Insulinaemia during pregnancy and implications for the dietary management of gestational diabetes mellitus

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Abstract

Amid the global obesity and type 2 diabetes epidemic, insulin resistance among women of child-bearing age continues to increase. Pregnancy is a natural state of insulin resistance and increased insulin secretion. When the physiological changes of pregnancy are superimposed on pre-existing insulin resistance, metabolic changes associated with pregnancy can become exaggerated. This can lead to an environment characterised by nutrient excess and inflammation, which is associated with adverse pregnancy conditions such as gestational diabetes mellitus (GDM) and foetal overgrowth. In the field of diabetes research, i.e. as a context separate from pregnancy, there has been growing interest in chronically elevated insulin, termed hyperinsulinaemia, and the role it plays in the aetiology of various cardiometabolic conditions. In this context, according to The Kraft Model of Hyperinsulinaemia, an elevated fasting and/or post-glucose load (100-gram glucose) plasma insulin response may be one of the earliest indicators for the development of type 2 diabetes later in life. While these concepts cannot be directly applied to pregnancy, it is likely that many women of child-bearing age will enter pregnancy with pre-existing insulin resistance and hyperinsulinaemia. As such, this may lead to further exaggerated changes in maternal metabolism (i.e. in the form of glucose, lipids, amino acids, and inflammatory markers). Moreover, since women who experience adverse pregnancy outcomes such as GDM appear to exist on a more adverse track toward later life chronic metabolic diseases, it is hypothesised that identifying hyperinsulinaemia (according to The Kraft Model) during pregnancy may aid in identifying these at-risk women sooner in pregnancy. Such early identification could provide an opportunity to enhance lifestyle management to mitigate the exaggeration of metabolic changes associated with pregnancy.

The overarching aim of this body of work was to investigate the relationship between insulin response patterns during pregnancy and adverse pregnancy outcomes. A further aim was to explore current dietary advice for the management of GDM. To investigate this aim, the first study was a systematic review (15 articles from 11 randomised controlled trials (RCTs), n = 3,614 participants) to extend knowledge on dietary interventions during pregnancy that may be effective for reducing the risk of adverse perinatal outcomes linked to maternal metabolic dysfunction (Chapter 3). The primary outcomes were neonatal cord blood insulin, c-peptide, and adiposity as markers of foetal hyperinsulinaemia and overnutrition. Findings demonstrated an overall protective effect of lifestyle-based interventions (including nutrition, physical activity, behaviour change, and monitoring) with elements of personalisation and dietary advice based on low glycaemic load (GL) approaches for reducing neonatal adiposity.

Maternal insulin response patterns and the prevalence of hyperinsulinaemia (applying the Kraft algorithm) according to varying degrees of glucose tolerance were then investigated in an observational study (Chapter 4). For this study, a historical dataset, dated mid-1970s to early-1990s, of results from presumed pregnant women (n = 926) who underwent three-hour oral glucose tolerance tests (OGTTs, 100-gram glucose load) with insulin assays was examined. Demographic information available included only participant age, weight, height, and date of testing. Further medical information and gestational age at time of testing was not available. Almost a third (31%) of the women with normal glucose tolerance demonstrated a delayed peak hyperinsulinaemia pattern (Kraft pattern III). Among the women with GDM (2010 American Diabetes Association criteria), the prevalence of Kraft pattern III hyperinsulinaemia was 75%. Kraft pattern IV hyperinsulinaemia was only observed in 3% of participants, the majority of which were categorised as GDM (GDM vs. normal: n = 13, 6% vs. n = 9, 1.5%; $p<0.001$).

To further explore the relationship between early pregnancy insulin response patterns and changes later in gestation, a case series of four pregnant women living in New Zealand was conducted (Chapter 5). Participants underwent an OGTT (75-gram glucose, 2-hour) at ≤ 14 weeks' gestation. Insulin response patterns were defined using a modified version of the Kraft algorithm to include four plasma insulin and glucose samples from the OGTT (fasting and 30-, 60-, and 120-minutes post oral glucose). Glycaemic measures, weight gain, foetal growth, dietary and lifestyle changes, and obstetric outcomes were examined throughout pregnancy. Two cases presented with Kraft pattern IIB hyperinsulinaemia early in pregnancy. For both of these women, difficulty during labour was observed (shoulder dystocia and surgically assisted delivery for Case #1, and emergency caesarean section for Case #4). A protective effect of healthy lifestyle choices to limit gestational weight gain (GWG) was postulated.

The final component of this research explored the current lifestyle management of GDM pregnancies by maternity-based health professionals in New Zealand in a qualitative study (Chapter 6). Key barriers to providing dietary advice included limited accessibility of health services, service delivery issues, fragmentation and conflicting information across health providers and alternative information sources (e.g. internet-based), and gaps in nutrition guidelines and clinical resources.

Collectively, this body of work demonstrated the potential significance of using insulin response patterns to recognise hyperinsulinaemia early in the gestational period. Several gaps in care were highlighted around the dietary management of women during early gestation at risk of GDM and those later in pregnancy once diagnosed. Recognising a spectrum of insulin response patterns may help to identify metabolic dysfunction much sooner in pregnancy than current screening programmes. Earlier identification of women with such an increased risk could further

enhance dietary and lifestyle management to be more proactive and personalised. Further research into this area could help inform the development of early screening tools for women with a higher risk of adverse outcomes and guide treatment decisions. In practice, a better understanding of metabolic phenotypes may aid in progressing therapeutic dietary advice to become more targeted and personalised for better maternal and offspring outcomes.

Yesterday I was clever, so I wanted to change the world.

Today I am wise, so I am changing myself.

-Rumi

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List of abbreviations

ACOG	American College of Obstetricians and Gynecologists
aRR	Adjusted relative risk
ANOVA	Analysis of variance
CHOICE	Choosing Healthy Options in Carbohydrate Energy
CI	Confidence interval
DALI	Vitamin D And Lifestyle Intervention for gestational diabetes prevention
DASH	Dietary Approaches to Stop Hypertension
DHA	Docosahexaenoic acid
ES	Effect size
GDM	Gestational Diabetes Mellitus
GWG	Gestational weight gain
GI	Glycaemic index
GL	Glycaemic load
GLUT4	Glucose transporter type 4
GLOW	Gestational weight gain and optimal wellness randomised controlled trial
HAPO	Hyperglycaemia and Adverse Pregnancy Outcomes study
HbA1c	Glycated haemoglobin, haemoglobin A1c
HDL	High density lipoprotein
HOMA	Homeostasis model assessment
HOMA-IR	Homeostasis model assessment of insulin resistance
HOMA-β	Homeostasis model assessment of beta-cell function
IGF	Insulin-like growth factor
IGF-1	Insulin-like growth factor-1
IOM	Institute of Medicine
IQR	Interquartile range
LDL	Low density lipoprotein particles
LED	Low energy diet
LIMIT	Limiting gestational weight gain in overweight and obese women during pregnancy to improve health outcomes
MAMI 1	Macronutrient adjustments in mothers with gestational diabetes study 1
MOMFIT	Maternal offspring metabolic family intervention trial
mTOR	Mammalian target of rapamycin
OGTT	Oral glucose tolerance test
OR	Odds ratio
PCOS	Polycystic ovarian syndrome

RCT	Randomised controlled trial
RR	Relative risk
ROLO	Randomised control trial of low glycaemic index diet in pregnancy
SD	Standard deviation
TNF-α	Tumour necrosis factor-alpha
UPBEAT	UK Pregnancies Better Eating and Activity Trial
USA	United States of America
VLED	Very low energy diet
VLDL	Very low density lipoprotein

Attestation of authorship

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person (except where explicitly defined in the acknowledgements), nor material which to a substantial extent has been submitted for the award of any other degree or diploma of a university or other institution of higher learning.

Sylvia Goedeke

List of publications arising from doctoral thesis

Papers published:

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North S, Zinn C, & Crofts C. Hyperinsulinemia during pregnancy across varying degrees of glucose tolerance: An examination of the Kraft database. *The Journal of Obstetrics and Gynaecology Research.* 2021 May;47(5):1719-1726. doi: 10.1111/jog.14731. Epub 2021 Mar 4. PMID: 33663017.

North S, Crofts C, & Zinn C. Health professionals' views and experiences around the dietary and lifestyle management of gestational diabetes in New Zealand. *Nutrition and Dietetics*. 2022 Apr;79(2):255-264. doi: 10.1111/1747-0080.12719. Epub 2022 Feb 6. PMID: 35128768.

North S, Crofts C, & Zinn C. Hyperinsulinaemia in pregnancy and gestational outcomes: A case series. *Journal of Insulin Resistance.* 2022 July; 5(1), 10. doi: 10.4102/jir.v5i1.69

Declaration of author contributions

Chapter 3	The role of maternal diet on offspring hyperinsulinaemia and adiposity after birth: a systematic review of randomised controlled trials	Goedeke (80%) Crofts (6%) Thoma (7%) Zinn (7%)
Chapter 4	Hyperinsulinemia during pregnancy across varying degrees of glucose tolerance: An examination of the Kraft database	Goedeke (80%) Zinn (10%) Crofts (10%)
Chapter 5	Hyperinsulinaemia in pregnancy and gestational outcomes: A case series	Goedeke (80%) Crofts (10%) Zinn (10%)
Chapter 6	Health professionals' views and experiences around the dietary and lifestyle management of gestational diabetes in New Zealand.	Goedeke (80%) Crofts (10%) Zinn (10%)

We, the undersigned, hereby agree to the percentages of participation in the papers outlined on page xiv.

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Christian Thoma

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Ethics approval

Ethical approval for research studies presented in this thesis was obtained from the following ethics committees:

- Chapter 4:
  - Auckland University of Technology Ethics Committee, 19/404, 23 October 2019
- Chapter 5:
  - Health and Disability Ethics Committees, 19/NTA/124/AM01, 19 June 2020
  - Auckland University of Technology Ethics Committee, 20/216, 22 July 2020
- Chapter 6:
  - Auckland University of Technology Ethics Committee, 19/405, 16 September 2020

Introduction

1.1 Background and Rationale

The obesity and diabetes epidemic has contributed to an increasing proportion of women of child-bearing age with insulin resistance. A change in the metabolic health landscape of women who may fall pregnant is evidenced by the rising incidence of conditions associated with insulin resistance. For example, in New Zealand, 27-32% of women of child-bearing age have obesity (Ministry of Health, 2020). The rising incidence of polycystic ovarian syndrome (PCOS) and advancing maternal age further illustrate an increasing population of potential mothers with insulin resistance (Anna, van der Ploeg, Cheung, Huxley, & Bauman, 2008; Kakoly, Earnest, Moran, Teede, & Joham, 2017; OECD Family Database, 2019). Particularly in the context of obesity, women with pre-existing insulin resistance who then conceive will enter pregnancy with an elevated risk of complications, in particular GDM, but also hypertensive disorders of pregnancy and foetal overgrowth (Catalano & Shankar, 2017). Thus, coinciding population trends in obesity and type 2 diabetes, increasing rates of GDM have been observed globally (Anna et al., 2008; Dabelea et al., 2005; Ferrara, 2007; Lavery et al., 2017; Paulo, Abdo, Bettencourt-Silva, & Al-Rifai, 2021; Zhu & Zhang, 2016). Specifically in an Australia and New Zealand context, this has been referred to as a tsunami that will likely overwhelm an already overstretched health system (Scott, Zhang, & Nolan, 2016).

Pregnancy is a natural and progressive state of increased insulin resistance and secretion; these physiological changes are expected and necessary to support the growth of a developing foetus (Butte, 2000). When this pre-pregnancy insulin resistance is combined with physiological adjustments to insulin metabolism, metabolic changes associated with pregnancy can become accentuated (Butte, 2000). This can lead to an environment characterised by nutrient excess (in the form of glucose, lipids, amino acids) and inflammation, which are associated with adverse pregnancy outcomes such as GDM and foetal overgrowth (Barbour & Hernandez, 2018a). Such adverse pregnancy outcomes are also associated with long-term health risks for women and offspring, including later life type 2 diabetes and metabolic syndrome (Bellamy, Casas, Hingorani, & Williams, 2009; Boney, Verma, Tucker, & Vohr, 2005; Damm et al., 2016; Godfrey et al., 2017; C. Kim, Newton, & Knopp, 2002; Retnakaran, 2018).

When we turn to the field of type 2 diabetes, it is now understood that decades before developing clinical hyperglycaemia, individuals exhibit chronic and progressive hyperinsulinaemia (Cooper, Brookler, Kyriakidou, Elliott, & Crofts, 2021; Crofts, Zinn, Wheldon, & Schofield, 2015). As pioneer in this field, Dr Joseph Kraft collected thousands of insulin

response patterns during OGTTs from patients and lay civilians over three decades (1970s to 1990s). A modern analysis of Kraft database showed that nearly three-quarters of people with normal glucose tolerance displayed hyperinsulinaemia (Crofts, Schofield, Zinn, Wheldon, & Kraft, 2016). This is important because excessive plasma insulin exposure observed in this condition has multiple effects on tissues which extend beyond glucose homeostasis. For example, the lipogenic and somatogenic effects of insulin can promote hyperlipidaemia and increased adiposity, which are both key characteristics of the metabolic syndrome (Crofts et al., 2015). Based on these and other metabolic effects, hyperinsulinaemia has been connected to the aetiology of various cardiometabolic diseases and could predict the development of type 2 diabetes as early at 10-20 years in advance (Crofts et al., 2015; Dankner, Chetrit, Shanik, Raz, & Roth, 2009; Hayashi et al., 2013). To this length, it has been suggested that identifying individuals with a hyperinsulinaemia insulin response pattern (see Terminology) would be one of the earliest biochemical markers of metabolic disease (Crofts et al., 2015; DiNicolantonio, Bhutani, Okeefe, & Crofts, 2017).

In a pregnancy context, the concepts described above cannot be applied directly due to the expected changes in maternal physiology. However, women of child-bearing age are not excluded from a potentially large proportion of individuals with hyperinsulinaemia. Thus, during the event of pregnancy, the effect that this hyperinsulinaemia has when superimposed on normal pregnancy physiology may underrecognized (Hufnagel, Dearden, Fernandez-Twinn, & Ozanne, 2022). However, when wider concepts surrounding hyperinsulinaemia and chronic metabolic disease are brought into the context of pregnancy, it is important to recognise that some changes in insulin secretion are expected, adaptive, and physiological (Butte, 2000). Therefore, the greatest challenge for defining hyperinsulinaemia in pregnancy is that there is no clear distinction between a normal insulin response pattern of pregnancy and one that might be considered harmful to the mother and offspring.

The role of a pre-existing and progressive factor in the aetiology of adverse pregnancy outcomes has been discussed by several authors. Adverse pregnancy outcomes such as GDM, hypertensive disorders of pregnancy, and pre-term birth are regarded as acute occurrences that exist on a continuum toward later-life chronic metabolic diseases (Ferranti, Jones, & Hernandez, 2016; Fu & Retnakaran, 2022; Hufnagel et al., 2022; Retnakaran, 2021). Moreover, population-based evidence has indicated that there is no clear inflection point at which hyperglycaemia in pregnancy leads to adverse outcomes in offspring and mothers (Bardugo et al., 2023; HAPO Study Cooperative Research Group et al., 2008). This suggests that instead of looking at GDM as an acute clinical condition, hyperglycaemia likely exists across a continuum which reflects maladaptive changes in maternal metabolism (Ferranti et al., 2016; Fu & Retnakaran, 2022). It

is plausible that the chronic and progressive effects of hyperinsulinaemia may contribute to this more adverse track toward later-life cardiovascular disease – before and during pregnancy, and in the post-partum period (Ferranti et al., 2016).

Within the field of GDM research, studies have examined insulin response patterns and metabolic sub-types (Bito, Foldesi, Nyari, & Pal, 2005; Grewal et al., 2012; Immanuel et al., 2021; Lapolla et al., 2008; Powe et al., 2016; N.-J. Zhang, Tao, Li, Zhao, & Wang, 2020). However, interpretation and comparison between studies is limited due to varying methodologies used and the lack of standardisation for insulin assays. There are also no specific reference intervals to define hyperinsulinaemia among pregnant women, therefore further limiting interpretation of previous research. Furthermore, current GDM management is surrounded by controversy; internationally, there is a lack of consensus regarding the optimal diagnostic criteria, glycaemic goals for treatment, specific dietary approaches, and medical therapies for best outcomes (Zera & Seely, 2021). Research into insulin response patterns during pregnancy has the potential to progress screening strategies to identify women with this pre-existing metabolic risk sooner in pregnancy. The challenge is that hyperinsulinaemia is not a concept that has been defined in pregnancy; therefore, exploring insulin response patterns to develop a definition may be beneficial for this field. A better understanding of metabolic responses among women at risk of GDM and those diagnosed could also help to improve lifestyle management to support optimal outcomes.

The importance of healthy dietary and lifestyle behaviours to promote positive maternal and offspring outcomes is well-established (B. Hill et al., 2020). However, the optimal diet to prevent or mitigate adverse outcomes among women with GDM, maternal obesity, and/or other conditions linked to pre-existing insulin resistance remains elusive (Hernandez & Brand-Miller, 2018; Mierzyński, Poniedziałek-Czajkowska, Sotowski, & Szydełko-Gorzkowicz, 2021; Parrettini, Caroli, & Torlone, 2020). Despite medical nutrition therapy being the first line of care for women diagnosed with GDM (Tsirou et al., 2019), guidelines for treatment are internationally inconsistent and, arguably, non-evidence-based (Hernandez & Brand-Miller, 2018; Tsirou et al., 2019). Moreover, since standard clinical practice for GDM management typically initiates screening from mid-to-late gestation (American Diabetes Association, 2023), the window of opportunity to introduce dietary modifications for glycaemic control and gestational weight gain (GWG) management is often brief. This reactive approach is a major challenge for providing timely and effective lifestyle advice. Similarly, other complications linked to maternal insulin resistance, such as hypertensive disorders, excess GWG, and placental or foetal growth abnormalities, can also occur in women who do not develop GDM (Catalano & Shankar, 2017; Corrales, Vidal-Puig, & Medina-Gómez, 2021). This means several months of pregnancy could

progress while the foetus is exposed to a sub-optimal metabolic environment. Proactive early screening approaches to identify women with metabolic dysfunction early in pregnancy (i.e. resulting from the effect of pre-existing insulin resistance and hyperinsulinaemia compounded by natural pregnancy changes), therefore, are important so that interventions could aid to mitigate adverse effects sooner in pregnancy (B. Hill et al., 2020).

As a dietitian, I was first exposed to GDM during my clinical training in a New Zealand public hospital diabetes service in 2015. Women newly referred to the service with GDM were provided with dietary advice on carbohydrate modification for glycaemic control. The majority of the women seen shared a number of key risk factors; they were overweight or obese, usually having exceeded their GWG goals, and from a higher risk ethnic demographic. The GDM diagnosis was a difficult experience for most women, requiring immediate lifestyle changes and intensive blood glucose monitoring. As dietitians, we would provide dietary advice with the belief that the changes would be beneficial. However, in reality, most women had a limited time frame (due to the gestational period) to implement dietary changes before medication would be recommended. Also due to clinical constraints, women often had limited contact with dietitians to develop a grasp of how to effectively implement the recommendations into their lifestyles. If the correct diet was so important for improving outcomes among these higher-risk pregnancies, it begs the question as to why these women did not receive this nutrition advice earlier. It was generally suggested from their risk factors that women who developed GDM had insulin resistance before their pregnancy, after all, a pre-existing metabolic defect is part of the underlying pathophysiology of GDM (Plows, Stanley, Baker, Reynolds, & Vickers, 2018). One may ponder whether there could be a better way to introduce lifestyle advice sooner in pregnancy before women face the discomfort of excess GWG and serious health risks associated with hyperglycaemia and/or hypertensive disorders. Together, these personal experiences as a clinician and interest in this wide body of literature that brought me to the central research question in this thesis.

1.2 Research aims

This research centres around exploring insulinaemia during pregnancy and several key aspects of the diagnosis and dietary management of GDM. This work aimed to investigate the relationship between insulin response patterns during pregnancy and adverse pregnancy outcomes. A further aim was to explore current dietary advice the prevention and management of GDM. To explore these overarching research themes, specific aims for each study were:

- **Literature review (Chapter 2 and 3):**

- To investigate insulin resistance, insulin response patterns, and hyperinsulinaemia during pregnancy, particularly in relation to adverse outcomes for women and offspring (Chapter 2).
- To explore dietary advice provision during pregnancy, specifically for GDM, and including evidence from intervention trials (Chapter 2).
- To systematically examine the relationship between maternal dietary exposures (from randomised controlled trials (RCTs)) and neonatal cord blood insulin, c-peptide, glucose, and adiposity (Chapter 3)

- **Kraft database analysis (Chapter 4)**:
  - To examine insulin response patterns (post 100-gram oral glucose load, 3-hour OGTT) and the prevalence of hyperinsulinaemia (using the Kraft pattern definitions) among a retrospective cohort of pregnant women characterised by glucose tolerance status (using the 1999 World Health Organization (WHO) GDM diagnostic criteria).
- **Pregnant women case series study (Chapter 5)**:
  - To examine the relationship between early pregnancy insulin response patterns and metabolic changes later in gestation.
  - To explore the feasibility of an OGTT test to identify hyperinsulinaemia during the first trimester of pregnancy as a potential strategy for identifying women at risk of adverse outcomes such as hyperglycaemia or excess GWG.
- **Qualitative study with health professionals (Chapter 6)**:
  - To investigate clinical experiences from health professionals providing dietary advice to women with GDM in New Zealand.
  - To explore challenges and gaps in care relating to dietary and lifestyle advice for GDM management.

1.3 Thesis overview

This thesis is presented as seven chapters. The structure is summarised in Figure 1. Terms used throughout this thesis can be given different meanings in various contexts. For this reason, important terms used consistently throughout this work are defined in Box 1.

It should be noted that this doctoral thesis follows a manuscript structure. Therefore, it is the nature of the thesis that there will be repetition in some areas. Chapter 2 presents a literature review relating to this research as a whole. Chapters 3 to 6 also each contain a background and literature review, with elements of repetition. These chapters contain a discussion relating to

the study described. Chapter 7 then concludes with a broader discussion of the combine research findings, which also includes some repetition.

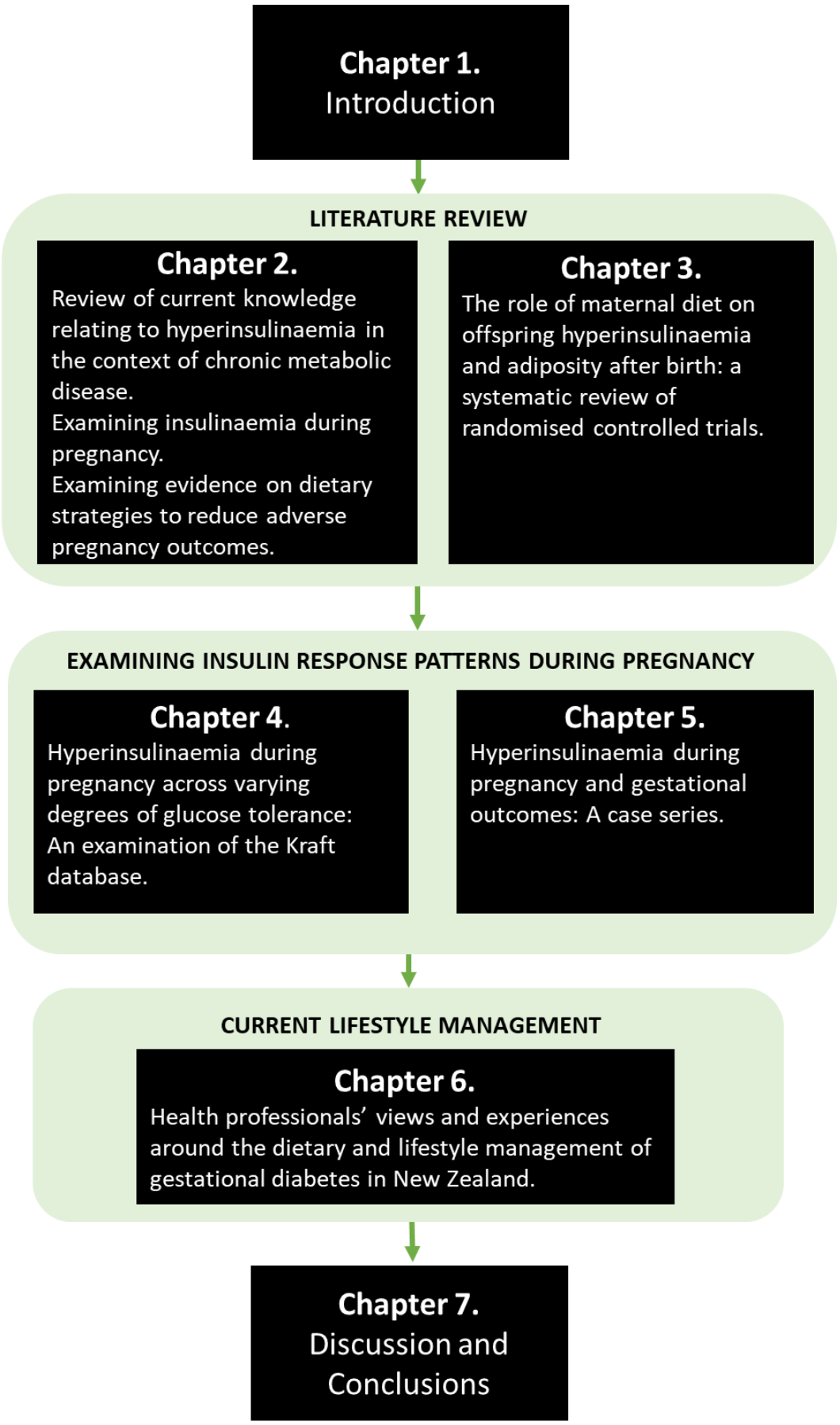


Figure 1. Flow diagram summarising thesis structure in seven chapters.

Insulin resistance

A metabolic condition characterised by impaired insulin signalling (James, Stöckli, & Birnbaum, 2021). This encompasses a depressed ability of insulin to activate insulin receptors on various cells, including glucose transport into tissues, particularly muscle and adipose, using the glucose transporter type 4 (GLUT4) transport system. In order to maintain homeostasis, insulin resistance is usually accompanied by compensatory hyperinsulinaemia. Insulin resistance is recognised as one of the earliest manifestations of a constellation of conditions, including type 2 diabetes and cardiovascular disease (otherwise referred to as cardiometabolic diseases).

Hyperinsulinaemia

Excessive levels of circulating plasma insulin and the effect of chronically elevated insulin signalling at insulin receptors of insulin-responsive tissues (A. M. Y. Zhang, Wellberg, Kopp, & Johnson, 2021). The effects of this exaggerated insulin signalling are linked to a range of metabolic and growth factor-related changes. Except for the very late stages of type 2 diabetes, hyperinsulinaemia invariably coexists with insulin resistance (Cooper, Brookler, Kyriakidou, et al., 2021; James et al., 2021). This condition can also be referred to as relative hyperinsulinaemia or compensatory hyperinsulinaemia.

There are multiple clinical definitions for hyperinsulinaemia. Therefore, for the purpose of this thesis, The Kraft Model of Hyperinsulinaemia will be used to define hyperinsulinaemia (Crofts et al., 2016; DiNicolantonio et al., 2017). This model characterises normal and dysfunctional insulin response patterns according to one or more of the following features: fasting plasma insulin, the timing and maximal insulin peak, and rate of decay, following an oral glucose load. As the Kraft patterns were determined from his original work conducted between the mid-1970s to early 1990s, absolute thresholds for the patterns are undetermined.

Insulin response pattern

The way in which insulin is released and used in response to changes in plasma nutrient levels following a standardised nutrient challenge (DiNicolantonio et al., 2017). This includes measuring plasma insulin levels over a defined time period following an oral or intravenous nutrient stimulus, typically glucose.

Metabolic dysfunction

Changes in metabolism that are associated with insulin resistance and the development of cardiometabolic diseases (James et al., 2021). These changes can include increased insulin resistance, hyperglycaemia, dyslipidaemia, hyperuricaemia, low-grade inflammation, and hypertension.

Cardiometabolic diseases

A group of medical conditions arising from a constellation of risk factors contributing to the chronic and progressive effects insulin resistance and metabolic dysfunction. These conditions include but are not limited to, type 2 diabetes, obesity, hypertension, non-alcoholic fatty liver disease, and cardiovascular diseases(Sattar, Gill, & Alazawi, 2020). This collection of conditions is also known as metabolic syndrome.

Box 1. Definitions of terms frequently used throughout the thesis.

1.4 Study delimitations

The boundaries of this research are as follows:

- In Chapter 4, insulin response patterns were examined from a pre-existing historical dataset, referred to as the Kraft dataset. A previous analysis of a sub-set of this same dataset formed the basis of the methodology applied. No further women were recruited for this research study.
- Analyses presented in Chapters 5 and 6 were specifically conducted in a New Zealand context. Participants were recruited locally, and therefore interpretation of findings pertained to perspectives from health professionals in New Zealand.

Chapter 2. Literature Review

The growing rise of chronic noncommunicable diseases, including obesity, type 2 diabetes, non-alcoholic fatty liver disease, cardiovascular diseases, and frailty, is a serious public health concern (Assar, Laosa, & Rodríguez Mañas, 2019; Lazarus et al., 2022; Powell-Wiley et al., 2021; Tahmi, Palta, & Luchsinger, 2021; van Herpt et al., 2020; World Health Organization, 2021). The number of people with type 2 diabetes has more than doubled globally in the last twenty years (Zimmet, Alberti, Magliano, & Bennett, 2016). Chronic metabolic diseases confer a substantial socioeconomic burden, contributing to a large proportion of healthcare costs to society (Barber, Kyrou, Randeva, & Weickert, 2021). Before we can explore the consequences of the population metabolic health crisis on pregnant women and their offspring, it is important to understand the underlying pathophysiological mechanisms at play in a broader, non-pregnancy context. Therefore, this first section of this review explores the concepts of insulin resistance and hyperinsulinaemia, and their associated metabolic perturbations. Later, we turn to explore the impacts of when the physiological changes observed during pregnancy are superimposed on this pre-existing state.

Insulin resistance is recognised as one of the earliest manifestations of a constellation of chronic metabolic diseases, particularly type 2 diabetes (James et al., 2021). The development of insulin resistance can be attributed to a range of environmental, genetic, and epigenetic factors. However, since genetics alone cannot explain the rise in obesity and chronic metabolic disease over the last century, environmental factors – particularly diet and exercise – are recognised as playing a key role (Hoffman, Powell, Barrett, & Hardy, 2021).

Modern-day “Westernised” lifestyles are characterised by a noisy, busy, stressful, sedentary, sleep-deprived, and technology-driven environment (P. Hanson, Weickert, & Barber, 2020). Together, a monopoly of intrinsic and extrinsic predisposing factors formulates a grand scenario for the development of obesity by promoting chronic excessive energy intake and reduced physical inactivity. Changes in the food environment over the last century are suggested as being one of the most significant causative factors. Technological advancements in modern agriculture and food production have led to the increasing availability of hyper-palatable, low-cost, nutrient-poor, and energy-dense food products. In a mindless culture, individuals are easily persuaded to consume based on availability, social norms, and expectations, which can sabotage appetite cues (P. Hanson et al., 2020).

The over-consumption of ultra-processed “Westernised” foods is well-recognised as having damaging effects on human health and is linked to the increased risk of multiple chronic

metabolic diseases (Xiaojia. Chen et al., 2020; Juul, Martinez-Steele, Parekh, Monteiro, & Chang, 2018; Nardocci et al., 2019; Suksatan et al., 2021). These ultra-processed foods are typically higher in refined carbohydrates, sugar, and total fat, and their consumption elicits an exaggerated physiological post-prandial insulin release in order to maintain glucose homeostasis (Erion & Corkey, 2017). In a world where ultra-processed food is hyper-available and hyper-palatable, over-consumption and chronic overnutrition leads to obesity, hyperinsulinaemia and insulin resistance (James et al., 2021).

2.1 Insulin resistance and hyperinsulinaemia

2.1.1 Insulin physiology

Insulin is a poly-peptide hormone secreted by pancreatic beta-cells (Aspinwall, Lakey, & Kennedy, 1999). It is recognised for its acute metabolic roles in energy metabolism, particularly glucose homeostasis. After a meal, elevated blood glucose levels and other metabolites trigger the release of insulin from pancreatic beta-cells. Binding of insulin to insulin receptors acts to normalise blood glucose levels after a meal through multiple well-regulated processes. These include activation of the GLUT4 transporter system in skeletal muscle and adipose tissue to facilitate glucose uptake; suppression of the release of glucose from the liver (hepatic glucose output); suppression of free fatty acid release from adipocytes (lipolysis); and increased lipid accumulation in liver and adipocytes (James et al., 2021).

In an evolutionary context, insulin is also closely related to insulin-like growth factors (IGF) genes and corresponding insulin-like peptides (A. M. Y. Zhang et al., 2021). While there are key differences between insulin and IGF in their downstream signalling and mechanisms, these peptides appear to share important growth factor-related and metabolic roles, particularly regulating energy storage and cell longevity (A. M. Y. Zhang et al., 2021). In a health and chronic disease context, excessive insulin signalling through these pathways is linked to obesity, cancer, accelerated ageing, and desensitisation of the insulin receptor (i.e. insulin resistance) (A. M. Y. Zhang et al., 2021). Excessive insulin signalling is required to maintain glucose homeostasis when insulin receptor sensitivity is reduced. This leads to a positive feed-forward loop of further increased insulin secretion, eventually manifesting as hyperinsulinaemia.

Insulin is secreted in a basal/bolus pattern. The mechanism and activity of bolus insulin is well-established for the regulation of glucose homeostasis in the postprandial state. Insulin has two phases of release following a nutrient stimulus (Figure 2) (Bilous & Donnelly; Vargas-Uricoechea, 2022). This first-phase of insulin release occurs within two minutes of glucose arriving in the blood steam and continues for 10-15 minutes. The second, more sustained, phase

of insulin release occurs until blood glucose levels and plasma insulin levels return to normal or near fasting levels. This second phase of insulin release may typically last between one and five hours.

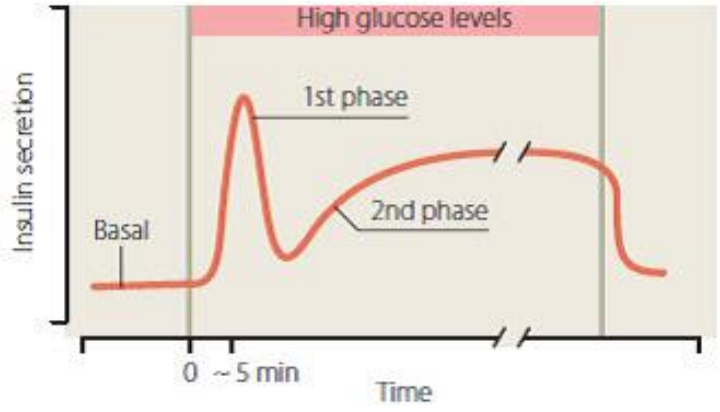


Figure 2. The biphasic glucose-stimulated release of insulin from pancreatic islets. Reprinted with permission from Bilous and Donnelly (2014).

Basal insulin secretion is not as well understood (Cooper, Brookler, Kyriakidou, et al., 2021). Insulin is released from the pancreatic beta-cells in a pulsatile manner. Blood insulin levels oscillate on small-amplitude high-frequency oscillations between 5 and 15 minutes apart with a background ultradian oscillation ranging from 80 to 180 minutes (Hellman, 2009; Satin, Butler, Ha, & Sherman, 2015; Schmitz, Rungby, Edge, & Juhl, 2008). More frequent and faster oscillations have been suggested as being an earlier indicator of insulin resistance.

2.1.2 Insulin resistance

The term “insulin resistance” was defined in the *New England Journal of Medicine* in 1929 as the significant variability in insulin dose required to reduce high glucose levels in a person with type 2 diabetes (Root, 1929). Following the pioneering work of Sir Harold Himsworth, insulin resistance was subsequently defined based on the degree of change in blood glucose level after administration of a defined quantity of insulin and glucose (Himsworth, 1936/2013, 1949). His differentiation of diabetes mellitus into the insulin-sensitive and insulin-insensitive types subsequently shaped modern understandings of type 2 diabetes (Himsworth, 1936/2013, 1949). Himsworth suggested that those with insulin resistance lack a factor (unknown at the time) that is required to facilitate insulin action. The important detail in Himswomth’s definition is the “defined quantity of insulin,” as in most situations (i.e. excluding type 1 diabetes and advances stages of type 2 diabetes) individuals with insulin resistance exhibit hyperinsulinaemia. When the pancreas fails to supply the excess insulin to compensate for insulin resistance, hyperglycaemia and glucose intolerance develop – the determining factors of type 2 diabetes (James et al., 2021).

In today's view, insulin resistance is characterised by a depressed ability of insulin to activate glucose transport into skeletal muscle and adipose tissues using the GLUT4 transport system (James et al., 2021). Insulin also suppresses the release of glucose from the liver and suppresses free fatty acid release from adipocytes (lipolysis). Thus, insulin resistant individuals, display impaired insulin-stimulated glucose disposal, increased hepatic glucose output, and increased circulating lipids (James et al., 2021). Although insulin resistance is largely recognised as a condition of glucose handling, the systemic and cellular effects of this progressive condition are widely recognised to have catastrophic effects on metabolism, leading to the development of many cardiometabolic diseases, in particular type 2 diabetes (James et al., 2021). In addition to metabolic changes observed in adipose, muscle, and hepatic tissues, insulin resistance is associated with maladaptive changes in tissues throughout the body. For example, insulin resistance is linked to alterations to nerve and bone metabolism, therefore providing a potential link to the development of other chronic metabolic diseases in these tissues, such as fragility and certain forms of dementia (Cooper, Brookler, & Crofts, 2021; B. Kim & Feldman, 2012).

2.1.3 Hyperinsulinaemia

Compensatory hyperinsulinaemia is a condition that is characterised by an excessive level of insulin circulating in the bloodstream (Crofts et al., 2015). However, there is great difficulty defining hyperinsulinaemia since, clinically and across literature, various definitions exist (A. M. Y. Zhang et al., 2021). Several criteria used to define hyperinsulinaemia include fasting levels, postprandial, 2-hour post-glucose load, or a combination of fasting and post-glucose load plasma insulin values (Crofts, Schofield, Wheldon, Zinn, & Kraft, 2019; Crofts et al., 2016; McAuley et al., 2001; Polonsky, Given, & Van Cauter, 1988). Unlike glucose thresholds that have been established for diagnosing type 2 diabetes, there is limited prospective data surrounding insulin measures and later life comorbidities. Instead of using clearly defined thresholds, various studies define hyperinsulinaemia based on quantiles (Dankner et al., 2009; Laakso, 1993; Lan-Pidhainy & Wolever, 2011; Nilsson, Nilsson, Hedblad, Eriksson, & Berglund, 2003).

To make an attempt at "defining" normal fasting plasma insulin, reference ranges are proposed by various laboratories. In most instances, reference ranges are typically developed using the mean of a given "healthy", normal glucose tolerant population, plus or minus three standard deviations from the mean. There is a general consensus that normal fasting plasma insulin sits below 30 µU/mL, which is consistent with Kraft's definition (described later in this section) (Kraft, 1975). However, inconsistencies for specific reference ranges exist between laboratories, even those within the same countries. For example, laboratories in the USA, UK, Australia, and New Zealand provide reference ranges for normal fasting plasma insulin up to 13-17.0 µU/mL

(Centres for Disease Control and Prevention, 2016; Labtests, 2023; National Health Service, 2023; Nutripath, 2023), whereas other pathology services in some of these countries also cite reference ranges up to 24.9 µU/mL (Auckland District Health Board, 2023; Clinical Pathology Laboratories, 2023; Mayo Clinic Laboratories, 2023). The Royal College of Pathologies Australasia cites that normal fasting plasma insulin may only be high as 10.0 µU/mL (The Royal College of Pathologies Austrialasia, 2023). Specific thresholds are often conflicting due to challenges arising from a lack of assay standardisation (as discussed later in section 2.1.5) and inconsistencies in the factors used for converting µU/mL to Système International units (pmol/L) (Knopp, Holder-Pearson, & Chase, 2019). These inconsistencies reflect the relatively short history of insulin measurement and major technological developments that have affected assay precision over the last century.

The greatest concerns surrounding hyperinsulinaemia definitions based on fasting levels come from the oscillatory nature of insulin secretion in the basal state (as described previously). Because of the issues interpreting fasting insulin measures, emerging literature suggests a 2-hour plasma insulin value, rather than fasting insulin, could be a stronger predictor for the development of type 2 diabetes. Hayashi et al. (2013) showed that approximately 38-48% of individuals with a lasting late insulin response (insulin peak at 2-hours post 75-gram oral glucose) developed type 2 diabetes in 10-11 years (pattern 3: OR 12.55, 95% CI 4.79–32.89; pattern 4: 8.34, 2.38–29.27). This was compared to 3-10% of individuals with peak plasma insulin at 30-minutes and 15% of individuals with peak plasma insulin at 1-hour post 75-gram oral glucose who developed type 2 diabetes at follow up. Compared to “normal” individuals, those with hyperinsulinaemia display larger insulin secretory pulses post oral glucose load, which is also characterised by a failure for plasma insulin to return to baseline between meals (Polonsky et al., 1988). Using data from 3-hour OGTTs (100-gram glucose load), Crofts et al. (2019) proposed that a 2-hour plasma insulin level > 30 µU/mL may identify an individual with hyperinsulinaemia.

Hyperinsulinaemia can manifest from either elevated basal/fasting circulating insulin, or because of excessive postprandial insulin secretion (A. M. Y. Zhang et al., 2021). Except for the very late stages of type 2 diabetes and in type 1 diabetes, compensatory hyperinsulinaemia typically coexists with insulin resistance (Cooper, Brookler, Kyriakidou, et al., 2021; James et al., 2021). Because insulin has effects on tissues throughout the body, compensatory hyperinsulinaemia refers to the systemic effects of excessive insulin signalling on insulin-responsive tissues. The resulting excessive stimulation of the insulin-responsive receptors is associated with metabolic derangements including, but not limited to, low-grade inflammation, hypertriglyceridaemia, hyperuricidaemia, and/or hypertension (Thomas, Corkey, Istfan, & Apovian, 2019; A. M. Y. Zhang et al., 2021). Due to this association, various authors have

theorised that hyperinsulinaemia may be the preceding defect toward the development of cardiometabolic diseases, including type 2 diabetes, cardiovascular disease, osteoporosis, certain forms of cancer, and certain forms of dementia (Cooper, Brookler, & Crofts, 2021; Cooper, Brookler, Kyriakidou, et al., 2021; Crofts et al., 2015; Thomas et al., 2019; A. M. Y. Zhang et al., 2021).

The Kraft Model of Hyperinsulinemia

Due to challenges related to defining hyperinsulinaemia, for the purpose of this thesis, hyperinsulinaemia will be referred to in the context of The Kraft Model of Hyperinsulinaemia. The Kraft Model of Hyperinsulinaemia is a theory based on the early work of Dr Joseph R Kraft (1975). His work involved examining insulin and glucose response patterns to a fasted oral glucose challenge (100-g) over three decades at St Joseph's Hospital, Chicago, Illinois, USA. The criteria for Kraft's definitions of hyperinsulinemia are described later in section 2.1.5. In brief, The Kraft Model defines hyperinsulinaemia according to one or a combination of the following: 1) the magnitude of fasting plasma insulin; 2) the presence/absence of a first-phase of insulin secretion and the magnitude and timing of the peak plasma insulin concentration; and 3) the rate of insulin decay following the peak plasma insulin response.

According to Kraft's hypothesis, an elevated fasting plasma insulin and/or exaggerated postprandial insulin signalling (measured as an insulin response to an oral glucose load) with normal glucose tolerance values was suggested as being the earliest indicator of type 2 diabetes (Kraft, 1975; Kraft & Sie, 1991). His work defined hyperinsulinaemia as diabetes mellitus *in situ* (occult diabetes); that is to say that, hyperinsulinaemia will invariably precede the development of hyperglycaemia in individuals with type 2 diabetes (Kraft, 1975).

The Kraft Model of Hyperinsulinemia and type 2 diabetes

To understand the progressive and chronic effects of insulin resistance, the important detail is this: in many people with defective glucose homeostasis (impaired fasting glucose and/or impaired glucose tolerance), there is a "relative insulin deficiency" in the face of insulin resistance, and not an absolute deficiency (Ferrannini & Mari, 2014). The majority of literature states that in individuals with type 2 diabetes, there is a significant loss in beta-cell function, resulting in insulin insufficiency to maintain glucose homeostasis (C. Chen, Cohrs, Stertmann, Bozsak, & Speier, 2017; Gray, Picone, Sloan, & Yashkin, 2015; Park, Gautier, & Chon, 2021). However, in people with type 2 diabetes, pancreatic beta-cell function loss occurs progressively along a continuum of the disease (Cerf, 2013; C. Chen et al., 2017; Esser, Utzschneider, & Kahn, 2020; James et al., 2021). Complete loss of beta-cell function is observed in the final stages,

where exogenous insulin therapy becomes a necessary part of the clinical management for type 2 diabetes.

According to The Kraft Model of Hyperinsulinaemia, individuals with type 2 diabetes may first present with elevated fasted and/or sustained post-glucose load insulin values a decade before the development of type 2 diabetes (Dankner et al., 2009; Hayashi et al., 2013). The progression of type 2 diabetes is also characterised by a state of relative compensatory hyperinsulinaemia until the late stages of the disease (James et al., 2021). Therefore, it has been suggested that evidence of this compensatory hyperinsulinaemia may be identifiable in a significant proportion of normoglycemic individuals, as shown in the Kraft dataset analysis (Crofts et al., 2016).

A progressive model from normal glucose and insulin responses across a type 2 diabetes spectrum was recently discussed in a review by Cooper and colleagues (2021), and is summarised in Table 1. A comprehensive review of the pathophysiology characterising these stages is beyond the scope of this review. In brief, a spectrum of type 2 diabetes phenotypes includes, first, those with hyperinsulinaemia and normal glycaemia. In stages two and three, there is persistent hyperinsulinaemia and mild (stage 2), then overt hyperglycaemia (stage 3). The final stage is characterised by hyperinsulinaemia and hyperglycaemia with morphological changes in pancreatic beta-cell mass, also described as the “pseudo type 1 diabetes”. Whilst it must be acknowledged that the model presented by Cooper and colleagues (2021) is a contemporary view which does not necessarily capture the complex aetiology of type 2 diabetes (Esser et al., 2020), on a conceptual level it has potentially useful implications from a public health perspective. Since hyperinsulinaemia exists very early in the progression across stages, recognising hyperinsulinaemia as a pathology of its own is crucial in the efforts to understand and mitigate chronic metabolic diseases.

Table 1. Hyperinsulinaemia and glycaemia spectrum as previously described by Cooper et al. (2021).

	Stage 1 Hyperinsulinaemia, normo-glycaemia	**Stage 2** Hyperinsulinaemia, mildly elevated glycaemia	**Stage 3** Hyperinsulinaemia, hyperglycaemia	**Stage 4** Hyperinsulinaemia, hyperglycaemia, morphological pancreatic beta-cell mass changes, "pseudo type 1 diabetes mellitus"
Venous plasma glucose (mmol/L)	< 6.0	6.1-7.0	≥ 7.0	≥ 7.0
HbA1c (mmol/mol)	≤ 37	38-49	≥ 50	≥ 50
	Compensatory hyperinsulinaemia adequately overcomes insulin resistance to maintain glycaemic control.	Chronic excess insulin levels are no longer able to mask insulin resistance.		

2.1.4 Stages of insulin resistance and hyperinsulinaemia

In many ways, it can be difficult to separate the conditions insulin resistance and hyperinsulinaemia. Essentially in all instances, hyperinsulinaemia and insulin resistance have a bi-directional relationship and contribute to the development of chronic metabolic diseases such as type 2 diabetes (Czech, 2017). The combined effects of cellular insulin resistance and systemic hyperinsulinaemia have catastrophic effects, leading to increased oxidative stress, chronic low-grade inflammation, lipotoxicity, and ectopic lipid accumulation (James et al., 2021). Here, the metabolic processes involved in insulin resistance and hyperinsulinaemia are discussed.

Insulin is a pleiotropic hormone, which means that it has impacts beyond glucose metabolism alone. In a glucose-centric model, elevated fasting and postprandial insulin primarily serves to maintain glucose homeostasis in the face of insulin resistance (Erion & Corkey, 2017). However, the selective insulin resistance paradox highlights other dysfunctional processes that may be exaggerated in a hyperinsulinaemic environment (Erion & Corkey, 2017; James et al., 2021). Selective insulin resistance suggests tissues such as hepatic, muscle, and adipose may remain sensitive to insulin's lipogenic effects while concurrently being resistant to insulin-mediated glucose transport (Erion & Corkey, 2017; James et al., 2021). Hyperinsulinaemia may, therefore,

exert negative effects by overstimulating pathways that remain sensitive to insulin, such as lipogenesis, protein synthesis, and certain transcription factors (James et al., 2021). Moreover, excessive insulin signalling has been shown to exert negative effects in various other tissues, such as kidney, bone, nerve, and vascular tissues (Artunc et al., 2016; da Silva et al., 2020; M. A. Hill et al., 2021; Salomaa, Riley, Kark, Nardo, & Folsom, 1995). For example, excessive insulin signalling can lead to diminished replenishment of osteocytes in bone tissues (Cooper, Brookler, & Crofts, 2021). In nerve tissue, hyperinsulinemia-induced insulin resistance leads to reduced activity of the serine/threonine kinase Akt, which is essential for the development of neurons (B. Kim & Feldman, 2012). Figure 3 summarises pathological changes associated with insulin resistance and hyperinsulinaemia.

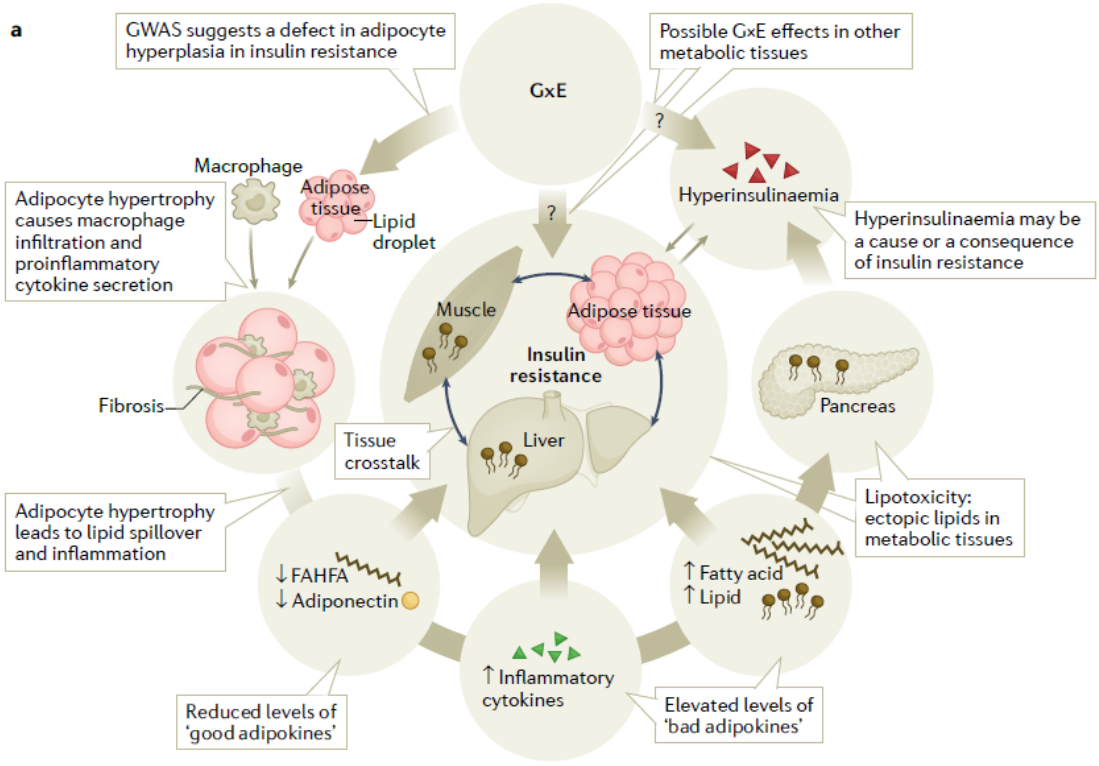


Figure 3. Extracellular factors that contribute to insulin resistance.
Reprinted with permission from James et al. (2021). Insulin resistance is triggered by a combination of genetic and environmental factors (G×E) that may lead to an inability of the fat cells to adequately store lipids. This culminates an array of changes, including infiltration of adipose tissue with macrophages, which is associated with increased inflammation and increased release of cytokines and lipids (including fatty acid esters of hydroxy fatty acids, FAHFAs). Lipid spillover from adipocytes whose storage capacity has been overloaded can result in the inappropriate deposition of lipids in a range of tissues, including muscle, liver, and pancreas, a phenomenon referred to as 'lipotoxicity'. Collectively, this results in the development of more advanced insulin resistance in muscle, liver, and adipocytes. This results in further hyperinsulinaemia, which can continue to exacerbate the development of insulin resistance.

Role of skeletal muscle, hepatic tissue, and adipose tissue

Currently, there is no consensus on whether insulin resistance starts in one particular tissue – skeletal muscle, adipose, pancreatic, or hepatic tissue (James et al., 2021). Some authors have suggested that skeletal muscle insulin resistance may be the earliest defect associated with metabolic syndrome (Petersen & Shulman, 2018; Shulman, 2018). Evidence from Shulman et al. (1990) shows that glycogen synthesis is impaired by ~50% in lean insulin-resistant, but otherwise healthy, offspring of individuals with type 2 diabetes. According to Petersen and Shulman (2018), impairments in insulin-stimulated glucose disposal at muscle tissue promotes compensatory hyperinsulinaemia. Elevated insulin is required to dispose of excess glucose through hepatic *de novo* lipogenesis. The exaggerated lipogenic effects of insulin on hepatic tissue leads to an increased lipid flux through the liver and subsequential development atherogenic dyslipidaemia (Petersen & Shulman, 2018; Shulman, 2018). Increased lipids in circulation further contribute to insulin resistance in subsequent tissues (primarily hepatic and adipose tissues) through ectopic fat deposition, as shown in Figure 3 (James et al., 2021).

A significant function of insulin is the suppression of lipolysis; therefore, adipose tissue that is resistant to insulin action presents with increased lipolysis, leading to an overabundance of lipids spilling over into circulation (Petersen & Shulman, 2018). As this lipid spill-over progresses in the context of low-grade chronic inflammation, ectopic lipids may be inappropriately deposited in metabolic tissues such as muscle, liver, pancreatic, and potentially other tissues. Collectively, the process of ectopic lipid deposition and lipotoxicity results in further insulin resistance and compensatory hyperinsulinaemia, which in turn breeds a destructive metabolic cycle of worsening insulin resistance (James et al., 2021) (Figure 3).

Adipose tissue dysfunction

It has been suggested that defects in the way adipose tissue expands may be one of the early events in the progressive development of insulin resistance and hyperinsulinaemia (James et al., 2021). Adipose tissue dysfunction is believed to be a core process linking overnutrition (through westernised diets and lifestyles) and increased lipids in circulation (James et al., 2021). Here, distinctions between metabolically healthy obesity and unhealthy obesity phenotypes demonstrate the key characteristics of dysfunctional adipose tissue (Blüher, 2020).

Adipose tissue expansion in response to overnutrition can occur either through hypertrophy (increase in cell size) or hyperplasia (increase in cell numbers) (James et al., 2021). Adipose tissue hyperplasia is generally considered healthy and adaptive; it is a key characteristic associated with the metabolically healthy obese phenotype (Ghaben & Scherer, 2019). When adipose tissue

expands by hyperplasia, it is associated with higher levels of adiponectin and better vascularisation (Ghaben & Scherer, 2019) (Figure 4). Metabolically healthy obese individuals tend to have lower visceral adipose tissue volume, be more insulin sensitive, and have more favourable lipid profiles (e.g lower triglycerides and higher HDL cholesterol) as compared to the metabolically unhealthy obese phenotype (Corrales et al., 2021; Tsatsoulis & Paschou, 2020).

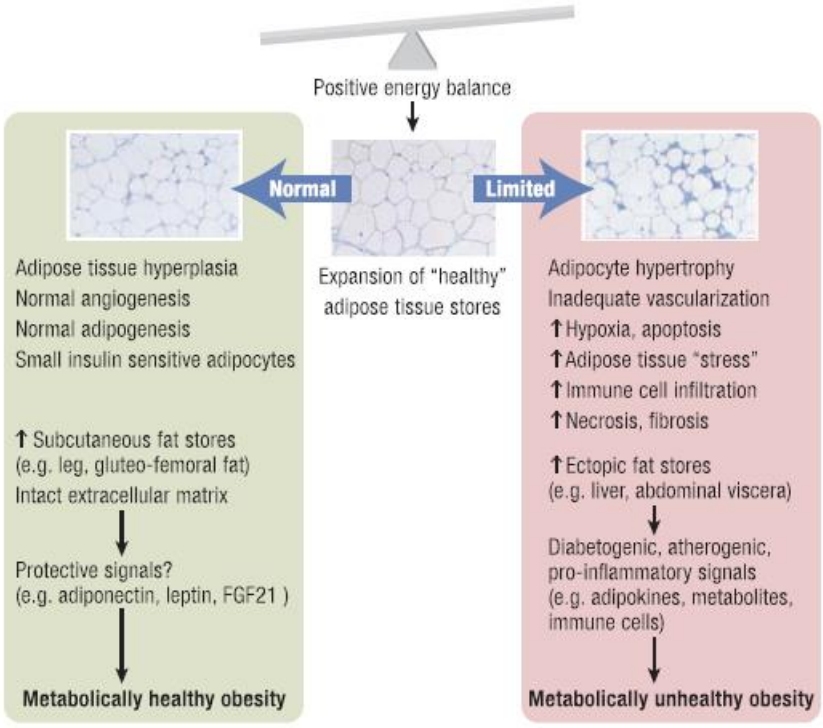


Figure 4. Adipose tissue dysfunction and development of metabolically unhealthy obesity. Open access figure reproduced with permission from Blüher (2020). In the face of positive energy balance, adipose tissue may expand by hypertrophy or hyperplasia. Adipose tissue dysfunction may develop if adipose tissues have an impaired capacity to respond to positive energy balance with ("healthier") hyperplasia, resulting in hypertrophy. Adipose tissue hypertrophy is associated with visceral fat deposits (i.e. in liver, abdominal visceral depots, skeletal muscle, pancreas) and dysfunctional tissue characteristics, including hypoxia, inadequate vascularisation, immune cell infiltration, apoptosis, and increased fibrosis (Blüher, 2020; James et al., 2021; Tsatsoulis & Paschou, 2020). Dysfunctional adipose tissue produces proinflammatory, diabetogenic, and atherogenic signals, which may contribute to the pathogenesis of cardiometabolic diseases in individuals with metabolically unhealthy obesity (Blüher, 2020).

In conditions of metabolically unhealthy obesity, adipocytes become hypertrophic and dysregulated, resulting in inflammatory changes in adipose tissue (Ghaben & Scherer, 2019; Huang, Chiu, Hsing, & Hsu, 2022). Impaired angiogenesis and tissue hypoxia have also been suggested as contributing factors in a cascade of metabolic and inflammatory changes, including macrophage infiltration, the increased production of proinflammatory cytokines (TNF-α and

IL-6), and increased undesirable adipokines (James et al., 2021). Dysfunctional, insulin resistant, adipose tissue demonstrates impaired metabolic flexibility, and impaired capacity to store dietary lipids, leading to enhanced lipolysis and elevated circulating free fatty acid levels (James et al., 2021; Petersen & Shulman, 2018).

2.1.5 Insulin measurement

Historical perspective on insulin measurement

The discovery of insulin was marked more than 100 years ago by the combined efforts of Banting, Best, Collip, and Macleod in Toronto, 1922 (Bliss, 1993; Sims, Carr, Oram, DiMeglio, & Evans-Molina, 2021) (Table 2). Soon after insulin could be integrated into the treatment of patients with diabetes mellitus, physicians first became aware of intra- and interindividual variabilities in glycaemic responses following insulin treatment, thus leading to the first reports of "insulin resistance" (Glassberg, Somogyi, & Taussig, 1927; Root, 1929). Later in the 1930s, insulin resistance diagnostics were pioneered by Sir Harold Himsworth (1949). Himsworth observed two phenotypes among individuals with diabetes mellitus – the insulin-sensitive and insulin-insensitive (Himsworth, 1936, 1936/2013). The classifications were not formally adopted by the National Diabetes Data Group until 1979 (Zaccardi, Webb, Yates, & Davies, 2016). From this historical perspective, Himsworth's definitions arguably shaped a glucose-centric model of type 2 diabetes. Himsworth proposed that the insulin-insensitive cases did not lack insulin but lacked a factor required to utilise insulin (Himsworth, 1936/2013). This has meant that treatments have subsequently oriented around increasing circulating plasma insulin (endogenously or exogenously) or enhancing insulin sensitivity (Zaccardi et al., 2016). The role of excess insulin secretion in the pathogenesis of insulin resistance could only be explored in the mid-late twentieth century when insulin measurement techniques were developed.

The development of insulin measurement assays

When compared to glucose assay, the history of insulin measurement is relatively short. A timeline of key discoveries in the development of insulin assays is provided in Table 2. Direct insulin measurement only first became possible in 1959 when radioimmunoassay (RIA) was developed by Berson and Yalow (Berson & Yalow, 1959a, 1959b, 1959c). The RIA technique was followed by further refined immunoassays (ELISA, AlphaLISA, HTRF, CLIA, and on-chip immunoassays), chromatography methods (MECC bottom-up method and LC-MS/MS top-down method), and electrochemical based on current and/or voltage to detect the binding of the analyte (Y. Shen, Prinyawiwatkul, & Xu, 2019).

Today, despite multiple insulin techniques being available, the most significant challenge hindering insulin assessment has been the lack of standardisation for insulin measurement (D. B. Sacks et al., 2002; Sharma, Matta, Haymond, & Chung, 2020). This is a critical issue when interpreting existing research, as it means that absolute insulin measurements cannot be compared across populations. These challenges are discussed further in section 2.1.5. In the following sections, techniques for measuring insulin resistance and insulin secretion patterns are explored as well as a discussion around the challenges related to interpreting fasting plasma insulin assays.

Table 2. Timeline of key discoveries leading to the development of modern insulin assays and insulin resistance measurements (Sims et al., 2021).

1921	Banting, Best, Collip, and Macleod discover insulin. Leonard Thompson was the first patient to receive pancreatic secretory extract.
1920s-1930s	Clinical observations of variable glycaemic responses to insulin treatments (Glassberg et al., 1927; Root, 1929).
1936	Sir Harold Himsworth describes two phenotypes among individuals with diabetes mellitus – the insulin-sensitive and insulin-insensitive (Himsworth, 1936, 1936/2013).
1959	Berson and Yalow developed the first radioimmunoassay allowing for quantification of insulin developed (Berson & Yalow, 1959a, 1959b, 1959c).
1970s and 1980s	Techniques to measure glucose disposal by insulin allowed for direct quantification on insulin resistance (DeFronzo, Tobin, & Andres, 1979; Reaven, 1983; S. W. Shen, Reaven, & Farquhar, 1970)
1975-1990	Two cite assays produced from monoclonal antibodies to insulin improves specificity of RIA method for quantifying insulin (Bürgi, Briner, Franken, & Kessler, 1988; Comitti, Racchetti, Gnocchi, Morandi, & Galante, 1987; Köhler & Milstein, 1975, 1976; Storch, Alexopoulos, & Kerp, 1989; Storch, Licht, Petersen, Obermeier, & Kerp, 1987; Toivonen et al., 1986).
1975-1993	Dr Joseph R. Kraft examined insulin response patterns to oral glucose and developed the Kraft patterns for defining hyperinsulinaemia (Kraft, 1975)
1979	National Diabetes Data Group proposed classifying diabetes as type 1 (insulin dependent), type 2 (noninsulin dependent), and “other” (National Diabetes Data Group, 1979b).
	Frequently sampled intravenous glucose tolerance test (Bergman, Ider, Bowden, & Cobelli, 1979).

1985	First description of homeostasis model assessment for steady-state estimation of insulin resistance and beta-cell function (Matthews et al., 1985)
	Quantitative insulin sensitivity check index (QUICKI) (Katz et al., 2000)
1990-2000s	Formulae based on OGTTs Cederholm and Wibell (1990), Belfiore, Iannello, and Volpicelli (1998), Matsuda and DeFronzo (1999), Stumvoll et al. (2000), and the dynamic oral glucose sensitivity (OGIS) index (Mari, Pacini, Murphy, Ludvik, & Nolan, 2001).

Quantification challenges for interpreting insulin measurements.

Since insulin assessment has progressed, there are notably several analytical and biological factors that affect the interpretation of assays. The original RIA immunoassay developed by Berson and Yalow relied on the competition between a constant amount of radioactive iodine-labelled insulin and insulin in a sample that would bind with a fixed amount of guinea pig anti-insulin serum; the concentration of insulin was determined from the ratio of antibody-bound radioactive insulin to free insulin (Berson & Yalow, 1959a). A key problem with the original RIA was an inefficient separation of the soluble antibody-bound insulin from free insulin until later techniques were developed (double antibody technique, salt precipitation, acid precipitation after enzyme destruction of free insulin, dextran or albumin coated charcoal, and ethanol) (Temple, Clark, & Hales, 1992).

Insulin RIAs have continued to encounter several problems affecting assay accuracy, which would lead to reporting disparities between different laboratories (Temple et al., 1992). Inaccuracies have been attributed to a range of factors, including the source of standard (Shishiba, Takino, Takagi, Sato, & Irie, 1982), properties of the antisera, adsorption of insulin onto glass and plastic tubes (Livesey & Donald, 1982), stability of insulin in plasma, and sample haemolysis (Livesey, Hodgkinson, Roud, & Donald, 1980). Moreover, immunoassays are not able to distinguish between human insulin, insulin analogues, and proinsulin, therefore making them inappropriate for research settings where individuals may be taking prescribed exogenous insulin (Y. Shen et al., 2019).

Importantly, the immunometric assays are dependent on the specificity of the antibodies used. Insulin antibodies used in the early version of the RIA method were known to cross-react with proinsulin, which was reported to be as high as 38% to 100% (Temple et al., 1992). Since plasma proinsulin is often raised in individuals with type 2 diabetes (Loopstra-Masters, Haffner, Lorenzo,

Wagenknecht, & Hanley, 2011; Tura et al., 2003), cross-reactivity would mean significant overestimation of plasma insulin status in some groups depending on their metabolic status. Challenges with immunoassay specificity improved through the 1980s with the development methods for producing monoclonal antibodies to insulin and the two-site (also called "sandwich") enzyme-linked immunoassays (ELISA) (Bürgi et al., 1988; Comitti et al., 1987; Hinsberg, Milby, & Zare, 1981; Kekow, Ulrichs, Müller-Ruchholtz, & Gross, 1988; Ruan et al., 1986; Storch et al., 1989; Storch et al., 1987; Toivonen et al., 1986). Despite having good selectivity toward insulin, some ELISA kits still showed cross-reactivity to intact proinsulin of around 54% (Y. Shen et al., 2019).

Chemiluminescence immunoassay is more widely used today. This technique combines a chemiluminescence technique – defined as the production of electromagnetic radiation from a chemical reaction – with an immunochemical reaction (Y. Shen et al., 2019). Monoclonal antibodies are coated on a test plate, and in the presence of insulin, the reacted complex produces chemiluminescence and the intensity is correlated with the insulin concentration (Y. Shen et al., 2019). The advantages of the chemiluminescence immunoassay are its high signal intensity, the absence of interfering emissions, reduced incubation time, and a wide dynamic range. Although these modern assays surpass the earlier RIA in terms of accuracy, the greatest challenge today is a standardisation in assessment techniques used. This means that any comparison between studies needs to be approached with considerations of these variables.

Insulin resistance measurement

Hyperinsulinaemic-euglycaemic clamp

The hyperinsulinaemic-euglycaemic clamp is referred to as the "gold" or reference standard measure of insulin sensitivity and was first described in 1979 (DeFronzo et al., 1979; S. H. Kim, 2011). The hyperinsulinaemic-euglycaemic clamp measures peripheral glucose uptake in response to a fixed infusion of exogenous insulin. After an overnight fast, insulin is administered at a continuous rate (5 to 120 μIU/m^2/min) to suppress endogenous insulin production and establish a new equilibrium at a higher concentration ("hyperinsulinaemia"). Blood glucose levels are then monitoring at intervals of 5- to 10-minutes while glucose is administered intravenously and continually adjusted to maintain euglycemia. Insulin sensitivity is calculated as "M", referring to the glucose infusion rate assumed as being equal to glucose being metabolised. "M" is adjusted for urinary losses and fat free mass. As opposed to the hyperinsulinaemic-euglycaemic clamp, the hyperglycaemic clamp technique raises blood glucose levels with an initial intravenous bolus followed by a continuous glucose infusion. Plasma glucose and insulin is measured every 2 minutes for the first 15-minutes of the initial

intravenous dextrose loading dose, and then every 5- to 10-minutes. The glucose infusion rate required to maintain steady-state hyperglycaemia is an index of insulin secretion capacity; an acute insulin response in measured during the first 10-minutes and late insulin response between minutes 10 and 120 of the test. Both techniques require laborious monitoring of glucose levels and manual modifications to the infusion rate, which can be subject to bias and user variability (S. H. Kim, 2011). The main limitation of the hyperinsulinaemic-euglycaemic clamp technique is that it does not reflect physiological conditions. An intravenous glucose infusion bypasses the first phase of metabolism through the hepatic portal vein. An effect from gut-derived peptide incretin hormones is also missed with this method (C. W. Chia & Egan, 2019). The technique also does not reflect conditions under physical activity. Therefore, modern interpretations may question the relevance of the clamp as being the "gold standard" for measuring insulin resistance. Further methods based on this reference standard should acknowledge the limitations of this test.

Frequently sampled intravenous glucose tolerance

The second early measure for insulin resistance, also introduced in 1979, is the frequently sampled intravenous glucose tolerance test (Bergman, Ider, Bowden, & Cobelli, 1979). The frequently sampled intravenous glucose tolerance test requires a minimum of 12 blood samples over an extended 180-minute testing period following an intravenous glucose bolus (Steil, Volund, Kahn, & Bergman, 1993). Insulin sensitivity is calculated as a ratio of two parameters that are defined in an "open-loop" minimal model, which describes the interactive effects of insulin and glucose on glucose disposal. The frequently sampled intravenous glucose tolerance test has been criticised as being poorly correlated with the hyperinsulinaemic-euglycaemic clamp due to under-estimating the first-phase insulin secretory response (S. H. Kim, 2011). Similar to the hyperinsulinaemic-euglycaemic clamp, the intravenous glucose tolerance test technique is laborious, typically making it only applicable in research settings and, therefore, inadequate for describing insulin resistance in a general population.

Fasting insulin measures: Homeostasis model assessment (HOMA) and quantitative insulin sensitivity check index (QUIKI)

More widely used measures for evaluating insulin resistance in research settings include the homeostasis model assessment of insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) (Katz et al., 2000; Matthews et al., 1985). Both models represent a calculated ratio using fasting plasma glucose and insulin; higher plasma insulin levels relative to glucose suggest insulin resistance. The homeostasis model assessment (HOMA) is a computer-solved method for assessing beta-cell function (HOMA-β) and insulin resistance (HOMA-IR) from fasting plasma glucose and insulin (Matthews et al., 1985; Wallace, Levy, &

Matthews, 2004). A non-linear calibrated computer model is also available but not as widely used (Wallace et al., 2004). QUICKI is nearly identical to HOMA-IR, only using a log transformation of fasting plasma glucose and insulin. HOMA-IR and QUICKI have been validated during pregnancy against the hyperinsulinaemic-euglycaemic clamp (HOMA-IR: $r = 0.53$, $p < 0.0001$; QUICKI: $r = 0.64$, $p < 0.0001$).

Sampling challenges with fasting insulin measures

Although widely used in research settings, the HOMA-IR and QUIKI measures based on a single fasting plasma insulin have been criticised for being a weak measure of insulin resistance when compared to the reference hyperinsulinaemic-euglycaemic clamp (S. H. Kim, 2011). The fundamental issue with using fasting measures alone is that they only reflect basal conditions. Interpreting basal conditions in complicated by the oscillatory pattern of insulin secretion in the basal state (Satin et al., 2015). HOMA-IR and QUIKI also provide no indication of the postprandial insulin secretion pattern when exposed to a nutrient stressor, which as discussed earlier, may be an important indicator of future type 2 diabetes risk.

The flaws with using models based on a single fasting insulin value have been described by DiNicolantonio et al. (2017). The first of these flaws is that insulin is released from the pancreatic beta-cells in a pulsatile manner. Blood insulin levels oscillate on small-amplitude high-frequency oscillations every 5-15 minutes with a background ultradian oscillation every 80-180 minutes (Cooper, Brookler, Kyriakidou, et al., 2021; Hellman, 2009; Satin et al., 2015; Schmitz et al., 2008). These oscillations could mean that an insulin value from a single sample could vary every 5-15 minutes, requiring an average of multiple samples taken to determine the true fasting insulin level.

Second, fasting insulin has been shown to have poor reproducibility, indicated by a coefficient of variation ranging between 25% and 50% (Mather et al., 2001). Correlation coefficients between HOMA-IR and “gold standard” measures can also vary with body composition, making it a poor measure of insulin sensitivity in lean, non-diabetic individuals (S. H. Kim, 2011). Wallace et al. (2004) have argued that HOMA measures should only be reported in the context of large cohort and epidemiological studies and not used for measuring insulin sensitivity and secretory function in isolation (i.e. they are not applicable for clinical practice).

OGTT formulae derived from plasma insulin and glucose

Several formulas based on OGTTs have also been established. These include Cederholm and Wibell (1990), Belfiore, Iannello, and Volpicelli (1998), Matsuda and DeFronzo (1999), Stumvoll et al. (2000), and the dynamic oral glucose sensitivity (OGIS) index (Mari, Pacini, Murphy, Ludvik,

& Nolan, 2001). These formulae are derived from plasma insulin and glucose measures taken during an OGTT (75-gram glucose, 2 hours). In their validation, calculations based on dynamic OGTT values tend to be more closely related to direct insulin sensitivity measures, compared to those based on fasting measures alone (S. H. Kim, Abbasi, & Reaven, 2004; Lorenzo, Haffner, Stancáková, & Laakso, 2010; Matsuda & DeFronzo, 1999; Yeni-Komshian, Carantoni, Abbasi, & Reaven, 2000).

OGTT calculations also have the capacity to introduce insulinogenic indices to estimate beta-cell function (i.e. insulin secretion). One of these calculations is a disposition index, calculated by the ratio of Δ (0–30 min) for insulin and glucose, divided by HOMA-IR (Y. Liu et al., 2018). Others include the insulinogenic index (calculated from the change in insulin and change in glucose over 30 minutes after an oral glucose load), the homeostatic model assessment of beta-cell function (HOMA-β), which is based on fasting glucose and insulin, and the Stumvoll first-phase estimate. The Stumvoll first-phase estimate is the only calculated measure of beta-cell function validated among pregnant women. Among a cohort of 40 pregnant women who underwent testing pre-pregnancy, during 12-14 week', and 34-36 weeks' gestation, the Stumvoll first-phase estimate was shown to correlate well with first-phase insulin response measured during the hyperinsulinaemic-euglycemic clamp (pre-pregnancy: $r = 0.44$, $p = 0.01$; 12-14 weeks': $r = 0.67$, $p = 0.0001$; 34=26 weeks': $r = 0.67$, $p = 0.0001$) (Powe, Locascio, Gordesky, Florez, & Catalano, 2022).

Unlike HOMA-IR, indirect measures following an OGTT are considered more accurate in individuals without diabetes (Mari et al., 2001; Matsuda & DeFronzo, 1999). This is due to an observation that postprandial insulin levels tend to be more attenuated in individuals with diabetes (S. H. Kim, 2011). Insulin assays following OGTT also provide an indication of insulin secretion patterns relative to insulin resistance, which has greater relevance for assessing metabolic health in individuals without diabetes (Crofts et al., 2016; S. H. Kim et al., 2004).

It is important to note that other than the Matsuda index and Stumvoll first-phase estimate, no other widely used insulin sensitivity or beta-cell function measures based on OGTTs have been validated among pregnant women against the gold standard hyperinsulinaemic-euglycemic clamp. This is important to recognise when interpreting research, given that glucose and insulin levels are substantially altered during pregnancy.

Insulin response patterns

Insulin response patterns to an OGTT are an emerging method for defining hyperinsulinaemia. This technique is merited for its capacity to characterise the timing and magnitude of the insulin

peak and post glucose load response, which is representative of physiological conditions (Crofts et al., 2019; DiNicolantonio et al., 2017). According to The Kraft Model of Hyperinsulinaemia, normal insulin responses are generally defined as those that model a healthy glucose response curve to an OGTT where insulin should rise within 30-60 minutes and return to near fasting levels after two hours (Kraft, 1975). Other criteria that define hyperinsulinaemia typically refer to dysfunctional insulin response patterns as those that have an exaggerated postprandial or post glucose load insulin response, with or without elevated fasting insulin (DiNicolantonio et al., 2017).

Patterns such as those defined by Kraft (1975), Crofts et al. (2016), Hayashi et al. (2013) and N.-J. Zhang et al. (2020) refer to a dysfunctional insulin response as one with a "delayed insulin peak" at 120-minutes or later following an oral glucose load (Table 3). That is, instead of the insulin secretory response presenting a peak within 30- to 60-minutes post oral glucose load before returning to near fasting levels within two hours, dysfunctional insulin patterns described by the authors above present a peak plasma insulin level at two-hours or later following an oral glucose load. It has been suggested that a delayed peak represents a defect in the first-phase insulin response, as an early marker for beta-cell dysfunction (Festa, Williams, Hanley, & Haffner, 2008; Y. Sun et al., 2016).

Kraft patterns

The Kraft patterns used to describe fasting and post-prandial insulin responses were first curated by Dr Joseph R Kraft (1975). His work examining insulin response patterns over three decades entailed collecting insulin and glucose tolerances to oral glucose (100-g glucose load) from patients referred by physician for diabetes testing at St Joseph's Hospital, Chicago, Illinois, USA. Kraft was affiliated with the Department of Clinical Pathology and Nuclear Medicine. Over 15,000 examinations were described in total (Crofts et al., 2016; Kraft, 1974, 1975, 1983, 1988; Kraft & Sie, 1991).

The standard protocol involved a four-hour OGTT with a 100-gram oral glucose load. Assays were taken at fasting, 30 minutes, and every hour thereafter. A limited number of physicians requested three- and five-hour procedures. Plasma glucose was determined by ferricyanide method (Autoanalyser) for the first ~3,000 examinations, and plasma glucose oxidase method used thereafter. Kraft noted that the procedures yielded interchangeable data (Kraft, 1983). Insulin was measured by RIA with automated gamma counting systems (Pharmacia Insulin RIA test) (Kraft & Sie, 1991).

Five insulin reference patterns were described from the cumulative data. A limited standard error of the mean for each timed value of the dynamic insulin assay was presented (standard error range from 0.6 to 16.8 for mean insulin pM values) (Kraft & Sie, 1991). The incidence of the insulin reference patterns also correlated with the diabetes diagnosis classifications from the National Diabetes Data Group (1979a) (Kraft, 1983; Kraft & Sie, 1991). A normal insulin response (Pattern I) was defined as a fasting insulin of 0-30 μU/mL, a peak value at 30- or 60-minutes above fasting range that returned to fasting range, and the second and third hour sum of less than 60 μU/mL (Kraft, 1975; Kraft & Sie, 1991). Pattern II was characterised as a normal insulin peak (30 or 60 minutes), with a delayed return to fasting range (second and third hour sum of > 100 μU/mL). Pattern III (hyperinsulinaemia) was characterised by a delayed insulin peak at the second or third hour post glucose load. High fasting insulin levels (>50 μU/mL), consistent with type 2 diabetes, was characteristic of pattern IV. A low insulin response across all time points characterised pattern V, hypoinsulinaemia, half of which cases were associated with hyperglycaemia (Kraft, 1975).

In recent years Crofts et al. (2016) reanalysed Kraft's original dataset according to redefined criteria. In brief, the original Kraft patterns from 1975 were determined to be overly complex and failed to classify participants with fasting insulin between 31 and 49 μU/mL. The revised algorithm was developed, combining Kraft's original work with information from his lay publication and additional information from recent data (Hayashi et al., 2013; Kraft, 2011). The analysis included 7755 participants (3953 men; 3802 women; mean age 55.5 ± 14.0 years, mean BMI 26.9 ± 5.3 kg/m^2). More than half (54%, n = 4185) of the participants had normal glucose tolerance; the remaining 21%, 23%, and 2% were classified as diabetes mellitus, impaired glucose tolerance, and impaired fasting glucose, each respectively according to WHO criteria (World Health Organization, 1999). The modern Kraft criteria comprise six insulin response patterns: Pattern I, Normal Insulin; Pattern IIA Borderline; Pattern IIB, III, and IV Hyperinsulinaemia; Pattern V Hypoinsulinaemia. A summary of the pattern criteria is provided in Table 3. As first described by Kraft, the patterns were modelled off a normal insulin response as being one with fasting insulin ≤ 30 μU/mL, an insulin peak at 30- or 60-minutes, and rapid clearance leading to the sum of the two- and three-hour insulin concentration being ≤ 60 μU/mL. The distinct difference compared to Kraft's original model was that pattern II was divided into IIA ("borderline") and IIB ("hyperinsulinaemia").

In the reanalysis of Kraft's original dataset, Crofts et al. (2016) described over 90% of people with either impaired glucose tolerance or type 2 diabetes had a hyperinsulinaemia pattern (Kraft Pattern IIB, III, or IV). The most important finding from this research was that among the people with normal glucose tolerance (n = 4,030), approximately 75% displayed hyperinsulinaemia, an

astounding prevalence. It should be noted that although limited demographic information is available, participants included patients and healthy volunteers referred for an OGTT at St. Joesph Hospital. Given Kraft's original observations further combined with modern prospective data (Dankner et al., 2009; Hayashi et al., 2013), it was proposed that the dynamic Kraft pattern methodology could be used to detect a person's risk of later-life metabolic disease (Crofts et al., 2016).

Hayashi et al. patterns

Hayashi et al. (2013) modelled dynamic insulin criteria in prospective research. Their findings showed that postprandial insulin levels could strongly predict type 2 diabetes development. Five patterns were developed from a cohort of 400 non-diabetic Japanese Americans from King Country, Washington, USA, who underwent a two-hour OGTT (75-gram glucose). Samples for plasma glucose and insulin were collected at fasting, 30-, 60-, and 120-minutes. Plasma glucose was assayed by an automated glucose oxidase method and plasma insulin by RIA (interassay coefficients of variation reported as 5 and 8% for insulin). The Hayashi et al. patterns are distinct from Kraft's in that peak concentration criteria for fasting or two-hour insulin levels are not defined. Instead, the five patterns refer to the insulin peak as being at 30- (Pattern 1 and 2), 60- (Pattern 2 and 3), or 120-minutes (Pattern 4 and 5) (Table 3). Patterns 4 and 5 were characterised by a delayed 120-minute insulin peak, similar to Kraft's Pattern III Hyperinsulinaemia. In their adjust model, the odds ratios for developing type 2 diabetes within a 10–11-year period was 12.55 (95% CI 4.79, 32.89; n = 28 cases/128 in total) for Hayashi Pattern 4 and 8.34 (95% CI 2.38, 29.27; n = 9 cases/24 in total) for Hayashi Pattern 5, compared to Hayashi Pattern 1 and 2.

Zhang et al. patterns

N.-J. Zhang et al. (2020) defined two insulin secretion patterns in a cohort of 2,432 pregnant Chinese women. Three-hour OGTTs (75-gram glucose load) were undertaken at 24-28 weeks' gestation as a part of usual screening/diagnostics for GDM. Methods used for glucose and insulin assays were not reported. Women were grouped according to their glucose tolerances as normal glucose tolerant (n = 1696, 69.7%) and GDM (n = 737, 30.3%) (IADPSG criteria) (International Association of Diabetes Pregnancy Study Groups Consensus Panel, 2010). The GDM group was also divided into subgroups based on plasma glucose abnormalities: in the GDM1 group (n = 89, 12.10%), only fasting plasma glucose was abnormal; in the GDM2 group (n = 516, 70.0%), only postprandial was abnormal; and in the GDM3 group (n = 132, 17.9%), both fasting and postprandial were abnormal. Using the insulin response data to the OGTT, two insulin release patterns were established based on the peak insulin response; a "normal" insulin pattern, termed "Type I", was characterised by an insulin peak at 30 minutes or 60 minutes. A "dysfunctional" "Type II" insulin pattern was defined by a delayed peak insulin at 120 or 180

minutes, which is similar to the Hayashi Patterns 4 and 5 and Kraft Pattern III (hyperinsulinaemia). Maternal and neonatal outcomes were later collected at delivery. These included incidences of preeclampsia, caesarean delivery, and postpartum haemorrhage, neonatal birth weight, and the occurrence of neonatal hypoglycaemia and admission to the neonatal intensive care unit. Zhang et al.'s Type II "dysfunctional" insulin pattern was represented in 62% of women diagnosed with GDM and 23% of women with normal glucose tolerance. A gradual increase in 2-hour plasma insulin was also shown across the normal glucose tolerant, GDM1, GDM2, and GDM3 groups ($p < 0.05$), with GDM3 representing the highest mean 2-hour insulin value. Logistic regression analysis showed that the delayed peak Type II insulin pattern was significantly associated with a higher risk of preeclampsia (adjusted OR 1.92, 95% CI 1.07, 3.44), large-for-gestational age infants (adjusted OR 1.15, 95% CI 1.05, 1.44), and neonatal hypoglycaemia (adjusted OR 1.42, 95% CI 1.01, 1.66), independent of GDM status. It should be noted that this was the only prospective study among pregnant women identified which used a dynamic insulin pattern analysis with an OGTT. To date, no such methods have been validated for use in pregnancy.

Another Chinese cohort study that included non-pregnant individuals also demonstrated a link between a delayed peak insulin secretion pattern at 120- or 180-minutes following a 3-hour OGTT (75-gram glucose) and risk for developing type 2 diabetes (Y. Sun et al., 2016). Participants were patients newly diagnosed as having type 2 diabetes (n = 694), impaired glucose tolerance (n = 419), and normal glucose tolerance (n = 558). Among those with a delayed peak insulin secretion pattern (insulin peak at 120- or 180-minutes, 24.91%), a quarter had normal glucose tolerance at the time of testing. Compared to those with a peak insulin response at 30-minutes, those with an insulin peak at 120- or 180-minutes had a higher risk of developing type 2 diabetes at 6 years follow up (RR 7.30, 95% CI 1.53, 34.72, adjusted for sex, age, BMI, and blood pressure), which is consistent with the associations described by (Hayashi et al., 2013).

Table 3. Criteria for defining hyperinsulinaemia using plasma insulin pattern analysis from OGTT

	Required assay	Insulin measurement	Criteria used
Kraft (modified) (Crofts et al., 2016)	OGTT (100-gram glucose), 180 to 300 min	RIA (Pharmacia Insulin and Diagnostic Product Cooporation Coat A Count insulin tests)	Kraft I, normal insulin: • Fasting insulin ≤ 30 μU/mL • 30- or 60-min peak • 120- + 180-min sum < 60 μU/mL Kraft IIA, borderline: • Fasting insulin ≤ 50 μU/mL • 30- or 60-min peak • 120- + 180-min sum ≥ 60, <100 μU/mL or • Fasting insulin 31-50 μU/mL • 30-or 60-min peak • 120- + 180-min sum < 60 μU/mL Kraft IIB, hyperinsulinaemia: • Fasting insulin ≤ 50 μU/mL • 30- or 60-min peak • 120- + 180-min sum ≥ 100 μU/mL Kraft III, hyperinsulinaemia: • Fasting insulin ≤ 50 μU/mL • Delayed peak (120- or 180-min) Kraft IV, hyperinsulinaemia: • Fasting insulin > 50 μU/mL Kraft V, hypoinsulinaemia: • All values < 30 μU/mL
Hayashi et al. (2013)	OGTT (75-gram glucose), 120 min	RIA (unspecified)	Pattern 1 • Peak at 30-min • 60-min > 120-min Pattern 2 • Peak at 30-min • 60-min ≤ 120-min Pattern 3 • Peak at 60-min Pattern 4 • Peak at 120-min • 30-min < 60-min Pattern 5 • Peak at 120-min • 30-min ≥ 60-min
Zhang et al. (2020) and Sun et al. (2016)	OGTT (75-gram glucose), 180 min	Zhang et al.: Unspecified Sun et al.: Chemiluminescence (Cobas e411 Analyzer, Roche Diagnostics)	Type I, normal: • 30- or 60-min peak Type II, delayed peak: • 120- or 180-min peak

min: minute; OGTT: oral glucose tolerance test; RIA: radioimmunoassay

2.2 Modern metabolic health concerns in the context of pregnancy

Women of child-bearing age are not excluded from wider societal changes in metabolic health discussed earlier in section 2.1. Maternal obesity and GDM are the most common metabolic concerns for pregnant women, for which the prevalence has continued to rise over the last two decades (Anna et al., 2008; Dabelea et al., 2005; Ferrara, 2007; Lavery et al., 2017; Paulo et al., 2021; Zhu & Zhang, 2016). Maternal obesity, in particular, is characterised by more advanced insulin resistance (Catalano, 2010; Catalano & Shankar, 2017), and is associated with significant perinatal and neonatal morbidity (American College of Obstetricians and Gynecologists' Committee on Practice Bulletins, 2021; Dodd, Grivell, Nguyen, Chan, & Robinson, 2011; Vats, Saxena, Sachdeva, Walia, & Gupta, 2021). Women with obesity during pregnancy also encounter greater risk of various adverse outcomes, in particular GDM, but also hypertensive disorders of pregnancy and foetal overgrowth (Catalano & Shankar, 2017).

First, to understand the relevance of pre-existing insulin resistance and hyperinsulinaemia in a pregnancy context, it is important to address physiological changes in maternal metabolism. Pregnancy is a natural state of increased insulin resistance and secretion; these physiological changes are expected and necessary to support the growth of a developing foetus (Butte, 2000). A progressive decline in insulin sensitivity and simultaneous rise in beta-cell insulin production drive physiological adaptations to ensure nutrient storage and transfer to support foetal needs (Armistead et al., 2020; Butte, 2000). This section discusses specific changes in nutrient metabolism as a result of this increased maternal insulin resistance and insulin secretion. Later, undesirable effects associated with adverse maternal metabolic changes will be discussed.

2.2.1 Physiological changes during pregnancy

A healthy pregnancy is characterised by two distinct phases: an "anabolic phase" and a "catabolic phase" (Armistead et al., 2020). The first trimester of pregnancy involves an acute increase in insulin sensitivity. Once the placenta is formed from around gestational week 10, surging levels of hormones such as human placental growth hormone, human placental lactogen, progesterone, oestrogen, and cortisol as well as inflammatory cytokines and adipokines lead to the progressive development of insulin resistance and hyperinsulinaemia (Armistead et al., 2020; Barbour et al., 2007; Butte, 2000; Catalano, Huston, Amini, & Kalhan, 1999). Combined, the anabolic effects of insulin resistance and hyperinsulinaemia allow pregnant women to develop adipose stores while preferentially transferring essential nutrients to support foetal needs (Armistead et al., 2020). In the third trimester, maternal metabolism

becomes increasingly "catabolic" as adipose stores are mobilised, and placental nutrient transport is altered to meet rapid foetal growth demands.

Glucose metabolism

Changes in glucose metabolism are an essential adaptation in a healthy pregnancy. From the beginning of pregnancy, a heightened state of insulin resistance and hyperinsulinaemia promotes maternal metabolism to be increasingly fuelled by non-carbohydrate substrates, sparing glucose for the foetus (Butte, 2000). Traditional views have been that since the foetus is unable (or has limited capacity) to undergo gluconeogenesis, they rely on a consistent supply of glucose from maternal metabolism (Cowett & Farrag, 2004). Recent *in vivo* evidence from human pregnancies has suggested glucose needs during pregnancy reflect a balance of both foetal and placental glucose consumption. That placental glucose needs likely modulate the maternal foetal-glucose gradient and glucose from maternal circulation is utilised to serve both placental and foetal needs (Michelsen et al., 2019).

As foetal and placental glucose demands increase across gestation, so does maternal glucose production and overall carbohydrate oxidative metabolism (Butte, 2000). For example, maternal basal hepatic gluconeogenesis rises by 16-30% from around 26 weeks' gestation (Bell & Bauman, 1997; Catalano et al., 1992). This increase in carbohydrate oxidative metabolism has been demonstrated by a higher respiratory quotient; in late pregnancy, carbohydrate oxidation was estimated at 282 grams per day, 73 grams higher than estimated six-month postpartum levels as demonstrated in a cohort of 76 pregnant women (40 lactating, 36 nonlactating with postpartum BMI's of 23.2 ± 3.7 kg/m^2 and 24.2 ± 4.3 kg/m^2, each respectively) (Butte, 2000).

Hyperinsulinaemia and insulin resistance of pregnancy and carbohydrate metabolism

The increase in carbohydrate oxidative metabolism during pregnancy is driven by a range of endocrine and cytokine signals that are mainly produced by the placenta, maternal adipose tissue, and maternal pituitary gland. Placental growth hormone, progesterone, oestrogen, cortisol, and tumour necrosis factor-alpha (TNF-α) drive a state of peripheral insulin resistance (Armistead et al., 2020; Handwerger & Freemark, 2000; Kaur, Muhlhausler, Roberts, & Gatford, 2021; McIntyre, Zeck, & Russell, 2009; Napso, Yong, Lopez-Tello, & Sferruzzi-Perri, 2018). Concurrently, lactogen hormones, which include placental lactogen and maternal pituitary prolactin, impose a stage of leptin resistance and stimulate hyperphagia to allow ongoing fat mass expansion.

Lactogen hormones also drive beta-cell hypertrophy and cell mass expansion from early-mid gestation, creating the physiological hyperinsulinaemia of pregnancy (Armistead et al., 2020;

Banerjee et al., 2016; Handwerger & Freemark, 2000; H. Kim et al., 2010; Newbern & Freemark, 2011; Parrettini et al., 2020; Parsons, Brelje, & Sorenson, 1992). By the end of pregnancy, maternal insulin levels may increase as much as 2- to 2.5-fold and insulin-mediated glucose disposal is reduced by ~50% (Barbour et al., 2007; Butte, 2000; Catalano et al., 1999). In this way, there can be many similarities drawn between these combined features of pregnancy, that is, insulin resistance, hyperinsulinaemia, leptin resistance, and low-grade inflammation, and pathological processes observed in metabolic syndrome. Thus, when pre-existing insulin resistance becomes augmented by these physiological processes, exaggerated metabolic effects such as hyperglycaemia can develop.

Maternal glucose and foetal overnutrition (The Pedersen Hypothesis)

The relationship between maternal glycaemia and foetal glucose homeostasis was first postulated by J. Pedersen (1952). Since maternal insulin does not cross the placenta, the Pedersen hypothesis suggests that glucose from maternal circulation to the foetus through a maternal-foetal gradient leads to the passive over supply of glucose. The foetal response to hyperglycaemia is to increase the production of foetal insulin, leading to foetal hyperinsulinaemia.

Freinkel et al. (1986) demonstrated that even the mildest form of GDM can cause accelerated maturation of foetal beta-cells and somatic development during foetal life. Because insulin has multiple effects on foetal metabolism in addition to increasing glucose transport into cells (Susa & Schwartz, 1985), foetal hyperinsulinaemia can lead to accelerated growth and adiposity and subsequent metabolic effects at delivery such as neonatal hypoglycaemia and hyperbiluriaemia (Barbour & Hernandez, 2018a; HAPO Study Cooperative Research Group et al., 2008; Metzger, Persson, et al., 2010).

Maternal glycaemia

Compared to non-pregnancy, maternal glucose levels are typically exaggerated in the postprandial state but, paradoxically, appear to be lower in the fasting state (Freinkel, 1980). This acute postprandial hyperglycaemia is thought of as having a role in enhancing the maternal-placental nutrient gradient to carry glucose to the foetus (Lain & Catalano, 2007). During the fasted state, increased glucose utilisation presents as lower fasting glucose levels (Lain & Catalano, 2007). Earlier research suggested fasting glucose levels might lower as much as 0.56-0.83 mmol/L by the third trimester (Catalano et al., 1992). A hospital-based study involving 7,946 pregnant women showed an average reduction in fasting glucose levels of 0.17 mmol/L in the first trimester, and a slight further reduction by the third trimester (Riskin-Mashiah, Damti, Younes, & Auslander, 2011). This observation may be surprising since it could

be expected that elevated insulin resistance would lead to a natural increase in fasting glucose levels throughout pregnancy. Other studies have shown little to no change in fasting and postprandial glucose levels across gestation while overall fasting, one- and two-hour OGTT glucose (Barbour, Farabi, et al., 2018), and 24-hour glucose area under the curve appear higher among women with obesity compared to their normal weight pregnant counterparts (Harmon et al., 2011).

Hyperglycaemia in pregnancy

Hyperglycaemia *first* recognised during pregnancy is diagnosed as GDM (American Diabetes Association, 2021a). GDM usually develops from mid-gestation when maternal insulin resistance exceeds a woman's capacity to compensate with pancreatic beta-cell insulin production despite hyperinsulinaemia. The "relative insulin deficiency" may result from pre-existing insulin resistance, a defect in beta-cell compensatory capacity, or both, augmented by maternal metabolic changes (Barbour et al., 2007; Plows et al., 2018). Women who present with abnormal glucose metabolism before or at the beginning of pregnancy also experience exacerbated hyperglycaemia and require earlier treatment. Most women with GDM show normal glucose control soon after delivery due to the loss of placental hormones (Barbour et al., 2007). However, a subset of women are found to have impaired glucose tolerance or type 2 diabetes postpartum, likely resulting from pre-existing abnormal glucose metabolism and more overt insulin resistance prior to pregnancy (Barbour et al., 2007).

In many ways, the metabolic processes leading to the development of GDM are an accelerated representation of changes that occur over several decades toward the development of type 2 diabetes. Evidence linking the pathological processes of GDM and type 2 diabetes is demonstrated by the close relationship between GDM and the development of type 2 diabetes later in life (Bellamy et al., 2009; Y. Xu et al., 2014). A meta-analysis of 20 cohort studies from 1960 to 2009 of 675,455 women showed that women with GDM had a seven-fold increased risk of developing type 2 diabetes compared to normoglycaemic pregnancies (RR 7.43, 95% CI 4.8, 11.5) (Bellamy et al., 2009). This risk of transitioning to type 2 diabetes is highest in the first five years after pregnancy (Bellamy et al., 2009; C. Kim et al., 2002). Recent prospective data from an Israli cohort (1,882,647 person-years, n = 177,241, n = 1,262 women diagnosed with type 2 diabetes) demonstrated a relationship between elevated blood glucose levels below the thresholds to diagnosing GDM and later life type 2 diabetes (Bardugo et al., 2023). For women with one abnormal OGTT result but not diagnosed with GDM (two-step Carpenter-Coustan thresholds, 100-gram oral glucose), the adjusted hazards ratio for type 2 diabetes in ~10 years was 9.11 (95% CI 7.64, 10.86; p<0·0001), and 11.81 (8.58–16·.5; p<0·0001) for women with an

isolated elevated fasting glucose. This is comparable to an adjusted hazards ratio of 24.84 (21.78–28.34; p<0·0001) among women previously diagnosed with GDM.

As discussed previously in section 2.1, the progression of type 2 diabetes is characterised by advancing insulin resistance and hyperinsulinaemia (Table 1). Eventually, hyperglycaemia develops when progressive compensatory hyperinsulinaemia is no longer adequate to overcome insulin resistance. Parallels can be drawn between the progressive changes seen in the development of type 2 diabetes and GDM. However, the key difference between the two conditions is that GDM is a transient state occurring at an accelerated rate during the gestational period. In both cases, hyperglycaemia eventually develops when compensatory insulin secretion is inadequate (Buchanan, 2001; James et al., 2021).

Glycaemic targets in pregnancy

What defines "good" glycaemic control in pregnancies affected by diabetes has been an ongoing source of controversy over the last century (Hernandez, 2015). Most international organisations recommend that adequate metabolic control may be achieved with a fasting blood glucose value of 5.3 mmol/L and postprandial values of 7.8 mol/L and 6.7 mol/L at 1- and 2-hours, each respectively. These thresholds were determined based on over three decades of evidence suggesting a reduction in large-for-gestational age, macrosomia, and improved perinatal outcomes when glycaemic targets are met (Hernandez, 2015).

The only systematic review to define normal glycaemic patterns in pregnancy was performed by Hernandez, Friedman, Van Pelt, and Barbour (2011). Using weighted averages from studies that measured glycaemic patterns in pregnant women from over five decades, mean glycaemic patterns during the third trimester were estimated as 3.9 ± 0.4 mmol/L for fasting blood glucose, 6.1 ± 0.2 mmol/L for 1-hour postprandial, 5.5 ± 0.6 mmol/L for 2-hours postprandial, and 24-hour mean blood glucose level of 4.9 ± 0.6 mmol/L. Findings showed that estimated population mean glycaemic patterns were significantly lower than glycaemic targets recommended to women with GDM. Hernandez et al. (2011) suggested that lower therapeutic targets should be explored for women with GDM or obesity in pregnancy due to the potential impacts of unrecognised hyperglycaemia in pregnancy that may result from lenient criteria.

The effect of tighter glycaemic targets during GDM pregnancies on serious maternal and perinatal outcomes was examined in a stepped-wedge, cluster-randomised trial (Crowther, Samuel, Hughes, et al., 2022). Ten New Zealand hospitals shifted between less tight targets (fasting plasma glucose <5.5 mmol/L, 1-hour <8.0 mmol/L, 2 hour postprandial <7.0 mmol/L) and tighter targets (FPG <5.0 mmol/L, 1-hour <7.4 mmol/L, 2 hour postprandial <6.7 mmol/L)

at four-monthly intervals over a two-year period. Findings showed no difference in the rate of large-for-gestational age infants (88/599, 14.7% versus 76/502, 15.1%; adjusted relative risk (aRR) 0.96, 95% CI 0.66 to 1.40, p=0.839). However, the composite of serious health outcomes of the infant (perinatal death, birth trauma, or shoulder dystocia) was apparently reduced in the tighter group (8/599, 1.3% versus 13/505, 2.6%, aRR 0.23, 95% CI 0.06 to 0.88, p=0.032).

Lipid metabolism

Changes in lipid metabolism are observed from as early as six weeks' gestation, resulting in physiological hyperlipidaemia of pregnancy. An initial increase in insulin sensitivity in the first six to eight weeks of gestation promotes fatty acid synthesis and increased lipoprotein lipase expression, enhancing triglyceride uptake into adipose stores (Wild & Feingold, 2000). After an initial decrease, circulating triglycerides, free fatty acids, cholesterol, and phospholipids steadily increase into the third trimester (Butte, 2000).

Placental oestrogen and increased insulin resistance are primarily responsible for the hypertriglyceridaemia of pregnancy (Butte, 2000). Oestrogen stimulates hepatic very-low density lipoprotein (VLDL)-triglyceride production (Barbour & Hernandez, 2018a). Concurrently, insulin resistance in adipose tissue promotes increased lipolysis, resulting in excess maternal triglycerides and free fatty acids available to the foetal-placental unit (Barbour & Hernandez, 2018a).

From 30 weeks' gestation, a surge in insulin resistance promoted by cortisol and inflammatory cytokines drives adipose tissue catabolism and decreased expression of hepatic lipoprotein lipase levels (Armistead et al., 2020). The result is the increased availability of lipid-based fuels to support maternal energy needs so that glucose and glucogenic amino acids are spared for the developing foetus. Higher circulating levels of lipoprotein particles also deliver essential cholesterol to the placenta for the production of steroid hormones (Armistead et al., 2020). The placenta expresses lipoprotein receptors to transfer triglyceride-rich very low-density- (VLDL), low-density- (LDL), and-high density lipoprotein particles (HDL) from maternal circulation. These contain fatty acid-binding proteins, which enable the preferential transfer of essential fatty acids, including docosahexaenoic acid (DHA) to support the foetal central nervous system (Herrera, Amusquivar, López-Soldado, & Ortega, 2006).

Endocrine functions of maternal adipose tissue

Maternal adipose tissue serves as an endocrine organ. As maternal fat mass expands and becomes progressively insulin resistant throughout gestation, there is an increase in the production of inflammatory cytokines (TNF-α, IL-6, and IL-1) and adipokines (leptin, adiponectin,

irisin, resistin) which contribute to a state of low-grade inflammation (Armistead et al., 2020; Mallardo, Ferraro, Daniele, & Nigro, 2021). One theorised function of increased generalised inflammation, is to compensate for the adaptive immune system, which is suppressed during pregnancy to support foetal-placental tolerance (Ingvorsen, Brix, Ozanne, & Hellgren, 2015).

The most recognised endocrine functions of adipose tissue are mediated by leptin and adiponectin. Leptin, secreted by white adipose tissue, signals to leptin receptors on the hypothalamus to suppress appetite and food intake; however, during pregnancy, these anorexic effects of leptin are blunted by human placental lactogen, which stimulates hypothalamic leptin resistance (Armistead et al., 2020). Leptin resistance and hyperleptinaemia allow women to maintain higher caloric and nutrient intake despite steadily developing adipose tissue stores throughout early and mid-gestation (Armistead et al., 2020; Ladyman, Augustine, & Grattan, 2010). Maternal adiponectin levels, also mainly secreted by white adipose tissue, are inversely associated with insulin resistance; lower levels also correspond to increases in endogenous glucose production (Ahlsson et al., 2013).

Effects of pre-existing insulin resistance on lipid metabolism during pregnancy

Increases in plasma free fatty acids, triglycerides, and total cholesterol in normal pregnancies are similar to the metabolic syndrome defined outside pregnancy (Ferranti et al., 2016). When women bring pre-existing insulin resistance into pregnancy, such changes in lipids are further augmented. In a nested case-control study, Bao et al. (2018) showed that women who develop GDM have higher circulating triglycerides in the first trimester (OR comparing highest versus lowest quartile: 3.15; 95% CI: 1.38-7.15; p=0.002) and lower HDL cholesterol at 10-14 weeks' (OR: 0.44; 95% CI 0.18–1.09; p=0.045) and 15-26 weeks' (OR: 0.23; 95% CI: 0.08–0.63; p=0.005). Moreover, altered lipid profiles and/or elevated circulating triglyceride levels have been described during pregnancy in women with obesity, pre-eclampsia, intrahepatic cholestasis of pregnancy, and those who deliver neonates with increased adiposity (Cho, Park, Shin, Oh, & Seo, 2016; Harville, Viikari, & Raitakari, 2011; Jin et al., 2016; Samsuddin et al., 2020; Tinius et al., 2020; Wiznitzer et al., 2009).

Adipose tissue is the main source of increasing circulating maternal lipids as gestation progresses (Armistead et al., 2020). Women with maternal obesity or excess GWG, in particular, display higher levels of this dysfunctional insulin-resistant adipose tissue (Corrales et al., 2021). Throughout pregnancy, it is plausible that a hyperabundance of circulating triglycerides and free fatty acids could further perpetuate worsening insulin resistance and hyperinsulinaemia through ectopic fat formation and visceral adiposity, as previously described in a chronic disease context (James et al., 2021). Moreover, there is increasing interest in the role that excess maternal lipids

(triglycerides and free fatty acids) have in contributing to increased birthweight and large-for-gestational age infants (Barbour & Hernandez, 2018a). Thus, taken together, the metabolic environment that is insulin resistance, hyperinsulinaemia, and hyperlipidaemia contributes to a metabolic storm that not only may perpetuate future cardiometabolic risk in the mother but also lead to later-life health risks in the offspring.

Amino acid metabolism

Adjustments in amino acid metabolism occur within several weeks of conception. Maintaining amino acid homeostasis is exceptionally important since foetal growth and development is dependent on the amino acids that are delivered across the placenta (Manta-Vogli, Schulpis, Dotsikas, & Loukas, 2020). Amino acids are almost exclusively derived from maternal dietary protein intake; both inadequate and very high protein intakes have been associated with growth restriction and low birth weight infants (Barker & Thornburg, 2013; M. A. Hanson & Gluckman, 2014; Imdad & Bhutta, 2011; Rodgers & Sferruzzi-Perri, 2021). An increase in maternal protein needs from as early as 16 weeks' gestation reflects changes in nitrogen metabolism that occur in the first trimester. Overall amino acid requirements are determined by the foetal rate of protein synthesis, interconversion to other substrates, and oxidation (Manta-Vogli et al., 2020). Foetal protein synthesis increases with gestational age before sharply dropping late-gestation as the foetus accumulates adipose stores. Mid-gestation is the period of highest foetal metabolic activity for protein synthesis, whereas during late-gestation, more amino acids are oxidised to meet rapid foetal growth and energy needs, resulting in increased urea output (Manta-Vogli et al., 2020).

The first study to estimate protein requirements during pregnancy using an amino acid oxidation direct calorimetry method was conducted by Stephens, Payne, Ball, Pencharz, and Elango (2015). Estimates suggested pregnant women in early and late gestation require 32% and 63% more dietary protein than non-pregnant adults (as compared to the estimated average requirement of 0.88 grams per kg per day recommended by the US Dietary Reference Intakes). Further, an Indian study that used a whole-body potassium counter method to estimate protein needs observed an 18% and 35% increase in early and late gestation, each respectively (Kuriyan et al., 2019). Authors suggest the p. 39 discrepancy between studies may be reflective of habitual protein take.

Requirements for individual amino acids are defined by the calculated placental clearance rate for foetal plasma (Manta-Vogli et al., 2020). Amino acids with the highest foetal plasma clearance are glutamate, leucine, serine, alanine, glycine, and tyrosine. Those with a higher clearance into maternal circulation are methionine, phenylalanine, isoleucine, leucine, valine,

tryptophan, threonine, histidine, and lysine (Regnault, de Vrijer, & Battaglia, 2002). Amino acids are transferred from the maternal circulation into the placenta following a concentration gradient, then actively transported by more than 20 different amino acid transporters under the regulation of placental growth hormone and IGFs (Manta-Vogli et al., 2020; Regnault et al., 2002).

Fasting levels of amino acids, including branch chain amino acids, have been shown to be higher among women with GDM (Metzger, Phelps, Freinkel, & Navickas, 1980; Phelps, Metzger, & Freinkel, 1981). Insulin resistance is associated with elevated maternal plasma alanine, which is used as a substrate for hepatic gluconeogenesis (Barbour & Hernandez, 2018b). Although maternal insulin does not cross the placenta, circulating insulin has the capacity to activate placental insulin/insulin-like growth factor 1 (IGF-1) signal transduction pathways. This somatogenic role of insulin to activate amino acid transfer across the placenta provides an additional pathway through which maternal hyperinsulinaemia may lead to foetal overnutrition and macrosomia. Jansson et al. (2013) demonstrated that maternal obesity was associated with overstimulation of amino acid transporters via insulin/IGF-1 signalling, therefore suggesting a link to the increased risk for high birth weight infants.

"Accelerated starvation" and "facilitated anabolism" of pregnancy

An extraordinary capacity for the maternal body to adapt to the metabolic demands of pregnancy was conceptualised in the pioneering work of Freinkel and colleagues (1980). Freinkel (1980) coined adaptations occurring in the fasted and postprandial state as the "*accelerated starvation*" and "*facilitated anabolism*" of pregnancy. Findings from Freinkel's seminal work described that in a fasted state, maternal glucose levels were lower in a normal pregnancy compared to non-pregnant controls. It was shown that maternal metabolism could rapidly divert metabolism to predominantly fat oxidation, thus sparing essential glucose for the foetal-placental unit. After as little as 12-hours of fasting, pregnant women experience enhanced fat oxidation and ketogenesis (Butte, 2000; Felig & Lynch, 1970), appearing much sooner and at an enhanced rate than non-pregnant controls (Metzger, Ravnikar, Vileisis, & Freinkel, 1982). Hence, adaptations typically occurring under starvation conditions in non-pregnancy appear at an *accelerated* rate in the pregnant state. Fasting adaptations allow stored energy in the form of fatty acids and glycerol to be utilised for maternal metabolism, while indispensable glucose and the glucogenic amino acid alanine are shunted to the foetus (Butte, 2000; Herrera et al., 2006).

It was further shown that after a meal, postprandial plasma glucose and triglycerides are much higher in pregnant women due to heightened insulin resistance, an exaggerated insulin

secretory response, and enhanced suppression of glucagon. A greater and prolonged postprandial hyperglycaemia was argued as "*facilitating*" glucose transport to the foetus across a transplacental gradient – elevated and attenuated glucose levels make the gradient larger, in essence, to "feed" the foetus (Freinkel, 1980). Thus, postprandial metabolism was coined "*facilitated anabolism"*. Table 4 provides a summary of the changes in maternal nutrient metabolism in the fasted and fed state as compared to non-pregnant women, as described by Freinkel (1980).

Table 4. Changes in fasting and postprandial nutrient serum levels during pregnancy as compared to non-pregnancy as described by (Freinkel, 1980).

Nutrient	**Fasted state "Accelerated starvation"**	**Postprandial state "Facilitated anabolism"**
Glucose	Decrease	Increase
Free fatty acids	Increase	Increase
Triglycerides	Increase	Increase
β-hydroxybutyrate	Increase	Decrease
Alanine	Decrease	Decrease

Ketogenesis during pregnancy

An increased tendency toward ketogenesis during pregnancy, has traditionally been met with caution under the assumption that ketonaemia is dangerous for the developing foetus (Metzger et al., 1982). Ketones readily cross the placenta. Elevated maternal ketones levels have been associated with poorer foetal and childhood outcomes, especially childhood neurological and cognitive development (John A Churchill & Berendes, 1969; J. A. Churchill, Berendes, & Nemore, 1969; Hamdi, Bastani, Mozafari, Hashemi, & Ghotbi, 2006; Onyeije & Divon, 2001; Rizzo, Metzger, Burns, & Burns, 1991; Silverman, Rizzo, Cho, & Metzger, 1998; Stehbens, Baker, & Kitchell, 1977). Although these observations have not been consistent; some studies report no association (Naeye, 1979; Persson & Gentz, 1984).

From a dietary perspective, concerns surrounding ketonaemia and offspring outcomes led to women being discouraged from skipping breakfast. Most guidelines advise pregnant women with GDM to avoid diets or dietary patterns that result in elevated ketones (Tanner, Dekker Nitert, Callaway, & Barrett, 2021). For GDM, this is communicated as a minimum carbohydrate intake and the spreading of carbohydrates across the day – carbohydrate modification in pregnancy is discussed further in section 2.6. However, data linking any specific dietary pattern or quantity of carbohydrate intake to ketonaemia and adverse foetal outcomes is lacking. In a

recent cross-sectional study of 108 pregnant women at 28 weeks' gestation, habitual carbohydrate intake (median 155 [126-189] g/day, measured by food frequency questionnaire) was shown to have no correlation with fasting serum β-hydroxybutyrate levels (Tanner et al., 2024). Due to a paucity of data, lower and upper safety thresholds for dietary carbohydrate remain undetermined.

The strength of evidence supporting concerns surrounding ketonemia in pregnancy is highly contended. This is due to studies reporting variable methodologies for analysing maternal ketone levels (i.e. urine dip stick versus serum β-hydroxybutyrate), a limited understanding of what defines "normal" ketone levels during pregnancy (both in a healthy and GDM pregnancy), and conflicting outcomes from observational studies reporting childhood IQ, among which confounding factors such as socioeconomic status are often not well-considered (Tanner et al., 2021). Moreover, since ketone production is closely related to fasting status (i.e. levels increase in the fasting state, and further with extended fasting), the effects of maternal ketogenesis cannot be isolated from the consequences of inadequate dietary intake as a whole (Butte, 2000). Consistent inadequate food intake would negatively affect foetal development by way of the reduced availability of energy, amino acids, nucleic acids, lipids, carbohydrate, and micronutrients (Butte, 2000).

Emerging views now challenge traditional caution around ketones in pregnancy; enhanced ketogenesis is not only a normal physiological adaptation during pregnancy, but ketone bodies freely cross the placenta and are used as a source of energy for the foetus (Bronisz, Ozorowski, & Hagner-Derengowska, 2018). During a physiological fasted state, β-hydroxybutyrate is required to complement glucose demands and provide essential metabolic and energy fuel to support foetal brain development (Steiner, 2019). Ketone oxidation may account for approximately one-third of foetal brain energy demands (Adam, Räihä, Rahiala, & Kekomäki, 1975). As well as serving as an energy source, maternally derived ketone bodies may also serve a role in the development of the foetal central nervous system (Bronisz et al., 2018). Although several neuroprotective mechanisms for ketone bodies have been hypothesised outside of pregnancy, specific roles in foetal development are uncertain (Bronisz et al., 2018).

In summary, from the very beginning of pregnancy, maternal metabolism undergoes extraordinary changes in nutrient handling to ensure a continuous supply of essential nutrients to meet the needs of a rapidly developing foetus, both in the fasting and postprandial/fed state. Together, changes in glucose, lipid, and amino acid metabolism are underpinned by physiological insulin resistance, increased insulin secretion, and low-grade inflammation.

However, the physiological demands of pregnancy present a challenge for women with pre-existing insulin resistance.

2.2.2 Risk factors that contribute to metabolic dysfunction during pregnancy

Maternal and offspring health is linked to many medical, environmental, social and demographic exposures occurring before conception (Fleming et al., 2018; Stephenson et al., 2018). Pre-pregnancy insulin resistance may develop due to multiple risk factors. A summary of factors associated with an increased risk of adverse pregnancy outcomes related to maternal insulin resistance is shown in Figure 5. Maternal obesity and GDM are the most common pregnancy conditions related to pre-existing maternal insulin resistance (Catalano & Shankar, 2017). Both of these conditions are associated with a range of adverse maternal and neonatal outcomes, which will be explored in greater detail in the following section (section 2.2.3). When pre-pregnancy insulin resistance is compounded by the pregnancy-related changes in metabolism discussed in section 2.2.1, many metabolic derangements, including increased inflammation, oxidative stress, and an overabundance of nutrients, subsequently develop (Barbour et al., 2007; Butte, 2000; Hernandez, Friedman, & Barbour, 2020). In most instances, there is a combination of several factors that contribute to greater insulin resistance pre-pregnancy, which, when superimposed on normal pregnancy physiology, may lead to adverse outcomes.

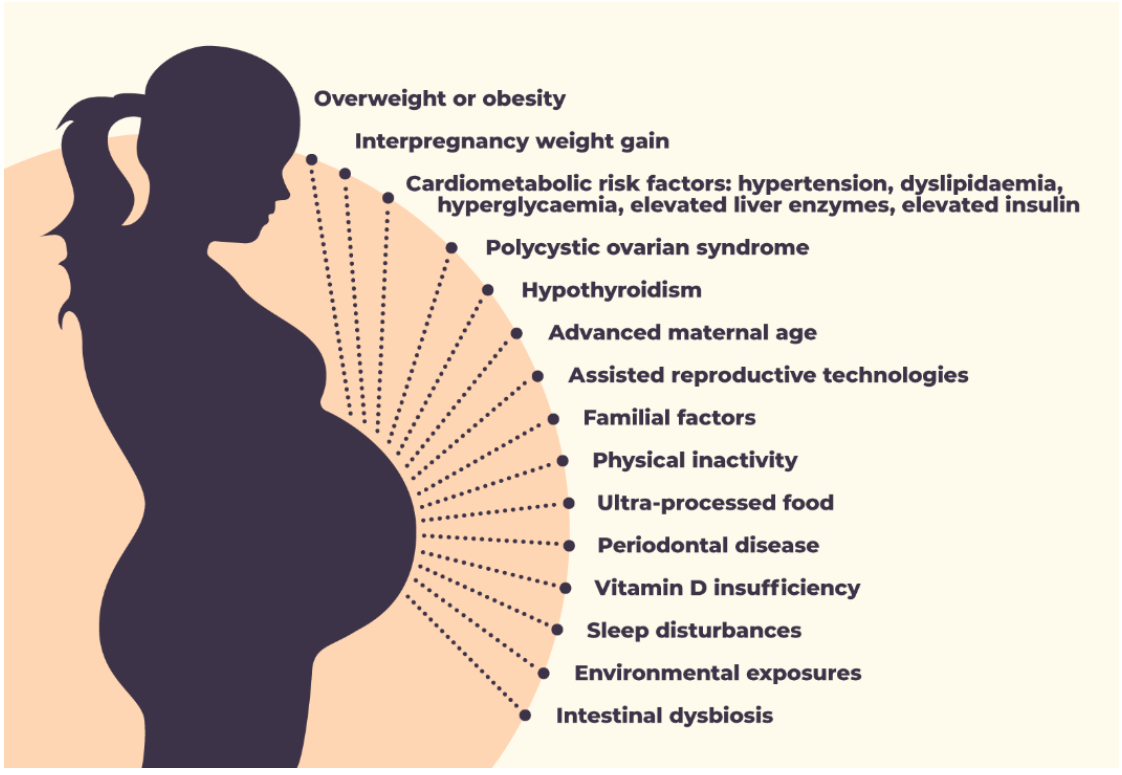


Figure 5. Risk factors associated with metabolic dysfunction during pregnancy.

Various metabolic, familial, and environmental risk factors before and/or during pregnancy which are associated with an increased risk for adverse outcomes characterised by maternal insulin resistance and hyperinsulinaemia.

Pre-pregnancy overweight or obesity

Maternal obesity is the leading health concern in pregnant women (American College of Obstetricians and Gynecologists' Committee on Practice Bulletins, 2021). Maternal obesity is invariably associated with insulin resistance and low-grade inflammation (Corrales et al., 2021). Therefore, during pregnancy, women with obesity experience significantly higher increases in insulin resistance across gestation compared to normal-weight pregnant women (Catalano & Shankar, 2017). Obesity in pregnancy has been linked to a 30-fold reduced expression of insulin-sensitive genes, which regulate placental trophoblast cell cycle and cholesterol metabolism. Compared to normal-weight pregnant women, those with overweight/obesity have poorer metabolic flexibility (reported as percent change in lipid oxidation at 4-hours post meal, overweight/obese 29.3 ± 34.3% vs. lean 48.0 ± 34.1%, $p = 0.035$), exhibit higher inflammatory markers (IL-6 $p = 0.003$, IL-1β $p = 0.028$), and elevated insulin secretion at fasting ($p < 0.05$) and 1-, 2-, and 4-hours postprandially in response to a high fat smoothie (Tinius et al., 2020).

Low-grade inflammation, insulin resistance, and hyperinsulinaemia associated with maternal obesity can be linked to many down-stream effects on maternal and neonatal health (Catalano & Shankar, 2017; Zehravi, Maqbool, & Ara, 2021). Since obesity is associated with endothelial dysfunction and cardiovascular disease risk outside of pregnancy, inflammatory and vascular changes manifesting during pregnancy can particularly affect placental development and function. Increased placental inflammation and endothelial dysfunction can induce ischemia of the placenta, leading to preeclampsia, spontaneous abortion, stillbirth, and small-for-gestational age infants (Spradley, Palei, & Granger, 2015).

There is extensive evidence describing the increased risk of both acute and long-term adverse outcomes among women with overweight/obesity in pregnancy. A meta-analysis by Vats et al. (2021) showed that an elevated pre-pregnancy BMI was associated with an increased odds of caesarean delivery (elective and emergency) (overweight: pooled OR 1.40, 95% CI 1.36, 1.43; obesity: 1.98, 95% CI 1.85, 2.11), GDM (overweight: pooled OR 2.10, 95% CI 1.89, 2.33: obesity: 4.10, 95% CI 3.50, 4.80), gestational hypertension (overweight: pooled OR 2.24, 95% CI 1.94, 2.59; obesity: 4.77, 95% CI 3.88, 5.85), preeclampsia (overweight: pooled OR 1.89, 95% CI 1.74, 2.05; obesity: 3.57, 95% CI 3.29, 3.87), induction of labour (overweight: pooled OR 1.23, 95% CI 1.17, 1.30; obesity: 1.55, 95% CI 1.36, 1.77), postpartum haemorrhage (overweight: pooled OR 1.18, 95% CI 1.11, 1.26; obesity: 1.38, 95% CI 1.25, 1.54), and premature rupture of membranes

(overweight: pooled OR 1.35, 95% CI 1.16, 1.59; obesity: 1.53 95% CI 1.23, 1.90) as compared to lean mothers. High BMI was also associated with neonates having an increased odds of intensive care unit admission (overweight: pooled OR 1.12, 95% CI 1.03, 1.21; obesity: 1.43, 95% CI 1.28, 1.58), Apar scores (a measurement reflecting neonatal breathing effort, heart rate, muscle tone, reflexes, and skin colour) less than 7 at 5 minutes (overweight: pooled OR 1.29, 95% CI 1.12, 1.48; obesity: 1.47, 95% CI 1.23, 1.75), large-for-gestational age (overweight: pooled OR 1.67, 95% CI 1.58, 1.77; obesity 2.36, 95% CI 2.17, 2.56), macrosomia (overweight: pooled OR 1.66, 95% CI 1.57, 1.76; obesity: 2.28, 95% CI 2.15, 2.41), and extreme pre-term birth <32 weeks' gestation (overweight: pooled OR 1.40, 95% CI 1.20, 1.63). Maternal obesity carries an increased risk for intrapartum complications, including anaesthesia problems, failed trial of labour, endometritis, wound rupture or dehiscence, and venous thrombosis (American College of Obstetricians and Gynecologists' Committee on Practice Bulletins, 2021). Neonates born to women with obesity are frequently large-for-gestational age, which can lead to maternal birth injury and neonatal trauma. Furthermore, the risk of spontaneous abortion and stillbirth is higher in women with a BMI ≥ 30 kg/m^2 (Metwally, Ong, Ledger, & Li, 2008; Yao, Ananth, Park, Pereira, & Plante, 2014), as well as incidence for overall congenital malformations (Dow & Szymanski, 2020). The incidence of spina bifida, neural tube defects, cleft lip and/or palate, and cardiac defects also show a strong correlation with maternal obesity (American College of Obstetricians and Gynecologists' Committee on Practice Bulletins, 2021; Dow & Szymanski, 2020). A meta-analysis of eight studies showed a 1.18 increased odds (95% CI: 1.11-1.26) of orofacial clefting in women with BMIs of 30 or greater (Blanco, Colombo, & Suazo, 2015).

Later in life, offspring of women with obesity are also more likely to be overweight or obese as children and early in adulthood. In a meta-analysis which included mother-child dyads from over 37 pregnancy and birth cohort studies (n = 162, 129), Voerman, Santos, Patro Golab, et al. (2019) observed higher maternal pre-pregnancy BMI and excess GWG were strongly associated with higher risks of childhood overweight/obesity, with the greatest effects occurring in late childhood/adolescence (ORs (95% CI) for overweight/obesity in early, mid, and late childhood, respectively: 1.66 (1.56, 1.78), 1.91 (1.85, 1.98), and 2.28 (2.08, 2.50) for maternal overweight; 2.43 (2.24, 2.64), 3.12 (2.98, 3.27, and 4.47 (3.99, 5.23) for maternal obesity; and 1.39 (1.30, 1.49), 1.55 (1.49, 1.60), and 1.72 (1.56, 1.91) for excessive GWG. *In utero* exposures also lead to an increased risk of chronic cardiometabolic disease later in life, therefore perpetuating the transgenerational cycle of obesity and metabolic dysfunction (Godfrey et al., 2017).

Postpartum weight retention, pre- and inter-pregnancy weight gain

Pregnancy is related to increases in fat mass that is typically mobilised in the postpartum period (Catalano & Shankar, 2017). However, postpartum weight retention is a significant contributor to the obesity epidemic among child-bearing women (Rasmussen et al., 2010). Women who retain weight gained from pregnancy, and/or go on to gain weight between pregnancies are more likely to enter future pregnancies with the additional metabolic risks associated with maternal obesity (Catalano & Shankar, 2017; Corrales et al., 2021). A prospective study examining changes in adiposity via computed tomography and dual-energy X-ray absorptiometry showed that compared to having zero births, pregnancy was associated with a greater increase in visceral adipose tissue (gain of 27.1 cm^2, 95% CI 14.5, 39.7, n = 14 vs. 9.2 cm^2, 95% CI 4.8, 13.6, n = 108; $p < 0.01$) (Gunderson et al., 2008). Since body fat is primarily mobilised from the lower body in the postpartum period (Sidebottom, Brown, & Jacobs, 2001; Sohlström & Forsum, 1995), weight retained may represent a great proportion of abdominal fat. Moreover, women who have had pregnancies tend to have higher waist circumferences and lower thigh circumference than nulliparous women (Lassek & Gaulin, 2006). Findings from the Danish National Birth Cohort study of 23,701 women showed that each 1 kg of postpartum weight retention at 6 months (as compared to pre-pregnancy weight) was associated with an average increase of 0.5 kg at 7 years follow up (Kirkegaard et al., 2014). Excess GWG presents as one of the greatest risk factors for postpartum weight retention, as shown in a meta-analysis by (Nehring, Schmoll, Beyerlein, Hauner, & von Kries, 2011). Weight gain above recommendations was associated with 3.06 kg (95% CI 1.50, 4.63, n = 34,235) and 4.72 kg (95% CI 2.94, 6.50, n = 2509) weight retention at 3 and ≥ 15 years postpartum, each respectively (9 observational studies).

Preconception and interpregnancy weight gain (meaning weight gained between pregnancies) across all BMI categories was shown in a meta-analysis of 61 studies to be significantly associated with an increased risk of GDM (OR 1.88, 95% CI 1.66, 2.14), hypertensive disorders (OR 1.46, 95% CI 1.12, 1.91), preeclampsia (OR 1.92, 95% CI 1.55, 2.37), and large-for-gestational age infants (OR 1.36, 95% CI 1.25) (Nagpal et al., 2022). When stratified by BMI OR for GDM and hypertensive disorders were greater in women with a BMI < 25 kg/m^2 (GDM: OR 2.01, 95% CI 1.54, 2.64; hypertensive disorders: OR 1.94, 95% CI 1.42, 2.64) versus BMI ≥ 25 kg/m^2 (GDM: OR 1.79, 95% CI 1.33, 2.40; hypertensive disorders: OR 1.07, 95% CI 0.58, 1.97) (Nagpal et al., 2022). In an umbrella review of systematic reviews, M. Daly, Kipping, Tinner, Sanders, and White (2021) presented moderate-certainty evidence that weight gain of greater than 2 kg/m^2 BMI units between pregnancies was associated with a greater risk of gestational hypertension compared to BMI maintenance (change of ≤ 2 kg/m^2 units) (OR 1.45, 95% CI 1.11, 1.80, n = 239,160, 6

studies). Weight gain of more than 3 BMI units between pregnancies, relative to BMI maintenance of ≤ 1 unit, was associated with a greater risk of caesarean delivery (adjusted OR 1.71, 95% CI 1.32, 2.24, n = 341,960), large-for-gestational age infants (adjusted OR 1.54, 95% CI 1.28, 1.86, n = 103,350), and GDM (adjusted OR 2.37, 95% CI 1.40, 3.34, n = 253,992, 5 studies), and to a lesser extent for weight gain of 1-3 kg/m^2 BMI units. Low-level evidence also suggested interpregnancy weight gain of > 2 units may be associated with an increased risk of preeclampsia (OR 1.39 95% CI 1.18, 1.60, n = 364, 943, 5 studies).

Cardiovascular risk factors

Metabolic conditions of pregnancy are known to be associated with an increased risk cardiovascular disease later in life (Retnakaran, 2018). Pooled analysis from over 5 million pregnancies showed that women with a history of GDM have a 2.3-fold increased risk of cardiovascular events in the first decade postpartum compared to their peers (RR 2.31, 95% CI 1.57, 3.39) (Kramer, Campbell, & Retnakaran, 2019). Both GDM and hypertensive disorders of pregnancy are associated with a significantly increased risk of type 2 diabetes later in life (Bellamy et al., 2009; G. Zhao, Bhatia, Jung, & Lipscombe, 2021). This increased risk for cardiovascular disease is ascribed to a dysfunctional metabolic phenotype; even before pregnancy, women who go on to develop gestational complications display cardiometabolic differences compared to healthy controls, thus suggesting background insulin resistance and hyperinsulinaemia (Retnakaran, 2021).

Biochemical markers that are associated with metabolic dysfunction in pregnancy are shared with classic cardiovascular risk markers for chronic metabolic disease. Population-based studies have shown that pre-pregnancy, women who develop GDM have higher glycated haemoglobin (HbA1c) and plasma glucose levels (both within subclinical parameters), insulin, LDL cholesterol, triglycerides, triglyceride-to-glucose ratios, liver enzymes (alanine aminotransferase, gamma glutamyl transferase), and lower HDL cholesterol (Gunderson et al., 2010; Harville et al., 2011; Retnakaran & Shah, 2020; Song et al., 2022; Sridhar et al., 2014). One population-based study showed among women who developed GDM, pre-pregnancy triglyceride (before pregnancy 1.25 ± 0.009 mmol/L vs 0.97 ± 0.003 mmol/L; preceding measurement 1.23 ± 0.009 mmol/L vs 1.00 ± 0.003 mmol/L, $p < 0.0001$) and fasting glucose levels (before pregnancy 4.95 ± 0.008 mmol/L vs 4.68 ± 0.003 mmol/L; preceding measurement 4.95 ± 0.008 mmol/L vs 4.92 ± 0.008 mmol/L, $p < 0.0001$) deteriorated at a worse trajectory over a 1.86-year period compared to their peers with healthier metabolic profiles (n = 101,161, 8,047 developed GDM) (Retnakaran & Shah, 2020). Furthermore, elevated triglycerides before pregnancy have also been linked to hypertensive disorders of pregnancy (adjusted RR 1.42, 95% CI 0.90-2.23), including

preeclampsia (adjust RR 1.70, 95% CI 1.08, 2.65) (n = 1142) (Harville et al., 2011). Women with chronic hypertension before pregnancy are at higher risk of preeclampsia (Catov, Ness, Kip, & Olsen, 2007; Chappell et al., 2008), preterm birth (Chappell et al., 2008; Odell et al., 2006), small-for-gestational-age infants, and GDM (Hedderson, Darbinian, Quesenberry, & Ferrara, 2011; Hedderson & Ferrara, 2008).

The presence of multiple cardiovascular risk factors and more advanced metabolic disease bears a further increased risk for adverse outcomes (Catov et al., 2007; Cho et al., 2016; El Jamaly, Eslick, & Weltman, 2022). Hedderson et al. (2011) demonstrated in a case control comparison study (n = 199 GDM cases, n = 381 controls) that three or more cardiovascular risk factors (including hypertension, hypercholesterolaemia, mild hyperglycaemia, and overweight/obesity) were associated with a 3.6-fold higher odds ($p < 0.001$, 95% CI provided visually) of GDM compared to those without risk factors. The most significant of these risk factors was a single random serum glucose level ≥ 4.8 mmol/L, which was associated with 3.1-fold increased risk of GDM compared to women with serum glucose < 4.8 mmol/L ($p < 0.001$, 95% CI provided visually).

Polycystic ovarian syndrome (PCOS)

PCOS is an endocrine metabolic disorder that affects 5% to 14% of women (Chatzakis et al., 2022; Escobar-Morreale, 2018). The link between PCOS and cardiometabolic health is well established; women with PCOS commonly present with hyperinsulinemia and insulin resistance, glucose intolerance, dyslipidaemia, hypertension, and high BMI (Dunaif, 1997; Osibogun, Ogunmoroti, & Michos, 2020). PCOS is associated with a 1.3-fold increased risk of cardiovascular diseases later in life, including ischaemic heart disease and stroke, compared to healthy controls (Okoth et al., 2020). Insulin resistance and hyperinsulinaemia are central to the pathophysiology of PCOS; hyperinsulinaemia fuels a vicious cycle between the overproduction of ovarian and adrenal androgens and endocrine mediators, including the downregulation of adiponectin and upregulation of TNF-α, interleukin-6, and leptin, which facilitate increased visceral adipose tissue (K.-W. Kim, 2021).

During pregnancy, PCOS is independently associated with a 2-fold increased risk for GDM (adjusted OR 2.19, 95% CI 2.02, 2.37, n = 14,882 with PCOS and n = 9,081,906 controls) (Mills, Badeghiesh, Suarthana, Baghlaf, & Dahan, 2020). An increased risk for hypertensive disorders, including pregnancy-induced hypertension and preeclampsia have also been reported in the order of 1.3- to 2-fold (Mills et al., 2020; Pan et al., 2021). PCOS is also associated with a greater risk of caesarean section, neonatal intensive care unit admission, and perinatal mortality (Boomsma et al., 2006; Chatzakis et al., 2022). A meta-analysis and meta-regression including

63 studies showed that independently of obesity, women with PCOS were more likely to miscarry (OR 1.71, 95% CI 1.19, 2.45, n= 3,196), develop GDM (OR 2.89, 95% CI 2.37, 3.54, n = 11,565), gestational hypertension (OR 2.58, 95% CI 1.95, 3.41, n = 2,698), and preeclampsia (OR 1.87, 95% CI 1.55, 2.25, n = 5,896), deliver by caesarean section (OR 1.39, 95% CI 1.23, n = 6,22), or receive an induction of labour (OR 2.55, 95% CI 1.23, 5,30, n = 769) (Bahri Khomami et al., 2019).

Hypothyroidism

The link between thyroid disease and the development of insulin resistance is well-established (Biondi, Kahaly, & Robertson, 2019; Yanachkova & Kamenov, 2021). Over time, the consequences of hypothyroidism, including progressive weight gain, hyperglycaemia, and insulin resistance can lead to the development of type 2 diabetes. Thus, the additional demands of pregnancy can further exacerbate pre-existing insulin resistance and impaired glucose metabolism related to hypothyroidism. A meta-analysis of ten cohort studies demonstrated that thyroid disease (thyroid stimulating hormone (TSH) levels >4.0 mIU/L) was associated with an increased risk for GDM in the order of 1.6-fold (TSH >4.0: OR 1.60, 95% CI 1.33,1.93) (Kent, Young, Akison, & Cuffe, 2021; Luo, Wang, Yuan, & Guo, 2021). Subclinical thyroid disease (TSH 2.5-4.0 mIU/L) was also associated with an increased risk of GDM only when accompanied by positive thyroid antibodies (Kent et al., 2021; Luo et al., 2021). Further, subclinical hypothyroidism was associated with 1.53-fold increased odds of preeclampsia compared to euthyroidism (3.6% vs 2.1%; OR 1.53, 95%CI 1.09, 2.15) in a meta—analysis that included 52 cohort studies (Toloza et al., 2022). Both higher and lower thyroid stimulating hormone levels were associated with an increased risk of preeclampsia.

Assisted reproductive technology

Assisted reproductive technology refers to a group of medical methods in which male and female gametes are used outside the body to achieve pregnancy, typically applied for the management of male and female infertility when trying to conceive (Zymperdikas, Zymperdikas, Mastorakos, Grimbizis, & Goulis, 2022). Two meta-analyses have reported a 1.5-fold higher risk of GDM among women who conceived from assisted reproductive technology (RR 1.53, 95% CI 1.39, 1.69, n = 37 studies; pooled RR 1.51, 95% CI 1.18, 1.93, n = 48 studies) (Bosdou et al., 2020; Mohammadi et al., 2020). Risk of hypertensive disorders, including gestational hypertension, and preeclampsia is estimated to be 54% to 79% higher following assisted reproductive technology (gestational hypertension: RR +79%, 95% CI 24%-157%; preeclampsia RR +75%, 95% CI, 50%-103%; all pregnancy related hypertension RR +54%, 95% CI, 39%, 70%) (Thomopoulos et al., 2017; Thomopoulos et al., 2013). Pregnancies conceived by assisted reproductive

technologies also experience a higher risk of perinatal mortality, preterm and very-preterm delivery, very-low birth weight and small-for-gestational age infants, and congenital malformations (McDonald, Murphy, Beyene, & Ohlsson, 2005).

The association between fertility treatment and maternal complications is unclear. The higher prevalence of GDM and hypertensive disorders may be explained by the aetiology of infertility, such as having a high BMI, PCOS, or advanced maternal age (Ashrafi et al., 2014; Mohammadi et al., 2020; Thomopoulos et al., 2013; Y. A. Wang, Nikravan, Smith, & Sullivan, 2013). These comorbidities that are likely to lead to fertility treatment also have a component of hyperinsulinaemia, as discussed previously. The experience of undergoing fertility treatment may also adversely affect metabolic health through excess stress and advice for women to limit their physical activity. A meta-analysis showed that ovarian hyperstimulation syndrome, which can occur as a result of fertility treatment, was associated with an 8.8-fold increased odds (95% CI 8.1, 9.5) of composite adverse maternal outcomes, including preterm birth, GDM, pre-eclampsia or pregnancy induced hypertension, intra-hepatic cholestasis of pregnancy, thromboembolic events or need for caesarean section (Buca et al., 2021). Ovarian hyperstimulation during treatment is linked to directly causing endothelial dysfunction and increased thrombosis, which may also lead to downstream cardiovascular events (Delvigne & Rozenberg, 2002; Henriksson et al., 2014). However, an independent effect of fertility treatment on cardiovascular events has been unsubstantiated (Udell Jacob, Lu, & Redelmeier Donald, 2013).

Familial and ethnic factors

Family history of metabolic syndrome, including diabetes, cardiovascular disease and/or hypertension, is associated with a higher risk of adverse pregnancy outcomes associated with insulin resistance, including preeclampsia and GDM (Giannakou et al., 2019; Kay, Wedel, & Smith, 2021; Y. Zhang et al., 2021). Genetic heritability explains part of the aetiology of metabolic dysfunction, however, evidence linking specific genes is limited and findings are inconsistent. A meta-analysis by C. Zhang et al. (2013) described minor alleles of nine single-nucleotide polymorphisms in seven genes as being associated with an increased risk of GDM. Most genes identified were involved in regulating insulin secretion. Learned behaviours and traditions around eating and lifestyle choices could also explain the familial nature of metabolic syndrome.

Prevalence rates of GDM have been found to vary between different countries, suggesting ethnic and geographical factors as having a role in the aetiology (McIntyre et al., 2019). Countries with multi-ethnic populations such as Australia, New Zealand, USA, Canada, and Israel show notable differences in prevalence rates between ethnic groups (Jaffe et al., 2020; McIntyre et

al., 2019; Pu et al., 2015). For example, in Australia, women with South Asian ethnicity have a four-fold increased risk of GDM (OR 4.33, 95% CI 4.12, 4.55) compared to European decent Australian or New Zealand women (Anna et al., 2008). Similar ethnic discrepancies are observed in New Zealand with higher rates of GDM observed among Māori, Pacific, and Asian women (Joshy & Simmons, 2006). Disparities for indigenous ethnic communities are recognised internationally; the disproportionate rates of chronic metabolic disease have been attributed to a complex host of social, environmental, genetic, and epigenetic causes (Wedekind, Mitchell, Andersen, Knowler, & Hanson, 2021). Genetic variation may also be part of the metabolic heterogeneity observed in the presentation of GDM. Candidate gene studies and genome-wide association studies over recent years have confirmed several diabetogenic variants that have also shown associations with GDM risk. Confirmed variants include those associated with obesity (FTO), impaired beta-cell function (KCNJ11, KCNQ1, MTNR1B, CDKAL1, CDKN2A/B, IGF2BP2), and insulin resistance and abnormal utilisation of glucose (PPARG, TCF7L2, GCK, GCKR) (Kasuga et al., 2017; Lauenborg et al., 2009; P.-C. Lin, Lin, Yeh, & Wung, 2016; Shaat et al., 2006; Tarnowski, Malinowski, Pawlak, et al., 2017; Tarnowski, Malinowski, Safranow, Dziedziejko, & Pawlik, 2017). Whether changes in the expression of these genes can explain heterogeneity in the presentation of GDM remains to be determined.

Physical inactivity

Physical activity is considered safe and beneficial to pregnant women; international guidelines recommend that pregnant women without contraindications should undertake regular physical activity throughout pregnancy (Tsakiridis, Bakaloudi, Oikonomidou, Dagklis, & Chourdakis, 2020). The lack of physical activity or increased sedentary behaviour therefore comes at a cost to maternal and offspring health. In the World Health Organization 2020 guidelines on physical activity and sedentary behaviour, pregnant and postpartum women are provided a “strong recommendation” to limit the amount of time spent being sedentary to reduce the risk of preeclampsia, gestational hypertension, GDM, excessive GWG, delivery complications, and postpartum depression (Bull et al., 2020).

There is strong evidence from randomised controlled trials that show low- to moderate-intensity exercise interventions reduce risk of GDM, gestational hypertension, preeclampsia, reduce GWG, and improve insulin sensitivity (Cremona, O'Gorman, Cotter, Saunders, & Donnelly, 2018; Danielli et al., 2022; Ming et al., 2018; Russo, Nobles, Ertel, Chasan-Taber, & Whitcomb, 2015; Sanabria-Martínez et al., 2015). Furthermore, women who exercise before pregnancy also have a lower risk of developing GDM (Tobias, Zhang, van Dam, Bowers, & Hu, 2011). A Cochrane review by Muktabhant, Lawrie, Lumbiganon, and Laopaiboon (2015) evaluated the effects of a

healthy diet, exercise, or the combination of both on the prevention of excessive GWG. Findings suggested an average 20% reduction in excess GWG from all three interventions. Muktabhant et al. (2015) indicated that exercise is an important part of controlling excessive weight gain in pregnancy, which may ultimately reduce the risk of multiple adverse outcomes associated with excess GWG. Mijatovic-Vukas et al. (2018) observed in a meta-analysis of 40 observational studies that greater than 90 minutes leisure time per week before pregnancy was associated with 46% decreased odds of GDM (OR 0.54, 95% CI 0.34, 0.87).

Westernised diet and consumption of ultra-processed food

The increasing consumption of highly palatable ultra-processed food is considered to be one of the most significant factors contributing to the global increase in obesity and chronic non-communicable metabolic diseases (Monteiro et al., 2018). A relationship between consumption of ultra-processed foods and chronic metabolic diseases has been described in multiple studies (Juul et al., 2018; Nardocci et al., 2019; Suksatan et al., 2021), including an increased risk for cardiovascular diseases, metabolic syndrome, overweight and obesity, maternal obesity, depression, irritable bowel syndrome, overall cancer, adolescent asthma, and frailty (Xiaojia. Chen et al., 2020). Ultra-processed foods categorically produce a high glycaemic and insulinogenic response with low satiety potential, which can lead to increased energy intake and weight gain (Crimarco, Landry, & Gardner, 2021). This means that in pregnancy, physiological adaptations already directed toward salvaging nutrients and adipose expansion can be appropriated by ultra-processed food choices. Additionally, food cravings and aversions experienced during pregnancy can lead to an increase in unhealthy food choices that may provide excess energy intake leading to increased GWG (Gomes, Malta, Benício, & Carvalhaes, 2021; Rohatgi et al., 2017), maternal obesity (Sartorelli, Crivellenti, Zuccolotto, & Franco, 2019), and greater risk of adverse maternal and neonatal outcomes (Casas, Castro Barquero, & Estruch, 2020).

Unhealthy “Western” style dietary patterns, often characterised by high consumption of ultra-processed foods such as refined sugar, refined grain products, processed meats, fried foods, and snack foods, have been associated with a higher risk of developing GDM and increased neonatal adiposity (L.-W. Chen et al., 2016; Hassani Zadeh, Boffetta, & Hosseinzadeh, 2020; Machairiotis, Vasilakaki, Minns, & Malakasis, 2021; Anne P. Starling et al., 2017; Zareei, Homayounfar, Naghizadeh, Ehrampoush, & Rahimi, 2018). Conversely, greater adherence to “healthy” dietary patterns such as the Mediterranean diet, often characterised by larger quantities of fruits, vegetables, legumes, nuts, unprocessed grains, extra virgin olive oil, moderate fish and meat, and low amounts of discretionary ultra-processed foods, is associated

with lower GWG (Cano-Ibáñez et al., 2020; Y. Li et al., 2021), reduced risk of excess GWG (Ancira-Moreno et al., 2019), reduced risk of GDM (Mijatovic-Vukas et al., 2018; Pajunen et al., 2022), and lower offspring BMI from 3 to 15 years of age (Monthé-Drèze et al., 2021). Poor compliance with national dietary guidelines is linked to high neonatal cord blood insulin (r = -0.365, p = 0.031) (Gesteiro, Rodriguez Bernal, Bastida, & Sanchez-Muniz, 2012), and adiposity (A. R. Chia et al., 2018; A. L. Shapiro et al., 2016).

There is mounting evidence from observational research that has described dietary patterns with higher risk attributes. Dietary pattern analysis has shown in various contexts that generally, western dietary patterns are associated with more adverse outcomes, such as increased GDM risk, and "healthy" or "prudent" dietary patterns lead to better outcomes (A. R. Chia et al., 2019; Lambert, Muñoz, Gil, & Román, 2023). However, specific components of these patterns are not well-defined due to varying methodologies used across geographically differing populations. In a systematic review by A.-R. Chia et al. (2019) of maternal dietary patterns and birth outcomes, "unhealthy" dietary patterns, characterised by high intakes of refined grains, processed meat, and foods high in saturated fat or sugar, were associated with lower birthweight (mean difference:−40 g; 95% CI −61,−20 g) and a trend towards a higher risk of pre-term birth (OR 1.17, 95% CI 0.99, 1.39). Conversely, healthy dietary patterns, characterised by high intakes of vegetables, fruits, wholegrains, low-fat dairy, and lean protein foods, were associated with lower risk of preterm birth (OR for top compared with bottom tertial 0.79, 95% CI 0.68, 0.91) and a weak trend towards a lower risk of small-for-gestational age (OR 0.86; 95% CI: 0.73, 1.01).

Vitamin D insufficiency

Vitamin D is recognised for many roles in maternal metabolic health, as well as being involved in fertilisation, placental development, and offspring health (Karras, Wagner, & Castracane, 2018). Extensive research has identified vitamin D as having a protective role by supporting cardiovascular and endothelial function, improving insulin sensitivity and carbohydrate metabolism, and modulating immune and inflammatory responses (Poniedziałek-Czajkowska & Mierzyński, 2021). During pregnancy, vitamin D inadequacy has been linked to complications such as preeclampsia, preterm birth, and GDM, as well as later life complications for the offspring such as asthma, psychomotor development, and cognitive disorders (Karras et al., 2018; Poniedziałek-Czajkowska & Mierzyński, 2021). Furthermore, there is an established relationship between vitamin D and obesity/adiposity (Bennour, Haroun, Sicard, Mounien, & Landrier, 2022).

In maternal metabolism, vitamin D deficiency is associated with epigenetic changes that lead to an obese phenotype, hyperinsulinaemia, and inflammation in the offspring (Bennour et al.,

2022). A meta-analysis including 68 prospective observational studies showed that higher vitamin D status conferred a lower risk for GDM, preeclampsia, and gestational hypertension, as compared to women with the lowest level (R. Zhao, Zhou, Wang, Xiong, & Hao, 2022). Vitamin D insufficiency (50-75 nmol/L) or deficiency (<50 nmol/L) has also been associated with a 1.4 to 1.5 increased odds of preeclampsia compared to women with replete vitamin D levels (>75 nmol/L) (K. L. Hu, Zhang, Chen, Zhang, & Hunt, 2022). Findings from 20 observational studies indicated a 45% increased risk of developing GDM among women with vitamin D insufficiency at varying stages of pregnancy (M. Lu, Xu, Lv, & Zhang, 2016; M.-X. Zhang et al., 2015). Despite research indicating a clear association between vitamin D status and various maternal health outcomes, supplementation with vitamin D has a limited or inconsistent effect on risk for GDM and preeclampsia (Palacios, De-Regil, Lombardo, & Peña-Rosas, 2016).

Advanced maternal age

The increasing number of women deferring motherhood to a later time in life is explained by cultural shifts in lifestyle choices, increasing infertility, and the availability of assisted reproductive technologies (Guedes & Canavarro, 2014). Advanced maternal age is traditionally defined as 35 years or older at the time of delivery and is recognised as an independent risk factor for maternal and perinatal complications (Lean, Derricott, Jones, & Heazell, 2017). The risk for adverse outcomes, including stillbirth, caesarean delivery, and maternal mortality increase with advanced age, with the greatest risks being in women from the 45-50 years and over 50 years age brackets (Saccone et al., 2022). Advanced maternal age has been shown to be associated with an overall 2.85 increased odds of GDM (OR 2.85, 95% CI 2.45, 3.32) with odds being as high as 3.82-4.81 among women over 40 years (40-49 years: OR 3.82, 95% CI 2.89, 5.04; ≥ 45 years: OR 4.81, 95% CI 2.65, 8.72) (Lean, Derricott, et al., 2017). Women over 35 years also have an increased risk of preeclampsia, placental abruption, neonatal intensive care unit admission, pre-term birth, stillbirth, and neonatal death.

Pregnancy is a natural human model of ageing (Giller, Andrawus, Gutman, & Atzmon, 2020). Women who enter pregnancy at an older age experience the combined effects of pregnancy and age-related metabolic changes to insulin sensitivity, oxidative stress, inflammation, changes in DNA methylation, and shortening of telomeres (Miller et al., 2022). Further evidence shows that an increased risk for preeclampsia and other placental abnormalities, such as placental abruption and foetal growth restriction, could reflect maternal cardiometabolic maladaptation and endothelial dysfunction (Miller et al., 2022). Maternal vascular abnormalities in preeclamptic pregnancies may be initiated by accelerated cellular senescence, including telomere shortening, altered mitochondrial autophagy, and activation of inflammatory and

stress-associated signalling pathways (Manna, McCarthy, & McCarthy, 2019). Placentas of women with advanced maternal age also show signs of accelerated placental ageing, described as reduced efficiency, altered nutrient transport, and vascular function (Lean, Heazell, Dilworth, Mills, & Jones, 2017). Rather than maternal age being a primary risk factor, it is plausible that metabolic dysfunction, hyperinsulinaemia, and low grade inflammation, which develop with age, are the likely drivers of vascular abnormalities during pregnancy (Jung et al., 2022). This background metabolic dysfunction may also explain the increased risk of cardiovascular diseases and other chronic non-communicable diseases of ageing observed among women with a history of preeclampsia (Manna et al., 2019).

Sleep disturbances

Sleep disturbances are a common challenge experienced during pregnancy due to considerable hormonal, respiratory, and cardiovascular changes, foetal movement, and frequent awakenings to urinate caused by a growing uterus (Lamberg, 2006). Sleep disordered breathing is one of the most common sleep disorders of pregnancy, estimated to affect 10 to 32% of pregnant women (Louis et al., 2018). Moreover, sleep disordered breathing is a known risk factor for metabolic dysregulation, often being associated with obesity, insulin resistance, elevated glucose and triglycerides that may lead to accelerated foetal growth and excess infant adiposity (S. S. Farabi, Barbour, & Hernandez, 2021). Sleep inadequacy has been shown in multiple studies to have detrimental effects on insulin sensitivity (Sondrup et al., 2022). The physiological stress of sleep restriction leads to increased cortisol levels and catecholamines that reduce insulin sensitivity. Concurrently, intermittent hypoxia and sleep fragmentation in women with sleep disordered breathing may lead to impaired placental oxygenation and inflammation that could impede placental function and foetal growth, contributing to the development of preeclampsia or small-for-gestational age infants (S. S. Farabi et al., 2021). A meta-analysis including 33 studies showed that obstructive sleep apnoea was associated with increased risk for gestational hypertension (adjusted OR 1.97, 95% CI 1.51, 2.56), GDM (adjusted OR 1.55, 1.26, 1.90), preeclampsia (adjusted OR 2.35, 95% CI 2.15, 2.58), caesarean section (adjusted OR 1.42, 95% CI 1.12, 1.79), postoperative wound complications (adjusted OR 1.87, 95% CI 1.56, 2.24), pulmonary oedema (adjusted OR 6.35, 95% CI 4.45, 9.50), preterm birth (adjusted OR 1.62, 95% CI 1.29, 2.02), and neonatal intensive care unit admission (adjusted OR 1.28, 95% CI 1.13, 1.46) (L. Liu, Su, Wang, & Zhu, 2019). A second meta-analysis of 120 studies demonstrated that sleep disturbances in pregnancy were significantly associated with an increased risk of preeclampsia (OR 2.80, 95% CI 2.38, 3.30), gestational hypertension (OR 1.74, 95% CI 1.54, 1.97), GDM (OR 1.59, 95% CI 1.45, 1.76), caesarean section (OR 1.47, 95% CI 1.31, 1.64), preterm birth (OR 1.38, 95% CI 1.26, 1.51), large-for-gestational age (OR 1.40, 95% CI 1.11, 1.77), and stillbirth (OR 1.25 95% CI 1.08, 1.45),

but not small-for-gestational age or low birth weight (Q. Lu et al., 2021). Morbidities related to sleep disturbances were higher among women with overweight/obesity before pregnancy and women aged 30 years or older. (S. S. Farabi et al., 2021)

Environmental exposures

There is increasing evidence linking exposure to environmental chemicals and long-term adverse health effects (Lite et al., 2022; Mohanto, Ito, Kato, & Kamijima, 2021). Endocrine-disrupting chemicals, which includes several classes of chemicals such as bisphenol, phthalates, and heavy metals, have been implicated in the development of obesity, type 2 diabetes, and insulin resistance (G. D. Shapiro et al., 2015; Q. Sun et al., 2014). Bisphenol and phthalates are ubiquitous in the environment due to common use in various products, including the lining of metal cans, toys, water pipes, paper products, and vinyl plastics (Philips et al., 2018). Their role in maternal metabolic health and offspring development is becoming increasingly recognised due to a range of potential obesogenic, oestrogenic, anti-androgenic, and thyroid disrupting effects (Xueping. Chen et al., 2014; De Coster & van Larebeke, 2012; Philips et al., 2018; Polinski et al., 2018). Evidence showing that bisphenols and phthalates also cross the placenta suggest further implications on foetal development and offspring health (Katsikantami et al., 2020; Schönfelder et al., 2002). Higher concentrations of first trimester urinary mono-ethyl phthalate was associated with higher early GWG (adjusted + 1.3kg at the 75th percentiles, lowest vs second quartiles, 95% CI 0.3-2.4) in an observational study with 347 women in Massachusetts USA (Bellavia et al., 2017). Higher urinary mono-3-carboxypropyl phthalate mid-late pregnancy was also associated with continued weight gain 5-10 years after pregnancy in a Mexican cohort of 178 women (adjusted + 0.33 kg per year for every unit increase 95% CI: 0.09, 0.56) (Rodríguez-Carmona et al., 2019). Two North American cohorts have shown associations between arsenic exposure and GDM risk. Among 532 women at 24 to 28 weeks' gestation, the highest quartile of blood arsenic exposure had 2.8 higher adjusted odds of impaired one-hour glucose tolerance test (>7.8 mmol/L, 50 g) than women in the lowest quartile of exposure (95% CI 1.1,6.9) (Ettinger et al., 2009). The highest quartile for urinary arsenic in a cohort of 1274 pregnant women was associated with an elevated odds for GDM (adjusted OR 3.7, 95% CI 1.4, 9.6), however, associations for phthalates, bisphenol, and other heavy metals were non-significant (G. D. Shapiro et al., 2015). Among a Chinese pregnant cohort, a three-fold increase in urine cadmium concentrations was associated with a 16% increased relative risk of GDM (RR 1.16, 95% CI 1.03, 1.33), with risk being highest among women with both overweight/obesity and high urinary cadmium (Xing et al., 2018). All studies provided adjustments for identified confounding variables (including but not limited to some of the following maternal age, ethnicity, pre-pregnancy BMI, energy intake, and education level). While current evidence describing

phthalates and heavy metals in relation to maternal outcomes is limited associations mostly observed in small cohorts, growing interest in environmental exposures suggests further research to determine any causal effect is required.

Associations between air pollution and exposure to agricultural chemicals and the increased risk of GDM and hypertensive disorders of pregnancy have been described in multiple observational studies (Jo et al., 2019; Malmqvist, Jakobsson, Tinnerberg, Rignell-Hydbom, & Rylander, 2013; Saldana et al., 2007). A recent meta-analysis showed particulate matter ($PM_{2.5}$ and PM_{10}) exposure during pregnancy was associated with a 1.04 (95% CI 1.02, 10.7) to 1.16 (95% CI 1.05, 1.29) increased odds of gestational hypertension (Cao et al., 2021). The included studies were highly heterogenous and all studies adjusted for age, BMI, multiple pregnancies, and prior chronic medical history as main causes of hypertensive disorders. Similar findings were reported in a meta-analysis which showed increased risk of hypertensive disorders in pregnancy in association with particulate matter ($PM_{2.5}$ and PM_{10}) (OR 1.57, 95% CI 1.26, 1.96) and nitrogen dioxide (OR 1.20, 95% CI 1.20, 1.00, 1.44) exposure during pregnancy (M. Pedersen et al., 2014). Although included studies adjusted for established covariates, high heterogeneity in studies relating to environmental exposures could be related to many unidentified confounders of air pollution such as geographical location, land-use, traffic density, and composition, which could influence the variation in exposure to air pollution. Nitrogen dioxide and particulate matter induce oxidative stress, lipid peroxidation, and the overproduction of proinflammatory cytokines, leading to a chronic low-grade inflammatory state, increased insulin resistance, and endothelial dysfunction (Lodovici & Bigagli, 2011). During pregnancy, the placenta is highly sensitive to vascular endothelial damage, which may lead to the development preeclampsia by causing disruptions to blood flow, oxygen transport, and angiogenesis (M. Pedersen et al., 2014).

Periodontal disease

Periodontal disease refers to an inflammatory condition initiated by bacteria in the oral cavity (Williams, 1990). In the course of severe disease, periodontitis can lead to a chronic systemic inflammatory response, which has been linked to the development of cardiovascular and other chronic non-communicable diseases (Conde-Agudelo, Villar, & Lindheimer, 2008). Periodontitis has been found to be positively associated with overweight/obesity in pregnancy (Foratori-Junior et al., 2022), excessive GWG (Jesuino, Foratori-Junior, Missio, Mascoli, & Sales-Peres, 2020), and preeclampsia (Conde-Agudelo et al., 2008). The impact of periodontitis on maternal metabolic health may be explained through the development of a chronic pro-inflammatory state. Bacteria can be released from the periodontal space during dental procedures or in the course of severe disease, stimulating an inflammatory response that may cause damage to the

cardiovascular system (Sanz et al., 2020). Both overweight/obesity and periodontitis induce local immune activation that causes increased bacterial translocation and an increased inflammatory response (Foratori-Junior et al., 2022; Jung et al., 2022). In pregnancy, it is suggested that reduced antimicrobial activity due to changes in the immune system may increase the proportion of anaerobic and aerobic bacteria (including *Bacteroides melaninogenicus, Prevotella intermedia and Porphyromonas gingivalis*) (Silva de Araujo Figueiredo, Gonçalves Carvalho Rosalem, Costa Cantanhede, Abreu Fonseca Thomaz, & Fontoura Nogueira da Cruz, 2017). It is hypothesised that in women who enter pregnancy with pre-existing inflammation associated with overweight/obesity, inflammatory changes associated with periodontitis may become more exaggerated, leading to worsened insulin resistance and lipotoxicity (Foratori-Junior et al., 2022; James et al., 2021).

Maternal intestinal dysbiosis

The role of human microbiota in regulating metabolism and the risk of non-communicable metabolic disease has become increasingly established. Gut dysbiosis has been implicated in the development of metabolic syndrome (Michels et al., 2022), type 2 diabetes (Fernández-Millán & Guillén, 2022; Portincasa et al., 2022), cardiovascular disease (Mahdavi-Roshan, Salari, Kheirkhah, & Ghorbani, 2022), and certain cancers (Sędzikowska & Szablewski, 2021). During pregnancy, the microbiome is directly and indirectly impacted by changes to maternal hormonal, immunological, and metabolic systems (Turjeman, Collado, & Koren, 2021). Over the course of gestation, total bacterial load increases and there is a substantial shift in the phylogenetic composition and structure (Collado, Isolauri, Laitinen, & Salminen, 2008; O. Koren et al., 2012). O. Koren et al. (2012) showed that reduced insulin sensitivity during pregnancy correlated with higher levels of inflammatory markers in the stool during the third trimester. In the same study, germ-free nonpregnant mice inoculated with stool samples from pregnant women in their third trimester were found to develop increased adiposity and insulin resistance compared to mice inoculated with first trimester samples. It was suggested that changes in the microbiota could therefore contribute to the low-grade proinflammatory state progressively increasing insulin resistance during pregnancy (O. Koren et al., 2012).

Changes in the microbiota composition have been described among women with GDM, maternal obesity, and preeclampsia as being characteristically different to “healthy” pregnant women (Hasain et al., 2020; Lv et al., 2018; Turjeman et al., 2021). Three meta-analyses have described evidence examining the impact of probiotic supplementation of glucose and lipid metabolism on pregnancy (M. M. Han et al., 2019; T. R. Peng, Wu, & Chao, 2018; Zheng, Feng, Zheng, & Xiao, 2018). From 10 RCTs, probiotic supplementation was suggested to produce

modest reduction in fasting blood glucose levels (mean difference −0.11 mmol/L, p = 0.0003), serum insulin levels (mean difference −2.06 µU/mL, p < 0.00001), total cholesterol (standardised mean difference −0.56, p = 0.03), and triglycerides levels (standardised mean difference -0.66, p = 0.04). A protective effect for reducing the risk of GDM following a probiotic intervention has also been suggested (RR 0.52, p = 0.003, three trials, probiotic/placebo n = 323/336), however, results from intervention trials have been contradictory, possibly due to varying study duration and probiotic strains administered (M. M. Han et al., 2019). Reviewing specific probiotic strains and their impact on maternal metabolism is beyond the scope of this review.

Knowledge of the human gut microbiome is still a relatively new field of research, therefore, there are various suggested mechanisms to explain the impacts of microbiota on metabolic health (O. Koren et al., 2012; Lv et al., 2018). Microbiota may alter dietary energy absorption and response to food by modulating gut-derived peptide incretin hormones. Higher gut-derived inflammation can also lead to translocation of lipopolysaccharides, contributing to the development of endotoxemia, which has been associated with reduced insulin sensitivity, weight gain, and the onset of type 2 diabetes and obesity (Cani et al., 2007).

Summary of risk factors associated with metabolic dysfunction in pregnancy.

In summary, maternal metabolic health is influenced by a multitude of intrinsic health factors, heritable traits, and environmental or lifestyle-related components (Figure 5). Many factors that lead to a higher risk phenotype are also likely interconnected and related to an individual's social circumstances. For example, dietary choices can influence periodontal health and the intestinal microbiome; familial factors may encompass learned lifestyle traits such as physical activity and dietary choices; lifestyle and environmental factors are strongly connected with social determinants of health which include housing conditions, income, education, food security, sanitation, social support, and access to health care (E. Wang, Glazer, Howell, & Janevic, 2020). That is to say that some risk factors for adverse maternal and neonatal outcomes may not directly point to causality but rather describe a suboptimal maternal environment. For example, food insecurity or limited disposable income can increase the likelihood of needing to rely on low-cost ultra-processed food. Lower cost housing may be more accessible in areas with greater air pollution and may be associated with suboptimal lifestyle behaviours such as sleep deprivation, poorer dietary behaviours from requiring lower-cost foods, and periodontal disease due to limited access to dental treatment. Impaired access to health care services or disengagement due to minority stress or perceived discrimination may mean delayed interventions for potentially avoidable obstetric complications.

Acknowledging risk factors discussed in this previous section could mean that most pregnant women categorically have some degree of "risk" for adverse outcomes in pregnancy. However, the presence of any one risk factor does not necessarily mean there is an immediate danger for the woman or her future offspring. That is to say, identifying one risk factor does not guarantee that a woman will develop pathological hyperinsulinaemia and insulin resistance in pregnancy. Therefore, clinical parameters and diagnostic criteria should be considered. Although some metabolic indicators described have clear clinical parameters, such as cardiovascular markers and BMI, the lack of diagnostic criteria to critically evaluate metabolic health for women with sub-clinical or borderline risk factors remains a challenge for clinical practice.

2.2.3 Adverse outcomes associated with metabolic dysfunction during pregnancy

Pregnancy is a sensitive period that does not come without risks to the mother and offspring's health (Fleming et al., 2018; Stephenson et al., 2018). Advances in medicine, such as the availability of insulin for the management of GDM (Retnakaran, 2021), pharmacological agents for the treatment of hypertensive disorders (Awaludin, Rahayu, Daud, & Zakiyah, 2022), and reproductive technologies to treat infertility means that more women can successfully conceive and carry to term (Zymperdikas et al., 2022). However, the increasing prevalence of maternal obesity (C. Chen, Xu, & Yan, 2018; Khajehei & Assareh, 2021; Ward et al., 2020), as well as other risk factors described in section 2.2.2 means that more women may enter pregnancy with pre-existing risk factors for adverse outcomes characterised by insulin resistance and hyperinsulinaemia in pregnancy. The following section discusses common adverse outcomes associated with metabolic dysfunction in pregnancy.

Excessive gestational weight gain (GWG)

The Institute of Medicine (IOM) provides BMI-specific weight gain targets during pregnancy, which have served as the basis for defining excess GWG since 2009 (Institute of Medicine & National Research Council, 2009, 2013). Excess GWG is associated with acute and long-term adverse effects on the mother and offspring, including epigenetic consequences across generations (Goldstein et al., 2018; M. A. Hanson, McAuliffe, Louise Killeen, Maria Jacob, & Hod, 2020). A meta-analysis by Goldstein et al. (2017) reported associations between GWG outside of the 2009 IOM guidelines and outcomes from over one million pregnancies. Excess GWG was associated with increased odds of caesarean delivery, and nearly two-fold increased odds of large-for-gestational age infants and macrosomia. In various other cohort studies, excess GWG is has been associated with an increased risk for developing preeclampsia, and in the offspring overweight/obesity and insulin resistance in later life (Houghton et al., 2016; Hrolfsdottir et al., 2015; Hung, Chen, Hsu, & Hsieh, 2015; Mamun, Mannan, & Doi, 2014). Particularly during the

first half of pregnancy, excess GWG conveys a greater risk for developing GDM (Carreno et al., 2012), especially in women with pre-existing overweight or obesity (Gibson, Waters, & Catalano, 2012). Studies have shown that high GWG in the first trimester is strongly associated with post-partum weight gain or weight retention (Fraser et al., 2011; Walter et al., 2015), therefore exposing the mother to risks associated with obesity in subsequent pregnancies and chronic metabolic diseases later in life.

Lipogenesis and fat storage is promoted by elevated insulin secretion in conjunction with increased cortisol, oestrogens, and progesterone (Butte, 2000). It has been postulated that increasing insulin resistance throughout pregnancy serves as an adaptation mechanism to conserve energy in the face of an increased basal metabolic rate and to make nutrients available for the foetal-placental unit (Catalano, Roman-Drago, Amini, & Sims, 1998; Eckel, 1992). Controlled studies have shown that insulin resistance during pregnancy has an inverse relationship with fat mass accumulation. Catalano et al. (1998) demonstrated in the first 14 weeks of pregnancy, decreased insulin sensitivity (measured by hyperinsulinaemic-euglycaemic clamp) was associated with reduced fat mass accumulation; changes in fat mass inversely correlated with changes in insulin sensitivity ($r = -0.52$, $p = 0.04$; $n = 6$ with normal glucose tolerance and $n = 10$ with pre-pregnancy abnormal glucose tolerance). Moreover, lean women with greater insulin sensitivity and appear to have significantly higher increases in fat mass throughout gestation as compared to women with obesity (Catalano & Shankar, 2017). However, outside of control studies, prospective research ($n = 621$ women) has shown that excess GWG was associated with greater maternal insulin resistance (HOMA-IR) and leptin levels at 28 weeks' gestation, but not at the beginning of pregnancy (Walsh, McGowan, Mahony, Foley, & McAuliffe, 2014). The accumulation of excess GWG further exacerbates peripheral insulin resistance and adipose tissue dysfunction, which leads to an increase in adipose tissue lipolysis, pro-inflammatory cytokines, lipotoxicity, and repartitioning of glucose and lipids throughout maternal circulation (Corrales et al., 2021). The independent effects of excessive GWG and pre-pregnancy obesity have not been well established since the obesity phenotype is likely to exacerbate GWG, and obesity can result from excessive GWG (Corrales et al., 2021; Gavard & Artal, 2014). Obesity has an additive effect when combined with excess GWG; risk for total adverse outcomes is greatest in women with both a high pre-pregnancy BMI and high GWG (Voerman, Santos, Inskip, et al., 2019).

Hypertensive disorders in pregnancy

Hypertensive disorders in pregnancy include preeclampsia, gestational hypertension or pregnancy-induced hypertension, and chronic hypertension with or without superimposed

preeclampsia (Garovic et al., 2022). Although hypertensive disorders in pregnancy can occur without prior risk factors, they occur most frequently in women with maternal obesity, GDM, PCOS, or other conditions associated with insulin resistance (Solomon & Seely, 2001). They also most commonly develop late in gestation as maternal insulin resistance and hyperinsulinaemia are most pronounced, therefore suggesting the role of insulin in the aetiology. Hypertensive disorders in pregnancy are defined as systolic blood pressure of 140 mm Hg or more or diastolic blood pressure of 90 mm Hg or more on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure (American College of Obstetricians and Gynecologists, 2020). Although the aetiology of specific hypertensive disorders can vary, hyperinsulinaemia and insulin resistance are arguably important factors in the development preeclampsia and gestational hypertension. During pregnancy, insulin has several roles regulating sodium and fluid balance, vascular resistance (Solomon & Seely, 2001), and angiogenesis of foetal-placental vasculature (Sobrevia et al., 2016).

Hypertensive disorders in pregnancy have long-term implications on maternal and offspring health. Preeclampsia is associated with an increased risk of hypertension, ischaemic heart disease, stroke, venous thromboembolism, and higher overall mortality within 15 years after delivery (Bellamy, Casas, Hingorani, & Williams, 2007). Signs of persisting insulin resistance are observed among women with a history of preeclampsia or gestational hypertension within a decade following delivery (Girouard, Giguère, Moutquin, & Forest, 2007). In particular, being diagnosed with preeclampsia or gestational hypertension earlier in pregnancy is linked to higher fasting glucose, insulin, triglycerides, and a greater prevalence of hypertension in two to five years postpartum (Veerbeek et al., 2015). The appearance of metabolic syndrome later in life suggests the progressive development of insulin resistance and hyperinsulinaemia several years after pregnancy.

Preeclampsia

According to the American Heart Association, preeclampsia is distinguished from gestational hypertension and chronic hypertension by the involvement of placental vascular dysfunction (Garovic et al., 2022). Diagnostic criteria from the American College of Obstetricians and Gynaecologists define preeclampsia as gestational hypertension (systolic blood pressure greater than 140 mm Hg or diastolic more than 90 mm Hg) with proteinuria, or new onset thrombocytopenia, renal insufficiency, impaired liver function, pulmonary oedema, or headache unresponsive to medication (American College of Obstetricians and Gynecologists, 2020). Preeclampsia is a multisystem metabolic disorder first initiated by increased production of pro-inflammatory cytokines, endothelial dysfunction, and impaired placental perfusion and ischemia, followed by maternal hypertension and proteinuria (Jung et al., 2022). As gestation

progresses, placentas affected by preeclampsia display increasing levels of vascular inflammation, endothelial dysfunction, maternal vascular injury, and infarction, which can eventuate as complete abruption (separation from the inner wall of the uterus before birth) (Garovic et al., 2022). Defects in placental function impede nutrient delivery to a growing foetus which can lead to growth restriction, small-for-gestational age infants, pre-term delivery, and perinatal death (M. Hu, Li, Baker, & Tong, 2021; Jung et al., 2022). In the mother, the consequences of advanced preeclampsia include maternal multiorgan dysfunction, maternal seizures, and eventual development of vascular dementia, coronary artery disease, heart failure, and chronic kidney disease later in life (Chappell, Cluver, Kingdom, & Tong, 2021; Garovic et al., 2022). Offspring affected by preeclampsia *in utero* have an increased risk of cardiovascular diseases later in life (Bellamy et al., 2007; E. F. Davis et al., 2012; Kajantie, Eriksson, Osmond, Thornburg, & Barker, 2009).

With vascular disease being central in the aetiology of preeclampsia, Jung et al. (2022) describes that placental ischemia develops from a failure in the transformation of the spiral arteries during placentation and the development of atherosis, a lesion specific to spiral arteries that is equivalent to atherosclerosis in coronary arteries. In their histological experiments, Jung et al. showed that ischemic atherotic arteries appear with lipid-laden macrophages and fat droplets, characteristics recognised as being linked to inflammation and endothelial cell dysfunction. The contribution of vascular inflammation and endothelial dysfunction suggests a role of hyperinsulinaemia in the aetiology of preeclampsia (Crofts et al., 2015). In healthy placentas, inflammatory cytokine and endocrine signals are produced in response to environmental changes, such as glucose availability, oxygen, and maternal insulin, to alter nutrient availability for foetal growth (Sobrevia et al., 2016). This capacity for the placenta to adapt to changes in the maternal environment could mean that abnormalities in carbohydrate and lipid metabolism may play a role in the aetiology and clinical progression of preeclampsia (M. Hu et al., 2021). These associations with abnormal nutrient metabolism and hyperinsulinaemia may provide a causal link for the increased risk of preeclampsia among women with pre-existing insulin resistance, GDM, metabolic syndrome, and obesity (Catov et al., 2007; Cho et al., 2016; Duckitt & Harrington, 2005; HAPO Study Cooperative Research Group et al., 2008; Schneider, Freerksen, Röhrig, Hoeft, & Maul, 2012; Z. Wang et al., 2013; Weissgerber & Mudd, 2015).

Gestational diabetes mellitus (GDM)

GDM is a condition that is typically identified in the second half of pregnancy (American Diabetes Association, 2023). Historically, GDM has been defined as carbohydrate intolerance resulting in hyperglycaemia or any degree of glucose intolerance with onset or first recognition during

pregnancy, usually from 24 weeks' gestation onwards (World Health Organization, 2013a). Whilst this definition has spearheaded a uniform strategy for detection and classification of GDM, the definition has limitations due to not distinguishing between women with unidentified pre-existing hyperglycaemia before pregnancy (American Diabetes Association, 2023). This understanding has led further modification of diagnostic criteria to encourage early screening among women with pre-existing risk factors (American Diabetes Association, 2023).

In women with GDM, hyperglycaemia develops following the rapid escalation in maternal insulin resistance, and this results in a disparity between maternal insulin secretion and insulin resistance. GDM is suggested to have various aetiologies; GDM may develop from a relative inadequacy in insulin production (termed beta-cell defect), excessive insulin resistance, or a combination of both (Powe, Hivert, & Udler, 2020).

GDM is considered to be the most common metabolic disorder during pregnancy (Choudhury & Devi Rajeswari, 2021). Estimated prevalence rates for GDM vary significantly between 6% and 25%, likely due to ethnic or regional factors and inconsistencies in screening programmes and diagnostic criteria used (Guariguata, Linnenkamp, Beagley, Whiting, & Cho, 2014; Paulo et al., 2021; D. A. Sacks et al., 2012; Zhu & Zhang, 2016). The increasing rates of GDM are a growing global concern. An increasing prevalence of women becoming pregnant with pre-existing risk factors for insulin resistance and hyperinsulinaemia, for example, advanced maternal age and obesity, are likely contributing factors (Dabelea et al., 2005; Ferrara, Kahn, Quesenberry, Riley, & Hedderson, 2004; Lavery et al., 2017).

GDM is associated with many adverse acute and long-term risks to the mother and offspring. For women, the acute impacts of GDM include a higher risk of hypertensive disorders of pregnancy, including preeclampsia, preterm birth, induction of labour, emergency caesarean section, perineal trauma, and postpartum haemorrhage (HAPO Study Cooperative Research Group et al., 2008; Martis et al., 2018). Infants from mothers with GDM have an increased risk of foetal growth restriction and being born small-for-gestational age, foetal overgrowth leading to macrosomia or large-for-gestational age infants (Ornoy, 2011; Young & Ecker, 2013). There is also a small risk for congenital abnormalities (T. N. Zhang et al., 2022). Larger babies are more likely to have difficulties during delivery (e.g. shoulder dystocia), which increases the risk of neonatal trauma such as bone fractures and nerve injury, although these events are uncommon (Kekki et al., 2021). Neonates exposed to hyperglycaemia *in utero* also have an increased risk of acute metabolic complications on delivery, such as hypoglycaemia, respiratory distress syndrome, and hyperbilirubinaemia (HAPO Study Cooperative Research Group et al., 2008). Risks for adverse outcomes are greater for women with poor glycaemic control (HAPO Study

Cooperative Research Group et al., 2008) and those with more advanced insulin resistance (Cosson et al., 2022; J. Lin, Jin, & Chen, 2021).

In 2008, the pivotal Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) trial, which included over 25,000 women, described associations between maternal glycaemia and pregnancy outcomes outside of overt diabetes (HAPO Study Cooperative Research Group et al., 2008). Primary outcomes included birth weight above the 90th percentile for gestational age, primary caesarean delivery, clinically diagnosed neonatal hypoglycaemia, and cord-blood serum c-peptide level above the 90th percentile. This seminal study demonstrated clear associations between increasing levels of fasting, 1- and 2-hour glucose (post 75-gram OGTT at 24 to 32 weeks' gestation) and large-for-gestational age, caesarean delivery, neonatal hypoglycaemia, and cord blood c-peptide >90th percentile. Furthermore, no distinct inflexion point at which the risk of adverse outcomes increase was identified; there was a continuous relationship between glucose levels and primary outcomes. Associations were observed at lower levels of glycaemia than expected. Findings from the trial led to new GDM diagnostic criteria from which thresholds were developed to identify women with a risk of large-for-gestational age infants, based on an odds ratio of 1.75 (Metzger, Gabbe, et al., 2010).

Both mothers and offspring exposed to GDM have an increased risk of metabolic syndrome later in life. In mothers, the risk of developing type 2 diabetes after pregnancy is well-established (Bellamy et al., 2009; Diaz-Santana, O'Brien, Park, Sandler, & Weinberg, 2022). Women who have had a GDM pregnancy are more than seven-times more likely to develop type 2 diabetes compared to those who have had a normoglycaemic pregnancy. A more recent analysis suggested the age-adjusted relative risk of type 2 diabetes declined in the most recent years from GDM diagnosis but remained elevated for over 35 years (HR at 6-15 years 3.97, 95% CI 2.60, 5.75; HR after 35 years 1.62, 95% CI 1.12, 2.33; n = 1,414 women with GDM) (Diaz-Santana et al., 2022). Moreover, women with a history of GDM enter a trajectory with a greater risk of developing chronic cardiometabolic diseases later in life, including hypertension, renal damage, liver disease, and cardiovascular diseases (B. Daly et al., 2018; Fadl et al., 2014; Kaul et al., 2015; Retnakaran, Luo, & Shah, 2019; Retnakaran & Shah, 2017; Shah, Retnakaran, & Booth, 2008; Tobias et al., 2017; Tranidou et al., 2021; Y. Xu et al., 2014; C. Zhang et al., 2019).

Offspring exposed to GDM *in utero* are more likely to be overweight or obese in childhood (Nehring, Chmitorz, Reulen, von Kries, & Ensenauer, 2013). They also encounter a life-long increased risk of cardiometabolic disease (Boney et al., 2005; Dabelea et al., 2000; Fraser & Lawlor, 2014; Ornoy, 2011), including an eight-fold risk of prediabetes or type 2 diabetes in early adulthood (Damm, 2009). Recent data from the HAPO Follow-Up Study, consisting of 3,317

maternal-child dyads revealed that having hypertensive disorder during pregnancy P (aRR 1.14; 95% CI, 1.04, 1.25) or having GDM (aRR 1.10; 95% CI 1.02, 1.19) was associated with a greater risk of having offspring that developed less-than-ideal cardiovascular health (ranked based on BMI, blood pressure, total cholesterol levels, and glucose level) at ages 10 to 14 years (Venkatesh et al., 2024). This means that as girls from GDM mothers enter child-bearing age, they are more likely to carry risk factors for GDM, fuelling the futile cycle of diabetes begetting diabetes.

Foetal hyperinsulinaemia

Among women with GDM, the foetal response to overnutrition is foetal hyperinsulinaemia, which can affect growth and development (McCance, 2011). In 1952, the Pedersen hyperglycaemia-hyperinsulinaemia hypothesis first suggested how foetal overgrowth could result from maternal hyperglycaemia (J. Pedersen, 1952). In Pedersen's view, the passive oversupply of glucose to the placenta was understood as being the main driver for foetal hyperglycaemia, which would stimulate foetal hyperinsulinaemia, resulting in excess growth. Maternal hyperglycaemia stimulates foetal pancreatic beta-cell hyperplasia and excessive production of insulin (Hellerström & Swenne, 1991). Since insulin has somatogenic effects, these exaggerated levels of circulating insulin have potent growth properties, leading to foetal overgrowth and excess adiposity (Barbour & Hernandez, 2018a; Freinkel et al., 1985). After delivery, neonates exposed to foetal hyperinsulinaemia can develop neonatal hypoglycaemia (McCance, 2011). Neonatal hypoglycaemia can cause serious neurological or cardiopulmonary disturbances, such as mental retardation, seizures, and developmental delay (Kc, Shakya, & Zhang, 2015; McCance, 2011). The metabolic effects of maternal hyperglycaemia on the foetus are shown in Figure 6.

Freinkel (1980) described the lasting consequences of foetal hyperinsulinaemia as a "fuel-mediated teratogenesis" on recognising that long term metabolic risk in the offspring (i.e. obesity and type 2 diabetes) could have intrauterine origin. More recent evidence suggests epigenetic effects of foetal hyperinsulinaemia that could have lasting effects on obesity and cardiometabolic risk of the offspring (Chu & Godfrey, 2020; Godfrey et al., 2017). Recognising the role of hyperinsulinaemia in the development of chronic metabolic disease (Crofts et al., 2015), it is plausible that the development of hyperinsulinaemia *in utero* could represent the beginning of a trajectory toward cardiometabolic disease that continues to progress through the lifespan. Thus, children exposed to hyperinsulinaemia during development experience a greater risk of metabolic syndrome and type 2 diabetes in early adulthood (Boney et al., 2005; Damm et al., 2016; Venkatesh et al., 2024).

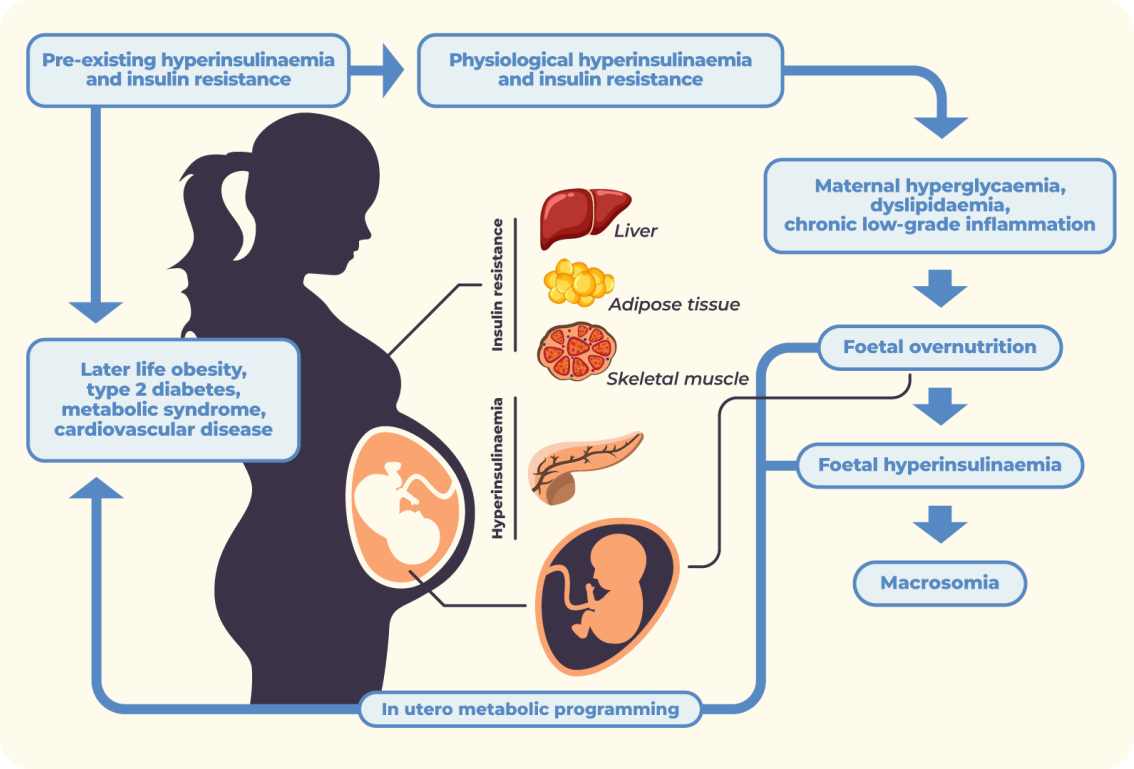


Figure 6. Hyperinsulinaemia and insulin resistance during pregnancy.
The metabolic demands of pregnancy for hyperinsulinaemia, insulin resistance, and low-grade chronic inflammation are augmented among women with pre-existing metabolic dysfunction (Hufnagel et al., 2022). Exaggerated hyperinsulinaemia, hyperglycaemia (in women with GDM only), dyslipidaemia, and chronic low-grade inflammation lead to foetal overnutrition. An oversupply of glucose across the placenta leads to foetal pancreatic beta-cell hyperplasia and hyperinsulinaemia (The Pedersen Hypothesis) (Freinkel et al., 1985; J. Pedersen, 1952). Excess nutrient transfer across the placenta and/or foetal hyperinsulinaemia can also lead to increased adiposity and macrosomia (Barbour & Hernandez, 2018a). Foetal overnutrition and hyperinsulinaemia alters epigenetic programming in the offspring. Long-term, both women and offspring have an increased risk of developing obesity, metabolic syndrome, type 2 diabetes, and/or cardiovascular disease later in life. Adults with hyperinsulinaemia and insulin resistance who do not become pregnant encounter similar risks for chronic metabolic disease later in life (James et al., 2021).

Foetal overnutrition

Maternal metabolic dysfunction, as seen in obesity and GDM, is linked to foetal-placental disturbances, which have serious immediate and long-term consequences on the offspring (Hebert & Myatt, 2021). Findings from the HAPO trial described that over three quarters (78%) of large-for-gestational age infants were born to women *without* GDM and that rates for large-for-gestational age infants were comparable between women with obesity (OR 1.73, 95% CI 1.50, 2.00) and GDM (OR 2.19, 95% CI 1.93, 2.47) (Catalano et al., 2012; Ryan, 2011). Thus, maternal BMI and glycaemia are both recognised as significant contributors to the risk of

large-for-gestational age infants (Catalano et al., 2012; HAPO Study Cooperative Research Group et al., 2008; Ryan, 2011). Since GDM and obesity are associated with a variety of endocrine and cytokine disturbances leading to a state of chronic low-grade inflammation and hyperinsulinaemia, these metabolic changes also have local effects on placental function (Newbern & Freemark, 2011). There is mounting evidence to show that a hyper-availability of maternal triglycerides and fatty acids to the placenta, as observed both in women with GDM and maternal obesity, may further drive foetal fat accretion and the development of excess neonatal adiposity (Barbour & Hernandez, 2018a). Placentas from women with obesity and/or GDM display mitochondrial dysfunction, leading to increased oxidative and nitrative stress (Hebert & Myatt, 2021); endoplasmic reticulum stress, further contributing to inflammation and to cellular insulin resistance; uncontrolled angiogenesis (Sobrevia et al., 2016); and altered lipid and amino acid transport (Hebert & Myatt, 2021; Sobrevia et al., 2016). Through these cellular changes in placental nutrient transfer, maternal dyslipidaemia and hyperinsulinaemia can drive an increase in lipid transport, leading to the development of macrosomia/foetal overgrowth (Corrales et al., 2021; Ruiz-Palacios, Ruiz-Alcaraz, Sanchez-Campillo, & Larqué, 2017; Sobrevia et al., 2016). Thus, it has been shown that maternal insulin levels In the third trimester correlate with foetal abdominal circumference (Ruiz-Palacios, Prieto-Sánchez, et al., 2017; Ruiz-Palacios, Ruiz-Alcaraz, et al., 2017). Furthermore, Sobrevia et al. (2016) suggest that altered lipid transport is also linked to reduced foetal DHA and altered HDL cholesterol particles, potentially linking the increase in neurological disorders and endothelial dysfunction in neonates from GDM pregnancies.

2.2.4 A life-course perspective on pregnancy

Previous literature has described pregnancy as a metabolic stressor that is superimposed upon a woman's existing track of cardiometabolic risk (Figure 7) (Fu & Retnakaran, 2022; Retnakaran, 2021; Torosyan, Aziz, & Quesada, 2022). Several similarities can be drawn between the physiological adaptations during pregnancy and metabolic syndrome defined outside of pregnancy (Ferranti et al., 2016). In this way, pregnancy serves as a metabolic stress test that may reveal metabolic abnormalities as a part of an evolving continuum across the life-course (Ferranti et al., 2016). Those who experience adverse pregnancy outcomes such as GDM, hypertensive disorders of pregnancy, or pre-term delivery are identified as having a substantially increased risk of cardiovascular disease later in life compared to women with healthy pregnancies (Torosyan et al., 2022). Even though abnormalities such as hyperglycaemia or hypertension typically resolve quickly within the postpartum period, the ongoing onslaught of environmental risk factors (i.e. poor diet and physical inactivity) may further a progression toward metabolic syndrome later in life (Ferranti et al., 2016) (Figure 7).

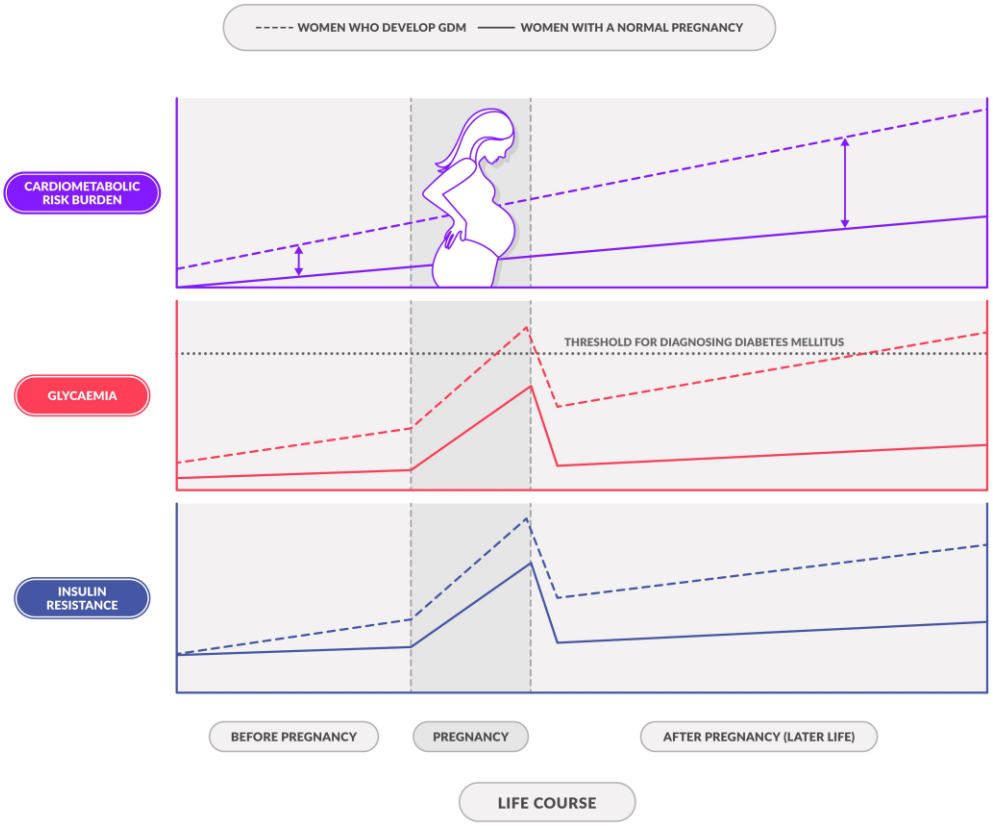


Figure 7. A conceptual life-course perspective of pregnancy as a life event superimposed upon an existing cardiometabolic risk burden.

Figure adapted from Retnakaran and colleagues (2022; 2021). Dotted lines indicate diverging trajectories of cardiometabolic risk among women who experience adverse pregnancy outcomes such as GDM, hypertensive disorders, or pre-term birth (Torosyan et al., 2022).

Since obesity typically coexists with insulin resistance and hyperinsulinaemia (Erion & Corkey, 2017; James et al., 2021), changes in body weight with the event of pregnancy provide a useful representation of metabolic health across the life-course. First, the event of pregnancy itself is associated with changes in body composition that may represent a higher risk, insulin resistant phenotype. Compared to having zero births, a history of pregnancy is associated with higher visceral adipose tissue and waist circumferences, meaning that weight gained or retained in the post-partum period is stored relatively centrally (as opposed to peripherally in the buttocks and thighs) (Gunderson et al., 2008; Lassek & Gaulin, 2006). In women who enter pregnancy with a higher BMI and/or have high GWG during pregnancy, there is a greater likelihood of long-term post-partum weight retention and the development of obesity later in life (Gunderson, 2009). The Danish National Birth Cohort (1996-2002) showed that excess GWG, postpartum weight retention at six months, and weight gain from six to 18 months postpartum contributed equally to an adverse weight status seven years after delivery (Kirkegaard et al., 2014). Having gained – and, later, retaining - excess weight during pregnancy can also mean women with an elevated BMI may enter subsequent pregnancies with an additional metabolic burden and a high risk for

adverse pregnancy outcomes such as caesarean delivery and neonatal intensive care unit admissions (Vats et al., 2021).

A life course perspective of pregnancy as it relates to the development of chronic cardiometabolic disease has been increasingly recognised in the context of GDM (Fu & Retnakaran, 2022; Retnakaran, 2021). As discussed previously in section 2.2.1, a relationship between GDM and later life type 2 is well-established (Bellamy et al., 2009; Y. Xu et al., 2014). In addition to this, recent data from an Israeli cohort suggested that the risk for later life type 2 diabetes is also sustained in women with hyperglycaemia below the threshold for diagnosing GDM (Bardugo et al., 2023).

Retnakaran and colleagues (2021, 2022) have presented several lines of evidence to describe GDM as a chronic cardiometabolic disorder, rather than one limited to pregnancy. First, evidence of a more adverse cardiovascular risk profile among women who go on to develop GDM is indicated by several biomarkers that can be observed during the first trimester (Retnakaran, 2021). In the first trimester, maternal glycaemic measures, fasting insulin, lipids (triglycerides and HDL cholesterol), adipokines (adiponectin and irisin), c-reactive protein, tissue plasminogen activator antigen, fatty acid-binding protein-4, under-carboxylated osteocalcin, and IGF axis biomarkers have all been described as being potential early markers for GDM (Pheiffer, Dias, Jack, Malaza, & Adam, 2021; Ruszała et al., 2021; Ryckman, Spracklen, Smith, Robinson, & Saftlas, 2015; Savvidou et al., 2010; Thong et al., 2022; X. R. Wang et al., 2019; Wolf et al., 2003; Zhu et al., 2016). Further, pre-pregnancy blood glucose abnormalities, dyslipidaemia (higher LDL cholesterol, higher triglycerides, and lower HDL cholesterol), and elevated liver enzymes may also predict GDM development (Gunderson et al., 2010; E. S. Han et al., 2016; Harville et al., 2011; Hedderson et al., 2011; Retnakaran & Shah, 2020; Sridhar et al., 2014). An important connection here is that these biomarkers linked to an increased risk of GDM have also been discussed in context of a metabolic milieu that is associated with insulin resistance and hyperinsulinaemia (Cooper, Brookler, Kyriakidou, et al., 2021; James et al., 2021). Therefore, it is plausible that metabolic markers linked to GDM also highlights a more adverse track toward chronic diseases later in life.

Furthermore, in a population-based study involving over 100,000 women from Canada among which 8,047 developed GDM, Retnakaran and Shah (2020) demonstrated diverging cardiovascular risk trajectories whereby those who develop GDM had higher annual increases in HbA1c (1.9-fold higher), random blood glucose (4.3-fold higher), and annual decline in HDL cholesterol (5.5-fold lower) compared to their peers. Finally, it has been shown in amniotic fluid that women who go on to develop GDM that signs of foetal overgrowth may be observed before

a GDM diagnosis (Sovio, Murphy, & Smith, 2016; Tisi, Burns, Luskey, & Koski, 2011), thus suggesting an impact of underlying metabolic changes on foetal development before hyperglycaemia develops.

2.3 Diagnosing hyperglycaemia during pregnancy

GDM is broadly defined as glucose intolerance during pregnancy occurring in women without a previous diagnosis of diabetes (Caissutti & Berghella, 2017). Several different criteria exist to screen for and diagnose GDM. Having been a source of controversy for many years, the different criteria weigh up the benefits for potentially over-diagnosing populations to include women with milder GDM, versus the burden of diagnosis to both women and healthcare systems (Caissutti & Berghella, 2017; Zera & Seely, 2021). To date, there is still a lack of consensus around whether strict versus more lenient criteria are optimal for overall maternal and neonatal outcomes.

Pre-existing diabetes

The increasing number of pregnant women with undiagnosed type 2 diabetes in early pregnancy is a growing concern (Feig et al., 2014; Jovanovič et al., 2015; T. Y. Peng et al., 2017). Screening for pre-existing diabetes is recommended across clinical practice guidelines, usually including a fasting or random plasma glucoses or HbA1c at the first antenatal appointment (American Diabetes Association, 2010; Blumer et al., 2013; Ministry of Health, 2014). The diagnostic criteria for pre-existing type 2 diabetes in pregnancy are the same as those used in the nonpregnant population (American Diabetes Association, 2021a). The American College of Obstetricians and Gynecologists (2018) recommends early pregnancy screening for undiagnosed type 2 diabetes at the initiation of antenatal care in women with a BMI ≥ 25 kg/m^2 and additional diabetic risk factors such as physical inactivity, having a first-degree relative with diabetes, high risk ethnicity, having previously given birth to an infant weighing ≥ 4000 g, previous GDM, PCOS, impaired glucose tolerance/impaired fasting glucose, HbA1c ≥ 39 mmol/mol, dyslipidaemia, hypertension, or history of cardiovascular disease.

Early pregnancy GDM

GDM diagnosed during the first trimester of pregnancy (before 20 weeks' gestation), frequently termed "early pregnancy GDM", and is estimated to occur in 0.7 to 36.8% of pregnancies (Hannah et al., 2022). A systematic review of 58 studies by Hannah et al. (2022) showed that compared to mid-gestation onset GDM, early pregnancy GDM may be associated with a greater risk of intrapartum adverse outcomes and postpartum dysglycaemia. Most clinical practice guidelines recommend early screening in the first trimester of pregnancy for women with pre-existing risk factors (i.e. HbA1c ≥ 39 mmol/mol or previous history of abnormal glucose

metabolism) (Tsakiridis et al., 2021). Women with sub-clinical abnormal glucose metabolism early in pregnancy (fasting plasma glucose of ≥ 6.1 mmol/L or HbA1c of ≥ 39 mmol/L) are more likely to require insulin treatment to maintain glycaemic control throughout gestation and are at higher risk of adverse outcomes(American Diabetes Association, 2010, 2023). Particularly among women with overweight/obesity with early GDM, a higher degree of insulin resistance has been associated with adverse pregnancy outcomes (Immanuel et al., 2021). Early identification of GDM, before 20 weeks' gestation, has been shown to lead to a modestly lower incidence of a composite of adverse neonatal outcomes (including birth at <37 weeks' gestation, birth trauma, birth weight of ≥4500 g, respiratory distress, phototherapy, stillbirth or neonatal death, or shoulder dystocia) (Simmons et al., 2018). A greater risk of adverse outcomes for women with sub-clinical abnormal glucose metabolism from the beginning of pregnancy likely reflects a much sooner or accelerated progression toward hyperglycaemia compared to normal GDM as pregnancy-related metabolic changes progress (Immanuel et al., 2021).

The most appropriate screening method used to test high-risk women with an otherwise normal fasting plasma glucose or HbA1c is unclear (Hannah et al., 2022). The National Institute for Health and Clinical Excellence (2015), International Federation of Gynecology and Obstetrics (Hod et al., 2015), and Australasian Diabetes in Pregnancy Society (Nankervis et al., 2014) recommend high-risk pregnant women, such as those who have had GDM previously, be screened for GDM with a two-hour 75-gram OGTT as soon as possible, be it in their first or second trimester. Testing for early pregnancy GDM in women with a previous history should be considered due to the high recurrence rate of GDM in subsequent pregnancies of 41-54% (Schwartz, Nachum, & Green, 2015). In women who have a normal result from first trimester testing, the OGTT should be repeated at 24 to 28 weeks of gestation (International Association of Diabetes Pregnancy Study Groups Consensus Panel, 2010).

2.3.1 Diagnostic criteria

Once a highly contentious topic on obstetric medicine, the diagnosis of GDM as it is today was shaped by two landmark RCTs that were published less than 20 years ago. The Australian Carbohydrate Intolerance Study in Pregnant Women trial (n = 490 intervention vs. n = 510 control) examined whether treatment of GDM would reduce perinatal outcomes (infants: death, shoulder dystocia, bone fracture, nerve palsy, and jaundice; women: induction of labour, caesarean delivery, general health, and psychological outcomes) (Crowther et al., 2005). Following an initial 50 g positive oral glucose challenge test, diagnosis of GDM was confirmed at 24 to 34 weeks' gestation, fasting plasma glucose of <7.8 mmol/L and 2-hour post 75-gram OGTT glucose value of 7.8 to 11.0 mmol/L, consistent with 1998 WHO criteria. Compared to routine

care, GDM treatment including dietary advice, blood glucose monitoring, and insulin therapy resulted in reduced serious perinatal complications, including neonatal death (intervention vs. control n (%): 0 (0) vs. 5 (1), p = 0.07), shoulder dystocia (7 (1) vs. 16 (3); aRR 0.46, 95% CI 0.19 to 1.10; p = 0.08), bone fracture (0 (0) vs. 1 (<1), p = 0.38), and nerve palsy (0 (0) vs. 3 (1), p = 0.11). The number needed to treat to benefit improvement in serious perinatal complications was 34 (95% CI 20 to 103). Rates of induction of labour and rate of admission to the neonatal intensive care unit were increased in the intervention group, which was thought to be related to the knowledge of the diagnosis by the attending physician. The number needed to treat to harm (i.e., the number of patients who would need to be treated for harm to occur in one patient) was 11 (95% CI 7 to 31).

The second seminal study from Landon et al. (2009) was a multicentre with 958 women (n = 485 intervention vs. n = 473 control) diagnosed as "mild" GDM following a 3-hour OGTT (100-gram glucose) using the criteria recommended from the Fourth International Workshop-Conference on Gestational Diabetes Mellitus (fasting glucose level of less than 5.3 mmol/L and two or three glucose values greater than 10.0 mmol/L at 1-hour, 8.6 mmol/L at 2-hours, or 7.8 mmol/L at 3-hours) (Crowther et al., 2005; Landon et al., 2009; Metzger & Coustan, 1998). Primary outcomes included perinatal mortality (stillbirth or neonatal death), neonatal hypoglycaemia, neonatal hyperbilirubinemia, neonatal hyperinsulinemia, and birth trauma. There was no significant effect of treatment on risk of stillbirth or perinatal death and several neonatal complications. However, treatment was found to be associated with reduced risk large-for-gestational age (n = 34/477 vs 66/454, RR 0.49 97% CI 0.32, 0.76), shoulder dystocia (n (%) 7 (1.5) vs. 18 (4.0); RR 0.37, 97% CI 0.14, 0.97), caesarean delivery (n (%) 128 (26.9) vs. 154 (33.8); RR 0.79, 97% CI 0.64, 0.99), and preeclampsia (n (%) 12 (2.5) vs. 25 (5.5); RR 0.46, 97% CI 0.22, 0.97). Treatment did not significantly reduce the risk of stillbirth or perinatal death and several neonatal complications.

Diagnostic practices to test for GDM vary across clinical practice guidelines using either a one or two-step approach (Tsakiridis et al., 2021). The one-step criteria (Table 5) by the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) (International Association of Diabetes Pregnancy Study Groups Consensus Panel, 2010) and the World Health Organization (2013a) was based on data from the landmark HAPO study (HAPO Study Cooperative Research Group et al., 2008). The HAPO study demonstrated a continuous relationship between glucose levels from an OGTT at 24 to 32 weeks' gestation and risk for large-for-gestational age infants, caesarean delivery, and neonatal hypoglycaemia. Diagnostic criteria for GDM were considered by the Consensus Panel of the IADPSG based on an OR of 1.75 relative to the mean for risk of large-for-gestational age. The single-step criteria, which are frequently referred to as the

"IADPSG criteria", are endorsed by the American Diabetes Association (2023), International Federation of Gynecology and Obstetrics (Hod et al., 2015), Australasian Diabetes in Pregnancy Society (Nankervis et al., 2014), and Endocrine Society (Blumer et al., 2013). The one-step strategy requires a fasting two-hour 75-gram OGTT. GDM is diagnosed if one or more a glucose levels is at or beyond 5.1mmol/L at fasting, 10.0mmol/L at one-hour, 8.5 mmol/L at two-hours.

Table 5. One-step strategy diagnostic criteria for GDM

	Plasma glucose threshold (mmol/L equal or greater than)		
Endorsing organisation	**Fasting**	**1 hour**	**2 hours**
ADA (2023)ǂ, ADIPS (Nankervis et al., 2014), ES (Blumer et al., 2013), and FIGO (Hod et al., 2015)	5.1	10.0	8.5

One-step strategy International Association of Diabetes Pregnancy Study Groups (IADPSG) (2010) and World Health Organization (WHO) (2013a) diagnostic criteria for GDM using 75-gram glucose OGTT at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes. One or more abnormal values diagnoses GDM.

ǂ ADA endorse both the one-step IADPSG and two-step Carpenter-Coustan criteria.

ADA: American Diabetes Association; ADIPS: Australasian Diabetes in Pregnancy; ES: Endocrine Society; FIGO: International Federation of Gynecology and Obstetrics.

A two-step approach based on the Carpenter and Coustan (1982) and O'Sullivan and Mahan (1964) criteria (Table 6), is endorsed by the Society of Obstetricians and Gynecologists of Canada (Berger, Gagnon, & Sermer, 2019), American College of Obstetricians and Gynecologists (American College of Obstetricians and Gynecologists, 2018), and New Zealand Ministry of Health (2014). The two steps include a non-fasting one-hour 50-gram oral glucose challenge test, as the first step. Screening thresholds for the one-hour glucose challenge vary between 7.2 to 7.8 mmol/L. A post-load glucose value that exceeds the threshold leads to the second step of diagnosis. The second step either requires a 75- or 100-gram two-hour OGTT. If the one-hour plasma glucose level following the 50-gram glucose challenge test is greater than 11.1 mmol/L, GDM is diagnosed without requiring the second step OGTT.

The recommendation to move to universal screening for all pregnant women at or beyond 24 weeks of gestation was made by the US Preventive Services Task Force in 2014 (Moyer, 2014). In a recent systematic review, the US Preventive Services Task Force presented evidence for a moderate net benefit of screening women for GDM after 24 weeks of gestation (US Preventive Services Task Force, 2021). Benefits for screening before 24 weeks of gestation was undetermined due to insufficient evidence of the balance of benefits and harms. Universal screening for GDM among all pregnant women at or beyond 24 weeks of gestation is widely

accepted across clinical practice guidelines (American Diabetes Association, 2021a; Berger et al., 2019; Blumer et al., 2013; Hod et al., 2015; Ministry of Health, 2014; Nankervis et al., 2014; Tsakiridis et al., 2021). One exception is the National Institute for Health and Clinical Excellence (2015) which recommends a targeted diagnostic OGTT only for women with risk factors for GDM, also at 24-28 weeks of gestation (75-gram glucose load, 2-hour). The later women are screened, the less opportunity there is to introduce interventions, therefore increasing risks to women and offspring. However, women may frequently be diagnosed beyond 24-28 weeks' gestation if testing is delayed, or if repeated testing is recommended due to risk factors such as suspected foetal overgrowth.

Table 6. Two-step strategy GDM diagnostic criteria plasma glucose thresholds

		Plasma glucose threshold (mmol/L equal or greater than)			
Step 1: Non-fasting glucose challenge	**Glucose load (g)**	**1 hour**			
ACOG (2018), NZMoH (2014)*, and SOGC (Berger et al., 2019)	50	Step 2 if ≥ 7.8 GDM if ≥ 11.1			
ADA (2021a, 2023)	50	Step 2 if ≥7.2, 7.5, or 7.8			
Step 2: Fasting OGTT	**Glucose load (g)**	**Fasting**	**1 hour**	**2 hours**	**3 hours**
Two or more abnormal values to diagnose GDM					
ACOG (2018)	100	5.3/5.8‡	10.0/10.6‡	8.6/9.2‡	7.8/8.0‡
ADA (2021a, 2023)	100	5.3	10.0	8.6	7.8
One or more abnormal values to diagnose GDM.					
SOGC (Berger et al., 2019)	75	5.3	10.6	9.0	-
NZMoH (2014)	75	5.5	-	9.0	-
National Institute for Health and Clinical Excellence (2015)[π]	75	5.6	-	7.8	

Two-step strategy Carpenter and Coustan and National Diabetes Data Group diagnostic criteria for GDM using OGTT at 24–28 weeks of gestation in women not previously diagnosed with diabetes.

*Women at high risk of GDM (HbA1c 41-49 mmol/mol) to receive a one-step 75-gram glucose OGTT.

‡ The left number represents plasma or serum glucose level from the Carpenter and Coustan conversion, right number represents plasma level from the National Diabetes Data group conversion.

π National Institute for Health and Clinical Excellence guidelines recommend a 2-hour 75-gram glucose OGTT in women with risk factors for GDM (previous GDM, BMI > 30 kg/m^2, previous baby weighing ≥ 4.5 kg, first-degree relative with diabetes, ethnicity with a high prevalence of diabetes. Initial non-fasting glucose challenge is not included.

ADA: American Diabetes Association; FIGO: NZMoH: New Zealand Ministry of Health; SOGC: Society of Obstetricians and Gynecologists of Canada.

There is still substantial disagreement on which criteria are most appropriate to diagnose GDM (Bilous, Jacklin, Maresh, & Sacks, 2021; Zera & Seely, 2021). Variability in diagnostic guidelines reflects different studies used as the basis of the criteria provided (Tsakiridis et al., 2021). The Carpenter and Coustan (1982) criteria (two step strategy) were based on thresholds from O'Sullivan and Mahan (1964), but converted to be applicable for plasma glucose assays (whole blood was previously used up until early-1980's) (Hernandez, 2015). The targets presented at the 1997 at the Fourth International Workshop-Conference were based on thresholds for

fasting, 1-, 2-, and 3- hour post OGTT (100-gram glucose) based on predicting maternal risk for type 2 diabetes after pregnancy (n = 792) (Metzger & Coustan, 1998; O'Sullivan & Mahan, 1964). In contrast, the more strict, one-step criteria endorsed by IASPSG and WHO were based on the HAPO data to represent thresholds to predict infant outcomes; criteria are based on upper glucose thresholds following a 75-gram glucose OGTT (one abnormal value) for an OR of 1.75 increased risk of large-for-gestational age infants (Metzger, Gabbe, et al., 2010).

The Gestational Diabetes Mellitus Trial of Diagnostic Detection Thresholds study (GEMS) in New Zealand (n = 4061) aimed to assess whether the detection of GDM using lower glycaemic criteria (IADPSG thresholds, Table 5), with subsequent treatment, would lead to lower perinatal morbidity without higher maternal health-related risk than such detection and treatment with the higher glycaemic criteria (New Zealand Ministry of Heath thresholds, Table 6)(Crowther, Samuel, McCowan, et al., 2022). OGTTs were performed at 24 to 32 weeks' gestation (75-gram glucose load, two-hour test) in women with no prior history of GDM or diabetes mellitus. It should be noted that women without a history of GDM in New Zealand would first undergo a 50-gram non-fasting screening glucose challenge test before being referred for the 75-gram, two-hour OGTT, which is a step that is usually not included in the one-step IADPSG criteria. GDM was diagnosed in 310 of 2022 women (15.3%) in the lower-glycaemic-criteria group and in 124 of 2039 women (6.1%) in the higher-glycaemic-criteria group. Study findings showed no difference in incidences of large-for -gestational age (lower-glycaemic-criteria group vs. higher-glycaemic-criteria group: 8.8% vs. 8.9%, adjusted RR 0.98, 95% CI 0.80, 1.19, p = 0.82). Secondary outcomes were also similar between groups, which included induction of labour (33.7% vs. 30.2%; adjusted RR 1.12, 95% CI 1.02,1.22), pharmacological treatment (metformin or insulin), infant anthropometric measures (weight, length, head circumference), small-for-gestational age, gestational age at birth, incidence of preterm birth. Neonates born to women with GDM in the lower-glycaemic-criteria group had a higher incidence of hypoglycaemia was detected than those with GDM treated in the higher-glycaemic-criteria group (10.7% vs. 8.4%, adjusted RR 1.27, 95% CI 1.05, 1.54). Follow-up data from five to six months also showed no difference in infant fat mass between control infants (2.05 kg) and exposure groups: A) GDM by lower but not higher criteria, treated (1.96 kg), adjusted mean difference (aMD) -0.09 (95% CI -0.29, 0.10); B) GDM by lower but not higher criteria, untreated (1.94 kg), aMD -0.15 (95% CI -0.35, 0.06); and C) GDM detected and treated using higher thresholds (1.87 kg), aMD -0.17 (95% CI -0.37, 0.03) (Manerkar et al., 2024).

Compared to the two-step approach, the one-step diagnostic strategy has been associated with a 54% reduced relative risk of large-for-gestational age infants (RR 0.46, 95% CI 0.25, 0.83), 51% reduced risk of neonatal intensive care admissions (RR 0.49, 95% CI 0.29, 0.84), a 48% reduced

relative risk of neonatal hypoglycaemia (RR 0.52, 95% CI 0.28, 0.95), and lower mean birth weight (mean difference -112.91 g, 95% CI -190.48, -35.33) (meta-analysis of four RCTs, n = 2,582) (Saccone, Khalifeh, Al-Kouatly, Sendek, & Berghella, 2020). Concerns reside around the lack of clinical trial evidence to confirm the overall benefit for the most strict one-step universal diagnostic strategy versus potential harm caused from increased obstetric monitoring and interventions (Cheung & Moses, 2018). Furthermore, universal IASPSG criteria adoption would lead to sizable increases in women diagnosed, therefore having extensive impacts on workload and resources (Ekeroma et al., 2015). Conversely, it might also be said that by maintaining lenient criteria, the underdiagnosis of GDM, while cost-saving at present, may only further contribute to the worsening obesity and diabetes epidemic as more infants could be born large-for-gestational age due to the teratogenic effect of *in utero* overnutrition (Barbour & Hernandez, 2018a).

To overcome these gaps, Doi et al. (2022) proposed a novel index using weighted average glucose values from an OGTT at 23 to 30 weeks' gestation in a USA cohort (n = 723, 75-gram OGTT), then validated in cohorts from Qatar (n = 1284, 75-gram OGTT) and South Africa (n= 220, 75-gram OGTT). Their modern criteria suggested expanding the pregnancy glycaemia spectrum into four categories i) normal gestational glycaemia (i.e. normal glucose tolerance), ii) impaired gestational glycaemia, iii) GDM, and iv) high risk GDM. Groups were based on cut-off points from weighted average glucose according to previous history of GDM and pre-pregnancy BMI. In the Qatar cohort, a progressive increase in odds of large-for-gestational age infants across categories as compared to normal gestational glycaemia was shown (iii) OR 2.86, $p < 0.001$; iv) OR 3.35, $p < 0.001$). In the South Africa cohort, a third of women in the iii) GDM group and three-quarters in the iv) high risk GDM group progressed to type 2 diabetes at 5 years. Their research group suggested that a broader spectrum for GDM diagnoses may aid better decision making in routine management, avoid potential over-diagnosis of women at lower risk of complications, and assist with diabetes prevention in higher-risk women after pregnancy.

In summary, GDM is diagnosed by an OGTT which is usually recommended during mid-gestation. Specific criteria recommended for diagnosing GDM vary internationally and are a source of considerable controversy. The main challenge for determining that best criteria involve weighing out the net benefit of diagnosing the most women to reduce their risk of adverse outcomes, while considering the overall economic cost to the health system and burden of over-medicalising pregnancy.

2.4 Defining hyperinsulinaemia during pregnancy

Pregnancy is characterised by adaptive increases in insulin resistance and secretion, which are essential for supporting the growth of a developing foetus (Butte, 2000). While insulin resistance in pregnancy is physiological, the global obesity and diabetes epidemic means more women enter pregnancy with pre-existing insulin resistance (Hernandez et al., 2020). When pre-pregnancy insulin resistance is combined with pregnancy-induced physiological adjustments to insulin metabolism, metabolic changes associated with pregnancy can become exaggerated (Butte, 2000). This can lead to an environment characterised by nutrient excess and inflammation, which are associated with metabolic conditions of pregnancy such as GDM and foetal overgrowth (Barbour & Hernandez, 2018a). Hence, such metabolic perturbations are linked to many adverse maternal and offspring outcomes, including a life-long increased risk of type 2 diabetes and metabolic syndrome for both mother and offspring (Bellamy et al., 2009; Boney et al., 2005; Damm et al., 2016; Godfrey et al., 2017; C. Kim et al., 2002; Retnakaran, 2018).

As outlined previously in section 2.1, knowledge from the wider field of type 2 diabetes has shown that decades before developing clinical hyperglycaemia, individuals may exhibit chronic and progressive hyperinsulinaemia (Cooper, Brookler, Kyriakidou, et al., 2021; Crofts et al., 2015). The Kraft Model of Hyperinsulinaemia suggests that excessive stimulation of insulin receptors (measured as fasting plasma insulin or as the insulin response to an oral glucose load) is implicated in the aetiology of cardiometabolic diseases and could predict the development of type 2 diabetes as early at 10-20 years in advance (Dankner et al., 2009; Hayashi et al., 2013). Thus, women of child-bearing age are not excluded from a potentially large proportion of glucose-tolerant and -intolerant individuals with pre-existing hyperinsulinaemia.

Furthermore, in a life-course perspective, several authors regard adverse pregnancy events such as GDM, hypertensive disorders of pregnancy, or pre-term birth as acute occurrences that exist on a continuum toward later-life chronic metabolic diseases (Ferranti et al., 2016; Fu & Retnakaran, 2022; Hufnagel et al., 2022; Retnakaran, 2021). It is plausible that, the chronic and progressive effects of hyperinsulinaemia may contribute to this more adverse track toward later-life cardiovascular disease – before, during, and post-partum period (Figure 7).

Finally, it is important to note that the concepts described above cannot be applied directly during pregnancy due to the expected changes in maternal physiology; increases in insulin secretion and reduced insulin sensitivity are expected, adaptive changes of pregnancy (Butte, 2000). Therefore, the greatest challenge for defining hyperinsulinaemia in pregnancy is that

there is no clear distinction between a normal insulin response pattern of pregnancy and one that might be considered detrimental.

2.4.1 Insulin secretion during normal pregnancy

An elevation in glucose-induced insulin secretion occurs from very early on in pregnancy (Kuhl, 1991). From approximately eight weeks' gestation, placental lactogen induces pancreatic beta-cell hypertrophy and cell mass expansion, resulting in increased insulin secretory capacity (Armistead et al., 2020). Earlier in section 2.1.1, we discussed the two phases of insulin secretion broadly in a non-pregnancy context, which is summarised in Figure 2. Initially, the increased secretory response seen during pregnancy is predominantly observed in the first-phase of insulin release (defined as the change in insulin concentration relative to the elevation in glucose concentration from zero to five minutes after intravenous glucose administration) (Butte, 2000) (Figure 2). As gestation progresses, both the first- and second-phases of insulin release increase significantly to levels 2 to 3.5-fold greater than early pregnancy and postpartum (Catalano, Tyzbir, Roman, Amini, & Sims, 1991; Kuhl, 1991). Following a secondary analysis of data collected by Catalano and colleagues (1991; 1992; 1999), Powe, Huston Presley, Locascio, and Catalano (2019) demonstrated marked increases in insulin secretion from early gestation prior to, and independently of, increased insulin resistance during pregnancy. This physiological hyperinsulinaemia of pregnancy promotes a "facilitated anabolism" to favour lipogenesis and fat storage in early gestation, and lipid transfer to the foetus (Butte, 2000; Freinkel, 1980).

2.4.2 Insulin measurement during pregnancy

Previously in section 2.1.5, insulin measurement techniques and challenges were discussed in a wider non-pregnant context. Since pregnancy involves major changes to insulin metabolism, this must be considered when interpreting insulin sensitivity measures and secretion patterns.

To date, the Matsuda index is the only measure of insulin sensitivity based on an OGTT that has been validated during pregnancy; compared to fasting measures (HOMA-IR and QUICKI), the Matsuda index was shown among 15 pregnant women (10 with normal glucose tolerance, 5 with GDM) to have significantly better correlation with the insulin sensitivity (hyperinsulinaemic-euglycaemic clamp validation) (univariate analysis for combined assays taken at pre-, early-, and late-gestation: $r = 0.74$, $p < 0.00$) (Kirwan, Huston-Presley, Kalhan, & Catalano, 2001; Matsuda & DeFronzo, 1999).

The Stumvoll first-phase estimate is the only calculated measure of beta-cell function validated among pregnant women. Among a cohort of 40 pregnant women who underwent testing

pre-pregnancy, during 12-14 weeks', and 34-36 weeks' gestation, the Stumvoll first-phase estimate was shown to correlate well with first-phase insulin response measured during the hyperinsulinaemic-euglycemic clamp (pre-pregnancy: r = 0.44, p = 0.01; 12-14 weeks': r = 0.67, p = 0.0001; 34=26 weeks': r = 0.67, p = 0.0001) (Powe et al., 2022).

To date, no dynamic insulin pattern analyses have been validated among pregnant cohorts against gold standard hyperinsulinaemic-euglycaemic clamp or intravenous glucose tolerance tests. This is noteworthy when applying such methods in pregnancy since changes in the first phase insulin response and postprandial/post glucose load insulin response have been documented (Powe et al., 2022).

2.4.3 Insulin response patterns and adverse pregnancy outcomes

Gestational diabetes mellitus

GDM is a highly heterogeneous condition which may arise from a range of aetiologies, in many ways similar to type 2 diabetes (Powe et al., 2020). Hyperglycaemia may develop during pregnancy from excessive insulin resistance, an insulin secretory defect, or a combination of both (Powe et al., 2020). The specific changes to insulin secretion and insulin resistance which define GDM phenotypes are yet to be established. This is partly due to a lack of standardisation for insulin measurement and techniques used to define insulin sensitivity and secretory issues. In this section insulin secretory responses in GDM pregnancies are discussed first in a historical context and in relation to evidence from more recent population-based cohort data.

Early reports of first-phase defects in insulin release

Among women with GDM, distinct differences in both the first- and second-phase of insulin release have been described. Defects in the first-phase of insulin release in women with GDM were described in early reports from the 1970s (Fisher, Sutherland, & Bewsher, 1980; Yen, Tsai, & Vela, 1971). Women with GDM were shown to have reduced insulin responses to intravenous glucose (steady state hyperglycaemic infusion and single glucose bolus tolerance test) compared to women without GDM or postpartum (Fisher et al., 1980; Yen et al., 1971). Yen et al. (1971) described women with obesity and GDM who had "blunted" insulin responses to intravenous glucose over a 60-minute period; those with GDM demonstrated no clear peak within the first 15-minutes following glucose infusion. These reductions in the peak insulin response reflect dysfunctional changes in the first-phase of insulin release (Freinkel et al., 1985; Kuhl, 1991).

A defect in the first-phase of insulin release seen here in women with GDM is not dissimilar to the secretory changes observed in type 2 diabetes (Di Giuseppe et al., 2023). In the early stages

of type 2 diabetes, this initial blunted the first-phase of insulin release is followed by an exaggerated second-phase. It is the exaggerated and prolonged second-phase of insulin release that contributes to elevated circulating plasma insulin levels, or hyperinsulinaemia (as described in section 2.1.3).

Buchanan (2001)

Seminal work from Buchanan (2001) described the reduced first-phase insulin secretory response in women with GDM as a pancreatic beta-cell defect. According to Buchanan (2001), women initially maintain glycaemic control in early pregnancy because of the ability of the pancreatic beta-cells to increase their insulin response. However, by late pregnancy, as insulin resistance increases, the insulin response is inadequate. Thus, there is a relative insulin deficiency in the face of excess insulin resistance. The hypothesis was tested using data from C. Homko, Sivan, Chen, Reece, and Boden (2001), who examined peripheral c-peptide concentrations during steady-state hyperglycaemia among pregnant women with and without GDM in their third trimester. Women with GDM were shown to have a 19% reduced insulin secretory rate (based on c-peptide kinetic studies) during steady-state hyperglycaemia with intravenous glucose infusion. Based on these data, Buchanan's work described a hyperbolic relationship between insulin sensitivity and insulin release; the "failure" for beta-cell insulin secretion to compensate for ambient insulin resistance results in hyperglycaemia (Figure 8).

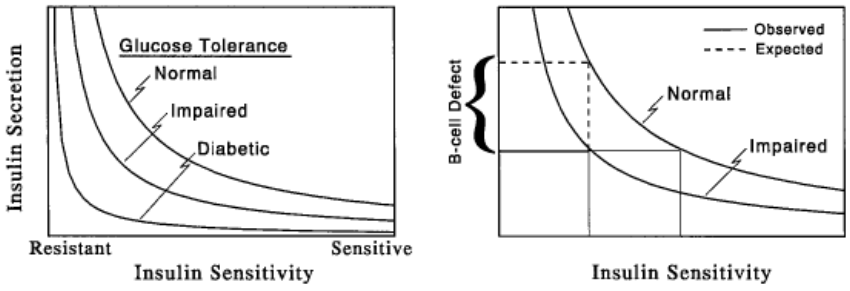


Figure 8. *Left,* Schematic representation of the hyperbolic relationship between insulin sensitivity and insulin secretion rates in a normal and GDM pregnancy. *Right*, Expected and observed insulin secretion in two groups of individuals with normal or impaired glucose tolerance.

Reprinted with permission from Buchanan (2002). Differences in insulin sensitivity predict differences in insulin secretion. Insulin secretion is the same in the two groups, indicating a beta-cell defect in the group with impaired glucose tolerance. The insulin secretion rate (y-axis) has been described using varying methodologies, one of these was pre-hepatic inulin secretion during steady state hyperglycaemia using plasma insulin and c-peptide concentrations and c-peptide kinetics.

An important detail in Buchanan's work is the terminology used in this context. A beta-cell deficit implies inadequate insulin production; however, this is actually described as the rate of insulin

production relative to plasma glucose, for example, at a given time point during an oral or intravenous glucose tolerance test (Buchanan, 2001; C. Homko et al., 2001; Xiang et al., 1999). This relative insulin deficiency is not an absolute lack of insulin. Therefore, it is dangerous to say women with GDM exhibit a lack of insulin as it may lead to a line of thinking where treatment must be centred around correcting this deficit or defect with exogenous insulin treatment. While exogenous insulin treatment is an important part of GDM care (see section 2.6.1), it is not the only strategy for addressing an imbalance between insulin secretion and resistance.

The Kraft Model of Hyperinsulinaemia (1975)

A defect in the first-phase of insulin release seen in women with GDM is not dissimilar to the secretory changes observed in type 2 diabetes (Di Giuseppe et al., 2023). Up until the late stages of type 2 diabetes, an initial blunted first-phase of insulin release is followed by an exaggerated second-phase (Cooper, Brookler, Kyriakidou, et al., 2021). It is the exaggerated and prolonged second-phase of insulin release which contributes to elevated circulating plasma insulin levels, or hyperinsulinaemia (as described in section 2.1.3).

In the context of pregnancy, we can only begin to identify the relevance of insulin's second-phase of release when insulin response patterns are observed for more than two-hours following a nutrient stimulus. Until this point of this section, the included studies have described insulin responses from women with GDM during the first 15- to 60-minutes following oral or intravenous glucose (i.e. the first-phase and early second-phase). The unique and important detail provided by Dr Kraft's pioneering work was that insulin response patterns to oral glucose were observed across at least three hours. Under normal conditions, the second phase of insulin release is elevated during pregnancy to promote nutrient transfer to "feed" the foetus (Butte, 2000). An exaggeration of the second-phase of insulin response (i.e. adjacently or independently of hyperglycaemia) therefore, has important implications for nutrient delivery and growth of the developing foetus. Authors have suggested that such an environment characterised by nutrient excess (in the form of lipids, glucose, and amino acids) may contribute to increased birth weight in women with obesity and/or GDM (Barbour & Hernandez, 2018a).

According to Dr Kraft (1975), hyperinsulinaemia was defined as elevated fasting plasma insulin level (> 0-30 uU/mL) or the increased sum of the second and third-hour insulin levels (> 60 uU/mL) following a 100-gram oral glucose load. In addition to his examinations in the broader population, Kraft's work from the 1970's to early 1990's included approximately 1,000 pregnant women (Kraft & Sie, 1991). From this work, Kraft argued that hyperinsulinaemia could be the *sine qua non* of the gestational diabetic state. He proposed hyperinsulinaemia, according to the Kraft pattern definitions (patterns IIb, III, and IV), is not a normal state of pregnancy, nor

non-pregnancy. It was therefore suggested that identifying an exaggerated insulin response post 100-gram oral glucose load early in pregnancy may provide a basis for prospective management of GDM (Kraft & Sie, 1991). He suggested that hyperinsulinaemia identified by glucose/insulin response patterns following OGTTs may be the earliest marker of GDM and type 2 diabetes (Kraft, 1975; Kraft & Sie, 1991).

While Kraft's definitions for hyperinsulinaemia in pregnancy have not been examined elsewhere, post-glucose load insulin response pattern phenotyping has become increasingly recognised in a wider type 2 diabetes context, which may also have relevance for further defining metabolic phenotypes in GDM (Cooper, Brookler, Kyriakidou, et al., 2021; Hayashi et al., 2013; Powe et al., 2020).

Observations from Kraft may at first appear entirely contrary to those of Buchanan (2001) who emphasised that GDM arose from an underlying beta-cell defect resulting in a relative "lack" of insulin. An important detail to interpret the apparent discourse between Buchanan's and Kraft's observations is the methodological differences in assays used (i.e. oral versus intravenous glucose load). In Buchanan's model, the beta-cell defect represents an inadequacy of insulin secreted relative to ambient insulin resistance (Buchanan, 2001). In Kraft's model, hyperinsulinaemia is defined according to the first- and second-phase of insulin release. This includes the net plasma insulin at fasting and post-oral glucose load (Kraft, 1975, 2011). However, in the literature cited in Buchanan's model, insulin responses are described as insulin secretion kinetics during steady-state hyperglycaemia – reflecting the first-phase of insulin release. Both models describe apparent changes in insulin release and action.

By taking into consideration the insulin response pattern over three hours following oral glucose, Kraft's hyperinsulinaemia patterns can demonstrate both phases of insulin release. Kraft pattern III hyperinsulinaemia, in particular, shows a defect in the first phase of insulin release which is followed by a "delayed peak" plasma insulin at 120- or 180-minutes following oral glucose. In this model, a defect in the first phase of insulin release is followed by ambient hyperinsulinaemia. This elevated plasma insulin and delayed rate of decay is what may have adverse effects. Kraft's model, therefore, demonstrates the significance of post glucose load or postprandial insulin measurement which other tests using fasting assays and glucose tolerance tests less than 60 minutes insufficiently show.

Finally, while Kraft's early work and more recent literature exploring this methodology holds promise, the greatest challenge when bringing these concepts specifically into a pregnancy context is the lack of standardised reference intervals which define i) what is a normal insulin

secretion pattern during pregnancy and ii) what characterises “defective” insulin secretion that may contribute to the aetiology of GDM.

Cohort studies

Evidence of the heterogeneity of insulin secretion responses and insulin resistance in women with GDM has been described in several large cohort studies. The Genetics of Glucose regulation in Gestation and Growth prospective pregnancy study examined insulin sensitivity and secretion patterns among pregnant women representing the general population of reproductive age in Québec, Canada (as reported in the main cohort: 95% European decent ethnicity, median age 28 years, IQR 25-31; median BMI 23.2, IQR 20.9-27.3 kg/m^2) (Guillemette et al., 2016; Powe et al., 2016). Among the 809 pregnant women included, 67 developed GDM (IADPSG criteria) (International Association of Diabetes Pregnancy Study Groups Consensus Panel, 2010). Plasma insulin and glucose levels following an OGTT (75-gram glucose, samples taken at fating, 1-, and 2-hours) at 24-30 weeks’ gestation was used to estimate insulin secretion (Stumvoll first-phase estimate)[1] and insulin sensitivity (Matsuda index) (Matsuda & DeFronzo, 1999; Stumvoll et al., 2000). Participants were grouped as having an insulin secretion defect, insulin sensitivity defect. Defective insulin secretion was defined as Stumvoll first-phase estimate below the 25th percentile of the participant group. Those with a Matsuda index below the 25th percentile were grouped as having an insulin sensitivity defect. Nearly a third of the women with GDM at 24-30 weeks’ gestation had a “defective” first-phase insulin secretion without insulin resistance (n = 20, 29.9 %), insulin sensitivity defect were observed in 51% of women with GDM (n = 34), and 17.9% of the women with GDM had both features (n = 12). Compared to normal glucose tolerant controls, GDM women who only had insulin secretion defects but not insulin resistance had similar BMIs (GDM secretion defect vs. control, median (IQR): 25.0 (23.7-28.3) vs. 26.6 (24.3-30.1) kg/m^2), fasting glucose (median (IQR): 76 (72-79) vs. 76 (70-79) mg/dL), infant birth weights (z score, median (IQR): 0.20 (-0.54-0.86) vs. 0.03 (-0.52-0.52)), and risk of any adverse outcomes (combined large-for-gestational age, caesarean delivery, neonatal hypoglycaemia: n = 6, 33.3% vs. n = 196, 23.2%). Women in the insulin sensitivity defect group had high BMIs (GDM sensitivity defect vs. control, median (IQR) 30.1 (26.9-37.7) vs. 26.6 (24.3-30.1) kg/m^2), larger infants (median (IQR) birth weight z score: 0.57 (-001-1.37) vs. 0.03 (-0.52-0.52)), and a greater risk for adverse outcomes compared to normal glucose tolerant controls (combined large-for--gestational age, caesarean delivery, neonatal hypoglycaemia: n = 19, 57.6% vs. n = 196, 23.2%). Those in the mixed GDM secretion and sensitivity defect group were similar to the normal glucose tolerant group in terms of outcomes. Findings suggested that women who

[1] The Stumvoll first phase index is defined as $1194 + 4.724 \times Ins_{0(pmol/l)} - 117.0 \times Gluc_{60(mmol/l)} + 1.414 \times Ins_{60(pmol/l)}$

develop GDM with a defective first-phase of insulin secretion, but without overt insulin resistance, encounter a risk of adverse outcomes at comparable rates to women without GDM, while those with a predominant insulin resistant presentation tend to have higher BMIs and encounter a greater risk for adverse outcomes related to GDM.

Y. Liu et al. (2018) described a prospective cohort of 456 pregnant Chinese women who underwent glucose tolerance with insulin testing (75-gram glucose OGTT) at 24-28 weeks' gestation. GDM was diagnosed in 206 women following the IADPSG criteria (International Association of Diabetes Pregnancy Study Groups Consensus Panel, 2010). Y. Liu et al. (2018) grouped women who developed GDM as having GDM with beta-cell dysfunction (n = 43, 21%), GDM with insulin resistance (n = 35, 17%), or "mixed" insulin resistance and beta-cell dysfunction (n = 79, 38%). Beta-cell dysfunction was defined as the disposition index (the ratio of Δ (0–30 min) for insulin and glucose, divided by HOMA2-IR) being below 25th percentile of the normal glucose tolerance group. Insulin resistance was defined as Matsuda index below the 25th percentile of the normal glucose tolerance group. Insulin secretion parameters following the OGTT showed that women in the "GDM-insulin resistance" group had higher fasting (GDM-insulin resistant vs. normal glucose tolerance median (IQR) µU/mL: 11.9 (4.9) vs. 8.3 (5.3)) and postprandial insulin at 30- (µU/mL: 106.9 (40.2) vs. 62.9 (48.9), $p < 0.001$), 60- (µU/mL: 122.0 (61.6) vs. 65.0 (46.0), $p < 0.001$), 120- (µU/mL: 126.7 (86.2) vs. 49.3 (53.2), $p < 0.001$), and 180-minutes (µU/mL: 63.0 (61.2) vs. 27.3 (38.2), $p = 0.003$), following the OGTT compared to those with normal glucose tolerance, consistent with hyperinsulinaemia patterns described by (Kraft & Sie, 1991). Women from the "GDM-beta-cell dysfunction" group had overall lower insulin responses at 30- (µU/mL: 37.0 (27.3) vs. 62.9 (48.9), $p < 0.001$) and 60- minutes (µU/mL: 46.0 (30.2) vs. 65.0 (46.0), $p = 0.001$) post glucose load as compared to the normal glucose tolerant group. Overall GDM-related complications including caesarean delivery, neonatal hypoglycaemia, and total adverse outcomes, appeared in higher frequencies among women from the "GDM-insulin resistance" and "GDM-mixed" groups compared to the normal glucose tolerant group, although non-significant. Interestingly, total adverse outcomes "GDM-beta-cell dysfunction" group were reported at comparable rates to the normal glucose tolerant group, suggesting that beta-cell dysfunction without insulin resistance may produce a lower risk phenotype that may be more responsive to treatment.

The third cohort that has evaluated insulin secretion and insulin resistance among women with GDM is the multicentre Vitamin D And Lifestyle Intervention for gestational diabetes prevention (DALI) trial, conducted across nine European countries (Immanuel et al., 2021). Participants included women with a BMI ≥ 29 kg/m^2 who underwent early-pregnancy glucose tolerance testing which included insulin assays (<20 weeks' gestation, 75-gram glucose). GDM was

diagnosed in 143 women out of 893 included in the study following the IADPSG criteria (International Association of Diabetes Pregnancy Study Groups Consensus Panel, 2010). In a *post hoc* analysis, Immanuel et al. (2021) described phenotypic groups of GDM women as either insulin resistant (defined as HOMA-IR above the median for the normal glucose tolerant group), impaired insulin secretion (Stumvoll first-phase estimate below median the median for the normal glucose tolerant group), or as a combination of both. Insulin secretion was estimated using the Stumvoll first-phase index formula ($1194 + 4.724 \times Ins_{0(pmol/l)} - 117.0 \times Gluc_{60(mmol/l)} + 1.414 \times Ins_{60(pmol/l)}$. Nearly two-thirds (n = 143, 60.6%) of the GDM women were in the insulin-resistant group with normal first-phase insulin secretion. Thirty-seven women (15.7%) were in the GDM-secretory defect group. The remaining 56 (23.7%) GDM women were groups as having a combination of both insulin resistance and impaired insulin secretion. As compared to the normal glucose tolerant controls, those in the GDM-insulin resistance group presented with higher fasting and 1- and 2- hour post glucose loads insulin (GDM-insulin resistant vs. normal glucose tolerance median (IQR) µU/mL: fasting: 21 (17-29) vs. 13 (9.6-17); 1-hour: 180 (140-230) vs. 88 (57-140); 2-hour: 140 (64-200) vs. 59 (40-94), all p values < 0.05). By contrast, women in the dysfunctional insulin secretion group had lower fasting and 1- and 2- hour post glucose loads insulin (GDM-insulin resistant vs. normal glucose tolerance median (IQR) µU/mL: fasting: 8.8 (7.8-9.7) vs. 13 (9.6-17); 1-hour: 61 (45-82) vs. 88 (57-140); 2-hour: 52 (22-70) vs. 59 (40-94), all p values < 0.05). Women in the insulin resistance group also had a higher incidences of metformin (n = 5, 3.5% vs. n = 2, 0.3%) and exogenous insulin (n = 14, 12% vs. n = 7, 1.1%) use throughout pregnancy, while medication use in the other GDM groups was comparable to normal glucose tolerant controls. Findings suggested that women in the insulin resistance group had a greater risk of large-for-gestational age infants (best fit adjusted OR 3.30, 95% CI 1.50, 7.50) and caesarean section (best fit adjusted OR 3.30, 95% CI 1.50, 7.50) as compared to the normal glucose tolerant group. No significant increased odds of adverse outcomes in the GDM-impaired secretion or GDM-both groups could be attributed to small participant numbers. A reduced risk of adverse outcomes among insulin sensitive GDM women with an impaired first-phase insulin secretory response is consistent with findings from Powe et al. (2016) and Y. Liu et al. (2018).

Previous work by Powe et al. (2016), Y. Liu et al. (2018), and Immanuel et al. (2021) as a whole suggests heterogeneity in insulin physiology among women with GDM that confers varying outcomes. However, the lack of reference standards to define “insulin resistance” and “secretory dysfunction” in GDM limits interpretation and comparison between these studies. Instead, their analysis used percentiles and references against the population median define dysfunctional physiology, therefore interpretation is limited to the population described.

Although the specific definitions varied across studies, the sub-groups described as being more "insulin resistant" displayed higher insulin sections following the OGTT. These insulin response patterns were consistent with Kraft's hyperinsulinaemia patters III and IV (Crofts, 2015; Kraft, 1975; Kraft & Sie, 1991). Therefore, these studies could be interpretated to suggest that an insulin resistant-hyperinsulniaemic phenotype conveys the greatest risk of adverse outcomes. Women with hyperglycaemia and a normal or suppressed insulin response may be those most responsive to treatment due to having less insulin resistance, therefore leading to better outcomes.

Further observational studies have also described an increased risk for adverse outcomes among women with GDM and higher insulin resistance determined by fasting insulin measures. Benhalima et al. (2019) presented a large multicentre prospective cohort study that included 1,813 pregnant women in Belgium (38% ethnic minority). Participants underwent glucose tolerance testing between 24 and 28 weeks' gestation (75-gram glucose); the IADPSG criteria for GDM were applied (International Association of Diabetes Pregnancy Study Groups Consensus Panel, 2010). Those diagnosed with GDM were grouped as insulin sensitive (n = 39, 17.1%) or high insulin resistance (n = 189, 82.9%) based on Matsuda index below the 50th percentile of women with normal glucose tolerance. GDM plus high insulin resistance was associated with higher rates of preterm delivery (8.5% vs. 4.7%, $p = 0.03$), induction of labour (42.7% vs. 28.2%, $p < 0.001$), caesarean section (28.7% vs. 19.4%, $p = 0.004$), neonatal hypoglycaemia (15.4% vs. 3.5%, $p < 0.001$), and neonatal intensive care unit admissions (16.0% vs. 8.9%, $p = 0.003$) compared to those with normal glucose tolerance. Similarly, GDM (IADPSG criteria) with a higher HOMA-IR has been consistently associated with a high risk of adverse outcomes such as excess GWG, hypertensive disorders, caesarean delivery, macrosomia, large-for-gestational age infants, and preterm delivery compared to GDM women a lower HOMA-IR (Cosson et al., 2022; J. Li et al., 2018; Y.-Y. Sun et al., 2020). These women with a higher HOMA-IR also appear to have more unfavourable characteristics including higher plasma glucose levels at screening, a more adverse glycaemic status (indicated by being diagnosed with GDM earlier in pregnancy), higher pre-pregnancy BMI and waist circumference and a family history of diabetes (Cosson et al., 2022). A higher HOMA-IR reflects a higher fasting plasma insulin relative to fasting glucose, therefore individuals classified as "insulin resistant" according to a HOMA-IR would have presented with an elevated fasting insulin, characteristic of hyperinsulinaemia.

When compared to the higher risk insulin-resistant GDM women, the small group of insulin-sensitive women with GDM described by Benhalima et al. (2019) were leaner (BMI 22.4 ± 2.7 kg/m^2 vs. 27.4 ± 5.3 kg/m^2, $p < 0.001$) and had lower fasting, 1- and 2-hour OGTT insulin levels (fasting insulin pmol/L median (IQR): 283 (209-348) vs. 583 (413-870); 1-hour: 415 (295-

517) vs. 834 (580-1083); 2-hour: 429 (325-522) vs. 870 (675-1263); 75-gram glucose; all p-values < 0.001). A lean, insulin-sensitive GDM phenotype has also been described among a Japanese cohort among which 70 women were diagnosed with GDM (IADPSG criteria) (Furukawa & Kobayashi, 2019). Participants were divided into subgroups as low or high insulin resistance based on a HOMA-IR cut-off value of 1.41; 64.2% of GDM women were classified as high insulin resistance. Beta-cell insulin secretory function was examined using the HOMA-β technique. Women in the low insulin resistance group were leaner (BMI: 20.9 ± 5.5 vs. 24.4 ± 5.5 kg/m^2, $p < 0.01$, and had significantly lower beta-cell function (HOMA-β: 95.5 ± 30.3 vs. 146.0 ± 70.1, $p < 0.01$) compared to GDM women with high insulin resistance. Further, a positive linear correlation between the BMI and HOMA-β was described ($r = 0.27$, $p = 0.02$).

Finally, as discussed in the previous section N.-J. Zhang et al. (2020) have also demonstrated a relationship between a "dysfunctional" post glucose load insulin pattern (75-gram glucose, "Type II" insulin pattern, Table 3) and gestational outcomes in a large Chinese cohort of pregnant women. Participants underwent standard diagnostic testing for GDM at 24-28 weeks' gestation (IADPSG criteria) (n = 2,432, 737 diagnosed as GDM) (International Association of Diabetes Pregnancy Study Groups Consensus Panel, 2010). Their analysis showed that independent of GDM status, a "dysfunctional Type II" delayed peak insulin response (insulin peak at 2- or 3-hours post glucose load) was significantly associated with a higher risk of adverse maternal and neonatal outcomes, including preeclampsia (adjusted OR 1.92, 95% CI 1.07, 3.44), large-for-gestational age infants (adjusted OR 1.15, 95% CI 1.05, 1.44), and neonatal hypoglycaemia (adjusted OR 1.42, 95% CI 1.01, 1.66).

To summarise, changes in insulin secretion patterns are highly heterogenous in women with GDM, and likely reflect varying aetiologies and degrees of metabolic decompensation (Powe et al., 2016). Numerous cohort studies have characterised two (or three) distinct phenotypes among women diagnosed with GDM. Although methodologically, definitions vary, the phenotypes include (i) Women with a predominant impaired first-phase insulin secretion defect. Those in this group may be leaner, have lower post prandial insulin secretion, and an overall lower risk for adverse outcomes; (ii) Women with insulin resistance and increased insulinaemia (fasting and/or post oral glucose load); this group may also include women with elevated fasted insulin (iii) Women with both insulin resistance and a defective first-phase of insulin secretion. The latter two phenotypes were associated with the highest risks for adverse outcomes such as preeclampsia, large-for-gestational age infants, and caesarean section. This suggests that among women with hyperglycaemia, more advanced insulin resistance and co-existing elevated compensatory insulin secretion are key determining risk factors for adverse outcomes in pregnancy. Within and beyond these subtypes there are also likely to be varying minor subtypes

such as what is been observed in individuals with type 2 diabetes (Powe et al., 2020). Developing reference standards to define dysfunctional insulin patterns may help to inform the management of GDM women with a greater risk of adverse outcomes.

Early gestation insulin assay as a predictor of GDM

Elevated post-glucose load insulin in the first trimester and early second trimester of pregnancy has been suggested as a predictor of GDM development in three pilot studies (Bito et al., 2005; Grewal et al., 2012; Lapolla et al., 2008). Bito et al. (2005) measured insulin and glucose responses following a 2-hour OGTT (75-gram glucose) in 64 Hungarian women in their first trimester of pregnancy (≤ 16 weeks' gestation) with one or more risk factors for GDM. Participants were divided into subgroups based off first-trimester insulin serum levels as follows: elevated fasting (≥ 30 mU/L) and 2-hour insulin (≥ 70mU/L) (n = 13); normal fasting (< 30 mU/L) but elevated 2-hour insulin (≥ 70 mU/L) (n = 18); normal fasting (< 30 mU/L) and normal 2-hour insulin (< 70 mU/L) (n = 33). Subsequent OGTTs (75-gram glucose) at 24-28 weeks' and 32-34 weeks' per performed to test for GDM (1998 WHO criteria) (World Health Organization, 1998). Findings showed that a fasting insulin ≥ 30 mU/L had a positive predictive value for GDM diagnosis of 0.9 by 24-28 weeks' gestation (69.2% sensitivity, 96.4% specificity) and 0.92 by 32-34 weeks' gestation (33.3% sensitivity, 96.4% specificity). An elevated 2-hour insulin in the first trimester had a positive predictive value of 0.75 by 24-28 weeks' gestation (92.3% sensitivity, 85.7% specificity) and 0.87 by 32-34 weeks' gestation (75.0% sensitivity, 85.7% specificity). In the multiple regression model, elevated fasting insulin was associated with a 16-fold increased odds of GDM at 24-28 weeks' gestation (OR 16.6, 95% CI 2.06, 134.2). In the multiple logistic regression model (remaining predictors included 2-hour glucose and insulin, HbA1c, and BMI), an elevated 2-hour insulin, the odds ratio for developing GDM by gestational week 32-34 was 13.3 (95% CI 3.07, 57.9).

A group in Italy, Lapolla et al. (2008), explored early pregnancy insulin sensitivity and beta-cell function and the risk of later pregnancy GDM among 866 pregnant women (Lapolla et al., 2008). Participants were given a 2-hour OGTT (75-gram glucose) with glucose and insulin assays at 16-20 weeks' gestation from which QUICKI and a dynamic oral glucose insulin sensitivity (OGIS) index were derived (Mari et al., 2001). The beta-cell function index was assessed as the ratio of area under the curve for insulin to the area under the curve for glucose. Ninety-two women developed GDM by 26-30 weeks' gestation, which was diagnosed applying the Carpenter and Coustan criteria (75-gram glucose, Table 6). Dynamic OGIS, but not QUICKI, was lower during early gestation (16-20 weeks') in women who developed GDM by 26-30 weeks' gestation compared to those who remained normal glucose tolerant (mean OGIS mL/min/m^2: 441 ± 60 vs. 468 ± 68, $p < 0.005$). Those who developed GDM also had higher insulin area under the curve

during the early OGTT as compared to the women who remained normal glucose tolerant (mean µU/mL h: 5460 ± 3149 vs. 4663 ± 2309, $p < 0.02$). Authors also indicated that insulin sensitivity indices based on fasting measures alone (QUICKI) could not distinguish between insulin-resistant women who developed GDM and non-GDM women.

The most recent and largest of the three studies was from a group in New Delhi, India. Grewal et al. (2012) recruited 298 normoglycaemic Asian Indian pregnant women for a 3-hour OGTT (100-gram glucose) before 12 weeks' gestation which included plasma insulin assays at fasting and each hour post glucose load. Of these women, 24 were diagnosed with GDM in the first trimester (GDM1), 16 were diagnosed between 24 and 28 weeks' gestation (GDM2), applying the Carpenter and Coustan criteria (100-gram glucose load, Table 6). HOMA-IR, QUICKI, and the Matsuda insulin sensitivity index were calculated based on first trimester measures. Among the GDM2 group, first trimester plasma insulin at fasting, 2-, and 3-hours post OGTT were significantly higher compared to normal glucose tolerance controls (mean plasma insulin µU/mL: fasting 9.7 ± 3.3 vs. 7.9 ± 5.0, $p = 0.03$; 2-hr 95.5 ± 73.6 vs. 45.2 ± 31.6, $p = 0.006$; 3-hr 62.1 ± 67.2 vs. 32.5 ± 32.8, $p = 0.02$). Insulin sensitivity measures were also significantly lower in the GDM2 group versus controls (HOMA-IR: 1.3 ± 0.3 vs. 1.1 ± 0.6, $p = 0.05$; QUICKI: 0.34 ± 0.02 vs. 0.37 ± 0.05, $p = 0.03$; Matsuda index: 5.7 ± 3.2 vs. 9.1 ± 5.8, $p = 0.01$). Authors conducted a receiver operating characteristic curve analysis to derive optimal cut-offs for insulin and insulin indices to predict GDM between 24 and 28 weeks' gestation. First trimester fasting plasma insulin greater than 7.45 µU/mL was able to identify women likely to develop GDM with sensitivity and specificity of 80% and 57.4%, each respectively. A post 100-gram glucose load 3-hour plasma insulin greater than 39.2 µU/mL, was suggested to predict GDM with a sensitivity and specificity of 66.7% and 73.4%, each respectively.

In summary, limited evidence from prospective studies suggests a possible association between post glucose load plasma insulin and the development on GDM. Studies are limited to small participant groups with limited ethnic representation. Methodologies vary in terms of glucose load and GDM diagnostic criteria applied. Larger studies would be needed to determine the clinical utility of an early pregnancy post glucose load plasma insulin assay.

Hypertensive disorders of pregnancy

The earliest reports identified describing hyperinsulinaemia among women with hypertensive disorders or pregnancy were by Bauman, Maimen, and Langer (1988) from New York, USA. Post glucose load insulin patterns following 5-hour OGTT (100-gram glucose) were described among 43 pregnant women at risk of intrauterine growth restriction in their third trimester. Participants were grouped as normotensive and hypertensive. Those in the hypertensive group had

significantly higher one- and two-hour post glucose load insulin levels (values reported graphically; 1-hr: $p < 0.003$; 2-hr $p < 0.02$). However, in a subgroup analysis, only half (n=8 out of 16) of the women with hypertension displayed an exaggerated insulin response. Their hypothesis was that women with superimposed hyperinsulinaemia and hypertension may represent a subgroup at greater risk of complications such as preeclampsia and hypertension later in life.

The relationship between hypertensive disorders of pregnancy and elevated plasma insulin responses has been described in several observational studies. Three controlled studies from the 1990's (Norway, Mexico, and Finland) showed that women with established preeclampsia had significantly higher fasting and post glucose load plasma insulin after an oral glucose load compared to healthy controls (2 hr OGTT, 75-gram glucose; observations reported between 29-40 weeks' gestation) (Kaaja, Laivuori, Laakso, Tikkanen, & Ylikorkala, 1999; Lorentzen, Birkeland, Endresen, & Henriksen, 1998; Martinez Abundis, Gonzalez Ortiz, Quiñones Galvan, & Ferrannini, 1996). Although study groups were matched for BMI and other potential confounding variables, associations were limited to small participant groups (n = 10-22 with preeclampsia) where the heterogeneity of insulin secretion patterns may not be well represented. Further, the cohort described by Kaaja et al. (1999) also showed that the women developing preeclampsia had decreased insulin sensitivity that persisted for at least three months postpartum compared to controls.

Other studies have also suggested that women with gestational hypertension tend to exhibit significantly higher fasting plasma insulin compared to normotensive pregnant controls (Z. Chen, Liu, Sun, & Zhu, 2017; Hamasaki, Yasuhi, Hirai, Masuzaki, & Ishimaru, 1996; Kaaja, Tikkanen, Viinikka, & Ylikorkala, 1995). Z. Chen et al. (2017) described Chinese women with gestational hypertension from which fasting plasma insulin and glucose were measured at ~32 weeks' gestation. Women with gestational hypertension (n = 50) displayed higher fasting plasma insulin (mmol/L: 15.78 ± 1.35 vs. 8.23 ± 1.92 p =. 0.022) and HOMA-IR (1.62 ± 0.58 vs. 4.34 ± 0.76, p = 0.014), and lower HOMA-β (225.49 ± 19.0 vs. 136.6 ± 25.4, $p < 0.001$) compared to the control group (n = 50). However, a higher BMI in the hypertensive groups could have confounded these observations (BMI in gestational hypertensive group vs. control: 32.5 ± 4.6 v. 26.6 ± 3.3 kg/m^2, p = 0.038). Although participants were reported as being without GDM according to medical records, fasting glucose was reported as being significantly higher in the hypertensive group ($p < 0.001$). Moreover, "impaired sugar tolerance" during pregnancy and medical history of chronic hypertension, diabetes mellitus, heart disease and nephropathy were described in the participant group. Thus, it is not clear whether associations are directly related to gestational hypertension or reflect undiagnosed GDM or a pre-existing pathology.

A Finnish cohort of 31 hypertensive pregnant women (8 with proteinuria) was described by Kaaja et al. (1995). Fasting serum insulin measured at 30-39 weeks' gestation was found to be significantly higher compared to a control group matched for BMI and gestational age (13.3 ± 6.6 vs 6.5 ± 2.4 mU/L , $p < 0.01$). Although women with a history of carbohydrate intolerance were excluded from the study, glycaemic measures were not reported and therefore could not be controlled for as a possible confounding variable.

In Japan, plasma insulin was measured in 84 pregnant women while undergoing usual diagnostic testing for GDM (75-gram glucose OGTT at 24-28 weeks' gestation) (Hamasaki et al., 1996). Among the 11 women who developed gestational hypertension, higher fasting plasma insulin (hypertensive vs. normotensive: 13.2 ± 7.9 IU/L vs. 7.9 ± 3.8; $p < 0.01$) and fasting plasma glucose (92.8 ± 8.2 mg/dL vs. 81.8 ± 8.2 mg/dL; $p <0.03$) was observed, which remained significant after adjusting for BMI. There was no significant difference in GDM incidence between the groups (n = 17/29, 58% vs. n = 23/55, 41.8%) (the diagnostic criteria applied was not reported). After controlling for maternal age, parity, pre-pregnancy BMI, and the gestational age at the time of 75-gram OGTT, multiple regression analysis suggested the relative risk of subsequently developing gestational hypertension for fasting insulin level (per 1.0 IU/L) was 1.19 (95% CI 1.03-1.38).

Evidence of a persisting adverse metabolic profile after a pregnancy complicated by preeclampsia and/or eclampsia was described in a meta-analysis from Alonso-Ventura et al. (2020). Findings from 41 observational cohort studies that evaluated metabolic and biochemical outcomes after delivery among women with preeclampsia and/or eclampsia were evaluated (n= 3300 preeclampsia/eclampsia and 13,967 controls). Women were followed up from 3 months to 32 years after delivery. In comparison to controls, preeclampsia was associated with more adverse metabolic profiles, including higher insulin (mean difference = 19.1 pmol/L, 95%CI 11.9 to 26.2), glucose (mean difference = 2.6 mg/dL, 95% CI 1.2 to 4.0), and HOMA-IR (mean difference = 0.7, 95% CI 0.2 to 1.2).

Taken as a whole, these studies are consistent with that concept that exaggerated insulin secretion and insulin resistance are putative factors in the aetiology of hypertensive disorders of pregnancy. However, it must be recognised that from the evidence identified, studies are limited to small cohorts where control of confounding variables (i.e. glycaemic factors and BMI) is limited. Moreover, physical activity and dietary factors have not described in any of the studies discussed in this section. Evidence suggesting that elevated insulin and insulin resistance may persist after pregnancies affected by preeclampsia is particularly noteworthy as it provides a link between pregnancy related hypertensive disorders and later-life manifestations of

cardiometabolic disease (Catalano, 2010). Exploring pre-existing evidence of altered insulin response patterns prior to the development of hypertensive disorders could therefore be of interest for the early detection of higher risk pregnancies.

Early gestation insulin assay as a predictor for hypertensive disorders in pregnancy

Although a link between hypertensive disorders of pregnancy and metabolic abnormalities linked to insulin resistance at the time of diagnosis has plausible aetiology (Catalano, 2010; Jung et al., 2022; Solomon & Seely, 2001), there are limited controlled studies that have explored whether first trimester dysfunctional insulin secretion and/or insulin resistance could predict the development of hypertensive disorders later in gestation. Kayemba-Kay's et al. (2013) studied a prospective cohort of 1,658 pregnant women who were tested for fasting plasma insulin levels at less than 15 weeks' gestation. Fasting plasma insulin was significantly higher among those who developed gestational hypertension compared to healthy controls (mean 16.9 ± 18.3 vs. 13.3 ± 13.5 mU/L; n = 155 vs. 1307; p = 0.02). BMI was also higher in the pregnancy induced hypertension group compared to controls (25.4 ± 5.1 vs. 23.5 ± 4.2 kg/m^2, p < 0.001) and women with GDM were reported separately (mean fasting plasma insulin 13.6 ± 17.0 mU/L). Similar associations were observed in an African-American cohort where fasting plasma insulin and glucose were measured at 18-25 weeks' gestation (Sowers, Saleh, & Sokol, 1995). Mean fasting plasma insulin (51.0 ± 12.0 vs. 29.2 ± 2.8 µU/mL) and the insulin/glucose ratio (0.59 ± 0.12 vs. 0.37 ± 0.03) were higher among women who went on to develop preeclampsia versus controls (n = 13 vs. 127; p-values not reported).

Further studies have taken to using insulin sensitivity indices as potential early predictors for preeclampsia. In a case-control study, first trimester insulin resistance was calculated using HOMA-IR among a pregnant Iranian cohort (Abhari, Ghanbari Andarieh, Farokhfar, & Ahmady, 2014). Among the 35 women who developed preeclampsia, HOMA-IR was shown to be higher during both first (3.09 vs. 1.9; p = 0.021) and third trimester (4.76 vs. 2.93; p = 0.001) compared to matched controls (matched for parity, BMI, maternal age, and gestational age). Average fasting insulin levels, but not glucose, were also shown to be significantly higher in the preeclampsia group compared to controls at both time points (graphically presented, p < 0.01). One study evaluated insulin sensitivity using HOMA-IR, QUIKI, and OGIS (OGTT with 75-gram glucose) among a prospective cohort consisting of 829 pregnant women (n = 53 developed preeclampsia) (Parretti et al., 2006). Testing was performed at early (16 to 20 weeks) and late gestation (26 to 30 weeks). Reduced insulin sensitivity, indicated by HOMA-IR above the 75th percentile or QUICKI below the 25th percentile, was shown to correlate with preeclampsia development for early (HOMA-IR >75th: 1.38, p = 0.0001; QUICKI <25th: 0.36, p =. 0.0001) and late gestation measures (HOMA-IR >75th: 1.70, p = 0.0001; QUICKI <25th: 0.35, p =. 0.0001)

according to the receiver operating characteristic curve index threshold value that yielded the highest combined sensitivity and specificity for the prediction of preeclampsia. Dynamic OGIS below the 25th percentile also showed potential to predict preeclampsia development at a cut of off 415 during early gestation (p = 0.03) and 404 during late gestation (p = 0.01). Taken together, these findings suggest clinical potential of first trimester insulin sensitivity indices for the prediction of hypertensive disorders in pregnancy. Given that insulin resistance is potentially a modifiable risk factor (e.g. with diet and lifestyle strategies), measures allowing the early detection of higher risk women hold potential important therapeutic implications.

Placental growth

O'Tierney-Ginn, Presley, Myers, and Catalano (2015) measured the insulin sensitivity of 40 pregnant women before pregnancy and at early (12-14 weeks) and late gestation (34-36 weeks) using an intravenous glucose tolerance test. They observed that early pregnancy insulin response, measured as the area under the curve from 0-60 minutes following intravenous glucose infusion (0.5 g/kg glucose bolus for women <120% of ideal body weight and 19 g/m^2 body surface area for women >120% ideal body weight over 3 minutes), was positively associated with placental weight (r = 0.42, p = 0.007) and neonatal adiposity in males (r = 0.59, p = 0.008, n=19), but not females. Adjusting for gestational age did not change results. Pre-pregnancy and late gestation insulin responses were not significant associated with placental size or neonatal adiposity outcomes. As discussed previously in section 2.2.1, insulin has somatogenic effects with potential to alter foetal growth. Maternal insulin binding insulin receptors on the maternal interface of the placenta activate insulin/IGF-1 signal transduction pathways which simulate nutrient transport to support foetal growth. Through altering placental development and nutrient transport, it is plausible that exaggerated maternal insulin secretion early in pregnancy could lead to accelerated growth of the placenta and foetus (Hufnagel et al., 2022).

In summary, evidence from a broad range of observational cohort studies suggests that elevated maternal insulin resistance and/or exaggerated insulin secretion is associated with an increased risk for a myriad of adverse gestational outcomes. Particularly for women with GDM, studies demonstrated significant heterogeneity in insulin resistance and secretory patterns, each of which conveyed varying risk profiles for adverse outcomes such as emergency caesarean or delivering large-for-gestational age infants (Benhalima et al., 2019; Immanuel et al., 2021; Y. Liu et al., 2018; Powe et al., 2016; N.-J. Zhang et al., 2020). However, due to the varying methodologies applied across the existing literature, insulin resistance and/or dysfunctional insulin response patterns have not yet been well defined, and therefore limited comparisons

between studies can be made. There is potential that assessing insulin sensitivity or secretion patterns could be used as an early indication of a woman's risk for adverse outcomes, and thus may provide a promising template to improve opportunities for lifestyle-based interventions.

2.5 Nutrition in pregnancy

Pregnancy is unequivocally an important life stage during which lifestyle choices have far-reaching impacts on maternal, offspring, and family health (M. A. Hanson et al., 2020; B. Hill et al., 2020). Section 2.2.2 highlighted how unhealthy lifestyle factors are associated with an increased risk for a plethora of adverse outcomes. Overweight/obesity, inter-pregnancy weight gain, unhealthy diets, and physical inactivity are some of the many factors that may have devastating effects on maternal and infant health. The American Dietetic Association acknowledges the importance of maintaining healthy dietary and lifestyle choices throughout childbearing years to reduce the risk of birth defects, suboptimal foetal development, and chronic health problems (Kaiser & Allen, 2008). The impact of various types of dietary and lifestyle interventions on the risk of adverse maternal and infant outcomes has been extensively studied in a range of different populations. This section will summarise current dietary recommendations and evidence from dietary and lifestyle interventions during pregnancy for the prevention of adverse outcomes.

2.5.1 Dietary and lifestyle advice during pregnancy

A healthy diet during pregnancy is one that should achieve both adequate GWG and satisfy nutrient requirements to support maternal and foetal metabolism (National Institute for Health and Care Excellence, 2010; World Health Organization, 2016b). Interventions to prevent excess GWG and adverse outcomes associated with maternal obesity begin with pre-conception care that encourages healthy lifestyle choices, and weight loss for women with a BMI of 30 kg/m^2 or over (National Institute for Health and Care Excellence, 2010; World Health Organization, 2013b). However, advice on what precisely constitutes an optimal diet during pregnancy is not well defined. The World Health Organization advises that pregnant women receive counselling about healthy eating and keeping physically active to stay healthy and to prevent excessive GWG (World Health Organization, 2016b). In a broad sense, undisputed healthy eating advice means to encourage consumption of adequate energy, protein, vitamins and minerals, obtained through a variety of foods, including green and orange vegetables, meat, fish, beans, nuts, whole grains, and fruit (World Health Organization, 2016b).

While a relationship between maternal metabolic dysfunction and an increased risk adverse outcomes is recognised, specific dietary recommendations during pregnancy for women with

pre-existing risk factors such as obesity are lacking (B. Hill et al., 2020; Parrettini et al., 2020). Gaps in dietary advice to prevent adverse outcomes were described by the Health in Preconception, Pregnancy and Postpartum Global Alliance; the highest ranked pregnancy research priority was to promote a healthy diet and nutrition during pregnancy (B. Hill et al., 2020). Not only is there a lack of specific guidance on which intervention components are most effective for promoting optimal maternal and offspring health, women's dietary intake is typically sub-optimal when compared to the USA national dietary guidelines (B. Hill et al., 2020; Moran, Sui, Cramp, & Dodd, 2013; Pick, Edwards, Moreau, & Ryan, 2005). In the case of maternal obesity and excess GWG, micronutrient inadequacy often co-exists with excessive energy intake (B. Hill et al., 2020; World Health Organization, 2016a). This gap in dietary advice does not necessarily reflect a lack of evidence to describe dietary approaches that are beneficial, but it represents a wider gap in public health policy to identify women with sub-optimal dietary behaviours and provide appropriate guidance that may facilitate healthy lifestyle choices occurring in the context of wider socioecological issues (B. Hill et al., 2020; E. Wang et al., 2020).

Weight gain recommendations during pregnancy

Weight gain during pregnancy is an essential adaptation that ensures adequate nutrition and energy availability to support maternal and foetal needs. Particularly in the latter half of pregnancy, maternal adipose stores, which make up nearly one third of maternal weight gain, provide energy in the form of lipid-based fuel to support maternal metabolism while a combination of maternal lipids and glucose is shunted to the foetus to support rapid growth and development of the foetus (Champion & Harper, 2020). The remaining weight gained during pregnancy encompasses the growing foetal placental unit (foetus, 27%; placenta, 5%; amniotic fluid, 6%; uterus 8%), increases in maternal blood volume (12%), extravascular fluid (~12%), and breast tissue (3%) (Champion & Harper, 2020).

Universal guidelines for optimal GWG based on pre-pregnancy BMI were provided by the Institute of Medicine (IOM) (Institute of Medicine & National Research Council, 2009, 2013). Weight gain guidelines are provided for women in four BMI categories: underweight, normal weight, overweight, and obesity (Table 7)(Champion & Harper, 2020). A systematic review and meta-analysis of more than one million pregnancies found that 47% of women had GWG greater than that IOM guidelines which was associated with a higher risk of large-for-gestational age infants (OR 1.85, 95% CI 1.76-1.95), macrosomia (OR 1.95, 95% CI 1.79-2.11), and caesarean delivery (OR 1.30, 95% CI 1.25-1.35), and lower risk of small-for-gestational age infants (OR 0.66, 95% CI 0.63-0.69) and preterm birth (OR 0.77, 95% CI 0.69-0.86) (Goldstein et al., 2017).

Table 7. Institute of Medicine 2009 gestational weight gain guidelines

Preconception BMI	Weight gain range
Underweight, <18.5 kg/m^2	12.5 – 18 kg
Normal weight, 18.5 – 24.9 kg/m^2	11.5 – 16 kg
Overweight, 25.0 – 29.9 kg/m^2	7 – 11.5 kg
Obesity, ≥ 30.0 kg/m^2	5 – 9 kg

Recreated from the Institute of Medicine and National Research Council (2009).

The IOM GWG guidelines do not include recommendations for obesity subgroups, which are: obesity class one, BMI of 30 to 34.9 kg/m^2; class two, BMI of 35 to 39.9 kg/m^2; and class three, BMI of 40 kg/m^2 or higher. Goldstein et al. (2017) showed that for women with obesity, weight loss during pregnancy was associated with a 5% lower risk of large-for-gestational age infants and macrosomia and 4% lower risk for caesarean delivery. Weight gain below the IOM guidelines was associated with 2% overall lower risk of all three outcomes. Weight loss had the greatest protective effect among women with class three obesity. Patterns of GWG differ across women from varying classes of obesity and by trimester (Most, Altazan, Hsia, Beyl, & Redman, 2020). Women with the more severe class three obesity gain less fat mass or lose more body weight and fat mass compared to women with class one or two obesity. Additional energy requirements during pregnancy are compensated by mobilisation of maternal adipose stores, suggesting that women with obesity should not require additional dietary energy (Most et al., 2019).

While weight gain below the IOM guidelines or weight loss during pregnancy may be beneficial for women with class three obesity, specific advice on an acceptable level of energy restriction and GWG guidelines for women with severe obesity during pregnancy is lacking (Parrettini et al., 2020). Guidelines remain conservative (i.e. weight gain recommendations are no different from women with class two or three obesity where a minimum GWG of 5 kg is advised) due to there being well-recognised risks associated with inadequate GWG or weight loss during pregnancy (Champion & Harper, 2020). In the meta-analysis by Goldstein et al. (2017), GWG below the IOM guidelines was associated with a higher risk of small-for-gestational age infants (OR 1.53, 95% CI 1.44-1.64) and preterm birth (OR 1.70, 95% CI 1.32-2.20). Inadequate GWG is also associated with intrauterine growth restriction and perinatal mortality (Champion & Harper, 2020; R. R. Davis, Hofferth, & Shenassa, 2014). Risk of neonatal death in pregnancies with inadequate GWG is greatest in women with underweight pre-pregnancy BMI (OR 6.18, 95% CI 2.45-15.56), with the odds decreasing in higher BMI categories (normal weight OR 1.47, 95% CI 1.08-2.01; overweight OR 2.11, 95% CI 1.30-3.42; obese OR 1.01, 95% CI 0.63-1.64) (R. R. Davis et al., 2014).

Weight loss or inadequate weight gain during pregnancy, particularly among women with a BMI < 30 kg/m^2, likely represents inadequate energy intake to support the nutritional demands of pregnancy (Kaiser & Allen, 2008). Sub-optimal food intake may also reflect inadequate intake of various micronutrients that are essential for foetal development, unless supplementation is considered (Kaiser & Allen, 2008; Marshall et al., 2021). Nutrient inadequacy and inadequate weight gain during pregnancy is especially problematic in groups with elevated nutrient needs, such as adolescent pregnancies that are complicated by additional energy and nutrient demands required for growth (Kaiser & Allen, 2008).

Increased ketogenesis is suggested as a mechanism through which foetal development can be adversely affected by maternal weight loss (Champion & Harper, 2020). However, a direct link between maternal ketones and adverse foetal outcomes remains disputed (Tanner et al., 2021). These controversies were discussed in further detail in section 0. In context of maternal weight loss, since ketone production is closely related to dietary intake (i.e. levels increase in the fasting state, and further with extended fasting), the effects of maternal ketogenesis cannot be isolated from the consequences of inadequate dietary intake itself (Butte, 2000). Reduced food intake would consequently lead to the reduced availability of energy, amino acids, nucleic acids, lipids, carbohydrate, and micronutrients essential for foetal development (Butte, 2000).

2.5.2 Evidence from dietary and lifestyle intervention studies

Extensive evidence from intervention studies indicates an overall protective effect of many types of combined dietary and exercise interventions on maternal and neonatal outcomes. Combined lifestyle interventions have been shown to lead to reduced GWG and risk of GDM, as well as some meta-analyses indicating a reduced risk of adverse outcomes including maternal hypertension, caesarean delivery, large-for-gestational age infants, macrosomia, and neonatal respiratory morbidity (Bain et al., 2015; Cantor et al., 2021; International Weight Management in Pregnancy (i-WIP) Collaborative Group, 2017; Lamminpää, Vehviläinen-Julkunen, & Schwab, 2018; Mohsenzadeh-Ledari et al., 2019; Muktabhant et al., 2015; Shepherd et al., 2017; Teede et al., 2022). Furthermore, interventions which provided general healthy eating advice without a physical activity component led to an overall 40% average reduced risk of GDM, 70% reduced risk of gestational hypertension, and lower GWG (-4.7 kg) compared to standard care (Tieu, Shepherd, Middleton, & Crowther, 2017).

Two Cochrane reviews described a clear benefit of dietary and exercise interventions to reduce incidence of excess GWG and GDM (Muktabhant et al., 2015; Shepherd et al., 2017). However, between the trials reviewed, authors acknowledge significant heterogeneity among the

interventions making it difficult to understand their optimal components. For example, Muktabhant et al. (2015) included varying "weight management" interventions where diets were low sugar, low glycaemic load (GL), "diabetic", energy-restricted, or low-fat. Additional monitoring with food diaries and/or regular body weighing and exercise components also varied. Characteristics of the lifestyle programmes reviewed by Shepherd et al. (2017) to reduce the risk of GDM included a dietitian- or health coach- delivered counselling either one-on-one or in group settings that encouraged healthy eating during pregnancy, some of which specified avoiding high-carbohydrate meals, substituting high- with low-glycaemic index (GI) foods, or energy restriction. In a meta-analysis by Teede et al. (2022), dietary-focused interventions were found to have a greater impact on limiting GWG, rather than physical activity alone or mixed interventions. They suggested that a positive effect was due to specific nutrition interventions having more intensive dietary information with the support of a dietitian or health coach, while those which did not clearly articulate structured diet and physical activity components were less effective. That is to say, the personal support and delivery of an intervention could be just as important as the content of advice provided. When compared to standard antenatal care, findings from meta-analyses clearly point to an overall protective effect of *any* lifestyle intervention that encourages health-promoting behaviours through the effect of monitoring and personalised support (Muktabhant et al., 2015; Shepherd et al., 2017; Teede et al., 2022). A positive impact of most lifestyle interventions is consistent with recommendations from Health in Preconception, Pregnancy and Postpartum Global Alliance which recognise the protective effect of lifestyle interventions in pregnancy reducing excess GWG and improving health outcomes (B. Hill et al., 2020). However, progress is needed to understand the most effective components of the interventions to support optimal maternal and neonatal metabolic health.

Although varying interventions were found to have a positive impact, the common element of "healthy diets" presented generally encourage consumption of nutrient-dense and minimally processed foods and discourage consumption of ultra-processed foods or "Westernised" dietary choices including foods that are high in sugar, refined carbohydrate, and refined oils. As it was described in section 2.2.2, ultra-processed food choices and physical inactivity are both well-recognised risk factors for adverse outcomes such as excess GWG. Hyperpalatable food choices can lead to excessive energy intake, while high sugar and refined carbohydrate-containing foods produce a high glycaemic impact which may appropriate the heightened maternal insulin response in pregnancy leading to increased adipose storage and worsening insulin resistance. Thus, it is expected that any intervention which directs women away from ultra-processed and hyperpalatable foods and encourages regular physical activity will have an overall benefit. As understanding of hyperinsulinaemia in pregnancy and

heterogeneity of different metabolic responses to diet evolves, future dietary research may look to provide targeted interventions for the most favourable glycaemic and insulinogenic responses. To further understand the metabolic impacts of varying types of dietary interventions, in Chapter 3 we present a systematic review examining the relationship between maternal dietary exposures and sub-clinical foetal hyperinsulinaemia and neonatal adiposity.

2.6 Nutrition in pregnancy: Challenges for women with GDM

2.6.1 Current treatment recommendations for GDM

For women who develop hyperglycaemia in pregnancy, lifestyle behaviour change is the first line of treatment to optimise glycaemic control and weight gain throughout pregnancy (American Diabetes Association, 2021b). Treatment for GDM starts with medical nutrition therapy, physical activity, weight management, and glucose monitoring. Medical nutrition therapy aims to ensure glycaemic targets are met, and therefore dietary lifestyle strategies that achieve glycaemic control are cornerstone in management (Duarte-Gardea et al., 2018; Hernandez, Mande, & Barbour, 2018). However, despite the importance of medical nutrition therapy having been established, the optimal diet for GDM remains elusive (Mahajan, Donovan, Vallee, & Yamamoto, 2019). Dietary recommendations for women with GDM have been criticised for failing to provide consistent and specific advice with limited consideration for specific macronutrient intake, quality of the nutrient choices, and/or dietary patterns (Hernandez & Brand-Miller, 2018; Mahajan et al., 2019). Two systematic reviews and meta-analyses of intervention studies have indicated room for improvement in current guidelines due to evidence showing an overall benefit of varying diet and lifestyle interventions when compared against standard care (S. Han, Middleton, Shepherd, Van Ryswyk, & Crowther, 2017; Yamamoto et al., 2018). This section reviews current clinical practice guidelines for the management of GDM, followed by a review of evidence from dietary intervention studies.

Medical nutrition therapy

In recognising that diet is an essential part of GDM management, medical nutrition therapy is advocated as the first line of care (American College of Obstetricians and Gynecologists, 2018; American Diabetes Association, 2021b; American Diabetes Association Professional Practice Committee, 2021b; Blumer et al., 2013; Duarte-Gardea et al., 2018; Ministry of Health, 2014). The goals of medical nutrition therapy are to encourage a healthy dietary intake which meets the nutritional requirements of pregnancy to deliver a healthy infant while maintaining glycaemic control (Duarte-Gardea et al., 2018; Vasile et al., 2021). Table 8 provides a summary of dietary recommendations from international governing bodies. In most instances, dietary

recommendations suggest the same Dietary Reference Intake values as those for all pregnant women, with consideration for the glycaemic impact of foods consumed.

Mustafa, Hofer, Harding, Wall, and Crowther (2021) presented a systematic review of 31 clinical practice dietary guidelines for women with GDM. Clinical practice guidelines were found to be inconsistent overall, occasionally contradicting each other. Significant gaps were identified around a paucity of evidence to support effective dietary interventions, including advice on meal distribution and specific macronutrient and energy intake. Similar findings were reported by Tsirou et al. (2019) in their systematic review of 21 clinical practice guidelines. To date, there is no clear evidence on the most appropriate nutritional approach to reduce the risks of adverse maternal-neonatal outcomes, such as preeclampsia, macrosomia, and perinatal complications (Hernandez & Brand-Miller, 2018; Martis et al., 2018; Mustafa et al., 2021).

Table 8. Current national guideline recommendations for medical nutrition therapy for women with GDM

American College of Obstetricians and Gynecologists (Committee on Practice Bulletins-Obstetrics, 2018)	• Nutrition goals: Achieve normoglycemia, prevent ketosis, provide adequate GWG based on maternal BMI and foetal growth. • Dietary energy distribution: 33-40% carbohydrate, 20% protein, 40% fat. • Complex carbohydrate choices, low GI, high fibre, carbohydrate allocated in three meals and between two and three snacks.
American Diabetes Association (American Diabetes Association, 2021b; American Diabetes Association Professional Practice Committee, 2021b)	• Nutrition goals: Achieve and maintain normoglycemia, promote adequate GWG and foetal growth. • Individual nutrition prescription and nutrition counselling developed between the women and a registered dietitian familiar with GDM management. • Intakes based on the recommended dietary reference intake for all pregnant women: At least 175 grams of carbohydrate, a minimum of 71 grams of protein, and 28 grams of fibre per day. • Emphasises monounsaturated and polyunsaturated fats while limiting saturated fats and avoiding trans fats. • The amount and type of carbohydrate will impact postprandial glycaemia. Simple carbohydrates will result in higher postprandial excursions. • Specific calorie or carbohydrate amounts are not provided.
Academy of Nutrition and Dietetics (Duarte-Gardea et al., 2018)*	• Nutrition goals: Achieve and maintain normoglycemia, promote adequate GWG and foetal growth. • Individual nutrition prescription and nutrition counselling. • Dietary energy distribution: 36.7-60% carbohydrate or >65% carbohydrate in the DASH diet. • At least 175 grams of carbohydrate per day, 28 grams of fibre per day, low or medium GI, with breakfast being low GI or

	15-60 grams of carbohydrate. Distribute carbohydrates across three meals and at least two snacks.
Diabetes Canada (Feig et al., 2018)	• Nutrition goals: Promote adequate intake without ketosis, achieve GWG glycaemic goals, and foetal growth. • Healthy diet for pregnancy. • At least 175 grams of carbohydrate per day, low GI, distributed over three moderate-size meals and at least snacks (one of which, at bedtime).
Endocrine Society (Blumer et al., 2013)	• Carbohydrate controlled meal plan that promotes adequate nutrition, appropriate weight gain, normoglycemia and absence of ketosis. • Healthy food choices, portion control, and good cooking practices, taking into account personal and cultural eating preferences, pre-pregnancy BMI, desired body weight, physical activity, and blood glucose levels. • Dietary energy distribution: 35-45% carbohydrate. • Distribute carbohydrate into three small-to-medium sized meals and between two and four snacks, with one evening snack. • Restrict energy to 1600-1800 kcal/day for women with overweight/obesity.
International Federation of Gynecology and Obstetrics (Hod et al., 2015)	• Based on personal and cultural eating habits, physical activity, Blood glucose levels, and gestation's physiological effects. • Dietary energy distribution: 35-45% carbohydrate. • At least 175 grams of carbohydrate per day, low GI, and distributed across three small-to-medium sized means and between two and four snacks. Evening snack needed to prevent overnight ketosis.
National Institute for Health and Clinical Excellence (2015)	• Carbohydrate-controlled meal plan promoting adequate nutrition and GWG, normoglycemia, and absence of ketosis. • Healthy diet for pregnancy. • Low GI and high fibre carbohydrates.
New Zealand Ministry of Health (Ministry of Health, 2014)	• Carbohydrate-controlled meal plan with specific dietary recommendations determined and regularly modified by individual assessment. • At least 175 grams of carbohydrates distributed evenly throughout the day between meals and snacks.

BMI: Body mass index; GI: Glycaemic index; GWG: gestational weight gain

*Most rigorous evidence-based analysis from all guidelines to date.

Pharmacological interventions

The medical management of GDM varies internationally regarding guidelines for first- and second-line therapies (Tsakiridis et al., 2021). Pharmacological interventions include insulin, oral hypoglycaemic agents, or both. They may be introduced at any point from GDM diagnosis with the aim of meeting maternal glycaemic targets to reduce the risk for foetal hyperglycaemia and foetal hyperinsulinaemia; they are usually offered as adjunctive therapy when lifestyle management alone fails to meet glycaemic targets (American College of Obstetricians and Gynecologists, 2018; American Diabetes Association Professional Practice Committee, 2021b; Blumer et al., 2013). The most used therapy is exogenous insulin, since unlike other oral hypoglycaemic agents, insulin does not cross the placenta into foetal circulation.

Insulin

Insulin therapy is the first-choice pharmacologic agent that is usually offered when lifestyle management alone fails to meet glycaemic targets (American College of Obstetricians and Gynecologists, 2018; American Diabetes Association Professional Practice Committee, 2021b; Blumer et al., 2013). Exogenous insulin therapy may be used to compensate for the relative insulin deficiency observed in GDM (J. Brown, Grzeskowiak, Williamson, Downie, & Crowther, 2017a). Unlike oral hypoglycaemics, exogenous human insulin dose not cross the placenta, therefore making it a preferred treatment. The main mechanism of action through which insulin lowers maternal glucose levels is by stimulating peripheral glucose uptake and inhibiting hepatic gluconeogenesis (J. Brown et al., 2017a; Girard, 2006). Insulin also inhibits lipolysis, proteolysis, and gluconeogenesis, and increases adipose storage and protein synthesis (J. Brown et al., 2017a; Girard, 2006). The recommendations supporting insulin therapy when lifestyle interventions inadequately achieve glycaemic control is based off two seminal clinical trials (described in section 2.3.1) (Crowther et al., 2005; Landon et al., 2009). Compared to usual care, Crowther et al. (2005) demonstrated that GDM treatment, where 20% of women received insulin therapy, led to reduced serious perinatal outcomes, defined as death, shoulder dystocia, bone fracture, nerve palsy, admission to neonatal intensive care unit, jaundice (1% vs. 4% RR 0.33 95% CI 0.14-0.75, $p = 0.01$). The trial by Landon et al. (2009) showed that GDM treatment, where 8% of the women received insulin therapy, was associated with a reduced risk of foetal overgrowth (large-for-gestational age: 7.1% vs. 14.5%, $p < 0.001$; birth weight > 4000 g: 5.9% vs. 14.3 %, $p < 0.001$), shoulder dystocia (1.5% vs. 4.0%, $p = 0.02$), caesarean delivery (26.9% vs. 33.8%, $p = 0.02$), and hypertensive disorders (8.6 vs. 13.6%, $p = 0.01$).

Evidence demonstrating the superiority of one insulin regimen or type of insulin over another is lacking (Zera & Seely, 2021). Varying protocols using a combination of long- or

intermediate-acting (glargine and detemir) and/or rapid-acting (aspart and lispro) insulin analogues have been used safely in pregnancy (Napoli, 2020). Each specific regimen is personalised by the clinician according to patient needs, with the overarching aim of achieving glycaemic goals throughout pregnancy (American College of Obstetricians and Gynecologists, 2018; Hod et al., 2015; Tsakiridis et al., 2021; Zera & Seely, 2021).

Metformin

Metformin is an oral anti-hyperglycaemia agent that improves insulin sensitivity, reduces hepatic gluconeogenesis, and enhances peripheral glucose uptake resulting in lowering of blood glucose (Eyal et al., 2010; Priya & Kalra, 2018). It has been established as an effective treatment for maintaining maternal glycaemic control with a minimal risk of hypoglycaemia and may help to limit GWG (Priya & Kalra, 2018). However, there is controversy regarding the use of metformin as a first-line medical treatment in GDM, resulting in general caution surrounding its use (Barbour & Feig, 2019). The main concern stems from knowledge that metformin freely crosses the placenta, potentially exposing the foetus to high concentrations of the drug (Eyal et al., 2010). The International Federation of Gynecology and Obstetrics (Hod et al., 2015) and National Institute for Health and Clinical Excellence (2015) recommend metformin for initial medical treatment if lifestyle therapies fail to meet glycaemic targets within the first two weeks of lifestyle changes. In contrary, the American Diabetes Association state that metformin should not be used as a first-line agent, recognising placental transfer (American Diabetes Association Professional Practice Committee et al., 2022). (American Diabetes Association Professional Practice Committee et al., 2022)

Meta-analyses have shown that compared to insulin therapy, metformin may lead to better maternal and neonatal outcomes (Balsells et al., 2015; Kitwitee et al., 2015; G. Li et al., 2015). Balsells et al. (2015) showed from 15 studies, metformin as compared to insulin therapy was associated with significant reductions in maternal weight gain, gestational age at delivery, and incidence of preterm birth (metformin vs. insulin: maternal weight gain mean difference -1.14 kg, -2.22 to -0.06); gestational age at delivery: mean difference -0.16 weeks, -0.30 to -0.02; preterm birth: RR 1.50, 1.04-2.16). A second meta-analysis including 11 studies demonstrated reduced rates of (Balsells et al., 2015)pregnancy-induced hypertension (RR: 0.53, 95% CI 0.31, 0.90, p = 0.02), GWG (mean difference: -1.28 kg, 95% CI -1.54 to -1.01, p < 0.0001), average gestational ages at delivery (mean difference: 0.94 weeks, 95% CI -0.21 to -0.01, p = 0.03), average birth weights (mean difference: -44.35 g, 95% CI -85.8 to -2.90, p = 0.04), incidence of hypoglycaemia (RR: 0.69, 95 % CI 0.55-0.87, p = 0.001), and neonatal intensive care unit admissions (RR: 0.82, 95% CI 0.67-0.99, p = 0.04) (G. Li et al., 2015). Further meta-analyses have shown equivocal maternal and perinatal

outcomes as compared to insulin therapy suggesting no clinically relevant difference in efficacy or safety between metformin and insulin (J. Brown, Grzeskowiak, Williamson, Downie, & Crowther, 2017b; Farrar et al., 2017; Poolsup, Suksomboon, & Amin, 2014; Yu et al., 2021; L. P. Zhao et al., 2015). However, a 43% increased risk for small-for-gestational age infants (RR 1.43, 95% CI 1.08, 1.89, p = 0.01), as shown in a meta-analysis by He et al. (2022), has led to caution around the use of metformin in pregnancies where there may be concerns relating to foetal nutrient supply (e.g. foetal growth restriction, maternal weight loss, women restricting food intake) (Barbour & Feig, 2019; Barbour, Scifres, et al., 2018).

Concerns for using metformin as a primary medical therapy are due to a limited long-term safety data with the knowledge that the foetus is exposed through placental transfer (Roy & Sahoo, 2021). Metformin has been shown to reach foetal concentrations equivalent to maternal levels, and therefore has potential to act on foetal and placental tissues in ways that could affect foetal and childhood development (Barbour, Scifres, et al., 2018). A meta-analysis by Tarry-Adkins, Aiken, and Ozanne (2019) showed that metformin exposure *in utero* is associated with lower infant birthweight (mean difference -107.7 g, 95% CI -182.3 to -32.7, p = 0.005), that may be followed by accelerated postnatal growth resulting in higher childhood BMI compared to children born to mothers treated with insulin alone (mean difference 0.78 kg/m^2, 95% CI 0.23-1.33, p = 0.005). Further, body composition outcomes at 9- years from the largest controlled study to date comparing metformin versus insulin treatment showed that (van Weelden et al., 2018; Q. Xu & Xie, 2019)metformin-exposed children in from the Auckland arm (n = 99) were heavier (37.0 ± 12.6 kg vs. 32.7 ± 7.7 kg, p = 0.049), had higher arm and waist circumferences (mid-upper arm: 23.0 ± 4.3 cm vs. 21.2 ± 2.9 cm, p = 0.02; waist circumference 69.1 ± 12.2 cm vs. 64.2 ± 8.4 cm, p = 0.04) and waist to height ratio 0.51 ± 0.08 vs. 0.47 ± 0.05, p = 0.02), and higher abdominal fat volume by MRI (subcutaneous fat: 3231 ± 2412cm^3 vs. 2398 ± 1566cm^3, p = 0.059; visceral fat: 941±629cm^3 vs. 722±365cm^3, p = 0.051) (Rowan et al., 2018). Seven-year follow-up analysis from the Adelaide are (n = 109) showed no differences in offspring weight of body composition. While metformin use in GDM pregnancies continues to be approached with caution as long-term health outcome data are established, treatment decisions require a balanced, personalised approach that weighs out the risks of inadequately managed hyperglycaemia when insulin therapy may be deems as inappropriate (Barbour & Feig, 2019).

2.6.2 Evidence from dietary interventions in women with GDM

There have been many and varied dietary intervention studies over the last three decades that have demonstrated efficacy for mitigating maternal hyperglycaemia and associated adverse outcomes among women with GDM (Allehdan, Basha, Asali, & Tayyem, 2019; Sarah S Farabi &

Hernandez, 2019). As several lifestyle interventions described in section 2.5.2 have been shown to be protective against excess GWG, the development of GDM, and other adverse outcomes, similar can be said for interventions provided after women are diagnosed with GDM. A pivotal meta-analysis by Yamamoto et al. (2018), which reviewed a range of interventions embedded into the treatment of GDM (18 randomised controlled trials), demonstrated that dietary manipulation to improve nutritional intake from usual behaviours resulted in better fasting and postprandial glucose, reduced need for medication treatment, and in neonates, reduced birth weight and macrosomia incidence. That is to say, findings showed that any type of dietary intervention which manipulates usual behaviour and encourages healthier choices has a likely overall benefit for maternal and neonatal health following a GDM-affected pregnancy. Yamamoto et al. (2018) concluded that the evidence pointed to room for improvement in usual dietary advice for women with GDM. Studies were highly heterogeneous and the quality of the evidence was low, which is a finding supported by earlier reviews (S. Han et al., 2017; Viana, Gross, & Azevedo, 2014). Despite mounting evidence from many dietary studies, speculation still remains around which dietary strategies are most effective for promoting positive maternal and infant outcomes in a GDM pregnancy while balancing concerns around excessive or unachievable restriction (Sarah S Farabi & Hernandez, 2019). A summary of the different types of dietary interventions that have been studied among women with GDM is provided in Table 9. Later, Chapter 3 aims to expand on and further refine this review of dietary evidence to investigate the impact of maternal dietary interventions on sub-clinical foetal hyperinsulinaemia and neonatal adiposity.

Table 9. Types of diets for the nutritional management of GDM

Diet	Definition	Meta-analyses and Trials
Low carbohydrate diet	Low carbohydrate diet: < 26% dietary energy or < 130 grams per day. Moderate carbohydrate diet: 26-45% dietary energy (Feinman et al., 2015).	Cui et al. (2022) Cypryk et al. (2007) S. Han et al. (2017) Hernandez et al. (2014) Hernandez et al. (2016) Moreno-Castill et al. (2013) Viana et al. (2018) Yamamoto et al. (2018)
Low GI diet	GI estimates the glucose response to intake of a carbohydrate food item. May be calculated as total dietary GI or provide qualitative recommendations based of types of food to encourages consumption of foods with a low GI ranking as opposed to foods classified as high GI. Food items with a GI of <55 are considered low GI foods (Augustin et al., 2015).	Balas-Nakash et al. (2010) Grant et al. (2011) S. Han et al. (2017) Louie et al. (2011) Ma et al. (2015) Moses et al. (2009) Perichart-Perera et al. (2012) Viana et al. (2018) Wan et al. (2016) Wei et al. (2016) Yamamoto et al. (2018)
Fat modification	Sunflower-oil enriched diet with ~30% dietary energy from fat and ~50% from carbohydrate.	S. Han et al. (2017) Lauszus et al. (2001) H. Wang et al. (2015) Yamamoto et al. (2018)
Mediterranean diet	High consumption of vegetables, fruit, nuts, seeds, legumes, olive oil, and unprocessed grains. Moderate intake of fish and poultry and limited consumption of dairy products, red meat, processed meats, or refined sugars (Assaf-Balut et al., 2018).	Assaf-Balut et al. (2017)
DASH	Diet abundant in fruits, vegetables, whole grains and low-fat dairy products, and low in saturated fat, cholesterol, refined grains and sweets (F. M. Sacks et al., 2001).	S. Han et al. (2017) S. Li et al. (2020) Yamamoto et al. (2018)
Energy restriction	Severe energy restriction: total intake of < 1500 kcal/day or 50% reduction from pre-pregnancy caloric intake. Moderate energy restriction: 1600-1800 kcal/day or 30% reduction from pre-pregnancy intake (Blumer et al., 2013).	Feng et al. (2021) S. Han et al. (2017) Kurtzhals et al. (2018) Tsirou et al. (2021) Viana et al. (2014) Yamamoto et al. (2018)

Carbohydrate modification

Dietary carbohydrate modification has been the central course of GDM management since the Pedersen hypothesis over 70 years ago (J. Pedersen, 1952). Pedersen proposed that postprandial glucose excursions in maternal circulation is the primary driver of passive foetal hyperglycaemia, leading to foetal hyperinsulinaemia and consequently foetal overgrowth. Early research by Jovanovic-Peterson and Peterson (1990) showed that dietary carbohydrate intake was significantly related to postprandial blood glucose and amniotic fluid insulin levels among women with GDM. Their anecdotal reports modifying carbohydrate intake according to frequent meter glucose monitoring and urine ketones assessments led to a recommended "euglycaemic" diet of 30% to 40% of energy from carbohydrates as a primary treatment to reduced the need for insulin therapy. Further dietary interventions oriented around the control of carbohydrates have varied significantly over the last three decades, both in the amount and type of carbohydrates (Mahajan et al., 2019). The most well-studied forms of dietary carbohydrate modification for the management of GDM are the low carbohydrate and low GI diets (Balas-Nakash, Rodríguez-Cano, Muñoz-Manrique, Vásquez-Peña, & Perichart-Perera, 2010; Cypryk, Kamińska, Kosiński, Pertyńska-Marczewska, & Lewiński, 2007; Grant, Wolever, O'Connor, Nisenbaum, & Josse, 2011; Hernandez et al., 2016; Louie et al., 2011; Ma et al., 2015; Moreno-Castilla et al., 2013; Moses, Barker, Winter, Petocz, & Brand-Miller, 2009; Perichart-Perera et al., 2012).

In a non-pregnancy context, a low carbohydrate diet is defined as less than 26% of daily energy from carbohydrate, or under 130 grams per day (Feinman et al., 2015; Wheatley, Deakin, Arjomandkhah, Hollinrake, & Reeves, 2021). Moderate carbohydrate restriction of up to ~40% energy from carbohydrate was used in the traditional dietary treatment for GDM up until the 2005 Fifth International Workshop Conference on GDM which subsequently resulted in the American Diabetes Association removing specific guidance on dietary energy percentage of carbohydrate intake from their practice guidelines (Metzger et al., 2007; Mulla, 2016). Most current clinical practice guidelines cite a minimum recommendation of 175 grams of carbohydrate per day for women with GDM (Table 8), therefore now leaning toward moderate or no carbohydrate restriction. Other authors have argued that amid the current global landscape where rates of maternal obesity have increased, 175 grams of carbohydrate per day may be considered as a low carbohydrate diet pattern for individuals consuming ≥2500 kcal/day as this may equate to ≤28% of energy intake (Hernandez & Rozance, 2023).

The 175 grams per day minimum carbohydrate threshold comes from the IOM; a threshold for minimum daily carbohydrate needs throughout pregnancy was calculated based on estimated

maternal and foetal brain glucose utilisation (Institute of Medicine, 2002/2005). Recent analysis based on the availability of new data estimating placenta glucose consumption, a further increase in the Recommended Daily Allowance for carbohydrate to 220 grams per day was proposed (Hernandez & Rozance, 2023). The historical (and current) 175-gram threshold is highly contested, especially given the growing popularity of carbohydrate-restricted diets (< 175 g/day or <40% energy intake) for achieving glycaemic control (Sweeting et al., 2021).

Dietary recommendations for GDM also frequently cite low GI carbohydrate guidance (Table 8), under the premise that low GI carbohydrate choices produce a more favourable glycaemic response for meeting glycaemic targets. The low GI diet encourages consumption of foods with a low GI rating, such as whole grains, vegetables, and legumes, while discouraging consumption of foods classified as high GI, for example, white bread and sugary foods (Augustin et al., 2015). Both low carbohydrate and low GI diets have overlapping characteristics; a low carbohydrate diet can also be low GI, and low GI can be, but is not always, low in carbohydrates. Other healthy dietary patterns, such as the Mediterranean diet, also encourage lower carbohydrate and GI choices. Overall, both low GI and low carbohydrate diets aim to blunt postprandial glycaemic excursions to improve glycaemic control and prevent foetal hyperinsulinaemia (Sweeting et al., 2021).

Both mechanistic evidence and findings from early trials have shown that carbohydrate restriction can improve glycaemic control (Jovanovic-Peterson & Peterson, 1990; Major, Henry, De Veciana, & Morgan, 1998; J. Pedersen, 1952). However, combined evidence from meta-analyses to suggest an overall advantage of carbohydrate-restriction versus other healthy but higher carbohydrate diets is unclear (Mahajan et al., 2019). A Cochrane Review by S. Han et al. (2017) demonstrated that between two trials, a low carbohydrate versus high carbohydrate diets (n = 182, 40% vs. 55%, and 45% vs. 65% of total energy from carbohydrate) led to no apparent differences for perinatal or obstetric outcomes (maternal hypertension, large-for-gestational age, perinatal mortality, caesarean section), nor was there a reduced need for insulin (Cypryk et al., 2007; Moreno-Castilla et al., 2013). Similarly, between four trials (n = 224) which compared low-moderate GI versus moderate-high GI diets in women with GDM, there was no clear difference between these diets for large-for-gestational age infants, severe hypertension, preeclampsia, eclampsia, or caesarean section (low and very-low quality evidence rating). In contrary, three meta-analyses have suggested an overall benefit of low GI diets as compared to standard care; they have shown a reduced risk of macrosomia (RR 0.27, 95% CI 0.10, 0.71; p = 0.008; 5 RCTs, n = 302) (Wei, Heng, & Gao, 2016) and need for insulin therapy (RR 0.767, 95% CI 0.60, 0.99; p = 0.039), and reduced average neonatal birth weight (mean difference 2161.9 g, 95% CI 2246.4, 277.4; p = 0.000) (Viana et al., 2014). However, no

statistically significant differences in the risks of caesarean section, large-for-gestational age, and small-for-gestational age were observed. Among ethnic Chinese women, low GI and low GL diet interventions have been shown improve glycaemic measures including fasting plasma glucose (low GI: mean difference -0.62, 95% CI -1.12, -0.13 mmol/L, 5 RCTs, n = 1038; low GL: -2.00, 95% CI -3.33, -0.67 mmol/L, 5 RCTs, n = 489), two-hour plasma glucose (low GI: -1.19, 95% CI -2.29, -0.09 mmol/L, 3 RCTs, n = 732; low GL: -3.12, 95% CI -4.91, -1.32 mmol/L, 4 RCTs, n = 375), HbA1c (low GI: -1.17, 95% CI -1.85, --0.49 %, 3 RCTs, n = 380; low GL: -1.06, 95% CI -2.01, -0.10 %, 5 RCTs, n = 489) as compared to standard care (Wan, Nankervis, Teede, & Aroni, 2019). A recent retrospective study of 265 Chinese women with GDM (IADPSG criteria, Table 5) examined the effect of a carbohydrate-restricted pattern (< 50% energy from carbohydrate) versus a high carbohydrate, healthy eating pattern. All participants were provided standard clinical care, which included a dietitian instructed meal plan and compliance ascertained by 3-day food diaries taken weekly over 3-4-week study period. The carbohydrate-restricted eating pattern was associated with delayed insulin treatment (initial treatment time 33.59 ± 3.45 weeks' gestation vs. 29.21 ± 4.07 weeks' gestation; p = 0.001)(Cui et al., 2022).

Variable outcomes from a wealth of experimental literature highlights many limitations which undermine the strength of the evidence (Hernandez et al., 2018). Mixed reports from intervention studies may be explained by different degrees of carbohydrate-restriction or modification among the included studies. A limited effect of the low GI interventions may be due to the diets being too similar in GI and the total amount of carbohydrate. For example, in one low GI intervention the reported dietary GI was 47 in the low GI group versus 48 in the control group, while total dietary energy from carbohydrates was between 46% and 48% across both groups (Perichart-Perera et al., 2012). In the low carbohydrate intervention by Moreno-Castilla et al. (2013), the intervention group reported a daily carbohydrate intake of 177 and 187 grams per day. The comparison control group reported 202 and 236 grams of carbohydrate per day in their dietary recalls. Therefore, suggesting a 25- to 49-gram difference between groups, which is the equivalent of approximately one medium-size potato. Additionally, carbohydrate quality (i.e. simple sugars versus complex, whole-food source) is not necessarily reflected in dietary comparisons. Differences reported in carbohydrate intake may also have less clinical significance when dietary recall inaccuracies are considered. Moreover, perhaps the strongest confounding variable when it comes to evidence from dietary interventions is participant adherence to a recommended eating regimen (Mustad, Huynh, López-Pedrosa, Campoy, & Rueda, 2020). Particularly during pregnancy, food cravings, palatability, hunger, and time pressure are recognised barriers to adherence (Carolan, Gill, & Steele, 2012). A specific effect of tested interventions on glycaemic control could also be highly confounded by the use of

medication, particularly exogenous insulin therapy, which is adjusted frequently throughout GDM pregnancies to achieve tight glycaemic control.

Outside of pregnancy, carbohydrate-restriction has gained recognition as an effective dietary strategy for type 2 diabetes, and gaps in evidence exploring further carbohydrate-restriction (i.e. below the IOM 175 g/day) in pregnancy are therefore a point of interest for GDM management (Sweeting et al., 2021). Carbohydrate-restricted eating patterns reduce HbA1c and the need for anti-hyperglycaemic medications in individuals with type 2 diabetes (Evert et al., 2019). The American Diabetes Association, Diabetes Australia, the British Dietetic Association, Diabetes UK, and the Scottish Intercollegiate Guidelines Network have endorsed carbohydrate-restricted dietary patterns for the management of type 2 diabetes to varying degrees as evidence has developed in recent years (American Diabetes Association Professional Practice Committee, 2021a; British Dietetic Association, 2018; Diabetes Australia, 2018; Diabetes UK, 2021; Scottish Intercollegiate Guidelines Network, 2010; Wheatley et al., 2021). However, further research is needed to expand current understanding of these dietary approaches in pregnancy since trials to date, as shown in Table 8, describe conservative and moderate carbohydrate-restriction.

There have been concerns that the higher fat intake in carbohydrate-restricted diets may adversely impact cardiovascular risk. However, higher fat carbohydrate-restricted diets have been shown to cause improvement in triglycerides, HDL cholesterol, but with limited or no effect on total and LDL cholesterol or blood pressure (Kirkpatrick et al., 2019; Meng et al., 2017; Sainsbury et al., 2018; Snorgaard, Poulsen, Andersen, & Astrup, 2017; Turton, Brinkworth, Field, Parker, & Rooney, 2019; van Zuuren, Fedorowicz, Kuijpers, & Pijl, 2018). Low carbohydrate dietary approaches are also not necessarily required to be high in total and/or saturated fat if the percentage of dietary energy from protein is increased and/or the types of fats are modified to include more mono- and polyunsaturated fatty acids. It should also be noted that there is a growing body of evidence changing conventional views of LDL cholesterol as a cardiovascular risk factor, especially when considered in the context of wider lipid (triglycerides and HDL cholesterol) and other cardiometabolic health biomarkers (Liou & Kaptoge, 2020; Packard, 2022). For example, varying subclasses of LDL particles (i.e. large buoyant versus small dense oxidised LDL) are recognised as having vastly differing atherogenicity (Austin, King, Vranizan, & Krauss, 1990; Gao et al., 2017; Krauss, 2014). Therefore, suggesting that conclusions drawn from dietary studies that have used calculated LDL as a primary end-point to describe the healthfulness of a diet may have limited application when considered through a modern lipidology lens.

The most recent critique of the traditional moderately carbohydrate-restricted dietary pattern for GDM argues that a greater percentage of dietary energy from fat may lead to increased lipid transfer to a developing foetus, resulting in overnutrition and macrosomia (Barbour & Hernandez, 2018a; Sarah S Farabi & Hernandez, 2019). Hernandez et al. (2014) conducted a randomised crossover study in which 16 women with GDM (ACOG Carpenter and Coustan criteria, Table 6) were provided with a controlled diet with a higher percentage of carbohydrates and a lower percentage of fat (60% carbohydrate, 25% fat, and 15% protein), named the Choosing Healthy Options in Carbohydrate Energy (CHOICE) diet. The comparison was a conventional diet with lower carbohydrates and higher fat (40% carbohydrate, 45% fat, 15% protein). The primary outcome was glycaemic control, and mean blood glucose was estimated with continuous glucose monitoring. Following the CHOICE diet, participants showed higher mean one-hour postprandial glucose for lunch (CHOICE vs. conventional: 114.8 ± 2.5 vs. 100.5 ± 3.3 mg/dL; $p \leq 0.001$), but not breakfast or dinner. Mean two-hour postprandial glucose was higher for the CHOICE diet for breakfast 110.5 ± 3.8 vs. 99.2 ± 2.9 mg/dL; $p \leq 0.01$) and lunch (104.4 ± 2.8 vs. 92.5 ± 2.9 mg/dL; $p \leq 0.001$), but not dinner. Day time (99,493 ± 2,136 vs. 93,663 ± 2,630 mg.min/dL; $p = 0.01$) and 24-hour glucose area-under-the-curve (136,730 ± 2,980 vs. 128,653 ± 3,810 mg.min/dL; $p = 0.02$) from continuous glucose monitoring data was also significantly lower in the conventional diet group. Despite these differences, glycaemic measures of both protocols were within the recommended glycaemic targets. The higher carbohydrate CHOICE diet also produced higher insulin and c-peptide area-under-the-curve levels compared to the conventional low carbohydrate diet (c-peptide: 2,121 ± 132 vs. 1,709 ± 93 ng.min/dL, $p \leq 0.001$; insulin: 29,374 ± 2,973 vs. 20,713 ± 2,344 µU.min/mL, $p = 0.0001$). Authors noted that the CHOICE diet led to lower postprandial free fatty acids (93,684 ± 6,153 vs. 115,449 ± 6,856 µEq.min/L, $p \leq 0.01$), which was proposed as being protective against foetal overnutrition. Triglyceride levels, however, were no different between groups. They argued that since plasma glucose area-under-the-curve was within the target range when following the CHOICE diet, a lower-fat diet with a higher intake of “healthy” carbohydrates may be an important strategy to prevent excess neonatal adiposity by blunting postprandial free fatty acids.

Higher insulin, c-peptide, and overall glucose values observed on the CHOICE diet beg the question as to whether worsened maternal hyperinsulinaemia could have detrimental effects on foetal growth by stimulating increased nutrient transport across the placenta via insulin/IGF-1 signal transduction pathways (Corrales et al., 2021; Hebert & Myatt, 2021; Ruiz-Palacios, Ruiz-Alcaraz, et al., 2017; Sobrevia et al., 2016). Furthermore, contrary to the hypothesis that carbohydrate restriction adversely affects lipid metabolism, an undisputed and consistent

outcome from low carbohydrate interventions in non-pregnant individuals is reduced triglycerides (Wheatley et al., 2021). This effect has been attributed to reduced hepatic fat content and improved lipid metabolism that may occur independently of weight loss. However, the effect of a carbohydrate-restricted, higher fat diet on maternal lipids, independent of weight loss and in a pregnancy context remains unclear (Barbour & Hernandez, 2018a). Improvements observed in triglyceride levels following low carbohydrate interventions are likely linked to reduced hepatic fat, achieved by reduced postprandial insulin secretion and reversal of primary mechanisms associated with hepatic fat accumulation and insulin resistance.

The metabolic effects the CHOICE diet on glucose and lipid profiles adipose tissue insulin resistance, and infant adiposity were further explored in a follow up study (Hernandez et al., 2016) and, more recently, in a randomised controlled trial (Hernandez et al., 2023). In the first of these studies, twelve women with GDM were randomised to either the CHOICE diet (n = 6, BMI 34.3 ± 1.6 kg/m^2) or the control conventional arm (n = 6, BMI 31.2 ± 0.4 kg/m^2) and provided diets for seven weeks from ~31 to ~37 weeks' gestation (Hernandez et al., 2016). After seven weeks on the CHOICE diet, the women demonstrated higher insulin suppression of lipolysis in adipose tissue biopsies (CHOICE vs. control, glycerol release % suppression: 55.8 ± 3.0% vs. 31.1 ± 10%, p = 0.01), which is suggested of improved insulin function and insulin sensitivity of adipose tissue, which may lead to reduced fatty acid transfer to the foetus, therefore being protective again foetal overnutrition (Barbour & Hernandez, 2018a). Reduced expression of proinflammatory biomarkers including interleukin-1b, TNF-α, toll-like receptor-4, cluster of differentiation molecule 11B (CD11B), CD11C, CD1D, and glycoprotein receptor 43 was also described (all p < 0.01). Changes in lipid metabolism and insulin action on lipid metabolism could be expected when diets consist of varying quantities of carbohydrate and fat. However, the clinical significance of changes in proinflammatory gene expression is unclear, especially since there were no significant differences in blood lipids observed between the women on the CHOICE diet and conventional lower-carbohydrate diet. Regarding neonatal adiposity outcomes, there was no significant differences in infant measures at 2 weeks postpartum (body fat percent measured by air displacement plethysmography method, PEAPOD). Higher insulin suppression of lipolysis could also be explained due to increased postprandial insulin, as exaggerated by the higher quantity of carbohydrate in the diet. Suppression of adipose tissue lipolysis may mean that additional lipid requirements for rapid foetal growth in the third trimester are met through hepatic *de novo* lipogenesis from dietary carbohydrates (Wheatley et al., 2021).

In the more recent RCT from Hernandez et al. (2023), there were 23 women with GDM in each group where the CHOICE diet was compared to the conventional "low carbohydrate" diet, providing a 100 gram of carbohydrate per day difference (CHOICE diet: 316 g/day carbohydrate;

conventional diet, 214 g/day carbohydrate versus the). The study showed no between-group difference in neonatal adiposity outcomes as well as cord C-peptide level, maternal 24-h glycemia, %TIR, or insulin resistance indices. Potentially the important detail reflecting the lack of between-group differences is the degree of carbohydrate-restriction. The diet providing 214 grams of carbohydrate per day is in line with standard dietary guidance for GDM (i.e. >175 g per day). This quantity is far greater than the level of carbohydrate-restriction that may be required to see measurable changes in insulinaemia, glycaemia, and circulating plasma lipid outcomes – as demonstrated outside of the context of pregnancy. To date, there remains a gap for well-controlled prospective RCTs comparing carbohydrate reduction of less than 165 grams per day (or approximately <30% total energy) and higher carbohydrate energy-balanced diets in pregnant women (Sweeting et al., 2021).

Various insulin secretory phenotypes with GDM, as described by Powe et al. (2016), Y. Liu et al. (2018), and Immanuel et al. (2021) may also be considered in the interpretation of findings from the CHOICE intervention. In an "insulin resistant- hyperinsulinaemic"-dominant phenotype, there is the potential that an up-regulation of *de novo* lipogenesis by means of exaggerated insulin secretion could lead to increased hepatic fat accumulation, increased triglyceride levels, and altered fatty acid composition of lipoprotein particles (Sobrevia et al., 2016). Since carbohydrate-restricted diets have shown to be beneficial for wider non-pregnant individuals with type 2 diabetes, larger trials over a longer gestational period are needed to confirm the impact of a higher-fat carbohydrate-restricted diet versus a lower-fat and liberal carbohydrate diet on neonatal outcomes. Contrary to the hypothesis presented by Hernandez et al. (2014), findings from interventions studies suggested that diets with a low GL (i.e a modest form of carbohydrate restriction and modification) were associated with reduced neonatal adiposity, which is consistent with the more widely accepted argument for carbohydrate-modified diets as the initial therapy in GDM (Mulla, 2016).

Before further carbohydrate-restriction in pregnancy (i.e. below ~40% energy as already described in existing trials (Sweeting et al., 2021)) can be explored, critical observations relating to safety must be considered. Two observational studies have described higher incidences of neural tube defects among infants born to mothers with lower carbohydrate intakes (defined as ≤5th percentile of the control or ~95/122 g/day) during the periconceptual period (~3 months to 1 year pre-conception, ascertained by food frequency questionnaire data) (Desrosiers, Siega-Riz, Mosley, & Meyer, 2018; Shaw & Yang, 2019). In a USA multi-centre cohort (n = 1,559 cases and n = 9,543 controls), adjusted OR for neutral tube defect affected pregnancy after lower carbohydrate intake pre-pregnancy was 1.30 (95% CI 1.02,1.67, adjusted for maternal race/ethnicity, education, alcohol use, folic acid supplement use, study centre, and energy

intake) (Desrosiers et al., 2018). Maternal age was not included in the adjusted model despite the carbohydrate-restricted cohort being older ($\chi^2 < 0.01$). Similar associations were suggested among a smaller California cohort, from 499 cases of pregnancies affected by neutral tube defects, a pre-pregnancy low carbohydrate dietary intake was twice as likely (adjusted OR 1.7, 95% CI 1.0, 3.0, adjusted for ethnicity, education, alcohol use, folic acid supplementation, and total energy intake) (Shaw & Yang, 2019). Importantly, the association was independent of folic acid deficiency. Given that the aetiology of neural tube defects remains elucidated (Finnell et al., 2021), it is unclear to which extent the reduced carbohydrate eating pattern may be a surrogate for low intake of other nutrients (for example, choline intake) or other higher risk behaviours associated with intake of a low carbohydrate intake in the periconceptional period.

Finally, findings from Hernandez et al. (2014) clearly demonstrate one of the challenges identified from meta-analyses which show that any type of controlled diet could help women achieve glycaemic goals (S. Han et al., 2017; Viana et al., 2014; Yamamoto et al., 2018). However, a possibly overlooked outcome was that the higher carbohydrate CHOICE diet produced more elevated postprandial insulin and c-peptide (a measure of insulin secretion) levels compared to the carbohydrate-restricted, higher-fat diet. Earlier parts of this literature review demonstrated the role of insulin resistance in the aetiology of hyperglycaemia in GDM, excess GWG, and foetal overnutrition, among other metabolic disturbances. Further work is needed to determine whether a benefit of reduced maternal plasma free fatty acids outweighs the possible harmful implications of exaggerated insulin secretion and glycaemia on maternal and neonatal outcomes. To explore associations between maternal diet and neonatal adiposity, a systematic review of intervention studies is presented in Chapter 3.

Fat modification

Few studies have exclusively examined fat-modification where the diets provided specifically aim to alter types of fatty acids in the diet. However, it should be noted that carbohydrate-restricted diets often lead to an increased percentage of dietary energy from fat, if protein intake is not increased (Hernandez et al., 2018). Therefore, the previous section could also theoretically be discussed in the context of fat modification. In order to examine the effect of a higher or lower carbohydrate intake without modifying fat in the diet, protein intake would need to be adjusted. This is an important consideration for further research since interventions with a higher dietary protein intake were not described in previous meta-analyses (S. Han et al., 2017; Viana et al., 2014; Yamamoto et al., 2018), and recent direct calorimetry research has suggested recommendations for protein intake during pregnancy may be significantly underestimated (Kuriyan et al., 2019; Stephens et al., 2015).

In the Cochrane review by S. Han et al. (2017), two trials comparing a diet high in unsaturated fat versus a diet low in unsaturated fat were found to produce no clear differences for large-for-gestational age infants, pre-eclampsia, hypertension in pregnancy, caesarean section, and diabetes from one to two weeks and four to thirteen months postpartum. The same two trials were also reviewed by Yamamoto et al. (2018) and showed no effect on glycaemic outcomes or neonatal birth size. Among these two trials, one five-week intervention included a diet rich in monounsaturated fatty acids from a hybrid high oleic acid (80%) sunflower oil from 33 weeks' gestation (intervention vs. control % fat: 37% vs. 30%; % carbohydrate: 50% vs. 46%). Compared to the treatment group (n = 12), women with GDM (diagnosed by local Danish criteria: 3 hour OGTT with 75-gram glucose, two or more plasma glucose samples above three standard deviations of the mean) receiving the standard comparison diet (n = 13) demonstrated increased in 24-hour diastolic blood pressure ($p < 0.04$) (Lauszus et al., 2001). The second trial was a polyunsaturated fatty acid-rich diet, which included 20 g of sunflower oil daily and 50-54% of total energy from fat (carbohydrate % intervention vs. control: 48% vs. 55%) (H. Wang, Jiang, Yang, & Zhang, 2015). There was no difference in glycaemic and pregnancy outcomes between the intervention and control groups. Types of dietary fat are also often modified in healthy dietary patterns such as the Mediterranean and DASH diets, usually by encouraging consumption of dietary fats high in mono-unsaturated fatty acids and limiting foods high in saturated fatty acids. However, conclusions on the effect of dietary fat modification cannot be drawn from these interventions due to varying confounding variables of an overall "healthy" eating pattern.

Healthy dietary patterns

The Mediterranean diet is a lower GI and anti-inflammatory eating pattern that encourages consumption of minimally processed foods including vegetables, fruits, nuts, seeds, legumes, unprocessed grains, and liberal use of olive oil (Assaf-Balut et al., 2018). There is moderate consumption of fish and poultry, and limited consumption of dairy products, red meat, processed meats, and refined sugars. From the trials included in meta-analyses by S. Han et al. (2017), Yamamoto et al. (2018), and Viana et al. (2014), the Mediterranean diet was not discussed exclusively as a type of treatment for GDM, however, a "Mediterranean style" eating pattern is commonly referred to as a part of healthy lifestyle interventions (Renault et al., 2014). Yamamoto et al. (2018) identified that a gap in the available evidence from dietary interventions is the lack of qualitative evaluation, including resemblance to healthy eating patterns such as Mediterranean diet. One randomised controlled trial demonstrated a reduced risk of GDM (IADPSG criteria, Table 5; n = 177 women diagnosed) among 434 women who received Mediterranean dietary advice from 8-12 weeks' gestation; intervention group received

additional advice to supplement their diet with extra virgin olive oil (>40 mL/day) and pistachio nuts (25-30 g/day), the control group were advised to restrict intake of dietary fat including extra virgin olive oil and nuts (Assaf-Balut et al., 2017). Rates of insulin treatment (intervention vs. control: (14/74 (19%) vs. 33/103 (32%); p = 0.002), prematurity (p = 0.023), GWG at 24-28 and 36-38 weeks' (p = 0.022 and 0.037, respectively), emergency caesarean section (p = 0.001), perineal trauma (p = 0.001), small-for-gestational age infants (p = 0.001), and large-for-gestational age infants (p = 0.006) were also significantly lower in the intervention group compared to controls.

Another diet considered beneficial for GDM is the DASH diet, originally developed in the late 1990s-early 2000s for controlling hypertension (F. M. Sacks et al., 2001). The DASH diet promotes the consumption of fruit, vegetables, fat-free/low-fat dairy, whole grains, nuts, and legumes, while limiting the intake of saturated fat, cholesterol, refined sugar, sodium, red and processed meats. The diet was developed during the era of "fat-free" and "cholesterol-free" eating recommendations, which had since been modified from the US Department of Agriculture dietary guidelines (Dietary Guidelines Advisory Committee, 2015), therefore questioning the relevance of some aspects of the diet today. During pregnancy, DASH diet interventions have been associated with a decreased risk of preeclampsia (RR 0.67; 95% CI: 0.45, 0.99, p = 0.043), macrosomia (RR 0.29; 95% CI: 0.12, 0.72, p = 0.043), and large-for-gestational age infants (RR 0.45; 95% CI: 0.21, 0.97, p = 0.041) among pregnant women with GDM, obesity, or hypertensive disorders of pregnancy (S. Li et al., 2020). In the Cochrane review by S. Han et al. (2017), three trials comparing a DASH diet intervention versus a control diet (n = 136) had no effect on the risk of preeclampsia for women with GDM. In two trials, the DASH diet was associated with a 47% reduced risk of caesarean section (RR 0.53, 95% CI 0.37, 0.76; n = 86).

A protective effect of healthy dietary patterns could be attributed to various components, especially the reduced intake of ultra-processed foods, including those high in refined carbohydrates and sugars, which negatively affect glycaemia. That is to say, interventions which encourage healthier eating and provide women with strategies to gather and prepare meals from minimally processed ingredients, as opposed to consuming ultra-processed foods, will undoubtably benefit mother and offspring. However, specific elements restricted in the Mediterranean and DASH diets may come at a cost to nutrient adequacy and not necessarily benefit maternal and neonatal health. For example, encouraging women to limit their intake of red meat during pregnancy increases the risk of inadequate iron intake, which can become problematic during a particular life-stage when iron deficiency is common (Kaiser & Allen, 2008). Advice to restrict dairy products and dietary cholesterol, often leading to limited egg consumption, may increase the risk of inadequate choline intake (Robb, Joubert, Jordaan,

Ngounda, & Walsh, 2021), which is essential during pregnancy to support foetal brain development (Derbyshire, Obeid, & Schön, 2021).

Energy restricted diets

Dietary energy restriction is frequently indirectly recommended to women with GDM and higher BMI's under the guise of avoiding excess GWG (Duarte-Gardea et al., 2018; Institute of Medicine & National Research Council, 2013). Outside of pregnancy, energy restricted diets have been shown to improve glycaemic control and lead to weight loss in adults with type 2 diabetes (A. Brown & Leeds, 2019), however, use in pregnancy is limited since adequate dietary intake for weight gain is an important part of a healthy pregnancy. Moreover, any reduction in dietary intake upon entering pregnancy is approached with grave caution due to recognised concerns associated with maternal weight loss, nutritional inadequacies, starvation ketosis, and potential detrimental effects on foetal development (discussed in section 2.5.1). Moderate energy restriction is defined as a ~30% reduction from pre-pregnancy caloric intake or ~1600-1800 kcal/day (Mahajan et al., 2019).

A pilot open-label and non-randomised study in Greece evaluated the effect of a very low energy diet (VLED, 1600 kcal/day, n = 19), or a low energy diet (LED, 1800 kcal/day, n = 24) among women with GDM (Tsirou et al., 2021). Those in the VLED group experienced lower GWG (median GWG: VLED: 5.9 kg; LED: 12.0 kg; p = 0.05). Negative urinary ketones were reported in all but 2 women on the LED and 3 women on the VLED. Both groups also experienced comparable obstetric and neonatal outcomes, suggesting feasibility for further research to explore the safety of energy-restricted diets for reducing GWG among women with GDM.

Earlier trials involving energy-restricted diets compared to standard GDM diets have suggested mild improvements in glycaemic control (pooled mean difference: -0.72mg/dL; 95% CI -7.10, 5.66mg/dL), while differences in birth weight, incidences of large-for-gestational age, and macrosomia, and neonatal hypoglycaemia were nonsignificant (6 RTCs, n = 1300 participants) (Feng, Zhao, Fu, Gao, & Zhang, 2021). Studies were found to have a high risk of bias, therefore concluding energy-restricted diets likely had a similar effect on maternal and neonatal outcomes and the standard GDM diet. S. Han et al. (2017) and Viana et al. (2014) also identified no difference in preeclampsia, caesarean section, large-for-gestational age infants, macrosomia, neonatal hypoglycaemia, or perinatal mortality in studies comparing energy-restricted versus control diets.

Limited success from energy-restricted diets may be related to other qualitative dietary components such as glycaemic impact and nutrient density. Overall, the diet must consider the

net benefit of body fat reduction or limiting weight gain, versus the risk of harm from potential nutrient inadequacies. Indeed, pregnancy is a particularly sensitive time where inadequate dietary intake could have life-changing effects on a developing foetus and potential long-term offspring health (Barker & Thornburg, 2013). Energy restriction during pregnancy is approached with grave caution due to concerns associated with maternal ketonemia and foetal development (Tanner et al., 2021). Further, although limiting portion sizes on an energy restricted diet can mean the GL in a meal is reduced, this may not always be the case for low energy-density but high carbohydrate-containing foods; for example, one slice of white bread which when consumed in isolation has a low energy density but can produce a high glycaemic response.

One Danish cohort study combined elements of an energy-restricted low GI "diabetes diet" intervention which was delivered to 382 women who were diagnosed with GDM at ~27 weeks' gestation (diagnosed by Danish criteria: OGTT, 75-gram glucose, 2-hour glucose value ≥9.0 mmol/L). Women who "adhered" to dietary restriction, as demonstrated by restricted weekly GWG (440, <350, <230 and <170 g/week for each BMI category), had a lower HbA1c ("restricted" vs. "excessive" GWG: 37.5 ± 5.1 mmol/mol vs. 39.6 ± 5.6 mmol/mol; $p < 0.017$) at the end of the study and delivered neonates with lower birth weights ("restricted" vs. "excessive" GWG birthweight z-score: 0.15 ± 1.1 vs. 0.59 ± 1.6; $p < 0.017$), without an increased incidence of small-for-gestational age infants (Kurtzhals et al., 2018).

In summary, the key goal of medical nutrition therapy in GDM is to reach glycaemic targets while also ensuring appropriate GWG and nutrient intake to meet maternal and foetal needs. Although the overall importance of diet and lifestyle in the management of GDM is undisputed, specific guidelines for meeting nutrition goals have been heavily criticised as being inconsistent, fragmented, and non-evidence-based (Hernandez & Brand-Miller, 2018). Despite many intervention studies with varying dietary approaches having been conducted over the last three decades, there is still a lack of consensus on which specific types of strategies or dietary components lead to optimal maternal and neonatal outcomes. One of the challenges in interpreting dietary intervention studies is that multiple dietary and behavioural change elements can confound the intervention's true effect. Even dietary strategies rooted in carbohydrate modification, which have been the central course of GDM management since the 1950's, have a considerably limited evidence-based due to significant confounding variables limiting interpretation of trials to date (Hernandez et al., 2018). While there is mechanistic evidence to suggest that carbohydrate-restricted diets among women with GDM would be beneficial for managing glucose intolerance and mitigating exaggerated insulin response patterns, well-controlled and appropriately powered intervention studies are lacking. Varying dietary approaches concerning the amount and percentage of dietary energy from

carbohydrates translates into variable clinical practice guidelines. Much work is needed in order to generate evidence to reveal optimal dietary strategies for women and infants affected by GDM (Hernandez & Brand-Miller, 2018).

2.7 Conclusion

Pregnancy places major metabolic demands on a woman's body with the overall goal of ensuring a continuous and adequate supply of essential nutrients for a developing foetus. These changes are facilitated by physiological increased in insulin secretion and insulin resistance. In women with pre-existing insulin resistance and hyperinsulinaemia, essential *physiological* changes are augmented to produce a dysfunctional state. Evidence shows that many adverse maternal and infant outcomes, such as GDM, gestational hypertension, preeclampsia, and foetal growth abnormalities, can be linked to pre-existing insulin resistance of the mother. These outcomes are also associated with an elevated long-term risk of cardiometabolic diseases of ageing later in life, for both the mother and offspring. Despite clear evidence that excessive insulin resistance is undesirable in pregnancy, there are limited public health strategies to identify high-risk women outside of standard GDM screening and diagnostic programmes. This is an important gap because adverse outcomes that are ascribed as being linked to maternal metabolic dysfunction also occur in women without GDM. Undoubtedly, healthy lifestyles play a major role in preventing adverse gestational outcomes by improving pre-pregnancy and maternal metabolic health. However, advice on how to first identify higher-risk women pre- and during pregnancy to provide appropriate lifestyle guidance that might mitigate these risks is lacking. The following chapters of this thesis address i) evidence linking maternal diet and neonatal cord-blood insulin, glucose, and adiposity outcomes (Chapter 3); ii) a cross-sectional study examining insulin response patterns during pregnancy across varying degrees of glucose tolerance from a legacy dataset of OGTTs in pregnant women (Kraft dataset) (Chapter 4); iii) a pilot study to explore insulin response patterns during pregnancy and later gestation effects (Chapter 5); and iv) a qualitative study exploring the dietary management of GDM in New Zealand from the perspective of health professionals (Chapter 6). Given the new findings, the final chapter (Chapter 7) discusses future directions for research for defining hyperinsulinaemia in pregnancy and implications for dietary advice that may mitigate the risk of adverse outcomes - before, after, and in women without a GDM diagnosis.

Chapter 3. The role of maternal diet of offspring hyperinsulinaemia and adiposity after birth: a systematic review of randomised controlled trials

Preface

The previous chapter examined metabolic changes during pregnancy and how physiological changes to insulin secretion and signalling are augmented in women with pre-existing insulin resistance. By describing risk factors and adverse outcomes associated with insulin resistance, a broad group of women who may benefit from lifestyle advice can be identified. It was also clearly shown in previous literature there are many types of dietary strategies that are, to varying degrees, beneficial for pregnant women at risk of and with GDM. However, dietary strategies for optimal maternal and infant health were unclear in the context of maternal insulin resistance and hyperinsulinaemia. Chapter 3 extends the literature reviewed around dietary interventions to reduce the risk of adverse outcomes for women with this exaggerated insulin resistance and the associated changes in nutrient metabolism. This chapter examines the relationship between maternal dietary exposures and foetal hyperinsulinaemia and neonatal adiposity. Neonatal cord blood c-peptide, insulin, and glucose measures and neonatal adiposity have been selected as surrogate indicators of *in utero* exposure to overnutrition. As described in the literature in the previous chapter, a sub-optimal maternal environment can influence metabolic programming in the offspring and lead to an increased risk of chronic health problems later in life. Recognising the adverse effects of maternal hyperinsulinemia on foetal development, neonatal outcomes could be more telling of the maternal metabolic environment. That is to say, although various lifestyle interventions have shown to be beneficial for reducing GWG, GDM, caesarean sections, and admissions to the neonatal intensive care unit, neonatal outcomes could provide a more complete picture of the true impacts of diet. The manuscript presented in this chapter was published in the *Journal of Developmental Origins of Health and Disease* in 2021 (doi 10.1017/S2040174421000623).

3.1 Abstract

In utero diet may be directly related to the risk of foetal hyperinsulinaemia and offspring metabolic health. This review examines the relationship between maternal dietary interventions during the perinatal period and neonatal cord blood insulin, c-peptide, or glucose levels, and neonatal adiposity. Articles were identified in MEDLINE, Web of Science, CENTRAL, CINAHL, SCOPUS, and SPORTDiscus (September 2019 - March 2021) using the PRISMA guidelines.

PROSPERO registration ID CRD42020146453. Studies were selected by two independent reviewers. RCTs involving a dietary intervention with pregnant women (healthy pregnancy, GDM, and obesity) and reporting foetal cord-blood insulin, c-peptide, glucose, or adiposity estimates were included. One author extracted all information on main study characteristics and outcomes. Risk of bias was assessed using the Cochrane Collaboration's bias risk assessment tool. A total of 733 articles were identified. Fifteen articles from 11 RCTs (3,614 participants) were included. Studies reviewed showed no specific effect of maternal diet on neonatal cord blood insulin, c-peptide, or glucose levels. Infants born to mothers who followed a low GL diet had lower skin fold thickness (SFT) at six months of age compared to controls. Interventions that provided individualised nutrition counselling on healthy eating for limiting GWG (e.g. low GI diet, reduced sugar and simple carbohydrate) were also associated with lower adiposity. The studies reviewed suggest that lifestyle/behavioural-based interventions (diet and physical activity education, coaching sessions, and monitoring components throughout) to improve glycaemia (low GL) and/or encourage limited GWG may have a protective effect against excess adiposity. Future studies should incorporate multi-modal interventions (nutrition, exercise, and behaviour change) with dietary counselling to support lifestyle changes throughout gestation and include assessments of maternal insulin resistance at recruitment.

3.2 Background

Maternal insulin resistance during pregnancy is a normal and essential adaptation that ensures adequate nutrition to support the life of a growing foetus (Barbour et al., 2007; Butte, 2000; Hernandez et al., 2020). Women with reduced pregravid insulin sensitivity compensate with an increased insulin response (hyperinsulinemia) (Freinkel et al., 1985), which could affect early placental growth and gene expression (Sobrevia et al., 2016). Maternal metabolism undergoes ongoing changes in insulin sensitivity mediated by circulating placental factors that drive excessive nutrient availability (Catalano & Shankar, 2017). When augmented by maternal insulin resistance, this may lead to an increased risk of complications for both the mother and neonate (Butte, 2000).

The global rise of insulin resistance syndromes such as obesity and polycystic ovarian syndrome among women of childbearing age has led to a growing interest in lifestyle-based strategies to mitigate pregnancy complications associated with pre-existing insulin resistance (Hernandez et al., 2020). Maternal obesity, a condition typically associated with more advanced insulin resistance, is associated with a milieu of metabolic derangements, including hyperglycaemia, hyperlipidaemia, and inflammation in the mother (Tinius et al., 2020). Maladaptive changes in maternal metabolism associated with pre-existing insulin resistance are associated with an

increased risk of developing GDM, hypertensive disorders, non-alcoholic fatty liver disease, cardiomyopathy, birthing complications (Hernandez et al., 2020; Yogev & Catalano, 2009), as well as a life-long increased risk of metabolic syndrome and type 2 diabetes (B. Daly et al., 2018).

Exaggerated maternal insulin resistance is known to have transgenerational impacts that beget childhood metabolic dysfunction. These genetic and epigenetic exposures *in utero* have lasting effects on the offspring's later life metabolic health (Hernandez et al., 2020; Juonala et al., 2011). Maternal insulin resistance has been shown to alter placental and foetal metabolism in ways that can lead to foetal overgrowth, endothelial dysfunction, and neurological disorders in the neonate (Sobrevia et al., 2016). Furthermore, alterations in the maternal insulin/IGF axis have been demonstrated in GDM pregnancies (Zhu et al., 2016), and are thought to have an important role in mediating foetal outcomes (Gęca & Kwaśniewska, 2020; Retnakaran, 2016).

The foetal response to maternal overnutrition is foetal hyperinsulinemia (J. Pedersen, 1952), which mediates developmental pathways involved with growth, body composition, and mitochondrial function in the offspring (Hernandez et al., 2020). In pregnancies complicated by diabetes mellitus, the maternal hyperglycaemia-foetal hyperinsulinaemia response leads to an increased risk of developmental and metabolic complications such as neonatal hypoglycaemia and macrosomia. Although interventions that reduce occurrence of adverse neonatal events are well-established in GDM pregnancies particularly (American Diabetes Association, 2020), there is growing interest in the long-term developmental impacts of *in utero* hyperinsulinaemia for infants born to women with normal-to-borderline hyperglycaemia.

Evidence from the largest blinded multinational study on adverse pregnancy outcomes, the HAPO cohort study (23,316 participants), highlighted the breadth at which foetal hyperinsulinaemia can be observed in pregnancies across a spectrum of clinical and sub-clinical maternal hyperglycaemia (HAPO Study Cooperative Research Group et al., 2008). The HAPO study showed an independent and continuous linear relationship between non-diabetic hyperglycaemia in pregnancy and cord serum c-peptide. Newborns with higher cord serum c-peptide (> 90th percentile) were also larger and fatter and had a higher clinical incidence of neonatal hypoglycaemia (Metzger, Persson, et al., 2010). Cord c-peptide has repeatedly been found to mediate the relationship between maternal body mass index (BMI) and infant size (I. L. Lee et al., 2020), and maternal hyperglycaemia and childhood adiposity (Josefson et al., 2021), thus providing a plausible link between *in utero* exposures and later life metabolic diseases (Muhlhausler, Gugusheff, Ong, & Vithayathil, 2013). This suggests all women carrying a risk of foetal hyperinsulinaemia, such as those with obesity, may benefit from interventions to mitigate excursions in nutrient excess, not only those affected by GDM.

Various dietary interventions have been implicated for reducing the risk of adverse outcomes in GDM pregnancies (S. Han et al., 2017). A meta-analysis by Yamamoto et al. of 18 studies showed various modified dietary interventions including the low GI and the DASH diet were associated with improved maternal glycaemia, lower neonatal birth weight, and reduced macrosomia (Yamamoto et al., 2018). Outside of GDM, various dietary interventions for pregnant women with overweight or obesity have been implicated for limiting gestational weight gain and preventing GDM incidence (Lamminpää et al., 2018). Among them, effective dietary interventions involve nutrient or energy restriction alongside behavioural and physical activity components. It is plausible that such interventions which reduce GDM occurrence also create a more favourable metabolic environment for foetal development.

Despite cord blood metabolites providing a promising marker of *in utero* exposures and infant metabolic development health, to our knowledge, there have been no systematic reviews published in the last five years that summarise current evidence from dietary studies on foetal insulin metabolism outcomes. Since it is unclear whether cord-blood metabolites, specifically insulin and c-peptide, from non-GDM pregnancies can provide a sensitive indicator of sub-clinical *in utero* exposures, excess infant adiposity is proposed to be both a plausible and measurable mediator of transgenerational metabolic dysfunction (Castillo, Santos, & Matijasevich, 2015; Catalano, Thomas, Huston-Presley, & Amini, 2003). Neonatal adiposity appears to be tightly linked to *in utero* foetal insulin levels (Stanley, Fraser, Milner, & Bruce, 1992), and altered cord-blood metabolites; reflective of altered fatty acid oxidation and mitochondrial dysfunction (Kadakia et al., 2018).

For this review, we aimed to examine the relationship between different dietary interventions in metabolically healthy and high-risk pregnant populations and neonatal cord blood insulin, c-peptide, or glucose levels, and neonatal adiposity.

3.3 Methods

This review was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009). The review protocol was registered in the PROSPERO International prospective register of systematic reviews (ID CRD42020146453). The Population, Intervention, Comparator, Outcomes, Study design (PICOS) criteria, used to define the research question and to select the studies, are presented in Table 10.

3.3.1 Search strategy

The literature search was performed using MEDLINE, Web of Science, Cochrane Controlled Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), SCOPUS, and SPORTDiscus using the keywords provided in Appendix C, Supplementary Table 1. The search was narrowed using filters of full text, peer-reviewed, journal articles, human, English language, and publication day from November 1985 to January 2021.

Table 10. Categories for formulation of the research question for a systematic review on effects of dietary interventions and associations of dietary intake with neonatal outcomes.

Category	**Result**
Population	Pregnant adult women (>18 years) and neonate up to 6 months of age.
Intervention/exposure	Dietary intervention (intervention studies).
Comparison	Control group (e.g, standard care as part of randomised controlled trial) or a different dietary intervention,
Outcome	Neonatal cord blood insulin, c-peptide, glucose, and neonatal adiposity up until 6 months of age.
Study designs	Intervention studies.

3.3.2 Inclusion and exclusion criteria

Inclusion criteria were as follows: i) RCTs involving a dietary intervention component that included either a macronutrient or dietary pattern modification, ii) dietary intake assessment ascertained by validated food frequency questionnaire (FFQ), multiple-day food diary, or 24-hour dietary recall method; iii) participants including pregnant adult women (aged >18 years, recruited at any point during their pregnancy) and their neonates up to 72 hours from birth (for cord blood) and up to six months of age (for adiposity); iii) articles from 1985 to present to capture lifestyle patterns of current times; iv) outcome measure examining foetal insulin secretion by cord blood metabolite analysis and/or infant adiposity. Valid outcome measures included cord blood c-peptide, insulin, and/or glucose measured at birth, or infant adiposity measured within six months of age using four-compartment or two-compartment model methods, i.e. air displacement plethysmography (ADP) or skin fold thickness (SFT).

Exclusion criteria were as follows: i) research investigating food security or malnutrition; ii) studies examining a nutritional supplement or supplemental food product; iii) dietary intervention component inadequately described; iv) full text article not available in the English

language; v) brief communications, case series, editorials, review studies; vi) pilot intervention studies without a control group.

3.3.3 Study selection

Suitable literature was identified following a three-step screening process (Figure 9). All literature retrieved was collated into Endnote and duplicates removed, then subjected to preliminary (title and abstract) and full-text review. Literature retrieval was performed by the first author (SN). Two independent reviewers (SN and CT) subsequently filtered the identified articles by evaluating titles and abstracts, and subsequently full texts and references based on the inclusion and exclusion criteria. Additional articles identified by hand searching of reference lists from previous review and selected studies were also considered. Any discrepancy in assessment between reviewers was resolved through discussion and rechecking of the full text.

3.3.4 Data extraction

Data were extracted from the included studies in the following domains: country; author; year; study design; number of participants; study groups; participant characteristics (maternal age, BMI, gestational age, GWG, neonatal birth weight, and prevalence of large-for-gestational age); primary outcomes; intervention protocol including intervention content and compliance assessment, timing, outcome measure of interest and study findings. Due to the heterogenicity of populations included in RCTs, results from women with GDM, BMI ≥ 25kg/m^2, and "healthy" populations were reported separately. Primary outcomes were reported as mean differences between groups (standard deviation, SD) and median (interquartile range, IQR), or relative risk if not otherwise available. Where mean differences were not reported in the manuscripts, between group differences were calculated using pooled SDs (Altman, 1991). In the instance where all data from included articles was not available, authors were contacted to obtain missing data.

3.3.5 Assessment and reporting quality

Risk of bias was assessed using the Cochrane Collaboration's bias risk assessment tool, where bias was classified into six domains: selection, performance, detection, attrition, reporting and other bias (Higgins et al., 2011). The 'other' domain referred to dietary intervention compliance, which was classified as low risk when the study design included compliance measures to evaluate participant adherence to assigned dietary intervention. Examples of low compliance bias included telephone or face-to-face dietary review sessions throughout the intervention period, and validated forms of dietary assessments by 24-hour food recall or three-day food

diaries. No dietary follow-up, low participant adherence, or the intervention group not achieving the intended dietary change was rated as a high risk of compliance bias.

3.4 Results

3.4.1 Study selection

The number of identified studies is shown in the flow diagram of the literature search in Figure 9. Titles of 868 articles were found from the search result and 733 were retained after removal of duplicates. Among the 733 that were screened for title and abstract, 136 articles were subjected to full text revision. Articles excluded were not dietary RCTs, did not provide an assessment of the outcome measures of interest, were a protocol paper or review article.

A total of 15 articles from 11 RCTs involving 3,614 pregnant women were included. The main characteristics from the included studies are summarised in Table 11. Five studies recruited women in their first trimester with a BMI ≥ 25 kg/m^2 (Ferrara et al., 2020; Garmendia, Casanello, Flores, Kusanovic, & Uauy, 2021; Rhodes et al., 2010; van Horn et al., 2018; Yi Zhang et al., 2019). Mean participant BMI for these studies ranged between 28.0 to 34.4 kg/m^2, which was reported pre-pregnancy (Ferrara et al., 2020; van Horn et al., 2018) or from first-trimester body weight (Garmendia et al., 2021; Rhodes et al., 2010; Yi Zhang et al., 2019). In the DALI study women were selected with a pre-pregnancy BMI ≥ 29 kg/m^2 (Harreiter, Simmons, et al., 2019; van Poppel et al., 2019), and UPBEAT study, participants had a pre-pregnancy BMI ≥ 30 kg/m^2 (N. Patel et al., 2017; N. Patel et al., 2018). Women with a previous infant born weighing > 4 kg were recruited for one study (mean BMI 26.5-27.2 kg/m^2 measured in the first trimester) (Donnelly, Walsh, Byrne, Molloy, & McAuliffe, 2015; Horan et al., 2016; Walsh, Mahony, Culliton, Foley, & McAuliffe, 2014). Kizirian et al. included women with at least one risk factors for GDM (Kizirian et al., 2016). Two studies recruited women diagnosed with GDM (Mijatovic et al., 2020; Rae et al., 2000). Among the remaining 9 studies, women were recruited in the first trimester and the prevalence of GDM ranged from 2% to 41% (Donnelly, Walsh, et al., 2015; Ferrara et al., 2020; Garmendia et al., 2021; Harreiter, Simmons, et al., 2019; Horan et al., 2016; Kizirian et al., 2016; N. Patel et al., 2017; N. Patel et al., 2018; Rhodes et al., 2010; van Horn et al., 2018; van Poppel et al., 2019; Walsh, Mahony, et al., 2014; Yi Zhang et al., 2019).

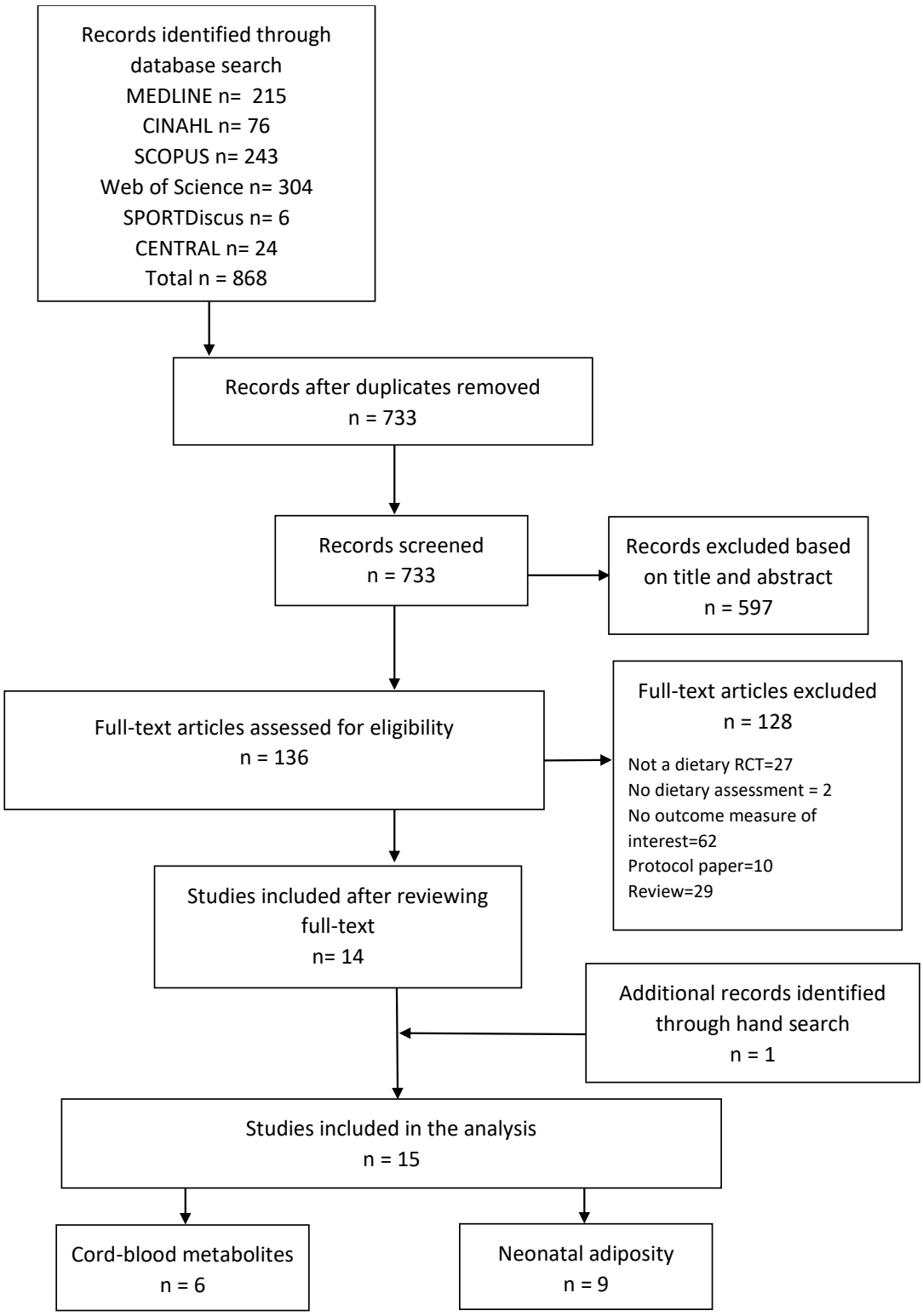


Figure 9. Flow diagram of literature search

3.4.2 Characteristics of interventions

The intervention characteristics are summarised in Table 11.

Intervention delivery

In five studies, the intervention was provided over between two and five individual dietitian- or nutritionist-led sessions (Donnelly, Walsh, et al., 2015; Garmendia et al., 2021; Horan et al., 2016; Mijatovic et al., 2020; van Horn et al., 2018; Walsh, Mahony, et al., 2014; Yi Zhang et al., 2019). Dietary interventions included home-based counselling to reduce sugar consumption alongside docosahexaenoic acid supplementation (2x2 factorial design) (Garmendia et al., 2021), eucaloric low GI diet (Donnelly, Walsh, et al., 2015; Horan et al., 2016; Kizirian et al., 2016; Walsh, Mahony, et al., 2014) (N. Patel et al., 2017; N. Patel et al., 2018), eucaloric low GI diet versus a low fat diet (Rhodes et al., 2010), low glycaemic load (GL) diet with a participant-driven mobile app (Yi Zhang et al., 2019); calorie-restricted diet (30% restricted) (Rae et al., 2000), modestly lower carbohydrate diet (135 grams per day) (Mijatovic et al., 2020); and the Dietary Approaches to Stop Hypertension (DASH) diet (van Horn et al., 2018). Two studies included one-on-one motivational interviewing techniques with participants to facilitate behaviour change for weight management (Ferrara et al., 2020; Harreiter, Simmons, et al., 2019; van Poppel et al., 2019). The UPBEAT study involved eight weekly health-trainer led sessions on reducing dietary GL without restricting dietary energy intake (N. Patel et al., 2017; N. Patel et al., 2018). Compliance checks in addition to study visits were food diaries (Kizirian et al., 2016; Rae et al., 2000) or 24-hour food recall (Ferrara et al., 2020; Kizirian et al., 2016; Mijatovic et al., 2020), telephone interviews (Harreiter, Simmons, et al., 2019; N. Patel et al., 2017; N. Patel et al., 2018; van Horn et al., 2018; van Poppel et al., 2019; Yi Zhang et al., 2019), and a logbook with weekly goals in one study (N. Patel et al., 2017; N. Patel et al., 2018).

Comparison group

Most studies described control groups as receiving usual care that included standard periodic antenatal visits and referral for medical care as indicated (i.e. following GDM diagnosis) (Donnelly, Walsh, et al., 2015; Ferrara et al., 2020; Garmendia et al., 2021; Harreiter, Simmons, et al., 2019; Horan et al., 2016; N. Patel et al., 2017; N. Patel et al., 2018; van Horn et al., 2018; van Poppel et al., 2019; Walsh, Mahony, et al., 2014). Among them, two studies specified providing nutrition advice to the control group as a part of routine care in alignment with national guidelines (Ferrara et al., 2020; Garmendia et al., 2021). Five studies compared two dietary interventions where the intensity of the treatment was similar between both groups. These included a low GL versus non-low GL dietary intervention (Yi Zhang et al., 2019), modestly lower- versus moderate-carbohydrate diet (Mijatovic et al., 2020), low GI versus high fibre, higher GI (Kizirian et al., 2016), energy-restricted and non-energy restricted diet (Rae et al., 2000), and a low GI versus a low fat diet (Rhodes et al., 2010).

Table 11. Study characteristics and results from randomised controlled trials

First author, publication year, trial name	Study design, country, population, primary outcome	Study period	Intervention (I) and control (C) groups	Subjects (-withdrawals)	Participant characteristics						Outcome measure of interest Difference between groups (mean difference, 95% CI)
					Age (years)	BMI	GDM (%) n/n with insulin treatment ¶¶	Gestational age at delivery (wk)	Gestational weight gain (kg)	Birth weight (g) (% LGA)	
(A) Participants with diagnosed GDM											
Rae (2000)	RCT, Australia Pregnant women with confirmed GDM Maternal insulin therapy, macrosomia incidence	GDM diagnosis (≤ 35 wk) to delivery	I: Moderate 30% dietary energy restriction (1590-1776 kcal/day) C: Non-energy restricted diabetes diet (2010-2220 kcal/day) Both: Standard treatment including diabetes education, control of hyperglycaemia, foetal and maternal surveillance.	I:66 C:58	I:30.2 C:30.6	I: 37.9± 0.7 C: 38.0±0.7	I: 12/66 C: 10/58	I: 37.8± 0.3 C: 37.6±0.2	I: 11.6±1.3 C: 9.7±1.5	I: 3461 (28.8) C: 3267±96 (24.6)	SFT-4, 5 days I – C: Subscapular (mm): 0.0 (-0.04 to 0.04) Suprailiac (mm): 0.3 (0.26 to 0.34) Triceps (mm): 0.0 (-0.04 to 0.04) Abdominal (mm): 0.2 (0.15 to 0.25)
Mijatovic (2020) MAMI 1	RCT, Australia Pregnant women with confirmed GDM	24-32 wk to delivery	I: Modestly lower carbohydrate diet of 135 g carbohydrate per day, without	I: 24 (-4) (7 ADP) C: 22 (-8) (8 ADP)	I: 32.5±0.9 C: 34.2±0.9	I: 25.8± 1.0 C: 27.8 ±1.5	I: 14/24 C: 12/21	I: 38.7±0.2 C: 38.6±0.2	I: 10.9±0.9 C: 8.2±1.5	I:3125±101 (0) C: 3278±79 (4.8)	ADP, delivery I – C: FM (%): -2.9 (-4.76, -1.04)

	Blood ketone level		energy restriction. C: Routine care carbohydrate range of 180-200 g per day.								
(B) Participants with BMI ≥ 25kg/m²											
Ferrara (2020) GLOW	Multicentre RCT, USA Pregnant women from antenatal and medical clinics with pre-pregnancy BMI 25-40 kg/m² Excess gestational weight gain	8-15 wk to delivery	I: Up to 13 x dietitian-delivered telehealth intervention with nutrition and physical activity behaviour change advice. C: Standard antenatal care including periodic health education newsletters, on recommended weight gain, healthy eating, and physical activity in pregnancy.	I: 199 C: 195	I: 32.4 ±4.1 C: 32.6 ±4.3	I: 29.3±3.4 C: 29.4±3.8	I: 16 (8) C: 16 (8)	I:39.2±1.8 C:39.0±1.8	I: 10.2±5.6 C: 12.4±5.3[a]	I: 3376±541 (12) C: 3384±507 (15)	Cord blood c-peptide, insulin, glucose I – C: C-peptide (ng/mL): -0.1 (-0.19 to -0.01) Insulin (pmol/L): 1.5 (-15.29 to 18.29) Glucose (mmol/L): 0.1 (-0.35 to 0.55)
Garmendia (2020) MIGHT	2 x 2 factorial RCT, Chile Pregnant women BMI ≥ 25 kg/m² at first antenatal visit	8-15 wk to delivery	I_1: Home-based dietary counselling and 800 mg DHA supplementation I_2: 800 mg DHA supplementation	I_1: 250 (-59) I_2: 252 (-80) I_3: 249 (-54) I_4: 251 (-79)	I_1: 28.4 ± 5.7 I_2: 27.3 ± 5.9 I_3: 27.6 ± 5.6	I_1: 32.1 ± 4.8 I_2: 32.9 ±4.7 I_3: 32.0 ± 4.7 I_4: 32.3 ± 4.4	I_1: 21.0 (41) I_2: 20.1 (40) I_3: 18.9 (39)	Not reported	I_1: 9.5±6.2 I_2: 9.0±5.5 I_3: 9.9±6.1 I_4: 9.2±6.3	I_1: 3424± 552 (25.9) I_2: 3435± 573 (26.3) I_3: 3359±596 (25.0)	Cord blood glucose, insulin I_1 and I_3 vs I_2 and I_4 (RR, 95% CI): Glucose (mg/dL): 0.04 (-0.01 to -0.10

	GDM, macrosomia, cord blood insulin		I_3: Home-based dietary counselling and 200 mg DHA supplementation I_4: 200 mg DHA supplementation		I_4: 28.1 ± 5.7		I_4: 20.9 (41)			I_4: 3393±581 (24.8)	Insulin (µU/mL): 0.01 (-0.15 to 0.17)
Harreiter (2019) DALI	Multicentre 2×(2×2) factorial RCT, Europe (nine centres) Pregnant women with a BMI ≥ 29 kg/m^2 GDM	<20 wk to delivery	I: Healthy eating (with or without physical activity intervention): 5 x individual lifestyle coach advice to reduce sugar and simple carbohydrate and fat intake, increase protein and fibre intake. Telephone and email support throughout. C: Usual care from midwife or obstetrician during pregnancy	I: 221 C: 215 Secondary analysis	I: 32.2±5.4 C: 31.7±5.3	I: 34.6±4.1 C: 34.4±3.8	I: 32 (19.4) C: 35 (20.2)	I: 39.5±2.6 C: 39.6±1.6	I: 7.0±4.4 [b] C: 8.5±4.7	I: 3477±574 (12.5) C: 3494±524 (15.2)	Cord blood c-peptide, glucose I – C: C-peptide (ng/mL): 0.03 (-0.06 to 0.12) Glucose (mmol/L): -0.3 (-0.06 to 0.12)
van Poppel et al. (2019) DALI				$I_{HE\&PA}$: 80 I_{HE}: 92 C: 80	$I_{HE\&PA}$: 32.5±5.3 I_{HE}: 32.4±5.5 C: 31.9±5.6	$I_{HE\&PA}$: 33.6±3.6 I_{HE}: 34.2±4.6 C: 33.7±3.7	$I_{HE\&PA}$: 11 (14) I_{HE}: 13 (14) C: 8 (10)	$I_{HE\&PA}$: 39.8±1.4 I_{HE}: 39.6±1.7 C: 39.7±1.4	$I_{HE\&PA}$: 6.4±3.9[c] I_{HE}: 7.6±4.9 C: 8.6±4.6	$I_{HE\&PA}$: 3480±504 (19)[≡] I_{HE}: 3485±629 (20)[≡] C: 3581±510 (23)[≡]	SFT-4, delivery, adjusted for time after birth $I_{HE\&PA}$ – C Subscapular (mm): -0.4 (-0.8 to 0.1) Suprailiac (mm): -0.5 (-0.9 to -0.1) Triceps (mm): -0.3 (-0.8 to 0.1)

											Thigh (mm): -0.7 (-1.3 to -0.03) Sum (mm): -1.8 (-3.5 to -0.2) I_{HE} – C: Subscapular (mm): -0.1 (-0.5 to 0.3) Suprailiac (mm): -0.2 (-0.6 to 0.2) Triceps (mm): -0.2 (-0.6 to 0.3) Thigh (mm): -0.4 (-1.1 to 0.2) Sum (mm): -0.8 (-2.5 to 0.8)
Patel (2017) UPBEAT	Multi-centre RCT, UK Pregnant women BMI ≥ 30 kgm^2 GDM, LGA incidence	15-18 wk to delivery	I: Complex behavioural intervention with low GL and reduced SFA dietary advice. Weekly health trainer-led sessions C: Usual antenatal care and recommended dietary and physical activity advice through	I: 342 C: 356	I: 31.3±5.0 C: 31.0±5.6	I: 36.2± 5.0 C: 36.3±4.7	I: 97 (28.9) C: 93 (26.9)	I: 39,5±2.0 C: 39.5±2.4	I:6.9±4.7 C:7.8±4.4[d]	I: 3479±529 (8.8) C: 3437±604 (7.6)	SFT-4, 6 mo I – C: Subscapular z-score: -0.26 (-049 to -0.02) Subscapular (mm): -0.38 (-0.70 to -0.06) Triceps z-score: -0.14 (-0.38 to 0.10) Triceps (mm) -0.22 (-0.64 to 0.20) Sum (mm): -0.63 (-1.30 to 0.04)

Patel (2018) UPBEAT			UK health care pathways	I: 169 C: 174 Secondary analysis	I: 31.0 (28.0-35.0) C: 31.0 (27.0-35.0)	I: 35.5 (33.0-39.1) C: 35.7 (33.0-38.5)	I: 59 (34.9) C: 52 (29.9)	I: 39.7 (38.7-40.7) C: 40.0 (38.7-41.0)	I:6.9±4.3 C:8.0±3.8	I: 3510 (3220-3790) C: 3590 (3190-3860) (LGA not available)	Cord blood c-peptide, insulin, glucose I – C: Insulin (U/ml): -0.135 (-0.000299 to 0.271) C-peptide (g/mL): 0.0329 (-0.0459 to 0.112)
Rhodes (2010)	Pilot RCT, USA Pregnant women BMI 25-45 kgm^2 Infant birth weight *z*-score	13-28 wk to delivery	Low GL: Low GI carbohydrates (45% carbohydrate, 35% fat, 20% protein) Low fat: Consistent with American Dietetic Association recommendations (55% carbohydrate, 25% fat, 20% protein, low-saturated-fat, high complex carbohydrate)	Low GL: 24 (-3) Low fat: 21 (-5)	Low GL: 33.7±3.9 Low fat: 33.2±3.7	Low GL: 32.1±4.6 Low fat: 31.2±3.1	Low GL: 0 (0) ¶ Low fat: 1 (4) ¶	Low GI: 39.3±1.1 Low fat: 37.9±3.1	I:6.4±4.5 C:6.9±4.2	Low GI: 3507±412 (8) Low fat: 3133±671 (14)	SFT-4, delivery Low GL-Low fat: Subscapular (mm): -0.4 (-0.97, 0.17) Triceps (mm): -0.5 (-1.01, 0.01) Suprailiac (mm): -0.1 (-0.67, 0.47) Thigh (mm): -0.3 (-1.09, 0.49)
Van Horn (2018) MOM FIT	RCT, USA Pre-pregnancy BMI 25-40 kg/m^2 Gestational weight gain	16 wk to delivery	I: Dietary Approaches to Stop Hypertension diet and physical activity intervention with individualised and group coaching with a	I:140 C:141	I: 33±4 C:34±4	I:31±4 C:31±4	I: 7 (5.3) C: 9 (7.1)	I:39±2 C: 39±2	I:10±6 C:12±6[e]	I: 3244±489 (5.8) C: 3213±524 (8.8)	ADP, <72 h I – C: FM (%): -0.7 (-1.71 to 0.31)

			smartphone application was used for self-monitoring. C: Usual antenatal care								
Zhang (2019)	RCT, China Pregnant women BMI ≥ 25 kgm^2 Maternal and neonatal insulin resistance	16 wk to delivery	I: Low GL Individualised dietitian-prepared diet plan and mobile app instructions C: Individualised dietitian-prepared diet plan to meet standard nutrition goals Both: 3 x dietitian consultation incorporated with routine antenatal care visits until delivery	I: 200 (-17) C: 200 (-14)	I: 28.0±3.7 C: 28.1±3.6	I: 28.0±3.0 C: 28.4±3.0	I: 45 (22.5) C: 43 (21.5)	I: 39.7±1.2 C: 39.8±1.7	I: 9.6±7.4 C: 11.2±63[f]	I:3514±522 C: 3453±527 (LGA not available)	Cord blood c-peptide I – C: C-peptide (ng/mL): 0.01 (-0.15 to 0.17)
(C) Participants with other pre-existing risk factor for foetal hyperinsulinaemia											
Donnelly (2015) ROLO	Nested case-control RCT, Ireland, Pregnant women with previous macrosomia (infant born > 4 kg) Infant birth weight	16 wk to delivery	I: Eucaloric low GI diet, 3 x dietitian sessions including dietary education and written information (14, 28 and 34 wk gestation) C: Usual antenatal care with no dietary advice	I: 126 C: 139	I: 32.7±3.8 C: 32.1±4.6	I: 27.2±4.9	I: 7/350 (2) C: 9/371 (2)†	40±2.7†	I: 14.1±11.1 C:13.8±4.5	I: 4034±510 (51% >400 g) C: 4006±497 (51% >400 g) †	SFT-4, <72 h from delivery I – C: Subscapular (mm): -0.04 (-0.41, 0.33) Triceps (mm): -0.09 (-0.45, 0.27) Biceps (mm): -0.1 (-0.46, 0.26)

											Leg (mm): 0.08 (-0.34, 0.50) Sum SFT (mm): -1.6 (-4.47, 1.27)
Horan (2016) ROLO				I: 138 C: 142	I: 33.2±3.8 C: 33.0±4.1	I: 26.0±4.3 C: 26.2±4.5					SFT-4, 6 mo I – C: Subscapular (z-score): 0.32 (0.05, 0.59) Triceps (z-score): 0.098 (-0.17, 0.36) Biceps (mm): -0.01 (-0.48, 0.46) Leg (mm): 0.25 (-0.41, 0.91) Sum SFT (mm): 0.85 (-0.53, 2.23)
									I: 12.2±4.4 C: 13.7±4.9†		
Walsh (2014) ROLO				I: 235 C:250 Secondary analysis	I: 32.7±3.8 C: 32.1±4.6‡	I: 27.2±4.9 C: 26.5±4.3‡					Cord blood c-peptide I vs C: (median, IQR): C-peptide (pg/mL): 206.6 (65.7-700.6) vs 206.4 (52.8-731.4), p = 0.96
Kizirian (2016) GI Baby 4	Pilot prospective follow up RCT, Australia Pregnant women with at least one of the following risk factors: BMI ≥30 kgm^2, age ≥35 y, polycystic ovary syndrome, previous GDM or glucose intolerance,	12-20 wk to delivery	Low GI: GI ≤ 50 High fibre: GI 60 Both: 5 x dietitian consultations throughout gestation. Diets matched by macronutrients (15–25% protein, 25–30% fat, 40–45% carbohydrate)	Low GL: 30 High fibre: 29	Low GL: 34.9±0.8 High fibre: 35.5±0.7	Low GL: 25.8±1.0 High fibre: 25.9±1.0	Low GL: 8 (27) High fibre: 9 (31)	Low GL: 39.4±0.3 High fibre: 39.9±0.2	Low GL: 10.6±1.0 High fibre: 10.7±1.0	Low GL: 3400±100 (0.0) High fibre: 3990±200 (6.9)	ADP, delivery, 3 mo, and 6 mo Low GL vs high fibre: FM (%): Birth: -1.1 (-3.56, 1.36) 3 mo: 0.6 (-2.10, 3.30) 6 mo: -1.1 (-3.37, 1.17) FM (index): Birth: -0.1 (-0.38, 0.18) 3 mo: 0.2 (-0.65, 1.05)

	previous infant born > 4 kg, first-degree relative with type 2 diabetes, or belonging to an ethnic group with a high prevalence of GDM	6 mo: 0.0 (-0.57, 0.57)
	Infant body composition	

BMI: Body mass index; CI: Confidence interval; C-peptide: cord blood c-peptide measured on delivery day; DHA: docosahexaenoic acid; FM: estimated fat mass; GI: Glycaemic index; GL: Glycaemic load; g: grams; h: hour; $I_{HE\&PA}$: DALI intervention group with healthy eating and physical activity; I_{HE}: DALI intervention group with healthy eating advice only; IQR; interquartile range; LGA: Large-for-gestational-age, defined as infants born >90th centile; mo: months; SFT-#: skin fold thickness and number of sites; wk: week. Study names: MAMI 1: Macronutrient adjustments in mothers with gestational diabetes study 1; MOMFIT: Maternal Offspring Metabolics Family Intervention Trial; DALI: Vitamin D And Lifestyle Intervention for GDM prevention; MIGHT: Maternal obesity/overweight control throuGh Healthy nutrition; UPBEAT: UK Pregnancies Better Eating and Activity Trial; LIMIT: Limiting weight gain in overweight and obese women during pregnancy to improve health outcomes; ROLO: Randomised Control Trial of Low Glycaemic Index Diet in Pregnancy; GLOW: Gestational Weight Gain and Optimal Wellness RCT.

Values reported as mean ± SD, median (IQR) or otherwise indicated.

≡ Birth weight >4000 g. LGA not reported.

† Reported from an earlier publication on the same population.

‡ Participant demographics reported from Donnelly., et al. (2015) DOI: 10.1111/j.2047-6310.2013.00216.x

¶ Participants with a glycated haemoglobin >6% at 36 weeks gestation.

¶¶ Participants treated with insulin in studies that included only women with GDM

Significant differences in gestational weight gain shown between intervention and control groups: [a]: p<0.0001; [b]: adjusted mean difference p=0.01; [c]: $I_{HE\&PA}$ versus control p<0.002; [d]: p=0.041 as reported by Poston et al. (2015) [e]: p=0.01 (adjusted p=0.02); [f]: p=0.02.

Table 12. Dietary intervention characteristics from randomised controlled trials

First author, year	Monitoring personnel	Main content of the intervention (I) and control (C)	Feedback	Dietary assessment, and compliance measures	Intended change in dietary intake or behaviour achieved
Ferrara (2020)	Dietitian	I: Telehealth-delivered motivational interviewing behaviour change for weight management (according to IoM guidelines) health eating (e.g. setting goals for eating healthy foods in appropriate portion sizes, total caloric intake, calories from fat), physical activity, and stress management. C: Standard antenatal medical care, seven antenatal visits on average from 7–10 weeks' gestation; Periodic health education newsletters, including the Institute of Medicine GWG guidelines, healthy eating, and physical activity information.	13 x weekly individual sessions, followed by optional maintenance telephone sessions.	Printed workbook and personalised graph to track weight gain. 24-h dietary recalls at baseline (8-15 weeks) and 29-38 weeks' gestation.	Change in dietary intake at end of intervention, I-C (mean difference, 95% CI): Energy (kcal/day): -107.3 (-192.2, 22.5; p = 0.13) No significant difference between groups for % energy from fat, saturated fat, or unsaturated fat, or physical activity (MET equivalents and self-reported)
Garmendia (2020)	Nutritionist	I_1 and I_3: Dietary intervention focused on reducing consumption of 7 most significant contributors to daily sugar consumption: refined sugar, cookies, processed fruit juices, sugar sweetened yogurt, sugar-sweetened beverages, powdered juices with added sugar, and bread	3 x sessions throughout pregnancy; game to assess participants' nutritional knowledge and specific personalised advice to address nutrition knowledge deficits.	FFQ (800 items; energy and sugar intake) at baseline and 35-37 weeks visits. Adherence defined as attendance to	Post intervention dietary intake not reported.

		All: Routine antenatal care and nutritional advice according to the national guidelines		dietary counselling	
Harreiter (2019) van Poppel et al. (2019)	Lifestyle coach	I: Lifestyle coach delivered motivational interviewing on healthy eating (with or without physical activity intervention). Advice to reduce sugar and simple carbohydrate and fat intake, increase protein and fiber intake, and regulate calorie intake by reducing portion sizes. C: Usual antenatal care.	5 x individual lifestyle coach sessions 4 x telephone and email support throughout. Toolkit with behaviour change materials and participant manual with weight management information. Coaching sessions evaluated by motivational interviewing trainer.	Self-reported 12-item dietary questionnaire at <20, 24-28, and 35-37 weeks' gestation.	Change in dietary intake at 35-37 weeks', I-C (mean difference, 95% CI): Sugar drinks (n/week): -3.3 (-5.1, -1.4; $p < 0.001$) Fat (n/week): -1.5, (-2.8,-0.3; $p<0.05$) Carbohydrates (n/week): -6.2, (-11.6, -0.9; $p < 0.05$) Portion size (n/week): -3.8 (-6.8, -0.9; $p < 0.01$) Sedentary time (MET hour/week): -1.6 (-3.3; 0.0; $p < 0.05$) Weight gain (kg): -1.5 (22.4; 20.5; $p < 0.01$) No significant difference between groups for fibre, protein, total physical activity, or moderate vigorous physical activity.
Kizirian (2016)	Dietitian	Low GI: GI ≤ 50 High Fiber: GI 60 Both: Diets matched by macronutrients (15–25% protein, 25–30% fat, 40–45% carbohydrate)	5 x dietitian consultations at 14–20, 18–24, 22–28, 26–32, and 34–36 weeks' gestation 3 x mid-study visits (visits 2, 3, and 4) 24-h recalls performed to check dietary	3-day food diary x 2 (12-20, 34-36 weeks).	Change in dietary intake at end of intervention, Low GI vs High Fibre (mean ± SEM) GI: 51±1 vs 57±1; $p < 0.001$ No significant difference between groups for energy, protein, total fat, saturated fat, carbohydrate, sugar, starch, fibre, % energy from protein, % energy from fat, % energy from carbohydrate.

			compliance (dietary GI was <50 in The Low GI group and >50 in the high fibre group. In the case of noncompliance, suitable alternative foods were encouraged. A selection of recipes was also provided.		
Mijatovic (2020)	Dietitian	I: Carbohydrate target of 135 g/day without energy restriction C: Carbohydrate target of 180–200 g/d.	3-4 x study visits with usual antenatal care. Pictorial booklet, showing carbohydrate content, a target number of portions, and GI.	3 × 24-h food diary. 3 x 2-day blood ketone diary. 24-h food recall at each study visit to assess compliance.	Change in dietary intake at end of intervention for study completers, I vs C (mean ± SEM): Energy (kJ): 7040 ± 240 vs 8230 ± 320; p < 0.01 Carbohydrate (g): 165 ± 7 vs 190 ±9; p = 0.04 Protein (g): 85± 4 vs 103 ± 4; p < 0.01 No significant difference between groups for sugar, starch, fibre, total fat, saturated fat, long chain omega-3 fatty acids, % energy from protein, % energy from fat, % energy from carbohydrate, GI, and GL.
Patel (2017), Patel (2018)	Health trainer (provided study-specific training)	I: Initial one-on-one health trainer-led interview followed by 8 weekly sessions. Dietary advice to decrease dietary GL (exchanging starchy foods with a medium/high GI for those with a lower dietary GI, and restricting the consumption of sugar-sweetened beverages (including fruit juice)), but not to restrict dietary energy intake.	8 x weekly trainer-led sessions (or phone call if not attended) Participant handbook, exercise DVD and pedometer.	FFQ at 15-18, 27-28, and 34-36 weeks.	Change in dietary intake at end of intervention, I vs C (mean difference, 95% CI): GL: -35.34 (-48.00, -22.67; p < 0.001 GI (0-100): -3.94 (-4.93, -2.94; p < 0.001) Total energy (kcal/day): -354.52 (-505.95, -203.10, p<0.001) Total fat (%E): -2.65 (-3.91, -1.38; p < 0.001)

		Physical activity advice to increase daily step count. C: Standard antenatal care, which may include referral to a dietitian. Authors suggest referral is infrequently implemented and women likely to only be weighed once in the first antenatal visit.	Logbook for recording weekly goals and steps as assessed by pedometer.		Saturated fat (%E): -1.93 (-2.64, -1.22; p < 0.001) Protein (%E): 2.70 (1.63, 3.77; p < 0.001) No significant difference between groups for carbohydrate, fibre, or exercise (MET; moderate and vigorous physical activity, or walking).
Rae (2000)	Dietitian	I: Moderate 30% dietary energy restriction (1590-1776 kcal/day) C: Non-energy restricted diabetes diet (2010-2220 kcal/day) Both: Standard treatment including diabetes education, control of hyperglycaemia, foetal and maternal surveillance.	Unspecified	3-day food diary x 3 throughout study period.	Change in dietary intake at end of intervention, I vs C (mean ± SEM): Total fat (g): 56 ± 2.0 vs 63 ± 2.4; p = 0.023 Total fat (%E): 31 ± 0.7 vs 34 ± 0.7; p = 0.11 No significant difference between groups for energy, carbohydrate, or protein.
Rhodes (2010)	Dietitian	Low GL: Low GI carbohydrates (45% carbohydrate, 35% fat, 20% protein) Low fat: Consistent with American Dietetic Association recommendations (55% carbohydrate, 25% fat, 20% protein, low-saturated-fat, high complex carbohydrate)	In-person maintenance visits at 2–4 week intervals.	24-h diet recall at 32-36 week.	Change in dietary intake at end of intervention, Low GL vs Low fat (mean ± SD): GI: 51.8 ± 6.9 vs 58.0±4.3; p = 0.002 GL (g/1000 kcal): 56.3±15.2 vs 69.1 ± 11.9; p = 0.005 Fibre (g/1000 kcal): 16.5 ± 5.0 vs 13.4 ± 4.5; p = 0.05

		Both: In-person and phone counselling, structured written guides.			No significant difference between groups for energy, percentage energy from carbohydrate, protein, fat, or saturated fat.
Van Horn (2018)	Dietitian	I: DASH diet and physical activity intervention with individualised and group coaching with a smartphone application was used for self-monitoring. C: Usual antenatal care	3 x individual dietitian led sessions, and 6 x group counselling by phone or webinar. Telephone, text message prompts, and e-mail reminders to encouraged adherence and website viewing.	24 h diet recall at baseline and 35 week.	Change in dietary intake at 35 weeks, I vs C (median, IQR): Dixon DASH score: 4 (3-4) vs 3 (3-4); p = 0.01 Fung DASH score:27 (25-30) vs 26 (22-29); p = 0.005 HEI 2010 score: 70 (62-77) vs 63 (56-75); p = 0.002
Walsh (2014), Donnelly (2015), Horan, (2016)	Dietitian	I: Eucaloric low GI diet 3 x group sessions (4-6 participants) and written information C: Usual antenatal care with no dietary advice	3 x dietitian education sessions (14, 28 and 34 weeks' gestation)	3-d food diaries at each trimester. FFQ at 12 and 28 weeks. Average weekly exercise. Maternal weight recorded at 12, 20, 28, 34, 36, 38, 40 weeks. Subjective dietary adherence based on 5-point Likert-type scale	Change in dietary intake, I vs C (mean ± SD): Trimester 2 energy (kcal/day): 1775.9 ± 396.6 vs 1961.9 ± 376.4; *P* < 0.001 Trimester 3 energy (kcal/day): 1858.0 ± 410.1 vs 2000.1 ± 449.8; *P* = 0.009 Trimester 2 protein (%E): 18.3 ± 3.2 vs 16.4 ± 2.7; p < 0.001 Trimester 3 protein (%E): 17.9 ± 3.2 vs 16.6 ± 3.1; p = 0.001 Trimester 2 carbohydrate (%E): 48.8 ± 5.7 vs 50.9 ± 5.6; p = 0.003 Trimester 3 carbohydrate (%E): 48.6 ± 5.5 vs 50.5 ± 6.2; p = 0.009 Trimester 2 GI: 56.2 ± 4.0 vs 57.7 ± 3.8; p = 0.003 Trimester 3 GI: 56.2 ± 3.9 vs 57.8 ± 4.1; p = 0.003

					Trimester 2 GL: 121.5 ± 29.5 vs 143.8 ± 31.2; p < 0.001 Trimester 3 GL: 127.1 ± 27.8 vs 146.4 ± 41.6; p < 0.001 No significant difference between groups for total fat, saturated fat, monounsaturated fat, and polyunsaturated fat.
Zhang (2019)	Dietitian	I: Individualised low GL dietary plan with mobile app instructions C: Individualised dietitian-prepared diet plan to meet standard nutrition goals Both: Standard nutrition and physical activity consultation according to the national recommendations of the Chinese Nutrition Society and gestational weight gain advice according to IoM guidelines. Individualise dietary assessment and planning. 3 x dietitian consultation incorporated with routine antenatal care visits until delivery	DietGI mobile app to allow personal tracking of meal and whole day diet GI and GL 3 x dietitian education sessions (16, 24-28, and 34-36 weeks' gestation) Telephone interview monthly to promote compliance.	24-h food recall at 3 visits.	Change in dietary intake at end of intervention, I vs C (mean ± SD): Trimester 2 GI: 64.8 ± 9.4 vs 62.8 ± 9.8; p = 0.05 Trimester 3 fibre: 11.6±8.0 vs 8.9 ± 5.6; p = 0.006 No significant difference between groups for dietary GL, energy, carbohydrate, protein, and fat intake in trimesters 2 and 3. No significant difference in dietary GI for trimester 3.

IoM guidelines: Institute of Medicine guidelines no more than 7 kg for women with pre-pregnancy BMI 25 · 0–29 · 9 kg/m_2 or 5 kg for women with pre-pregnancy BMI 30 · 0 kg/m_2 or higher.

DASH, dietary approaches to stop hypertension; FFQ, food frequency questionnaire; GI, glycaemic index; GL, glycaemic load; h, hour; IQR, interquartile range; SD, standard deviation; SEM, standard error from the mean.

Effects of interventions on dietary intake

Change in dietary intake or behaviour at the end of the intervention are described in Table 12. Women receiving the telehealth-delivered behavioural intervention for weight management in the GLOW trial reported lower energy intake and a lower incidence of excess gestational weight gain (intervention: 41% vs control: 66%, $p < 0.001$) (Ferrara et al., 2020). In the DALI trial (Harreiter, Desoye, et al., 2019), the intervention resulted in lower intake of sugar drinks, fat, and carbohydrate, as well as reduced portion sizes, and sedentary time. GWG was significantly lower in the group receiving the combined healthy eating and physical activity intervention compared to standard care (p=0.002) (van Poppel et al., 2019). In the GI Baby 4 RCT (Kizirian et al., 2016), the Low GI intervention group had a significantly lower dietary GI, while there was no difference in energy and other nutrients. In the MOM FIT RCT, the intervention group presented with significantly higher Dixon DASH and Fung DASH scores, and higher HEI 2010 scores indicating compliance to the prescribed DASH diet (van Horn et al., 2018). In the ROLO study, the intervention group was shown to have a significantly lower dietary GI, GL, and percentage energy from carbohydrates (Donnelly, Lindsay, et al., 2015; Horan et al., 2016; Walsh, Mahony, et al., 2014). The study intended to provide eucaloric diets, however, the intervention group had lower energy intake in trimesters two and three. Compared to the control, intervention group from the UPBEAT study reported lower dietary GL, GI, total energy intake, total percentage energy from fat, saturated fat, and high percentage energy intake of protein (N. Patel et al., 2017; N. Patel et al., 2018). Rhodes et al. (2010) reported significantly lower dietary GI and GL in the Low GL intervention group. However, there was no significant difference in dietary fat (as a percentage of energy intake) when compared against the “Low Fat” control group. Yi Zhang et al. (2019) showed no significant difference between study groups for dietary GI, however, a total reduction in GL, energy, and carbohydrate intake was observed in both groups over the duration of the study.

The following studies did not achieve the intended dietary change. The moderately energy restricted intervention by Rae et al. (2000) indicated no significant difference between groups for total energy intake. In the moderately lower carbohydrate intervention study by Mijatovic et al. (2020), the intervention group had significantly lower total energy, carbohydrate, and protein intake. However, groups did not vary in percentage of dietary energy from carbohydrate, protein, fat, GI, GL, and total sugar, starch, and fibre. Only 20% of participants in the intervention group were reported meeting the target carbohydrate intake compared with 65% in the control group. Garmendia et al. (2021) did not provide a post-intervention comparison of participant dietary intake in the main study findings. Adherence to the lifestyle intervention was defined as

attendance to dietary counselling sessions, for which overall attendance was 69% and 31% attended all sessions.

3.4.3 Neonatal outcomes for each intervention

3.4.3.1 Cord blood c-peptide, insulin, and glucose

Six of the included studies examined neonatal cord blood. Among them, c-peptide was measured in five studies (Ferrara et al., 2020; Harreiter, Simmons, et al., 2019; N. Patel et al., 2018; Walsh, Mahony, et al., 2014; Yi Zhang et al., 2019), insulin was measured in three studies (Ferrara et al., 2020; Garmendia et al., 2021; N. Patel et al., 2018), and four studies reported glucose (Ferrara et al., 2020; Garmendia et al., 2021; Harreiter, Simmons, et al., 2019; N. Patel et al., 2018).

In two studies which delivered a behaviour change intervention to facilitate healthy eating and physical activity for appropriate weight gain, there was no significant difference between groups for cord blood c-peptide, glucose (Harreiter, Simmons, et al., 2019), or insulin (Ferrara et al., 2020), despite there being difference in dietary intake between the intervention and control group in one of these studies (Harreiter, Simmons, et al., 2019). Garmendia et al. (2021) found no significant difference in cord blood glucose and insulin between participants who received home-based dietary counselling to reduce sugar consumption and controls who received no dietary education. In the RCT by Yi Zhang et al. (2019), when compared to a dietitian-prepared control diet, the low GL intervention had no significant effect on neonatal cord blood c-peptide. In the secondary analysis from the UK UPBEAT low GI study (N. Patel et al., 2018), there was no significant difference between groups in cord blood insulin or c-peptide. Similarly, the Irish ROLO study found no significant difference in median cord blood c-peptide among participants who received a eucaloric low GI diet provided over three dietitian-led education sessions (Walsh, Mahony, et al., 2014).

3.4.3.2 Neonatal adiposity

Eight of the included studies examined neonatal adiposity. Among them, two studies measured SFT at delivery (Donnelly, Walsh, et al., 2015; Rhodes et al., 2010; van Poppel et al., 2019), two studies used ADP at delivery (Mijatovic et al., 2020; van Horn et al., 2018), two studies measured SFT at six months of age (Horan et al., 2016; N. Patel et al., 2017), and one study used ADP at both delivery and six months of age (Kizirian et al., 2016).

Among the four studies that investigated a low GL dietary intervention, the UPBEAT UK RCT, showed a reduction in subscapular SFT at six months of age (mean difference -0.38 mm (-0.70

to -0.06), p = 0.021), but not triceps SFT (N. Patel et al., 2017). In a secondary analysis of the DALI trial, neonates born to mothers in the healthy eating with physical activity intervention group had lower SFTs (n = 80; thigh: p = 0.04; subscapular: p = 0.03; sum of SFT: p = 0.03) and estimated fat mass (percentage: p = 0.04, grams: p = 0.04). There were no significant associations between the intervention and adiposity outcomes in the ROLO low GI study (Donnelly, Walsh, et al., 2015; Horan et al., 2016), GI Baby 4 study (Kizirian et al., 2016); MOM FIT DASH dietary intervention (van Horn et al., 2018); the MAMI 1 modestly lower carbohydrate intervention (Mijatovic et al., 2020), moderately energy restricted diet (Rae et al., 2000), and pilot low GL RCT (Rhodes et al., 2010).

3.4.4 Quality assessment and risk of bias

Based on the Cochrane risk of bias assessment tool (Higgins et al., 2011) the majority of the included studies had a low risk of selection bias due to randomisation and blinded allocation to treatment groups (Donnelly, Walsh, et al., 2015; Ferrara et al., 2020; Garmendia et al., 2021; Harreiter, Simmons, et al., 2019; Horan et al., 2016; Kizirian et al., 2016; N. Patel et al., 2017; N. Patel et al., 2018; Rae et al., 2000; Rhodes et al., 2010; van Horn et al., 2018; van Poppel et al., 2019; Walsh, Mahony, et al., 2014; Yi Zhang et al., 2019) (Appendix C, Supplementary Table 2).

Due to the natural of dietary intervention studies, true binding of participants is not feasible. Performance bias also refers to personal involved in delivering the intervention. A low risk of performance bias was suggested in the four studies where the intervention and comparison group were provided with matched intensity (Kizirian et al., 2016; Mijatovic et al., 2020; Rae et al., 2000; Yi Zhang et al., 2019). These studies did not inform participants on their intervention arm. A high risk of performance bias was identified in six studies where the control group received standard antenatal care and specific dietary input was not explicitly described (Donnelly, Walsh, et al., 2015; Ferrara et al., 2020; Garmendia et al., 2021; Harreiter, Simmons, et al., 2019; Horan et al., 2016; N. Patel et al., 2017; N. Patel et al., 2018; van Horn et al., 2018; van Poppel et al., 2019; Walsh, Mahony, et al., 2014).

Most of the included studies reported blinding for outcome assessments (neonatal cord blood analyses and adiposity) (Donnelly, Walsh, et al., 2015; Ferrara et al., 2020; Garmendia et al., 2021; Harreiter, Simmons, et al., 2019; Horan et al., 2016; Kizirian et al., 2016; N. Patel et al., 2017; N. Patel et al., 2018; Rhodes et al., 2010; van Horn et al., 2018; van Poppel et al., 2019; Walsh, Mahony, et al., 2014; Yi Zhang et al., 2019). Blinding during SFT assessments was unclear in one study (Rae et al., 2000).

A low risk of attention bias was identified in fourteen studies that used intention-to-treat analysis and adequately described participant withdrawals (Donnelly, Walsh, et al., 2015; Ferrara et al., 2020; Garmendia et al., 2021; Harreiter, Simmons, et al., 2019; Horan et al., 2016; Kizirian et al., 2016; Mijatovic et al., 2020; N. Patel et al., 2017; N. Patel et al., 2018; Rhodes et al., 2010; van Horn et al., 2018; van Poppel et al., 2019; Walsh, Mahony, et al., 2014; Yi Zhang et al., 2019). There was a high risk for attention bias in one study where missing data or drop-outs were not reported (Rae et al., 2000). There was a low risk of reporting bias in 12 studies (Donnelly, Walsh, et al., 2015; Ferrara et al., 2020; Garmendia et al., 2021; Harreiter, Simmons, et al., 2019; Horan et al., 2016; Kizirian et al., 2016; Mijatovic et al., 2020; N. Patel et al., 2017; Rae et al., 2000; Rhodes et al., 2010; van Horn et al., 2018; van Poppel et al., 2019; Walsh, Mahony, et al., 2014; Yi Zhang et al., 2019) which reported all present outcomes from their protocol. One study did not specifically report cord blood insulin and c-peptide outcomes by intervention groups and the authors were contacted for these data, from which the unpublished results are included in Table 11 (N. Patel et al., 2018). A low risk of compliance bias was identified in 12 studies which provided multiple points of participant contact and dietary assessments to ensure the intervention was adequately followed (Donnelly, Walsh, et al., 2015; Ferrara et al., 2020; Garmendia et al., 2021; Horan et al., 2016; Kizirian et al., 2016; Mijatovic et al., 2020; N. Patel et al., 2017; N. Patel et al., 2018; Walsh, Mahony, et al., 2014; Yi Zhang et al., 2019).

The dietary assessment tool used by Harreiter, Simmons, et al. (2019) introduced a potential risk of compliance bias; although there was frequent participant contact with a personal lifestyle coach as well as telephone contact, dietary assessments were self-reported according to a short (12-item) questionnaire and not analysed for nutritional intakes. The analysis was also not appropriate to compare adiposity outcomes due to low subject number. The UPBEAT RCT was considered to be low risk for compliance bias, however, it should be noted that the involvement of any dietitian in the control group by standard antenatal referral pathways was not reported although suggested to be minimal (N. Patel et al., 2017; N. Patel et al., 2018). Four studies which reported non-significant differences between groups for the intended dietary change at the end of the intervention received an overall “high” risk for other bias (Garmendia et al., 2021; Mijatovic et al., 2020; Rae et al., 2000; Rhodes et al., 2010). Although reporting no differences between intervention groups, Yi Zhang et al. (2019) indicated a net effect of both study arms on dietary GI.

3.5 Discussion

3.5.1 Principal findings

This review aimed to systematically examine the effect of maternal diet on foetal hyperinsulinemia measured at birth. Due to limited data assessing cord blood insulin or c-peptide (to indicate foetal hyperinsulinaemia), we also included neonatal adiposity as a surrogate marker for *in utero* hyperinsulinaemia. To our knowledge, this is the only review published in the last five years to summarise experimental evidence on the impact of maternal diet on foetal insulin metabolism and neonatal (up until six months of age) adiposity.

The main results from the included studies do not show any effect of an intervention on neonatal cord blood insulin, c-peptide, or glucose. Among the studies that measured neonatal adiposity, the Low GL diet from the UPBEAT study showed a significant reduction in adiposity as compared to standard care (subscapular SFT -0.38 mm, 95% CI -0.7 to -0.06, p = 0.02; subscapular SFT z-score -0.26, 95% CI -0.49 to -0.02, p = 0.03) (N. Patel et al., 2017). Compared to the usual antenatal care arm, estimated neonatal adiposity was also significantly lower among neonates born to participants of the DALI study who received life coach-delivered behaviour change advice on healthy eating and physical activity to limit GWG below 5 kg (Sum of SFT−1.8 mm; 95% CI −3.5 to −0.2; p = 0.03; FM −63 g; 95% CI −124 to −2; p = 0.04; FM% −1.2%; 95% CI −2.4% to −0.04%; p = 0.04) (van Poppel et al., 2019). There was a trend toward improved neonatal adiposity outcomes in the ROLO study (low GI intervention) and DASH diet study (Donnelly, Walsh, et al., 2015; van Horn et al., 2018).

From the studies which showed no effect of the intended dietary intervention on the outcomes examined in this review, it was noteworthy that the majority of these did not achieve all aspects of the expected dietary change (Mijatovic et al., 2020; Rae et al., 2000; Rhodes et al., 2010; Yi Zhang et al., 2019), or did not report follow up dietary assessment information (Garmendia et al., 2021) (Table 12). Further, two studies were pilot studies with small participant group numbers, suggesting inadequate statistical power to detect differences between groups in neonatal adiposity (Kizirian et al., 2016; Mijatovic et al., 2020). Data included from the DALI trial was a secondary analysis, which authors reported was inadequately powered to detect differences in neonatal outcomes (Harreiter, Desoye, et al., 2019). It should be noted that none of the included studies were adequately powered to examine neonatal cord blood or adiposity outcomes as the primary outcome.

Low GI dietary interventions are well-recognised as a feasible and effective strategy in the medical nutritional management of GDM (S. Han et al., 2017). The most recent meta-analysis

and systematic review of low GI diets provided to women with GDM clearly demonstrated that these diets improve glycaemic control (J. Xu & Ye, 2020), which is key for reducing the risk of maternal and neonatal complications (American Diabetes Association, 2020). Consistent with findings in our current review, the benefits of a low GI diet appear to exist wider than GDM pregnancies. In a meta-analysis by R. Zhang et al. (2018) authors concluded low GI diets provided during healthy pregnancies and to those with GDM were associated with a reduced incidence of infants born large-for-gestational age, as well as improved maternal fasting and two-hour postprandial glucose levels.

A trend toward reduced adiposity was also observed in the UPBEAT trial during which women with obesity (BMI ≥ 30 kg/m^2) were provided with a low GL intervention. Among participants where over a quarter of the women developed GDM, the intervention was associated with reduced neonatal subscapular SFT (N. Patel et al., 2017). Similarly, the ROLO study showed a trend toward lower neonatal SFTs at delivery (Donnelly, Walsh, et al., 2015). Participants were women with a previous macrosomia pregnancy, but only two percent of the women developed GDM. It is plausible that low GL dietary strategies could improve glycaemic control in women with pre-existing insulin resistance, reducing the risk of foetal overnutrition. The greater incidence of GDM among participants from the UPBEAT trial may explain significantly better outcomes among the participants who received this specific low GL intervention. This could be interpreted in two ways; women with greater baseline insulin resistance at the beginning of pregnancy have larger capacity to improve metabolic markers following lifestyle changes. Secondly, interventions provided through usual GDM care may have an independent treatment effect on foetal development thereby being additive to low GL dietary advice. Interventions for women with GDM including glucose monitoring, pharmaceutical interventions (oral hypoglycaemics or insulin), and increased obstetric monitoring all aim to reduce the risk of foetal hyperinsulinemia and related obstetric complications (American Diabetes Association, 2020).

A trend towards a lower neonatal body fat percent among women receiving a DASH dietary intervention is consistent with results from the recent systematic review and meta-analysis (S. Li et al., 2020). Among six studies providing a DASH dietary intervention to pregnant women, the DASH diet was associated with a decreased risk of preeclampsia, macrosomia, large-for-gestational age infants, and overall lower ponderal index. Although the DASH diet was found to have a significant lowering effect on maternal fasting plasma glucose, the maternal homeostasis model assessment of insulin resistance was unaffected. Comparisons were not adjusted for maternal energy intake or GWG over the course of the interventions, therefore limiting interpretation of whether the diets were confounded by these factors. Consumption of a DASH diet may improve maternal glucose levels by having a lower glycaemic impact.

Improvements in maternal glycaemia may prevent nutrient excess, foetal hyperinsulinaemia, and resulting excess growth (Ornoy, 2011). This supports findings from our systematic review to suggest that adherence to a glycaemic DASH diet in women with an elevated pre-pregnancy BMI could reduce neonatal adipose development that is associated with the risk of macrosomia and large-for-gestational age babies.

Despite limited associations between any one type of intervention and neonatal outcomes, our findings point to an important role of dietary education. There were associations between interventions and lower estimated neonatal fat mass percent and SFT in studies that compared a personalised lifestyle intervention to standard antenatal care (no specific nutrition or lifestyle advice) (Donnelly, Walsh, et al., 2015; N. Patel et al., 2017; van Horn et al., 2018). Common elements from these interventions included dietary personalisation with a dietitian or 'health trainer', written education resources, and multiple points of contact to reinforce the provided advice and promote adherence. However, in studies that provided the comparison group with a similar level of support, e.g. personalised meal plan, written resources, compliance checks (Kizirian et al., 2016; Mijatovic et al., 2020; Yi Zhang et al., 2019), no significant effect of a low GI, low GL, or moderately carbohydrate restricted diet was observed. What this suggests is that personalised dietary advice, including follow up support and goal setting throughout gestation, may be just as, if not more, important than the specific dietary intervention alone. From the included studies, the interventions did not differ significantly in terms of practical dietary changes recommended (i.e. reduce sugar, increase fruit and vegetable intake, unrefined carbohydrate choices), making it difficult to distinguish any specific effect of one dietary change. These findings also highlight that general healthy eating education may be overlooked during usual antenatal care, particularly for women who carry risk factors for insulin resistance but are not diagnosed with GDM. Individualised advice allows women to understand their risk factors, respond to feedback throughout pregnancy, set measurable goals, and make realistic behavioural adjustments. Communicating health advice within the context of an individual's lifestyle is key to supporting healthy behaviours which could impact maternal, infant, and life-long family metabolic health (Procter & Campbell, 2014).

The impact of broader lifestyle changes ought to be considered for any dietary intervention; nutrition behaviours exist in the context of a person's wider lifestyle choices including physical activity, stress, sleep patterns, and food behaviours. While this review specifically aimed to examine dietary interventions, many of the interventions also included lifestyle changes such as physical activity and stress management (Ferrara et al., 2020; Harreiter, Simmons, et al., 2019; N. Patel et al., 2017; N. Patel et al., 2018; van Horn et al., 2018). Physical activity could explain the reduced SFTs observed following the complex behavioural intervention on the UPBEAT trail

(N. Patel et al., 2017), healthy eating and physical activity intervention in the DALI study (van Poppel et al., 2019), and trend toward lower infant adiposity in the MOM FIT study (van Horn et al., 2018). Physical activity is known to have many protective effects on maternal and offspring health by promoting appropriate weight gain in pregnancy and enhancing insulin sensitivity (Cremona et al., 2018; Ferrari & Joisten, 2021). In the World Health Organization 2020 guidelines on physical activity and sedentary behaviour, pregnant and postpartum women are provided a "strong recommendation" to limit the amount of time spent being sedentary to reduce the risk of preeclampsia, gestational hypertension, GDM, excessive GWG, delivery complications, and postpartum depression (Bull et al., 2020).

An important detail in reviewing the efficacy of the included interventions was the effect on GWG, albeit this was not a primary outcome of the review. Among the included studies, five trials described significant differences in maternal GWG (less GWG in the intervention versus control groups) (Ferrara et al., 2020; Harreiter, Simmons, et al., 2019; van Horn et al., 2018; van Poppel et al., 2019; Y. Zhang et al., 2019), this included the UPBEAT trial where significant reductions in neonatal adiposity (subscapular SFT) were observed (N. Patel et al., 2017; Poston et al., 2015). Maternal obesity and excessive GWG are associated with increased neonatal fat mass (Goldstein et al., 2017; Sewell, Huston-Presley, Super, & Catalano, 2006; A. P. Starling et al., 2015). Therefore, reduced neonatal adiposity could be an expected effect of any intervention which successfully supports appropriate maternal weight gain among women with obesity (Poston et al., 2015). A lack of an effect of reduced GWG on neonatal adiposity could be due to the studies not being appropriately powered to observe changes in neonatal adiposity, as it was not the primary outcome. Moreover, the lack of an effect on GWG in the remaining studies could also explain limited associations between interventions and neonatal adiposity outcomes.

A further explanation for the lack of associations between any of the included dietary interventions and cord blood metabolites (c-peptide, insulin, glucose) may be due to challenges associated with the metabolic analyses used. Although umbilical cord blood is considered one of the most useful samples in neonates instead of early peripheral blood examination (N. Wang, Eerdun, Dong, Hao, & Li, 2021), insulin measurement has limitations since degradation increases in the presence of slight haemolysis (O'Rahilly, Burnett, Smith, Darley, & Turner, 1987). While c-peptide is a more stable and useful marker of foetal metabolic exposures (I. L. Lee et al., 2020), no difference in c-peptide between intervention and control groups was observed in any of the five studies with this outcome measure. This suggests that these biomarkers may not be suitable to determine the specific metabolic impact of maternal dietary modifications in women without gestational hyperglycaemia.

Previous research suggests adipokines may be a more sensitive marker of placental-foetal nutrient transfer. In the HAPO study, lower cord blood levels of adiponectin and c-reactive protein were associated with a higher neonatal adiposity (Lowe et al., 2010). Adiponectin has been negatively associated with birth weight and estimated percentage fat mass (Lowe et al., 2010). Leptin has also been linked to adipose development and insulin metabolism (Telschow et al., 2019), which was identified in a secondary analysis from the ROLO study, as being associated with greater neonatal adiposity, while foetal c-peptide was not significant after adjustments (Donnelly, Lindsay, et al., 2015).

3.5.2 Strengths and limitations

A strength of this review is the inclusion of studies from diverse populations of pregnant women from varying cultural backgrounds. Studies reviewed included pregnant women with varying risk factors including GDM and obesity. The potential for replication bias introduced from seven individual references from three study populations (UPBEAT, ROLO, and DALI) is a limitation. Heterogeneity among the sampled participants may also limit the practical application of diet advice to specific populations. It is also possible that participant heterogeneity may have confounded a specific effect of individual dietary changes. Among the included studies, maternal insulin resistance was not exclusively examined in the recruitment criteria. This is important because maternal insulin resistance before pregnancy is a fundamental determinant of placental-foetal metabolism, nutrition status, and subsequent foetal development (Barbour & Hernandez, 2018a; Hernandez et al., 2020). Variability in the prevalence of GDM diagnosis among the participants in the included studies is a limitation. GDM diagnosis and treatment has the potential to influence lifestyle behaviours through additional monitoring and interventions. A higher prevalence of GDM in the included studies where a significant effect of the intervention on neonatal adiposity was observed limits our interpretation. Also noteworthy is the possibility for confounding obstetric variables such as time in labour, placental attachment, cord blood clamping to influence cord blood analysis.

3.5.3 Recommendations for future research

Future research investigating the impact of lifestyle interventions should consider a multi-modal approach to address maternal insulin resistance syndrome as it impacts placental-foetal metabolism. This means dietary factors must be considered alongside other environmental determinants such as physical activity, gestational weight gain, sleep quality, smoking, and maternal stress (Gaillard, Wright, & Jaddoe, 2019). To reduce heterogeneity from lifestyle factors within studies, RCTs may consider a multi-level intervention design to provide women relevant, personalised interventions based on pre-pregnancy behaviours.

Dietary intervention studies require specific dietary prescriptions that are measurable and repeatable in clinical practice. This means that research examining maternal dietary intake requires thorough, valid dietary assessments, such as three-day food diaries or the use of diet tracking apps throughout gestation with attention to macronutrient intake, types of carbohydrates, and micronutrient adequacy. We recommend that future studies examining neonatal metabolic outcomes should be assessed alongside first trimester maternal insulin resistance to better understand early gestation developmental impacts among mothers with varying patterns of gestational hyperinsulinaemia (North, Zinn, & Crofts, 2021). Consistent methodology for examining neonatal metabolites at birth must be considered. This includes accounting for technical variables such as neonatal cord clamping and time in labour.

3.6 Conclusions

This systematic review indicates gaps in experimental evidence to demonstrate a specific relationship between dietary interventions during pregnancy to prevent subclinical foetal hyperinsulinemia, measured by cord-blood metabolites and neonatal adiposity. Limited evidence from RCTs suggests dietary strategies that are known to improve glycaemic control in GDM pregnancies may have a protective effect against excess adiposity by a similar mechanism. Additionally, findings from RCTs suggest that antenatal dietary counselling appears to have a protective effect and should be offered to all pregnant women with overweight or obesity. The reviewed studies identified challenges with dietary research where an impact on sub-clinical metabolic changes may be confounded by lifestyle factors and participant adherence issues. Future large dietary RCTs should consider a multi-modal design to explore the specific effect of dietary modification, particularly in the context of environmental risk factors for maternal insulin resistance such as physical activity, stress, and sleep. Further research is needed to confirm if specific nutrient modifications, independent of energy balance, in non-GDM pregnancies reduce the risk of foetal hyperinsulinemia and foetal overgrowth in women with underlying insulin resistance.

Chapter 4. Hyperinsulinaemia during pregnancy across varying degrees of glucose tolerance: An examination of the Kraft database.

Preface

A main component of this research was to investigate how examining insulin patterns early in pregnancy could be used to identify women with pre-existing insulin resistance, which when augmented by normal pregnancy changes may lead to adverse outcomes. As it was shown in Chapter 2, there is rationale to suggest that changes in insulin metabolism are a hallmark of metabolic dysfunction in pregnancy. Considering this literature as a dietitian, I had pondered on how defining a woman's insulin response pattern could alter my dietary advice in clinical practice – just as self-measured blood glucose levels inform personalised dietary guidance for women with GDM. Since there have been mixed results from modified carbohydrate interventions (shown in Chapters 2 and 3), perhaps a woman's insulin response could influence the protective nature of any one type of diet. Before embarking on this research journey, I became familiar with the work of my supervisors, Associate Professor Zinn and Dr Crofts. Previous work by Crofts et al. exploring hyperinsulinaemia as it relates to chronic metabolic disease, especially type 2 diabetes was discussed in Chapter 2. What I found most compelling about previous research using the Kraft patterns was the hypothesis from Crofts et al. and other research groups that hyperinsulinaemia could be used as an early indicator for the development of chronic metabolic disease. This led to one of my research questions: could a similar line of thought be applied to predict the development of GDM and other perinatal complications typically observed more frequently among women with insulin resistance before pregnancy (e.g. large-for-gestational age infants)? An unanalysed data sub-set of presumed pregnant women from the Kraft dataset previously examined by Crofts et al. (2016) presented an opportunity to explore insulin response patterns among a pregnant demographic.

It must be noted that analysing these data came with many limitations. First, assays were collected over a time period (mid-1970s to early 1990s) when methods for insulin measurement were only first being developed. Early versions of the RIA assays had problems with specificity for measuring insulin due to cross-reactivity with proinsulin. To date, insulin measurement techniques have not been standardised, which limits comparisons between Kraft's data and other datasets. However, one important thing to note with Kraft's methodology is that patterns are characterised based on the timing of the peak insulin response (i.e. 30-60 minutes for a

"normal" or "borderline" insulin response verses 2 or 3 hours for pattern III hyperinsulinaemia) as well as thresholds of fasting and post glucose load plasma insulin. A further limitation was a significant lack of demographic and technical information on the participants and how analyses were conducted. Some of these gaps were filled from further information in an unpublished manuscript from Kraft and Sie (1991) which was addressed to the New England Journal of Medicine, January 28, 1991. This archived manuscript was sent to us from Kraft's family.

The study presented in this chapter is a modified from a manuscript that was published in *The Journal of Obstetrics and Gynaecology Research* in 2021 (doi:10.1111/jog.14731).

4.1 Abstract

Hyperinsulinaemia is a known underlying driver of metabolic disease, however, its role in pregnancy complications is less understood due to insulin measurement not being a part of standard clinical assessments. This study aimed to characterise hyperinsulinaemia in pregnancy by glucose tolerance status using Kraft methodology. We analysed historical data from 926 pregnant women who underwent OGTTs (3-hour assays with 100-gram glucose), which included insulin measurement. Gestational age, obstetric, and medical information of the participants were unavailable. Subjects were grouped by GDM diagnosis status ("Normal", "Borderline", "GDM") using the 2010 American Diabetes Association thresholds and insulin responses were compared between groups. "GDM" was diagnosed in 20.1% of the subjects and 13.2% were grouped as "Borderline". The prevalence of hyperinsulinaemia using the Kraft algorithm was 33% for Kraft IIB and 42% for Kraft III. Compared to normal glucose-tolerant mothers, individuals from the "Borderline" group had an exacerbated insulin response, although not to the same magnitude as those with "GDM". Dynamic OGTT insulin measurement during pregnancy may provide a meaningful assessment of metabolic risk among women who would otherwise not be diagnosed with GDM.

4.2 Introduction

Hyperinsulinaemia may be the most wide-spread, yet under-recognised, metabolic condition contributing to the development of chronic inflammatory diseases, including atherosclerosis and type 2 diabetes (Crofts et al., 2015). Previous research indicates that a substantial proportion of the population with normal, non-diabetic, glucose tolerance may be considered hyperinsulinaemic (Crofts et al., 2016); authors suggest that public health initiatives for the early detection of hyperinsulinaemia may be pivotal to reduce the global burden of metabolic disease (Crofts et al., 2019).

Increased insulin resistance and secretion during pregnancy is a normal and expected physiological state (Butte, 2000). During a normal pregnancy, hormonal shifts affecting insulin sensitivity and secretion drive changes in carbohydrate and lipid metabolism to facilitate nutrient accretion and transfer to the growing foetus (Butte, 2000). Complications arise in mothers with pre-existing insulin resistance when pregnancy-related changes are augmented (Catalano & Shankar, 2017; Grieger et al., 2018). These changes change result in a metabolic environment characterised by nutrient excess and low-grade inflammation, which is associated with an increased risk of many maternal disorders including GDM, hypertensive disorders, non-alcoholic fatty liver disease, sleep-disordered breathing, cardiomyopathy, birthing complications, and lactation failure (Hernandez et al., 2020). Through multiple pathways, is may be postulated this exaggerated hyperinsulinaemia and insulin resistance of pregnancy also has wide-spread implications on foetal development being linked to growth abnormalities, neurological disorders, and endothelial dysfunction in the neonate (Hufnagel et al., 2022; Sobrevia et al., 2016).

There is a growing body of evidence to show that hyperinsulinaemia in early gestation precedes gestational metabolic complications such as GDM (Bito et al., 2005; Lapolla et al., 2008), which is usually first diagnosed in the second or third trimester (from 23 weeks' gestation) (American Diabetes Association, 2020). This suggests similarities between rapid pathological metabolic changes that can happen over nine months' gestation, and the progression of hyperinsulinaemia in non-pregnant adults which develops over decades (Crofts et al., 2015).

Outside of pregnancy, hyperinsulinemia is recognised to directly, or indirectly, affect nearly every biological system of the human body, which, over many years, contributes to the pathogenesis of various chronic disease states (Crofts et al., 2015). However, its role in pregnancy-related complications such as blood pressure complications and foetal growth abnormalities is unknown. Moreover, insulin is not included in routine assessment and there are no standardised diagnostics. Identifying hyperinsulinaemia in the first trimester, as opposed to diagnosing GDM or other metabolic abnormalities mid-to-late gestation, could mean that mothers are equipped earlier with first-line lifestyle modifications and clinical support to mitigate potential risks.

Defining hyperinsulinaemia in pregnancy is a challenge. First, in the context of pregnancy, an important detail is this: hyperinsulinaemia is an expected, adaptive, physiological effect (Butte, 2000). However, recognising that women with insulin resistance symptoms, such as obesity, also likely display compensatory hyperinsulinemia in the non-pregnant state, this already elevated insulin response must be further exaggerated for pregnancy. The greatest challenge for defining

hyperinsulinaemia in pregnancy is that there is no clear distinction between a normal insulin response pattern of pregnancy and one that might be considered detrimental, resulting in negative maternal and offspring effects. These challenges also exist around the diagnostics for GDM, where a consensus around clear cut-off points for maternal glucose tolerance is also lacking (Hod, Kapur, & McIntyre, 2019).

Due to a limited of knowledge on the significance of exaggerated insulin response patterns in pregnancy, particularly for those unaffected by GDM, further work is needed to establish pregnancy-specific criteria. Advanced understanding of how hyperinsulinaemia presents among pregnant women with varying degrees of glucose tolerance may help to identify those at risk of late-gestation complications including GDM and other metabolic abnormalities affecting foetal development. This study aims to characterise insulin response patterns according to the Kraft algorithm for defining hyperinsulinaemia and the American Diabetes Association 2010 criteria for GDM among a retrospective cohort of approximately 1,000 pregnant women.

4.3 Methods

4.3.1 Subjects

Subjects included 926 healthy women of child-bearing age referred for an OGTT as part of routine medical care at St Joseph's Hospital, Chicago. IL. USA. This group is a subset of the complete Kraft dataset which includes the results from approximately 15,000 OGTTs with insulin assays, collected between approximately 1972 and 1992. The patient population consisted of approximately two-thirds Caucasian with the remainder being Asian, Black, and Hispanic. Patients were physician referred for diabetes testing, however specific information on the varying reasons for referred testing was not available. Whether women underwent a screening non-fasting glucose challenge test prior being referred to Kraft is unknown. Demographic information included weight, height, and age. Further demographic and medical information, including gestational age and obstetric history of pregnant participants, were unavailable. Data collected included plasma glucose, plasma insulin, age, and sex. The group of women were presumed pregnant at the time of testing (raw data file and column markers indicating pregnancy); however, information on the gestational age, pre-pregnancy weight, or parity of the subjects was not described. Subjects included in this study were previously excluded from a previous Kraft data subset analysis and characteristics of the wider population have been reported previously (Crofts et al., 2016).

Subjects included in the current analysis were over the age of 20 and under the age of 45 years to reduce the effect of variation in insulin resistance and insulin responses in adolescent

pregnancies and women with advanced maternal age (Hackmon et al., 2007; Sprague, Gandica, & Kelsey, 2020). Although unconfirmed for these data, it is also presumed that subjects under 20 years may have received a smaller glucose dose for the OGTT; a standard practice at the time.

4.3.2 Study protocol

The complete study protocol for this work has previously been described in detail (Crofts et al., 2016). In brief, subjects were fasted overnight for 10-16 hours. Subjects first provided a fasting venous blood sample, before ingesting 100 grams of a glucose solution (Glucola, Miles/Ames, Elkhardt, IN.). Up to six subsequent venous samples were collected at 30 minutes, 60 minutes, and each successive hour for between three and five hours. The duration of sampling was determined by the patients' physician. Data from five time points over three-hours of testing were included in the current analysis. Plasma blood samples were analysed for glucose concentration using an Autoanalyzer ferricyanide method for the first 26 examinations (1972-1973). These examinations were adjusted downward by 10 mg/dL to account for the systematic error, according to the methods of Passey, Gillum, Fuller, Urry, and Giles (1977). Plasma glucose oxidase methodology was applied for the majority of the measurements. Precision was not reported for either glucose assays; however, precisions have been reported as CV < 5% for ferricyanide and CV < 3% for plasma glucose oxidase methods (Passey et al., 1977; Purcell, Behenna, & Walsh, 1979). Plasma insulin was determined by the Phadebus Insulin Test (Pharmacia insulin RIA 100, Pharmacia Diagnostics AB, Uppsala, Sweden). Precision was reported as SD = 5 lU/mL up to 150 lUmL (Kraft, 1975). Data re-analysis was granted ethical approval by Auckland University of Technology Ethics Committee (New Zealand) on 23 October 2019 (approval reference: 19/404).

4.3.3 Analysis

Subject classification

Glucose tolerance

Glucose tolerance was defined using the 2010 American Diabetes Association criteria for diagnosing GDM (American Diabetes Association, 2010). These criteria were selected as they are the most modern criteria applicable to the 100-gram glucose bolus OGTT used in this study protocol. According to these criteria, GDM is diagnosed in those with two or more of the venous plasma glucose levels greater or equal to the given thresholds for each timepoint (fasting glucose ≥ 5.3 mmol/L, 60 minutes ≥ 10.0 mmol/L, 120 minutes ≥ 8.6 mmol/L, 180 minutes ≥ 7.8 mmol/L). We defined two additional groups: the "Borderline" group included subjects with only one value

above the American Diabetes Association thresholds and the “Normal” group included subjects with all glucose values below the American Diabetes Association thresholds.

Insulin response patterns

Insulin response patterns were was defined using the previously established Kraft pattern criteria (Table 13) (Crofts et al., 2016). The Kraft insulin patterns apply the same principles of glucose homeostasis, where insulin returns to near fasting levels in healthy people after two hours. Kraft patterns were only determined in subjects from which a complete set of fasting, 30-, 60-, 120-, and 180-minute insulin values were obtained. Previous work by Crofts et al. (2016). defined normal insulin metabolism as Kraft I (fasting insulin ≤ 30 μU/mL, 30-min or 1-h peak, and 2-h + 3-h sum < 60 μU/mL), Kraft IIA as borderline hyperinsulinaemia (fasting insulin ≤ 50 μU/mL, 30-min or 1-h peak, 2-h + 3-h sum ≥ 60 μU/mL and < 100 μU/mL, or fasting insulin 31–50 μU/mL, 30-min or 1-h peak, and 2-h + 3-h sum < 60 μU/mL), and hyperinsulinaemia as Kraft IIB (fasting insulin ≤ 50 μU/mL, 30-min or 1-h peak, and 2-h + 3-h sum ≥ 100 μU/mL), Kraft III (fasting insulin ≤ 50 μU/mL, delayed peak at 2- or 3-h), and Kraft IV (fasting insulin > 50 μU/mL). Kraft pattern V is hypoinsulinaeima (all values ≤ 30 μU/mL), with similar features expected in individuals with type 1 diabetes.

Table 13. Kraft pattern algorithm for defining hyperinsulinaemia in non-pregnant adults.

Kraft Pattern	Description
Pattern I (normal non-pregnant insulin)	Fasting insulin ≤ 30 µU/mL 30-min or 1-h peak 2-h + 3-h sum < 60 µU/mL
Pattern IIA (borderline)	Fasting insulin ≤ 50 µU/mL 30-min or 1-h peak 2-h + 3-h sum ≥ 60 µU/mL, < 100 µU/mL or Fasting insulin 31–50 µU/mL 30-min or 1-h peak 2-h + 3-h sum < 60 µU/mL
Pattern IIB (hyperinsulinaemia)	Fasting insulin ≤ 50 µU/mL 30-min or 1-h peak 2-h + 3-h sum ≥ 100 µU/mL
Pattern III (hyperinsulinaemia)	Fasting insulin ≤ 50 µU/mL Delayed peak (2 or 3 h)
Pattern IV (hyperinsulinaemia)	Fasting insulin > 50 µU/mL
Pattern V (hypoinsulinaemia)	All values ≤ 30 µU/mL

Kraft patters are derived from plasma insulin samples taken fasting, and at 30, 60, 120, and 180 minutes following an oral glucose tolerance test with a 100 g glucose bolus. Adapted from Crofts et al. (2016).

Calculations and statistical analysis

Insulin response levels at each of the five timepoints from the three-hour OGTT (fasting, 30-, 60-, 120-, and 180-minutes) were compared across each GDM diagnostic group. Subject demographics and Kraft insulin response patterns (Kraft I, IIA, IIB, III, IV, and V) were also calculated and compared across the three groups. One-way analysis of variance (ANOVA) was used to determine mean difference in demographic variables between groups for normally distributed nominal variables and Pearson's chi-square was applied to categorical variables. The difference in insulin between the three groups for all five timepoints from the OGTT was examined using a repeated measures ANOVA. Differences in insulin levels were compared across time and between GDM groups. The Greenhouse-Geisser correction was applied to within-subject effects in cases where Mauchly's test indicated violation of the sphericity assumption. Simple effects were calculated when a significant interaction between the GDM diagnostic groups and time was observed. To examine mean differences in insulin and glucose between GDM groups, pairwise comparisons (using the Bonferroni adjustment) were performed on the estimated marginal means and effect size (ES) expressed as Cohen's d. A small effect was defined as > 0.2, a medium effect as > 0.5, and large effect as > 0.8. ES was expressed as partial

eta squared for normal variables, otherwise epsilon squared for non-normal variables, and Cramer's V for categorical variables. Statistical significance was set at a two-sided *p* value 0.05 throughout. Statistical analysis was performed using Microsoft Excel 2010 or IBM SPSS Statistics 25.

4.4 Results

4.4.1 Subject characteristics

A total of 926 subjects from the existing Kraft dataset of approximately 15,000 were included in this study (Table 14). Demographic information on individuals in the wider dataset have been reported elsewhere (Crofts et al., 2016). Subjects had a mean age of 28.0 years (SD 5.0) and a mean BMI of 27.8 kg/m^2. One fifth (n = 186, 20.1%) of the subjects had two or more abnormal glucose values, sufficient to diagnose GDM according to the American Diabetes Association diagnostic criteria (American Diabetes Association, 2010). Using the previously described glucose tolerance criteria, 123 (13.3%) were characterised as "Borderline" (one glucose value meets or exceeds the American Diabetes Association thresholds), and nearly two-thirds (n = 616, 66.6%) of the subjects were placed in the "Normal" group. The repeated measures ANOVA confirmed differences between all groups for age ($F(2, 922) = 21.7239$, $p < 0.001$), height ($F(2,913) = 3.47$, $p = 0.032$), weight ($F(2, 921) = 6.09$, $p = 0.002$), and BMI ($F(2,912) = 12.78$, $p < 0.001$). Post-hoc tests showed women with GDM and those classified as "Borderline" were significantly older than those with normal glucose tolerance (mean age 30 ± 6 yr vs. 28 ± 5 yr vs. 27 ± 5 yr, $p < 0.001$). When compared to the "Normal" group, those with GDM had a significantly higher mean weight (75.6 ± 20.6 kg vs. 70.4 ± 16.6 kg, $p = 0.023$) and BMI (29.9 ± 7.9 kg/m^2 vs. 27.1 ± 6.1 kg/m^2, $p < 0.001$).

Table 14. Subject characteristics grouped by GDM diagnosis status.

	Total	Normal	Borderline	GDM	p-value	Effect size
n	926	616 (66.5)	122 (13.2)	186 (20.1)		
Age (years)	28 ± 5	27 ± 5	28 ± 5	30 ± 6	<0.001[a]	0.045
Height (m)	1.61 ± 0.11	1.61 ± 0.10	1.61 ± 0.11	1.59 ± 0.12	0.032[a]	0.008
Weight (kg)	71.6 ± 18.2	70.4 ± 16.6	72.0 ± 19.8	75.6 ± 20.7	0.002[a]	0.013
BMI (kg/m^2)	27.8 ± 6.9	27.1 ± 6.11	28.0 ± 7.88	29.9 ± 7.93	<0.001[a]	0.026
Kraft I	63 (6.8)	58 (9.4)	4 (3.3)	1 (0.5)	<0.001[c]	0.291
Kraft IIA	127 (13.7)	118 (19.2)	9 (7.3)	0 (0.0)		
Kraft IIB	305 (33.0)	226 (36.7)	47 (38.2)	32 (17.2)		
Kraft III	390 (42.2)	191 (31.0)	57 (47.3)	142 (76.3)		
Kraft IV	26 (2.8)	11 (1.8)	5 (4.1)	10 (5.4)		
Kraft V	14 (1.5)	12 (1.9)	1 (0.8)	1 (0.5)		

Variables reported as mean ± SD, otherwise n (%).
GDM diagnosis groups: "Normal" includes subjects with no abnormal glucose values from the oral glucose tolerance test using thresholds from the American Diabetes Association (American Diabetes Association, 2010); "Borderline" includes subjects with one abnormal glucose value; "GDM" includes subjects with two or more abnormal glucose values.
[a] Kraft pattern categories defined by the Kraft algorithm for defined hyperinsulinaemia (Crofts et al., 2016).
[b] ANOVA between-group comparison adjusted for age and BMI, effect size reported as partial eta-squared.
[c] Pearson χ^2, effect size reported as Crammer's V.
BMI: Body mass index.

4.4.2 Hyperinsulinaemia and glucose tolerance status

Kraft pattern prevalence

The prevalence of each Kraft insulin response pattern across the three GDM diagnostic groups is shown in Table 14. There were differences between the three groups for the prevalence of each of the six Kraft patterns ($\chi^2(8) = 159.0$, $p < 0.001$). The majority of the subjects were characterised as having either a Kraft pattern IIB or III insulin response (Kraft IIB: 33.0%, n = 305; Kraft III: 42.2%, n = 390). Kraft pattern IIB was found in over a third of the "Normal" group (n = 226, 36.7%) as well as the "Borderline" group (n = 47, 38.2%). A Kraft pattern III was most common among subjects with hyperglycaemia; three quarters (n= 142, 76.3%) of women with GDM were found to have a Kraft pattern III insulin response, while the prevalence was nearly half among those from the "Borderline" group (n = 57, 47.3%). Kraft pattern I was observed in less than a tenth of the subjects (n = 63, 6.8%), the majority of whom had normal glucose tolerance (n = 58). Kraft pattern IV and V were the least common, representing 1.5% in total.

Glucose and insulin response comparison between groups

We examined the difference in glucose and insulin responses between the GDM diagnostic groups using a repeated measures ANOVA. The analysis confirmed differences between individual timepoints across the three-hour OGTT, differences between GDM groups, and an interaction between time and group for glucose (time main effects: $F(4, 3564) = 36.66$, $p < 0.001$; between subject effects GDM group main effects $F(2, 908) = 570.796$, $p < 0.001$; interaction main effects: $F(8, 3564) = 107.75$, $p < 0.001$) and insulin (time main effects: $F(4, 3580) = 19.94$, $p < 0.001$ sig; GDM group main effects: $F(2, 895) = 56.03$, $p < 0.001$; interaction main effects: $F(8, 3580) = 53.15$, $p<0.001$).. Due to the significant interaction of time and group on insulin, the simple effect sizes are shown in Appendix C, Supplementary Table 3.

Pairwise comparison for insulin at each timepoint

The mean difference between the three GDM groups for insulin and glucose levels at each timepoint across the three-hour OGTT was assessed using pairwise comparisons (Figure 10). Significant differences in estimated marginal mean insulin levels for "Normal" versus "Borderline" were found at time 0 min ($p = 0.042$, Cohen's d = 0.245), 60 min ($p < 0.001$, Cohen's d = 0.44), 120 min ($p < 0.001$, Cohen's d = 0.59), and 180 min ($p = 0.003$, Cohen's d = 0.33). For "Normal" versus "GDM", estimated marginal mean insulin levels were significantly lower at time 0 min ($p < 0.001$, Cohen's d = 0.44), 60 min ($p < 0.001$, Cohen's D = 0.52), 120 min ($p < 0.001$, Cohen's d = 1.20), and 180 min ($p < 0.001$, Cohen's D = 1.08). Estimated marginal means were also significantly lower in the "Borderline" versus "GDM" group at time 0 min ($p = 0.02$, Cohen's

d = 0.20), 120 min (p < 0.001, Cohen's d = 0.55), and 180 min (p < 0.001, Cohen's d = 0.73). Glucose levels were significantly different between the three GDM groups at all times points.

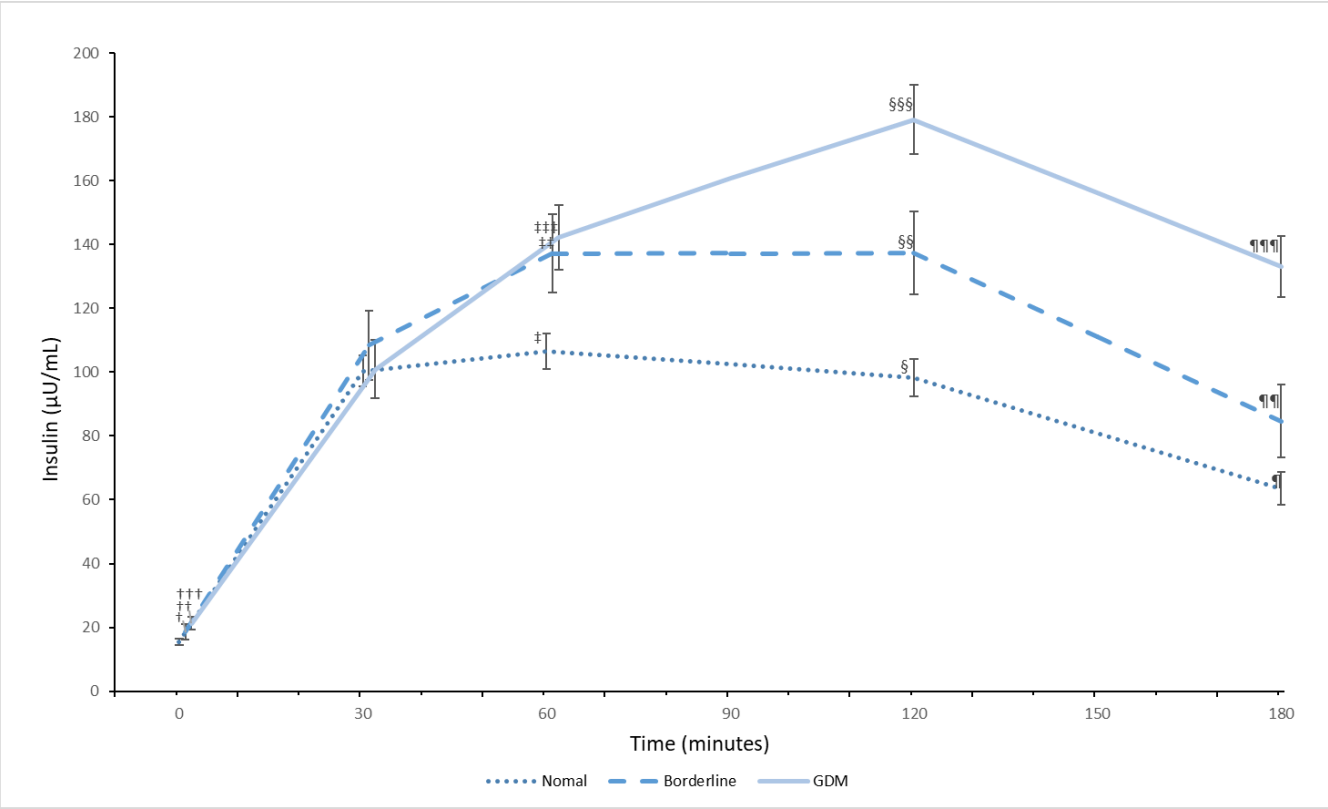


Figure 10. Estimated marginal means (95% CI) for insulin at 0, 30, 60, 120, and 180 minutes for each GDM diagnostic group.
0 minutes: † Normal vs GDM, p=0.42; †† Normal vs Borderline p<0.01; ††† Borderline vs GDM p=0.02.
30 minutes: No significant differences between all groups.
60 minutes: ‡ Normal vs GDM, p<0.001; ‡‡ Normal vs Borderline p < 0.001; ‡‡‡ Borderline vs GDM p<0.001.
120 minutes: § Normal vs GDM, p< 0.001; §§ Normal vs Borderline p<0.001; §§§ Borderline vs GDM p<0.001.
180 minutes: ¶ Normal vs GDM, p<0.001; ¶¶ Normal vs Borderline p=0.003; ¶¶¶ Borderline vs GDM p<0.001.
Individual datapoints at 0, 30, and 60 minutes are presented staggered by 1 unit across the x axis for visual clarity.

4.5 Discussion

This study examined the presence of hyperinsulinaemia in a large cohort of presumed pregnant women[2] attending a routine OGTT. Applying the American Diabetes Association diagnostic criteria for GDM (American Diabetes Association, 2010), one fifth of the subjects were diagnosed with GDM, while 14% had one abnormal glucose value (the "Borderline" group). The prevalence of GDM was considerably higher than expected compared to reported populated trends from the USA at the time (approximately 1.2 to 11.3% between 1980 to 1985) (Lavery et al., 2017). Due to lacking ethnicity, co-morbidity, and pregnancy information (parity and gestational age) from this cohort, no further assumptions can be made to explain the high prevalence of diagnosed GDM and thus, is a limitation of this study.

We identified hyperinsulinaemia (Kraft IIB or III) among three-quarters (75.1%) of the subjects. Kraft pattern I, recognised as a "normal" insulin response in non-pregnant adults, was identified in less than 10% of the subjects. Additionally, among the 616 subjects from the "Normal" group in this study, Kraft patterns IIB and III were represented in over two-thirds (68%). When compared to an earlier analysis of non-pregnant adults from the wider Kraft dataset which applied the same criteria for defining hyperinsulinaemia, Crofts et al. (2016) previously showed a significantly higher prevalence of Kraft I ("normal" insulin response) in subjects with normal glucose tolerance (24%), while only 19% were characterised as Kraft III (hyperinsulinaemia).

The higher prevalence of Kraft IIB and III, and lower prevalence of Kraft I is consistent with an expected physiological increase in insulin secretion among the pregnant subjects in this study. During a normal pregnancy, insulin sensitivity progressively decreases throughout gestation while the insulin secretory response increases. In response to the maternal "facilitated anabolism" pregnant women experience greater, and prolonged post-prandial hyperinsulinaemia and hyperglycaemia which becomes more pronounced across gestation (Freinkel, 1980). The very low prevalence of the Kraft I "normal" insulin response in our study suggests most subjects were beyond gestational week eight to fourteen. From the late first trimester, maternal insulin resistance and secretion is significantly altered alongside rising placental hormones including oestrogen, progesterone, prolactin, cortisol, human chorionic gonadotropin, human placental growth hormone, human placental lactogen, and leptin (Butte, 2000). Gestational age could not be confirmed among the subjects of this study, however, it is

[2] Pregnancy can only be presumed due to limited information associated with the dataset. This data sub-set from the Kraft dataset was labelled "PREG". The number of subjects and demographic information available is also consistent with an unpublished manuscript from Kraft and Sie (1991) where pregnant participants were described.

possible the limited cases with a “normal” Kraft pattern I response were in their first trimester of pregnancy, thus before anti-insulinogenic hormones have exerted their dramatic effect on maternal metabolism.

Our study showed that pregnant women with only one elevated glucose level following an OGTT (“Borderline” group) had significantly higher fasting and post-prandial insulin levels compared to those in the “Normal” group. This suggests a higher prevalence of hyperinsulinaemia among women with borderline or subclinical glucose intolerance whose pregnancies would otherwise not be diagnosed with GDM. It is plausible that this hyperinsulinaemia combined with “Borderline” glucose intolerance may contribute to an unfavourable *in utero* environment characterised by nutrient excess and inflammation (Barbour & Hernandez, 2018a). It has been suggested that an excess of maternal lipids can drive foetal overgrowth, leading to infants being born large-for-gestational age with a greater risk of delivery complications. The relationship between maternal insulin secretion and “Borderline” glucose intolerance could explain pivotal observations from the large multicentre HAPO cohort study (n = 25,505) that showed an increased risk of foetal overgrowth (birth weight above the 90th centile, OR ranged from 1.38 to 1.46), primary caesarean delivery (OR ranged from 1.08 to 1.11), elevated cord-blood c-peptide (OR ranged from 1.37 to 1.55), and neonatal hypoglycaemia (OR ranged from 1.08 to 1.13) in mothers with mild-to-moderately elevated glucose levels (HAPO Study Cooperative Research Group et al., 2008).

Kraft III hyperinsulinemia was most common among the subjects from our study in the “Borderline” (45.3%) and “GDM” (75.5%) groups, which was similar to previous findings among non-pregnant adults with type 2 diabetes (Crofts et al., 2016). Outside of pregnancy, a delayed insulin peak (60-min insulin peak higher than 30- and 60-min level post 75-gram glucose OGTT) characteristic of Kraft III has been associated with an increased risk of developing type 2 diabetes (Hayashi et al., 2013). Growing evidence now shows that this delayed-peak hyperinsulinaemia may also have vast consequences for pregnant mothers. Among Chinese mothers at 24-28 weeks gestation (n = 2,432), a delayed peak insulin response was associated with a greater risk of gestational complications including pre-eclampsia, large-for-gestational-age, and neonatal hypoglycaemia (N.-J. Zhang et al., 2020). Similarly, earlier pilot studies have suggested hyperinsulinaemia precedes later gestation hyperglycaemia and GDM development (Bito et al., 2005; Lapolla et al., 2008). Both studies showed that the two-hour dynamic insulin response to an OGTT, rather than the fasting level, was a stronger indicator of insulin sensitivity and potential predictor of GDM risk. This further supports findings from our study which have shown that an elevated two-hour insulin level, characteristic of the delayed peak in Kraft pattern III, is suggestive of hyperinsulinaemia or metabolic dysfunction in pregnancy.

Current understanding of the consequences of metabolic dysfunction during pregnancy have largely been established among mothers with obesity in pregnancy or GDM. Pre-existing maternal metabolic dysfunction exacerbates the physiological insulin resistance of pregnancy, resulting in further metabolic derangements such as impaired glucose metabolism, worsening insulin resistance, impaired fat oxidation, and inflammation (Butte, 2000; Tinius et al., 2020). This metabolic dysfunction could impact maternal and neonatal health in many ways (Sobrevia et al., 2016). However, due to the significant limitation from this study's cohort, the clinical implications of hyperinsulinaemia are unknown. Further work is needed to explore links to perinatal and neonatal outcomes.

Identifying a high prevalence of hyperinsulinaemia in the "Borderline" or "Normal" groups in this study who would have otherwise not been diagnosed or identified as being at risk of gestational complications may have important clinical significance. Due to a lack of research around hyperinsulinaemia in pregnancy, independent of GDM, type 2 diabetes, or obesity, it is unclear whether hyperinsulinaemia characterised as Kraft III in pregnancy is physiologically normal or whether it suggests an increased metabolic risk to the mother and infant. Women with one abnormal value from the OGTT ("Borderline" group in our study) have been shown to have a significantly increased risk of many adverse pregnancy outcomes including foetal overgrowth, neonatal hypoglycaemia, caesarean delivery, maternal hypertensive disorders, and neonatal intensive care unit admission, with rates being comparable to women who have GDM (Roeckner, Sanchez-Ramos, Jijon-Knupp, & Kaunitz, 2016). Additionally, among women who receive a "false positive" result following the 50-gram, non-fasting, glucose challenge test (a test used to first screen for GDM risk) but are otherwise not diagnosed with GDM, also experience a greater incidence of infants born large-for-gestational age and adverse pregnancy outcomes such as caesarean delivery, shoulder dystocia, and antenatal death (Ezell, Peters, Shill, & Cassidy-Bushrow, 2015; Ruangvutilert, Uthaipat, Yaiyiam, & Boriboonhirunsarn, 2020; Stamilio, Olsen, Ratcliffe, Sehdev, & Macones, 2004; Yee, Cheng, Liddell, Block-Kurbisch, & Caughey, 2011). Authors recommend that mothers with such borderline results would benefit from early pregnancy lifestyle interventions to reduce this risk. Findings from our study suggest that pregnant women with a "borderline" or "false-positive" result following the standard OGTT or glucose challenge test may present with hyperinsulinaemia if this were included in clinical assessments.

Insulin measurement, especially in the dynamic OGTT format, is not standard clinical practice for expectant mothers. Our study has highlighted an important area where further research is needed. We have identified a gap where insulin measurement is needed in the diagnosis of metabolic dysfunction during pregnancy. Longitudinal research should explore outcomes

related to hyperinsulinaemia across gestation and beyond pregnancy. Additionally, further work is needed to characterise hyperinsulinaemia prevalence among varying demographic groups. Detecting metabolic risk early in pregnancy may allow for early lifestyle interventions to mitigate risk and potentially lead to long-term benefits for maternal and infant health.

This study is unique in that the data came from a pre-existing historical dataset which was collated over two decades, however, we acknowledge several limitations. During the period these data were collected, two assays for measuring glucose were used leading to potential sampling bias. Insulin assays were collected using an RIA for which the precision could only be presumed from previous literature. Insulin measurement from this particular time period (1970s-1990) comes with many challenges due to the limitations surrounding assay precision from this time. No further information could be obtained on the ethnicity or medical and pregnancy history of the subjects. As this dataset was cross-sectional, no longitudinal information on pregnancy outcomes such as infant size or maternal diabetes (GDM or type 2 diabetes) outcomes limits our interpretation. A key strength was the large sample size and extended period over which these data were collected. These data were collected through a large non-profit teaching hospital (St Joseph's Hospital, Chicago, IL, USA) in accordance with the best medical practice of the time. The methodology for insulin assessment was unique including a dynamic three-hour insulin assay with up to five timepoints.

By characterising pregnant subjects by glucose tolerance status, we demonstrated a spectrum of hyperinsulinaemia, whereby women with a "Borderline" GDM diagnosis as well as those with GDM had significantly higher post-prandial insulin levels compared to their normal glucose tolerant counterparts. This study showed a high prevalence of hyperinsulinaemia among women who would have otherwise not been diagnosed with GDM. The clinical significance of this finding is that, although hyperinsulinaemia may have implications for maternal and infant health, measuring insulin in pregnancy, particularly in the dynamic OGTT format used in this study, is not a part of standard clinical care. Limited research to confirm diagnostic thresholds for hyperinsulinaemia in pregnancy means there is no clear criteria to determine when normal physiological changes to insulin metabolism become potentially harmful. Further longitudinal research is needed to better understand the implications of varying magnitudes of hyperinsulinaemia at different stages in gestation on maternal and infant health.

Chapter 5. Hyperinsulinaemia during pregnancy and gestational outcomes: A case series

Preface

The analysis of the Kraft data subset provided an indication of expected insulin response patterns during pregnancy across women with varying glucose tolerances. The most interesting finding from these data was a broad representation of hyperinsulinaemia (according to the Kraft definitions) across women with varying glucose tolerances; notably, nearly a third of women with normal glucose tolerance demonstrated hyperinsulinaemia (as according to the Kraft pattern definitions). This leaves one to consider how many women may have entered pregnancy with pre-existing hyperinsulinaemia. Since a large proportion of these women with Kraft Pattern IIB and III did not meet the diagnostic criteria for GDM, it is also unlikely that, at this point in their pregnancy, they would have received formal lifestyle advice. However, according to the Kraft Model of Hyperinsulinemia, it could be said that women who enter pregnancy with Kraft Pattern IIB and III but normal glucose tolerance, sit on a more adverse track toward later life cardiometabolic disease. It is also, therefore, plausible that they may also encounter a greater risk of adverse outcomes.

If hyperinsulinaemia (i.e. as a pre-existing issue) could be identified from the beginning of pregnancy, there may be grounds for earlier interventions. Although the "optimal" diet may still be a source of controversy, previous chapters showed that lifestyle interventions that promote healthy diet and physical activity behaviours generally mean better outcomes overall when compared to standard care. As a health professional, it was important for me to undertake research in a way that would develop my understanding of pregnant women's experiences so that findings could be translatable into clinical practice.

The Kraft Model methodology comes with challenges surrounding the clinical application and overall acceptability of the test – especially when working with pregnant women in the early stages of pregnancy. In bringing the Kraft Model into this modern context for this study, two components from the original Kraft protocol were modified. These changes included reducing the test length from three to two hours and reducing the oral glucose load from 100- to 75-grams. The greatest limitation of these changes was that neither the original nor modified Kraft Pattern criteria have been validated in a pregnancy context. However, the purpose of this study was to demonstrate where future research may be continued in this space. The following case series was designed to explore whether an early pregnancy insulin response test could identify

women with pre-existing dysfunctional insulin response patterns. It was hypothesised, according to the Kraft Model of Hyperinsulinaemia, that such testing could provide an indication of the woman's metabolic health and therefore reflect her risk for adverse outcomes.

The study presented in Chapter 5 is in the form of a manuscript published in the *Journal of Insulin Resistance*, 2022 (DOI: https://doi.org/10.4102/jir.v5i1.69).

5.1 Abstract

Insulin resistance is an expected part of pregnancy. When this pre-pregnancy insulin resistance is combined with the physiological adjustments to insulin metabolism, there's an increased risk for complications such as GDM and preeclampsia. Individuals with insulin resistance also exhibit hyperinsulinaemia. While increased insulin secretion is physiological in pregnancy, currently, there is no clear distinction between a normal insulin response pattern of pregnancy and one that might result in negative maternal and offspring effects. This study aimed to explore the relationship between first-trimester insulin response patterns and gestational outcomes. The setting was Auckland, New Zealand. Participants included four pregnant women with pre-pregnancy BMI ≥ 25 kg/m^2 and aged 25 to 35 years. Glucose and insulin response patterns were examined following a 120-minute OGTT (75-gram glucose) at 12-15 weeks of gestation using a modified Kraft methodology. Outcomes assessed at 25- and 35-weeks of gestation included GWG, blood pressure, fasting capillary blood glucose, and foetal growth. Lifestyle and medical information were collected during each trimester. After delivery, total GWG, infant size, delivery method, and clinical outcomes were recorded. Kraft pattern IIB hyperinsulinaemia was identified in two cases. Among them, Case #1 experienced excessive GWG, induction of labour, and surgically assisted delivery. Case #4 delivered by emergency caesarean and the neonate required intensive care admission for 17 hours. No cases developed hyperglycaemia or hypertension. Infant weights were between 3.75-3.86 kg. Insulin response pattern analysis provides a promising template to assess metabolic risk in the first trimester of pregnancy. Identifying hyperinsulinaemia early in pregnancy may mean that lifestyle-based initiatives could be introduced earlier to mitigate excess GWG and potential adverse outcomes.

5.2 Introduction

The global obesity and type 2 diabetes epidemic has risen in parallel with insulin resistance syndromes in pregnancy that have widespread implications for maternal and infant health (Egan et al., 2017; Lavery et al., 2017; Paulo et al., 2021; Ward et al., 2020). In New Zealand, 27-32% of women of child-bearing age have obesity (Ministry of Health, 2020). Women who conceive

with insulin-resistant obesity will enter pregnancy already at risk of complications, such as GDM, preeclampsia, and foetal overgrowth (Catalano & Shankar, 2017).

Changes to maternal insulin metabolism are a normal and essential part of human pregnancy. From the late first trimester, placental hormones, including human placental growth hormone and maternal adipokines drive the increase in maternal insulin resistance (Armistead et al., 2020; Barbour et al., 2007). Concurrently, human placental lactogen stimulates the compensatory expansion of maternal pancreatic beta-cells to enhance insulin secretion and maintain glucose homeostasis (Armistead et al., 2020). The resulting progressive physiological hyperinsulinaemia and insulin resistance of pregnancy ensure nutrient and energy availability for a growing foetus. However, in women with pre-existing insulin resistance, these physiological gestational changes become augmented, leading to exaggerated changes in insulin metabolism, nutrient excess, and low-grade inflammation (Butte, 2000; Catalano & Shankar, 2017; Tinius et al., 2020).

Pre-pregnancy insulin resistance combined with pregnancy is linked to a milieu of metabolic derangements, including low-grade chronic inflammation, oxidative stress and altered nutrient transport (Ingvorsen et al., 2015; Sobrevia et al., 2016). Infants born to mothers with either GDM and/or obesity experience an increased risk of foetal growth restriction (infants born small-for-gestational-age) or overgrowth (macrosomia or infants born large-for-gestational age) (Catalano & Shankar, 2017; Dow & Szymanski, 2020; HAPO Study Cooperative Research Group et al., 2008; Wendland et al., 2012). There is also an increased risk of delivery complications, including induction of labour, shoulder dystocia, emergency caesarean delivery, and neonatal metabolic complications, including hypoglycaemia and respiratory distress. Maternal metabolic dysfunction exposes offspring to overnutrition *in utero,* which is linked to later life poor health outcomes including childhood obesity, type 2 diabetes in early adulthood, and/or metabolic syndrome later in life (Boney et al., 2005; Damm, 2009; Hrolfsdottir et al., 2015; Nehring et al., 2013; Voerman, Santos, Patro Golab, et al., 2019).

Outside of pregnancy, hyperinsulinaemia is both cause and consequence of insulin resistance (James et al., 2021). Research shows that hyperinsulinaemia plays an important underlying role in the pathogenesis of cardiometabolic and other chronic metabolic diseases (Crofts et al., 2015). In non-pregnant, glucose tolerant adults, hyperinsulinaemia could predict the development of type 2 diabetes as early as 20 years in advance (Dankner et al., 2009). One method used to identify hyperinsulinaemia is plotting a curve based on insulin release in response to an OGTT (Crofts et al., 2019; Crofts et al., 2016; DiNicolantonio et al., 2017; Hayashi et al., 2013). Using the Kraft Model of Hyperinsulinaemia, a dysfunctional insulin response

pattern is characterised by an elevated fasting plasma insulin level, a delayed insulin peak (2- or 3-hour post oral glucose load) and/or loss of the first phase of insulin release, and delayed rate of decay. Other widely used measures, such as the homeostasis model assessment HOMA system, based on fasting insulin and glucose, are considered inappropriate for defining hyperinsulinaemia due to the oscillatory nature of insulin release in the basal state (Crofts et al., 2019; DiNicolantonio et al., 2017).

Although increased insulin secretion is an expected part of pregnancy, insulin response patterns vary in women with GDM. N.-J. Zhang et al. (2020) conducted a large prospective study that included a 180-minute OGTT (75-gram glucose) with insulin assay alongside routine screening for GDM at 24-28 weeks of gestation. Among the 1,695 women diagnosed as having GDM, 62% had a "dysfunctional" insulin pattern, which was defined as a delayed peak at 2- or 3-hours post glucose load. Regardless of GDM status, this "dysfunctional" insulin pattern was significantly associated with a higher risk of adverse maternal and neonatal outcomes, including preeclampsia, large-for-gestational age infants, and neonatal hypoglycaemia. Similarly, our previous analysis of a pregnant cohort showed that a delayed peak hyperinsulinaemia pattern (i.e. loss of the first phase of insulin response, followed by an extended second phase) was characterised among 75% of women with GDM and 31% of those with normal glucose tolerance (North et al., 2021).

Pilot studies have endeavoured to describe an association between hyperinsulinemia in early gestation (~16 weeks and earlier), the risk of GDM development (Bito et al., 2005; Grewal et al., 2012; Lapolla et al., 2008), and hypertensive disorders in pregnancy (Hamasaki et al., 1996; Kayemba-Kay's et al., 2013; Solomon & Seely, 2001; Sowers et al., 1996). Although these first trimester measures have variable sensitivity and specificity for GDM (Bito et al., 2005; Grewal et al., 2012), there is an argument that dynamic insulin measurement could be used as a predictor of other adverse gestational outcomes, independent of GDM status. That is to say, the associations between mid-gestation hyperinsulinaemia and the adverse outcomes described by N.-J. Zhang et al. (2020) could also exist for first trimester insulin assays. The ability to identify women in their first trimester with a metabolic phenotype associated with an increased risk for adverse outcomes could mean that lifestyle-based strategies (Griffith et al., 2020; Lamminpää et al., 2018) are introduced sooner. A key challenge to investigate this hypothesis further is that, aside from those outlined in the existing research, there are currently no established criteria for defining hyperinsulinaemia specific to pregnancy. Furthermore, there are varying techniques used for measuring insulin (i.e. immunoassays, chemiluminescence, chromatography) that are not standardised internationally, limiting any comparison between populations.

This case series aimed to explore the relationship between a woman's first-trimester insulin response pattern and gestational outcomes, including glycaemia, GWG, foetal growth, and obstetric outcomes. We applied a modified version of the Kraft algorithm to define hyperinsulinaemia in a clinical setting using a two-hour OGTT with a 75-gram glucose load which is common practice when screening pregnant women for GDM. It was hypothesised that identifying hyperinsulinaemia in the first trimester of pregnancy could be used to describe a woman's risk of adverse pregnancy-related outcomes, therefore providing an earlier opportunity to introduce dietary and lifestyle measures. We present a case series of four New Zealand women identified to have at least one risk factor of GDM who underwent an OGTT (75-gram glucose) with insulin assays in the first trimester of pregnancy.

5.3 Methods

We conducted a prospective observational case series of four women living in Auckland, New Zealand. Participants were women at less than 14 weeks of gestation with a naturally conceived singleton pregnancy. Selection criteria included those with a pre-pregnancy BMI ≥ 25 kg/m^2 and aged between 25 and 35 years. Women were invited to participate by convenience sampling, which included advertising on social media in targeted private Facebook groups (e.g. "New Zealand Mums"). Eligible participants confirmed their involvement in the study by providing written informed consent.

Participants were invited to attend an OGTT in the first trimester of pregnancy (< 14 weeks of gestation) at their nearest community pathology clinic (Labtests New Zealand). Venous blood samples were taken at fasting, then 30, 60, and 120 minutes following a 75-gram glucose drink (Carbotest™). Samples were measured by the commercial pathology service (Labtests New Zealand). Insulin was measured using a two-site sandwich immunoassay with chemiluminescence technique (ADVIA Centaur Insulin assay, CV 3.2-7.5%). Plasma glucose was measured by hexokinase method (ADVIA Chemistry Glucose Hexokinase_3 Concentrated Reagents, CV 0.3-2.0%). Plasma glucose results were examined according to the New Zealand Ministry of Health diagnostic criteria where either a fasting plasma glucose ≥ 5.5 mmol/L or 120-minute plasma glucose ≥ 9.0 mmol/L is diagnostic for GDM (Ministry of Health, 2014).

To examine insulin response patterns among the cases, we developed a modified version of the Kraft algorithm for classifying insulin response patterns. With careful consideration for the practical application of insulin response pattern assessment, two components from the original criteria previously described by Crofts et al. (2016) were modified for this study. These changes included reducing the test length from three to two hours and reducing the oral glucose load

from 100- to 75-grams. The resulting revised Kraft protocol aligned more closely with the standard OGTT performed for GDM diagnostic testing in New Zealand (also a 75 gram glucose load and two-hour testing protocol), therefore having better overall acceptability among pregnant women with greater potential to translate into clinical practice.

In the original criteria, Kraft patterns I, IIA, and IIB are determined based on the 120- and 180-minute sum value, as shown in Table 15. The procedures for determining the new 120-minute plasma insulin cut-off (i.e. to replace the 120- and 180-minute sum values which determine patterns I, IIA, and IIB) were as follows. A subset of non-pregnant, glucose tolerant individuals (n = 7755) from the wider Kraft dataset previously analysed by Crofts et al. (2016) was used to model the abbreviated criteria. First, a suitable range to model a new cut-off value was estimated at one standard deviation above the mean 120-minute insulin value from subjects in Kraft pattern groups I and IIA (Kraft I, mean ± SD: 27.9 ± 10.3 μU/mL; Kraft IIA: 51.9 ± 13.6 μU/mL). Four models were created using a 120-minute lower cut-off value of ≤ 35 μU/mL, ≤ 36 μU/mL, ≤ 37 μU/mL, and ≤ 38 μU/mL (for Kraft pattern I and IIA), and upper cut-off of ≥ 64 μU/mL, ≥ 65 μU/mL, ≥ 66 μU/mL, and ≥ 67 μU/mL (for Kraft pattern IIA and IIB). Each model was tested to estimate the frequency of misclassified individuals. The estimated percentages of misclassified individuals in the final model are shown in Figure 11. The final model was selected to minimise the proportion of individuals misclassified as Kraft I or IIA (i.e. being misclassified as being healthier than they are), while allowing for a higher percentage of individuals who could be misclassified as having more advanced hyperinsulinaemia. We chose these more cautious criteria, as opposed to the more lenient criteria, to model how initial management strategies for hyperinsulinaemia could be based on reinforcing healthy lifestyle practices such as healthy eating and physical activity. A summary of the original and modified criteria is shown in Table 15.

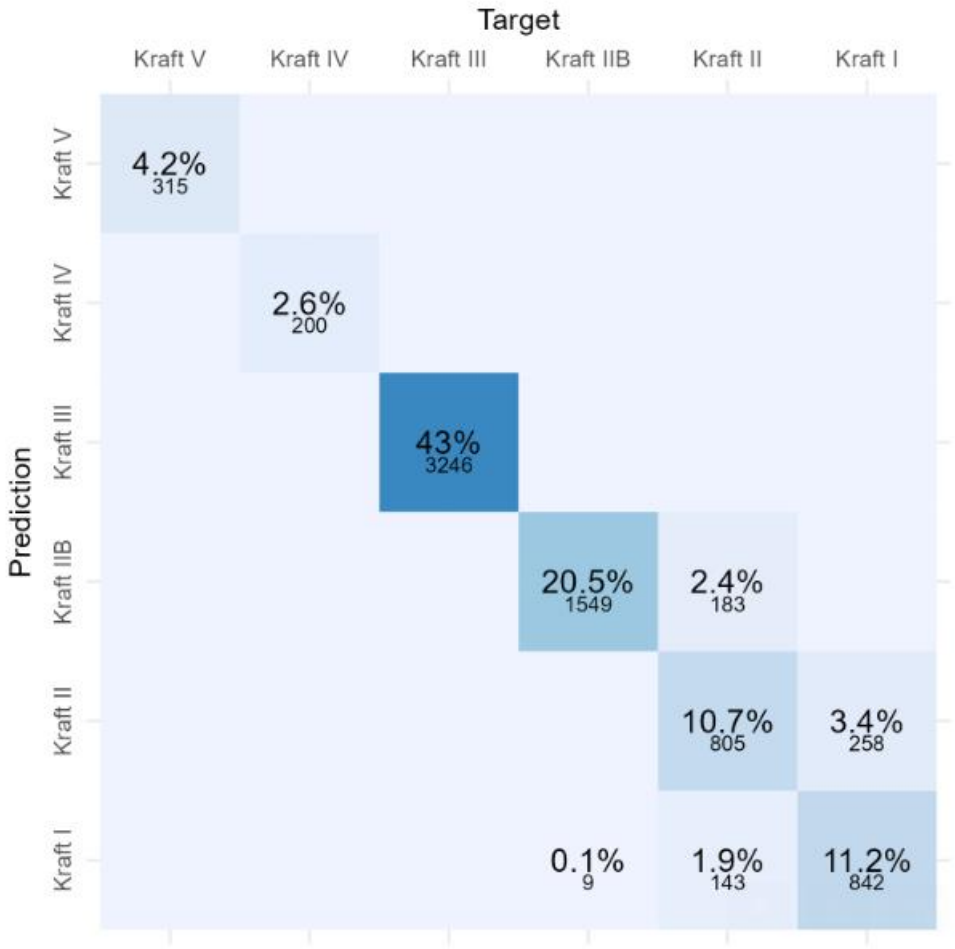


Figure 11 Confusion matrix indicating the proportion of subjects misclassified in the final model of the modified Kraft pattern criteria, based on classifications previously applied by Crofts et al. (2016).

Modified criteria were tested on a subset from the Kraft dataset of glucose tolerant non-pregnant adults (n=7755). Frequencies across the diagonal line indicate a true match between the "prediction" from the modified criteria and the "target" original Kraft pattern criteria. Those indicated in boxes below or above the diagonal indicate misclassifications. In the final model, the 120- +180-minute sum plasma insulin value used to define Kraft patterns I, IIA, and IIB was replaced with a lower 2-hour threshold of ≤36 µU/mL and upper two-hour threshold of ≥65 µU/mL. No changes to Kraft patterns III, IV, and V were made.

Table 15. Modified Kraft pattern criteria to identify hyperinsulinaemia from a 120-minute oral glucose tolerance test.

Kraft Pattern	Original	Modified
Pattern I (Normal insulin)	Fasting insulin ≤ 30 µU/mL 30- or 60-minute peak 120- + 180-minute sum ≤ 60 µU/mL	Fasting insulin ≤ 30 µU/mL 30- or 60-minute peak 120-minute ≤ 36 µU/mL
Pattern IIA (Borderline)	Fasting insulin ≤ 50 µU/mL 30- or 60- minute peak 120- + 180-minute sum > 60, < 100 OR Fasting insulin 31-50 µU/mL 30- or 60-minute peak 120- + 180-minute sum < 60 µU/mL	Fasting insulin ≤ 50 µU/mL 30- or 60-minute peak 120-minute > 36, < 65 OR Fasting insulin 31-50 µU/mL 30- or 60-minute peak 120-minute ≤ 36 µU/mL
Pattern IIB (Hyperinsulinaemia)	Fasting insulin ≤ 50 µU/mL 30- or 60-minute peak 120- + 180-minute sum ≥ 100 µU/mL	Fasting insulin ≤ 50 µU/mL 30- or 60-minute peak 120-minute ≥ 65 µU/mL
Pattern III (Hyperinsulinaemia)	Fasting insulin ≤ 50 µU/mL Delayed peak (120-minutes or later)	
Pattern IV (Hyperinsulinaemia)	Fasting insulin > 50 µU/mL	
Pattern V (Hypoinsulinaemia)	All values < 30 µU/mL	

Kraft pattern criteria modified from Crofts et al. 2016.

Health, dietary, and lifestyle information of the participants was collected during face-to-face interviews at the time of each OGTT. This information included gestational age, self-reported pre-pregnancy weight and height, recent medical history including any prescription medications and supplements, and lead maternity carer details. A dietary and lifestyle assessment included a 24-hour food recall, a 20-item food frequency questionnaire, and qualitative questions describing the woman's diet pattern, recent dietary changes, exercise pattern, and recent changes to physical activity. This questionnaire was repeated at 25- and 35-weeks of gestation by a remote video or phone interview. Participants collected their own capillary fasting blood glucose levels for seven days at 25- and 35-weeks of gestation (FreeStyle Optium Neo meter and glucose test strips). The date, time, and glucose reading result were recorded and emailed to the researcher on a log sheet.

Participants were provided with an additional written questionnaire to complete with their lead maternity carer as part of standard antenatal assessments. They were also asked to provide a record of metabolic parameters (first trimester glycated haemoglobin (HbA1c), blood pressure, recommended total GWG, and current weight), foetal growth ultrasonography measures (timing and frequency according to lead maternity carer guidance), and medical concerns (e.g. thyroid problem, weight gain, iron deficiency, or foetal abnormalities). This questionnaire was repeated at 25- and 35-weeks of gestation and returned by email.

Women received standard antenatal care from their community lead maternity carer. Maternal and foetal obstetric outcome information was collected during a postnatal telephone interview with the women. Information collected included gestational age at birth, delivery method, medical interventions used, and neonatal birth weight, length, and respective percentiles according to the INTERGROWTH-21st project neonatal growth charts (Villar et al., 2014).

Ethical approval for this study was obtained from the Northern Health and Disability Ethical Committee (19/NTA/124/AM01) and Auckland University of Technology Ethics Committee (20/216).

5.4 Case Presentation

Insulin and glucose assays performed following a 120-minute OGTT measured between 12+1 (weeks plus days) and 14+5 weeks of gestation for each case are presented in Figure 12. All women had normal fasting insulin levels ≤ 30 µU/mL, as compared to the criteria in Table 15. Insulin responses from all four women had an insulin peak at either 30- or 60-minutes following the 75-gram glucose load, which is suggestive of a normal first-phase insulin secretory response. Cases #1 and #4 had an elevated 120-minute insulin value ≥ 65 µU/mL (Case #1: 117.5 µU/mL; Case #4: 107.8 µU/mL), which is characteristic of Kraft pattern IIB hyperinsulinaemia. Cases #2 and #3 presented with normal insulin response patterns. For Case #2, the insulin response peaked at 60-minutes (55.4 µU/mL), while for Case #3 a peak insulin of 51.9 µU/mL was established at 30-minutes. All women had normal glucose tolerances according to the New Zealand Ministry of Health diagnostic criteria for GDM (Ministry of Health, 2014).

Baseline characteristics from the four case studies are presented in Table 16. No medical concerns (e.g. hyperglycaemia or thyroid abnormalities) were indicated at baseline assessments. Information on medications, nutritional supplements, and dietary information collected at each trimester are included in Appendix C, Supplementary Table 6.

Table 16. Baseline characteristics

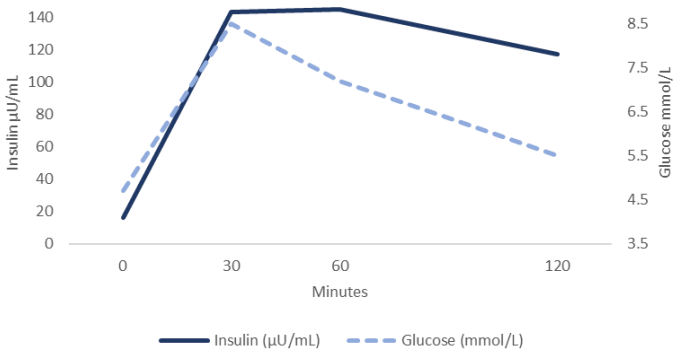
	Case 1	Case 2	Case 3	Case 4
Age (years)	30	30	30	28
Parity	0	1	0	0
Pre-pregnancy weight (kg)	82.0	75.0	80.0	92.0
Pre-pregnancy BMI (kg/m^2)	28.4	26.6	25.5	37.8
HbA1c 1st trimester (mmol/mol)	33	31	33	35

BMI: Body mass index; HbA1c: glycated haemoglobin

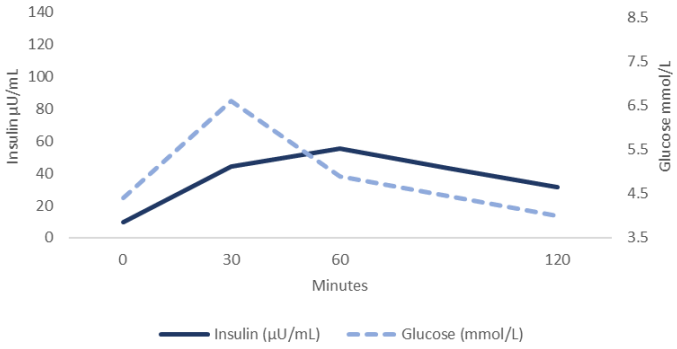
5.4.1 Case #1: Kraft pattern IIB (Hyperinsulinaemia)

Case #1 was a 30-year-old primigravida Caucasian woman with no pre-existing medical conditions. Self-reported body weight before conception was 82 kg (BMI 28.4 kg/m^2). She had conceived naturally after ceasing contraception (medroxyprogesterone acetate (Depo Provera™) injection) 24-months prior and had a normal HbA1c of 33 mmol/mol. Metabolic parameters collected at 25- and 35-weeks of gestation are shown in Table 17. Total GWG was 19.0 kg, 7.5-12 kg in excess of New Zealand Ministry of Health and IOM guidelines for women with a BMI between 25-29.5 kg/m^2 (Institute of Medicine & National Research Council, 2013; Ministry of Health, 2014). Lead maternity care antenatal clinical notes indicated foetal growth above the 90th percentile, which resulted in additional growth scans during the third trimester (Appendix C, Supplementary Table 5). Foetal ultrasonography measured taken at 27+2, 32+3, and 36+3, but not 34+2 weeks indicated foetal biparietal diameter above the 95th percentile and between the 50th and 95th percentile for head and abdominal circumference and femur length (National Women's Health, 2021). Dietary information from 24-hour food recall and food frequency questionnaires collected at each trimester indicated no remarkable dietary changes (Appendix C, Supplementary Figure 1). Self-reported physical activity included walking, which was reduced in the third trimester.

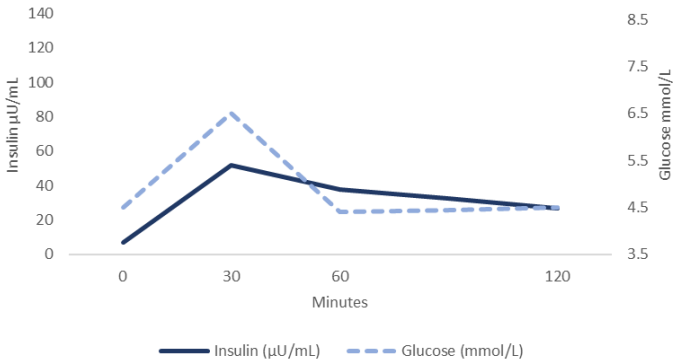
Labour was induced by misoprostol at 39+5 weeks of gestation. She received epidural anaesthesia and oxytocin. Delivery was assisted by ventouse and forceps, requiring episiotomy. Complications included meconium present in amniotic fluid, foetal shoulder dystocia, and a 3rd degree perineal tear. The neonate was born weighing 3.80 kg (50th to 90th percentile) and length 51 cm (50th to 90th percentile) (Villar et al., 2014).



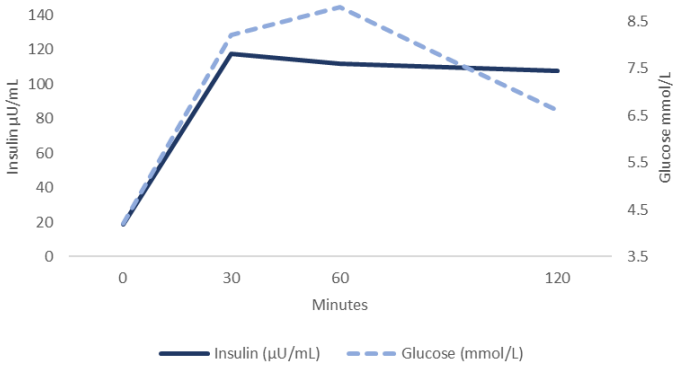
Case #1: Normal glucose tolerance, Kraft IIB hyperinsulinaemia, 12+1 weeks' gestation.



Case #2: Normal glucose tolerance, Kraft I normal insulin tolerance, 14+5 weeks' gestation.



Case #3: Normal glucose tolerance, Kraft I normal insulin tolerance, 11+6 weeks' gestation.



Case #4: Normal glucose tolerance, Kraft IIB hyperinsulinaemia 14+5 weeks' gestation.

Figure 12. Insulin and glucose response patterns following a 75-gram oral glucose tolerance test

Table 17. Metabolic parameters collected throughout gestation

	Case 1	**Case 2**	**Case 3**	**Case 4**
Weight 25 wk (kg)	91.6	68.5	85.4	91.0
Weight 35 wk (kg)	98.0	80.0	91.7	94.8
Weight 38 wk (kg)	101.0	84.0	92.5	96.0
Total GWG (kg)	19.0	9.0	12.5	4.0
Blood pressure 1st tri (systolic/diastolic, mmHg)	122/80	110/60	110/60	100/65
Blood pressure 2nd tri (systolic/diastolic, mmHg)	118/70	104/63	110/66	92/62
Blood pressure 3rd tri (systolic/diastolic, mmHg)	120/75	90/60	120/70	102/72
SMBGL 25 wk (mmol/L) mean (range)	3.9 (3.5-4.1)	4.4 (4.2-4.8)	4.2 (4.1-4.4)	4.4 (3.7-4.8)
SMBGL 35 wk (mmol/L) mean (range)	4.0 (3.8-4.1)	4.3 (4.1-4.8)	4.0 (3.8-4.2)	4.2 (3.8-4.4)

GWG: Gestational weight gain; SMBGL: Self measured fasting capillary blood glucose 7-day average; Wk: weeks. Tri: Trimester

Table 18. Foetal growth and infant birth outcomes

	Case 1	**Case 2**	**Case 3**	**Case 4**
Foetal growth (2nd tri)				
Gestational age (wk+d)	27+2	No growth scan, anatomy scan normal	No growth scan, anatomy scan normal	28+5
BPD (percentile)¶	77 (> 95th)			74 (50th-95th)
HC (percentile)¶	265 (50th-95th)			279 (50th-95th)
AC (percentile)¶	251 (50th-95th)			262 (50th-95th)
FL (percentile)¶	53 (50th-95th)			56 (50th-95th)
EFW (g)	1296			1488
Foetal growth (3rd tri)				
Gestational age (wk+d)	36+3¥	No growth scan	34+6	37+4
BPD mm (percentile)¶	97 (> 95th)		94 (>95th)	92 (5th-50th)
HC mm (percentile)¶	336 (50th-95th)		333 (50th-95th)	324 (5th-50th)
AC mm (percentile)¶	351 (50th-95th)		320 (50th-95th)	352 (50th-95th)
FL mm (percentile)¶	71 (50th-95th)		67 (50th-95th)	70 (5th-50th)
EFW (g)	3406		2817	3340
Delivery				
Gestational age (wk+d)	39+5	39+1	39+4	40+5
Sex	Male	Male	Male	Male
Birth weight kg (percentile)¶¶	3.80 (50th-90th)	3.86 (90th-97th)	3.76 (50th-90th)	3.75 (50th-90th)
Birth length cm (percentile)¶¶	51 (50th-90th)	50 (50th-90th)	51.5 (50th-90th)	55 (> 97th)

BPD: Biparietal diameter; d: day; HC: Head circumference; AC: Abdominal circumference; FL: Femur length; Wk: weeks. Tri: Trimester

¶National Women's Health (2021). https://www.nationalwomenshealth.adhb.govt.nz/assets/Uploads/Fetal-Growth-Chart.pdf

¶¶Villar et al (2014) International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. *Lancet* 2014: 384: 857-68.

¥Additional growth scans from Case #1 at 32+3 and 34+2 weeks' gestation not shown.

5.4.2 Case #2: Kraft pattern I (Normal insulin response pattern)

Case #2 was a 30-year-old secundigravida Caucasian woman. Self-reported pre-pregnancy weight was 75 kg and BMI 26.6 kg/m^2. First trimester antenatal assessments confirm normal HbA1c of 31 mmol/mol and blood pressure of 110/60 mmHg, which remained stable during the second trimester. Self-measured capillary fasting glucose levels were within normal ranges at 25 weeks (4.2-4.8 mmol/L) and 35 weeks of gestation (4.1-4.8 mmol/L) (Table 16). Case #2 did not

undergo further screening or diagnostic tests for GDM at 24 weeks of gestation. Total GWG throughout pregnancy was 9 kg, within the recommended 7-11.5 kg (Institute of Medicine & National Research Council, 2013; Ministry of Health, 2014)

According to lead maternity care records from 35 weeks of gestation, Case #2 presented with low blood pressure (90/60 mmHg) and irregular uterine contractions, noted by the lead maternity carer as an "irritable uterus", as a threat for pre-term labour. Self-reported physical activity reduced in the third trimester due to pain, discomfort, and heat exhaustion reduced during this time. Total energy from self-reported dietary intake from 24-hour food recall at each time point was remarkably lower than expected requirements (~38-43% of 9800 kJ/day vs recorded 3741-4231 kJ/day) (National Health and Medical Research Council, Australian Government Department of Health and Ageing, & New Zealand Ministry of Health, 2006). At each of these time points, Case #2 reported that her intake was lower than usual and that she experienced nausea in trimester 1, acute gastroenteritis from foodborne illness in trimester 2, and lethargy related to iron deficiency in trimester 2 and 3. Reduced intake during trimester 1 is also consistent with 6.5 kg weight loss observed between pre-pregnancy and weight at 25 weeks of gestation.

Case #2 delivered a male neonate at 39+1 weeks of gestation. The labour and birth were unassisted without complications to the neonate. The neonate was born weighing 3.86 kg (90^{th} to 97^{th} percentile) and length 50 cm (50^{th} to 90^{th} percentile) (Villar et al., 2014). Partial placental attachment and maternal haemorrhage shortly after the birth indicated admission to Middlemore Hospital requiring surgical intervention.

5.4.3 Case #3: Kraft pattern I (Normal insulin response pattern)

Case #3 was a 30-year-old primigravida Caucasian woman with no pre-exiting medical conditions. Although medically primigravida, she suspected miscarrying a conceptus at 4-5 weeks of gestation, two months prior to the confirmed pregnancy. Pre-pregnancy weight was 80.0 kg, and BMI 25.5 kg/m^2. First trimester antenatal assessments confirm a normal HbA1c of 33 mmol/mol and blood pressure of 110/60 mmHg, which remained stable throughout gestation. First trimester antenatal biochemistry also revealed mild thrombocytopenia, which continued into the second trimester. Self-measured capillary glucose levels were non-remarkable at 25 weeks (4.1-4.4 mmol/L) and 35 weeks of gestation (3.8-4.2 mmol/L) (Table 17). Total GWG was 12.5 kg, 1 kg excess of the recommended 7-11.5 kg (Institute of Medicine & National Research Council, 2013; Ministry of Health, 2014). Case #3 did not undergo further screening or diagnostic tests for GDM at 24 weeks of gestation. Dietary information collected at

each trimester indicated no remarkable dietary changes (Appendix C, Supplementary Table 5). She followed a healthy dietary pattern consisting of mostly minimally processed foods. It is also noteworthy that Case #3 sought nutrition advice from a Registered Nutritionist prior pregnancy which likely further supported healthy dietary behaviours. Physical activity in the first trimester included weight training and running, which was replaced by walking and yoga in the second and third trimesters.

Foetal growth ultrasound performed on 34+6 weeks of gestation reported foetal biparietal diameter above the 95th percentile and head and abdominal circumference and femur length within the 50th-95th percentile (National Women's Health, 2021). Case #3 gave birth to a male neonate at 39+4 weeks following a natural labour. Birth weight was 3.76 kg (50th to 90th percentile) and length 51 cm (50th to 90th percentile) (Villar et al., 2014). No maternal or neonatal complications were reported.

5.4.4 Case #4: Kraft pattern IIB (Hyperinsulinaemia)

Case #4 was a 28-year-old primigravida Caucasian woman. Her self-reported pre-pregnancy weight was 92 kg (BMI 37.8 kg/m^2) and antenatal biochemistry confirmed a normal HbA1c of 35 mmol/mol (Table 17). Self-measured capillary glucose levels at 25 weeks ranged from 3.7 to 4.8 mmol/L and 3.8-4.4 mmol/L 35 weeks (Table 17). A secondary OGTT performed at 27+5 weeks of gestation confirmed normal glucose tolerance (fasting venous glucose 4.0 mmol/L; 2 hours post 75 g OGTT 7.4 mmol/L).

Case #4 was advised by her lead maternity carer in trimester 1 to avoid excessive GWG due to the risks associated with obesity in pregnancy. She reported changing her dietary habits at the beginning of pregnancy to "eat healthier", which included an increased daily intake of vegetables, fruit, and protein-rich foods (meat, eggs, and dairy), and reduced intake of sugar and ultra-processed snack foods. As a result, Case #4 gained a total of 4 kg during pregnancy after an initial 2 kg weight loss in the first trimester (Table 17). Foetal growth ultrasonography from 28+5 weeks suggested normal growth patterns between the 50th and 95th percentiles for all measures. At 37+4 weeks of gestation, biparietal diameter, head circumference, and femur length were recorded in the 5th to 50th percentile (Table 18) (National Women's Health, 2021).

Dietary information from food frequency questionnaires collected at each trimester indicated an increase in processed meat and sugar-free drink consumption and decreased consumption of refined grains, nuts, and spreads. Dietary recall analysis from 24-hour showed no remarkable change in food intake between the three trimesters (Appendix C, Supplementary Table 5).

Self-reported physical activity included daily walking, which was replaced for swimming in the second trimester.

Labour commenced naturally at 40 weeks of gestation and remained in the latent stage for five days. The posteriorly positioned foetus was delivered by an emergency caesarean section with epidural anaesthesia. The male neonate weighing 3.75 kg (50^{th} to 90^{th} percentile) and length 55 cm (>97^{th} percentile) (Villar et al., 2014) was compromised on delivery (heart rate of 55 bpm) and admitted to neonatal intensive care for 17 hours for oxygen, intravenous glucose, and enteral feeding.

5.5 Discussion

We presented four clinically healthy pregnant women with BMIs > 25 kg/m^2 who had varying obstetric outcomes. Insulin response patterns examined from 12-15 weeks of gestation varied between the participants. Presented cases included two women with Kraft IIB hyperinsulinaemia and two women with normal insulin response patterns (Kraft I).

Observations from our study can be compared against previous literature that has, to a limited degree, drawn associations between varying descriptions of hyperinsulinaemia and adverse pregnancy outcomes. In a recent prospective observational study that included 2,432 pregnant women, N.-J. Zhang et al. (2020) defined a “dysfunctional” insulin pattern as one that has a delayed 120- or 180-minute peak insulin response following an OGTT (75-gram glucose), which is similar to Kraft pattern III (hyperinsulinaemia) used in our study. Logistic regression analysis showed that Zhang et al.'s Type II delayed-peak insulin secretion pattern was significantly associated with a higher risk for pre-eclampsia, large-for-gestational age infants, and neonatal hypoglycaemia, in both normal glucose tolerant and GDM women. Further, three large cohort studies have characterised metabolic phenotypes among women with established GDM based on insulin secretory responses and insulin resistance (Immanuel et al., 2021; Y. Liu et al., 2018; Powe et al., 2016). Although using varied methodologies, these studies showed that women grouped as being “insulin resistant-GDM”, with or without first-phase beta-cell dysfunction, have exaggerated postprandial insulin responses, and experience the greatest risk for adverse pregnancy outcomes compared to GDM women with greater insulin sensitivity. GDM women grouped as having an “insulin secretion defect”, without insulin resistance, had lower postprandial insulin responses and similar outcomes as their non-GDM pregnant counterparts.

Outside of pregnancy, Hayashi et al. (2013) demonstrated a temporal relationship between a lasting late insulin response pattern (120-minute plasma insulin peak, greater than 30- and 60-minute insulin level post 75-gram glucose load) and the development of type 2 diabetes over a

5 to 11-year period. This “lasting late insulin response” pattern shares characteristics with Kraft pattern III and the Type II delayed-peak pattern described by N.-J. Zhang et al. (2020) by demonstrating a potential loss of the first phase of insulin release and a delayed rate of decay. None of the cases presented in this study developed GDM, preeclampsia, or delivered large-for-gestational age infants, however, it is noteworthy that Cases #1 and #4 both experienced difficulties in labour requiring delivery assistance (Case #1) and an emergency caesarean (Case #4).

Case #1 experienced excess GWG throughout pregnancy and in the second and third trimesters, foetal biparietal diameter measured above the 95th centile. Due to the presumed risks associated with excess GWG and foetal overgrowth, Case #1 received a medical induction at 39+5 weeks of gestation, which was complicated by shoulder dystocia and meconium aspiration, requiring surgical assistance (ventouse, forceps, and episiotomy). These delivery complications, however, did not appear to be directly a result of foetal overgrowth since the infant born to Case #1 was a normal weight and length for gestational age (between the 50th and 95th percentiles) (Villar et al., 2014). According to the recently revised clinical practice guidelines for the induction of labour in New Zealand, it is suggested that maternal obesity or suspected foetal macrosomia without other risk factors (i.e. non-GDM women) does not indicate induction of labour due to insufficient evidence for any proposed benefit (Ministry of Health, 2019). Further, Chandrasekaran (2021) argues that third trimester ultrasound lacks the required precision to diagnose large-for-gestational-age infants and recommends shared decision making to outweigh perceived risks and benefits of interventions. Although infant birthweight from Case #1 was in the upper range of the 50th-90th percentile, it is likely that neonatal shoulder dystocia was unrelated to maternal insulin resistance. Instead, difficulties during labour may have occurred as a result of the medical interventions Case #1 received during her induction of labour. Ironically, a potentially unnecessary induction may have been recommended for Case #1 due to the *perceived* risks from excessive GWG. That is to say, hyperinsulinaemia at the beginning of pregnancy predisposed Case #1 to excess GWG, ultimately leading a path to maternal and neonatal birth trauma via medical intervention.

Shoulder dystocia is one of many established birthing complications that occur more frequently in women with excess GWG, BMI ≥ 25 kg/m^2 (Dow & Szymanski, 2020), and/or hyperglycaemia in pregnancy (HAPO Study Cooperative Research Group et al., 2008). It often results from foetal macrosomia (D. D. Davis, Roshan, Canela, & Varacallo, 2022). The J. Pedersen (1952) hypothesis describes that excess foetal growth is driven by the passive oversupply of maternal glucose (hyperglycaemia), resulting in foetal hyperglycaemia and hyperinsulinaemia. Thus, Pedersen implied maternal glucose levels were the primary driver of foetal overgrowth via the foetal

insulin response. However, hyperglycaemia alone does not explain how infants born large-for-gestational age can occur at near equivocal rates in non-GDM mothers with obesity (OR 1.73, 95% CI 1.50, 2.00) as those with GDM (OR 2.19, 95% CI 1.93, 2.47)(Catalano et al., 2012; Ryan, 2011), thus suggesting an alternate mechanism at play.

It is recognised that in women with pre-existing insulin resistance, changes in maternal nutrient metabolism may be augmented during pregnancy, leading to an environment characterised by nutrient excess (Butte, 2000; Hernandez et al., 2020). It is plausible that normal glucose-tolerant women who display an exaggerated insulin response may also demonstrate changes in nutrient metabolism (lipids, glucose, amino acids), albeit below the threshold for diagnosing diabetes. Exposure to an excess of maternal lipids have also been proposed as a driver of foetal fat accretion; when in excess, maternal triglycerides and free fatty acids can lead to higher birth weight and large-for-gestational age infants (Barbour & Hernandez, 2018a). Our Case #1 presented with Kraft pattern IIB hyperinsulinaemia in the first trimester. Further, excess GWG could have amplified insulin resistance and hyperinsulinaemia as gestation progressed, increasing the risk of foetal overgrowth (Margerison Zilko, Rehkopf, & Abrams, 2010). These changes occurred independently of glucose status since both the OGTT at 26 weeks of gestation and fasting capillary glucose levels suggest normoglycaemia; however, it should be noted that occult hyperglycaemia could still have occurred without having continuous glucose monitoring of participants.

There are several mechanisms that could explain the relationship between maternal hyperinsulinaemia and foetal overgrowth. Hypersecretion of insulin may drive an exaggerated hepatic lipogenic response leading to increased circulating triglycerides and VLDL particles (Barbour & Hernandez, 2018a; Petersen & Shulman, 2018). Insulin binding placental insulin receptors have the potential to activate insulin/IGF-1 and mammalian target of rapamycin (mTOR) signal transduction pathways to enhance nutrient transport across the placenta (Desoye et al., 1997; Hiden et al., 2006; Jansson et al., 2013). Sobrevia et al. (2016) proposed that hyperinsulinaemia leads to endoplasmic reticulum stress that drives activation of maternal adipokines and dyslipidaemia. Furthermore, Sobrevia et al. discuss that hyperinsulinaemia could be the mechanistic driver in GDM pregnancies that alters placental vasculature and nutrient delivery, leading to increased fatty acid transfer, reduced docosahexaenoic acid, and altered composition of HDL particles in fetoplacental circulation. Increased lipid transport as an energy supply to the foetus may explain a higher incidence of foetal overgrowth, particularly in the context of mothers with normal glycaemia. Interestingly, altered placental vasculature function may also be implicated in placental retention (Auger et al., 2021), which was observed in Case

#2, implying a hypothetical role of hyperinsulinaemia in the pathogenesis of this condition (Siddiqui & Hladunewich, 2011).

Diagnostic and therapeutic targets to define normal glycaemic patterns in pregnancy have received considerable controversy. The landmark HAPO trial, which included over 25,000 women worldwide, suggested that maternal glucose levels below the previously accepted diagnostic thresholds for GDM were predictive of large-for-gestational age and foetal hyperinsulinaemia (HAPO Study Cooperative Research Group et al., 2008). In response, the International Association of Diabetes in Pregnancy Study Group and the American Diabetes Association recommended new lower diagnostic criteria for GDM (Metzger, Gabbe, et al., 2010). Further, glycaemic targets for women with GDM have also been a source of controversy. Hernandez et al. (2011) performed a systematic review and collated glycaemic patterns from healthy pregnant women in 11 studies between 1975 and 2008. Their results showed remarkably lower glycaemic patterns than targets set for women with GDM, suggesting stricter glycaemic targets are required to reduce the risk of foetal overgrowth among women with GDM and obesity in pregnancy. Indeed, the proportion of undetected hyperglycaemia in pregnancy due to lenient criteria is unknown. When compared against the stricter thresholds proposed by Hernandez et al. (2011), Case #1 and Case #4 from our study, both of whom were characterised as having hyperinsulinaemia in trimester 1, could be described as borderline hyperglycaemic based on fasting (proposed normal: 3.4-4.4 mmol/L, versus 4.7 mmol/L for Case #1), 1-hour (proposed normal: 5.3-6.8 mmol/L, versus 7.2 mmol/L for Case #1 and 8.8 mmol/L for Case #4), and 120-minute glucose levels following the OGTT (proposed normal: 4.9-6.1 mmol/L, versus 6.6 mmol/L for Case #4). Noting this relationship in Cases #1 and #4, it is possible that these "normal glycaemic" women may have had excess maternal glucose available throughout pregnancy which, in line with the Pedersen hypothesis (J. Pedersen, 1952), could drive foetal hyperinsulinaemia.

GWG is one of the most significant and modifiable factors in pregnancy, affecting maternal and foetal health. Dietary and lifestyle interventions that encourage healthy GWG observe a reduced risk of GDM (Lamminpää et al., 2018), and other associated adverse outcomes such as caesarean delivery, macrosomia, neonatal respiratory morbidity, and maternal hypertension (Muktabhant et al., 2015). Excess GWG also has been positively associated with higher neonatal adiposity (Crozier et al., 2010; Jedrychowski et al., 2011; A. P. Starling et al., 2015) and large-for-gestational age incidence (Goldstein et al., 2017) in numerous cohort studies. Varying GWG outcomes for Cases #1 and #4, both of whom had Kraft IIB hyperinsulinaemia in our study, may explain differences in obstetric outcomes observed. Case #1 (pre-pregnancy BMI 28.4 kg/m^2) gained 19 kg throughout pregnancy, amounting to an excess of 7.5-12 kg. However, Case #4's

(pre-pregnancy BMI 37.8 kg/m^2) total GWG was below the recommended 5-9 kg (Institute of Medicine & National Research Council, 2013; Ministry of Health, 2014). These GWG differences were reflected in nutrition and physical activity behaviours described by Cases #1 and #4. During the study period, Case #4 noted changes in dietary behaviours toward a "healthier" eating pattern to circumvent gestational risks associated with obesity in pregnancy. Lower GWG experienced by Case #4 could have mitigated her risk of foetal overgrowth or hyperglycaemia, thus allowing natural labour. Unfortunately, delivery was ultimately complicated by an emergency caesarean due to a prolonged latent phase of labour and posterior foetal position. Comparing outcomes between Case #1 and #4, it could be argued that had Case #1 been provided with lifestyle-based strategies early in pregnancy to achieve GWG within the Institute of Medicine guidelines (Institute of Medicine & National Research Council, 2013; Ministry of Health, 2014), induction of labour and birth trauma may have been avoided. Interestingly, these experiences are contrasted against Case #3 whose GWG was within 1 kg of recommendations (Institute of Medicine & National Research Council, 2013; Ministry of Health, 2014) and had a natural labour and delivery without adverse outcomes. We speculate that Case #3's appropriate GWG and normal insulin response pattern were likely contributing factors to a low risk profile for adverse outcomes.

This is the first study that, to our knowledge, examines maternal outcomes across the gestational period in relation to a first trimester insulin pattern. A strength of this study was that we compiled personal dietary and lifestyle information as well as clinical changes that are known to influence gestational outcomes. Since it is known that the presence of a certain risk factor does not guarantee an adverse outcome, this case series design allowed contextualised interpretation of individual risk factors and outcomes. A further strength is that we have modelled a modified Kraft pattern criteria to make the algorithm applicable to a 120-minute OGTT (75-gram glucose), versus the original criteria that required a 180-minute insulin value to diagnose hyperinsulinaemia (Patterns I, IIA, and IIB). These criteria are more practical to apply clinically as the majority of OGTTs used in clinical practice involve a 120-minute test (75-gram glucose). This is especially important for pregnant women who may find it difficult to fast for more than two hours following the glucose bolus, especially after an overnight fast.

Further work is needed to validate criteria to define both normal insulin response patterns during pregnancy and one that might indicate pre-existing insulin resistance and hyperinsulinaemia. The Kraft patterns have not been validated in a pregnancy context. Larger prospective research is needed to explore relationships between insulin response patterns and outcomes and to presented in context alongside established indicators of insulin resistance. The lack of any consensus definition for normal insulin response patterns during pregnancy in a

limitation of this work. Timing for insulin assessment must also be defined in pregnancy since insulin secretion and sensitivity progressively changes after placental formation near the end of the first trimester, at approximately 10-12 weeks of gestation (Burton & Jauniaux, 2018). Placental-induced hyperinsulinaemia may have been a confounding variable in two women from our study (Case #2 and Case #4) who underwent OGTT testing at 14+5 weeks of gestation due to practical limitations.

The key limitation of this study is that the interpretation of case series data is limited to speculation. As a result, we cannot draw any conclusions or make any associations with certainty from this participant group. We also acknowledge there are many confounding characteristics of human pregnancy that can increase the risk of adverse outcomes. These include various intrinsic maternal and paternal factors, as well as external antenatal and birth care influences. Due to the individual nature of pregnancy and delivery, even the absence of risk factors does not guarantee that pregnancy comes without vulnerabilities. A further limitation is that the foetal growth assessments used were requested at the discretion of the women's lead maternity carers. Sequential growth measures in trimester 3 were only available for Case #1 and were not plotted on customised growth charts, therefore limiting interpretation. We, therefore, recommend that this study be repeated with a broader sample size to further explore the heterogeneity of insulin patterns in early gestation and establish statistical power that may draw associations toward adverse gestational outcomes.

5.6 Conclusions

Insulin response pattern analysis provides a promising template that could assess a woman's metabolic risk early in gestation. Future studies should look toward validation of insulin response pattern analysis among pregnant women to progress this work. Further studies with larger participant cohorts are also needed to characterise the metabolic phenotype of women with hyperinsulinaemia in pregnancy according to different Kraft patterns. Analyses from larger cohorts examining risks for clinical endpoints such as gestational hypertension, preeclampsia, hyperglycaemia, and large-for-gestational age infants could also be used to inform future screening tools applicable in a clinical setting. Identifying these women early in pregnancy could mean that lifestyle-based initiatives could be introduced sooner to mitigate excess GWG and potential adverse maternal and neonatal outcomes.

Chapter 6. Health professionals' views and experiences around the dietary and lifestyle management of gestational diabetes in New Zealand.

Preface

The previous chapters exploring insulin response patterns during pregnancy invited speculation as to whether early pregnancy dietary interventions could be beneficial for reducing the risk of adverse outcomes among women who present with hyperinsulinaemia. Combined findings from studies in Chapters 4 and 5 as well as previous literature suggest that women with pre-existing insulin resistance and hyperinsulinaemia are likely to benefit from lifestyle interventions during pregnancy. Although literature presented in Chapters 2 and 3 demonstrated uncertainties around what type of advice is best for positive outcomes, many successful trials would incorporate an element of personalisation with a nutrition professional (i.e. dietitian). The health professional's role in promoting positive outcomes was also identified and discussed in one of the case studies in the previous chapter; we speculated that guidance from Case #4's midwife initiated healthy lifestyle changes during pregnancy that may have been contributed to this woman achieving healthy GWG. The following study aimed to gain a broader perspective on current lifestyle advice available to pregnant women. Qualitative methodology was incorporated for the final component in this series of studies with the aim of further contextualising an understanding of how first trimester screening for hyperinsulinaemia could support and/or enhance current practice. The study presented this chapter was published in *Nutrition & Dietetics* in 2021 (doi: 10.1111/1747-0080.12719).

6.1 Abstract

This study aimed to investigate New Zealand health professionals' views and experiences around the dietary and lifestyle management of GDM. Semi-structured interviews were conducted remotely with health professionals; sessions were recorded and transcribed. Core themes were extracted using inductive thematic analysis using a framework method. Twenty-seven health professionals were interviewed (13 diabetes dietitians, 8 specialist diabetes midwives, two community midwives, one antenatal clinic midwife, one obstetrician, and two endocrinologists). Themes were organised into three central domains: (1) Social and cultural barriers, (2) Service provision, and (3) Nutrition advice. Enabling themes included professional collaboration, innovation, and creating trusting and supportive environments. Key barriers identified included accessibility, cultural barriers, overwhelmed service, fragmentation and conflicting information,

and nutrition resource gaps. Findings highlight foremost a deficit in primary antenatal nutrition advice that may play a significant role in the fragmentation identified. Investment in community-inclusive services providing antenatal nutrition and diabetes education appears critical to overcome barriers associated with misinformation and poor outcomes. Pathways to include nutrition education from various primary care health providers should be investigated to ease the burden from specialist gestational diabetes clinicians and allow effective delegation of dietetic resources. Revision of current nutrition guidelines for the management of GDM in New Zealand is needed to facilitate consistent messaging and standards of care.

6.2 Introduction

GDM is one of the most common pregnancy complications that is estimated to affect 6.2% of pregnancies in New Zealand and up to 13% of pregnant women globally (Lawrence, Wall, & Bloomfield, 2019; Zhu & Zhang, 2016). The rising prevalence has grown in parallel with the rise in obesity and insulin resistance syndromes affecting women of child-bearing age and is at the centre of the "diabetes begetting diabetes" vicious cycle (Egan et al., 2017; Kampmann, Knorr, Fuglsang, & Ovesen, 2019; McIntyre et al., 2019). GDM is a condition where physiological gestational changes become augmented by maternal insulin resistance, leading to exaggerated maternal hyperinsulinaemia, carbohydrate intolerance and hyperglycaemia (Hernandez et al., 2018). Poorly controlled gestational blood glucose concentrations are associated with adverse acute maternal and neonatal outcomes such as pre-eclampsia, large-for-gestational age infants, shoulder dystocia, and neonatal metabolic complications such as hypoglycaemia and respiratory distress syndrome (Corrado et al., 2009; HAPO Study Cooperative Research Group et al., 2008; H. S. Kim et al., 2002). Mothers and infants also experience a significantly increased risk of adverse metabolic outcomes later in life, especially, type 2 diabetes and cardiovascular disease (B. Daly et al., 2018; Damm, 2009; Succurro et al., 2021; Tranidou et al., 2021).

Lifestyle modifications are recognised as an essential first-line therapy for the management of GDM (American Diabetes Association, 2020; Duarte-Gardea et al., 2018; Ministry of Health, 2014). Under the guidance of a specialist registered dietitian, medical nutrition therapy for GDM aims to provide adequate nutrition to promote foetal and maternal health, achieve glycaemic goals, and promote appropriate gestational weight gain (American Diabetes Association, 2020; Duarte-Gardea et al., 2018; Ministry of Health, 2014). Internationally, many governing bodies recommend dietetic guidance over a course of regular and frequent visits to optimise outcomes (Duarte-Gardea et al., 2018; Tsirou et al., 2019). Although specialised dietary advice for women diagnosed with GDM in New Zealand has received a "strong" recommendation, clinical practice guidelines surrounding timing and frequency of dietetic involvement are not specified (Ministry

of Health, 2014). Medical nutrition therapy and physical activity may serve as a complete therapy for many women or be combined with pharmacotherapy as gestation and maternal insulin resistance progresses (American Diabetes Association, 2020; Ministry of Health, 2014).

Despite the importance of nutrition in GDM being undisputed, global inconsistencies in dietary guidelines have led to uncertainly around which specific type of dietary advice is best (Hernandez & Brand-Miller, 2018). Inconsistencies in dietetic practice were demonstrated in a recent survey among New Zealand dietitians which identified varying compliance with evidence-based guidelines (Lawrence, Wall, Bloomfield, & Crowther, 2017). Specifically, a key challenge was adherence to recommendations regarding minimum carbohydrate intake, which in some instances, advice from practicing dietitians was inconsistent with the Ministry of Health guidelines for pregnant women (Ministry of Health, 2014). A further challenge was also identified in service delivery; less than half of dietitians reported seeing referrals within a week (39%) and less than a third (28%) had capacity to offer the minimum of three dietetic consultations as recommended by Academy of Nutrition and Dietetics (American Diabetes Association, 2020). Such practice barriers could also limit the degree to which nutrition advice can be personalised to meet women's needs, a concept which is integral to the New Zealand Ministry of Health's recommendations for GDM care (Ministry of Health, 2014).

Various gaps around medical nutrition therapy delivery were also identified in an Australian survey interviewing diabetes educators, dietitians, endocrinologists, obstetricians, and midwives; one-third of respondents indicated that diet advice may be provided by anyone in the multidisciplinary team, contrary to consensus guidelines which recommend specialist dietitian input (Meloncelli, de Jersey, Barnett, & Pelly, 2019). Although nutrition therapy is always presented as the first-line approach (Duarte-Gardea et al., 2018; Ministry of Health, 2014), it is plausible that in under-resourced clinical settings second-line pharmacotherapy might receive greater emphasis. GDM management in New Zealand also follows a multidisciplinary model where women are offered input from specialist health professionals who oversee various aspects of the women's glycaemic control, foetal development, and pharmacotherapy (Ministry of Health, 2014). This means that women may be provided with multiple points of contact where lifestyle advice is offered. There has been little published literature examining the nutrition management of GDM from a local multidisciplinary perspective. Therefore, the aim of this exploratory qualitative study was to investigate views, opinions, and experiences around the dietary and lifestyle management of GDM from the perspective of GDM-specialist health professionals in New Zealand. This study aimed to explore the research question: what are the challenges and gaps in care relating to dietary and lifestyle advice for GDM management in New Zealand?

6.3 Methods

Participants included in this qualitative study were health professionals who provide care to women diagnosed with GDM in New Zealand and could comment on their experience offering nutrition advice to these women. Purposive sampling was used to gain representation from each professional group in the GDM multidisciplinary team, and to represent rural and urban areas. Invitations to participate were circulated through GDM specialist interest group email newsletters and private online groups (Dietitians New Zealand and New Zealand College of Midwives, newsletters, and their respective Facebook groups). Recruitment flyers were also distributed across Auckland maternity and primary care practices. Personal invitations were sent to health professionals working within GDM services from Auckland, Counties Manukau, and Waitemata District Health Boards District Health Boards, from which the study was granted independent review by each of the District Health Board's respective Clinical Governance review committees. Participation was based on voluntary decisions and informed consent provided before interviews. Ethical approval for this research was granted by Auckland University of Technology Ethics Committee (19/405).

Individual semi-structured interviews were conducted remotely by video-call (Zoom Video Communications Inc., 2021) between September 2020 and May 2021 by the first author (SN, PhD student with MSc in nutrition and dietetics, New Zealand registered dietitian, previous experience conducting qualitative interviews and dietetic experience working in GDM specialist clinics). The decision to use video-calls exclusively resulted from social restrictions in response to the Covid-19 pandemic. When potential participants were colleagues from the same discipline and workplace, a group interview was offered by video-call. In consideration of privacy in these instances, participants were always offered the opportunity to opt out of group interviews to have an individual interview if desired. The main research objectives of the interviews were shared beforehand, enabling participants to be prepared. Questions aimed to explore three key inquiry domains which were: 1) Clinical role in the care of women diagnosed with GDM, 2) Experiences providing nutrition and lifestyle advice (positive experiences and challenges), 3) Gaps where existing systems or resources could be improved to support best outcomes. Indicative questions and contextual probing questions are provided in Appendix C, Supplementary Table 6.

Interviews were transcribed following a two-pass method by the primary researcher (formal training in thematic analysis conducted at Auckland University of Technology, October 2018). Transcribed texts were analysed and coded using NVivo software (version 2021) to perform inductive thematic analysis using The Framework Method (Gale, Heath, Cameron, Rashid, &

Redwood, 2013). Codes identified from the primary transcript analysis were defined and categorised into central themes and sub-themes. A sub-set of transcripts (n=5) were analysed and independently coded by a second reviewer (Associate Professor in health psychology with extensive experience in qualitative research). Any discrepancies in codes and theme categories were discussed to produce the Coding Framework (Appendix C, Supplementary Table 6). Secondary coding was then performed to ensure all codes fit within the framework. Codes were eventually categorised into main themes and subthemes.

6.4 Results

Twenty-seven health professionals participated in the study (Figure 13). Participants were specialist diabetes dietitians (n=13, from an estimated pool of 33), specialist diabetes midwives (n=8, from an estimated pool of 60-90), community lead maternity care midwives (n=2), an antenatal clinic midwife (n=1), endocrinologists (n=2, from an estimated pool of 18-25), and an obstetrician (n=1, from an estimated pool of 18-25). All participants were employees from District Health Boards across New Zealand. More than half of the participants (n=18) were in the upper North Island (Auckland, Counties Manukau, Waitemata District Health Boards), three from the central North Island (Tairāwhiti, Midcentral, and Bay of Plenty District Health Boards), four from the lower North Island (Capital and Coast, Wairarapa, and Hutt Valley District Health Boards), and two from Southern District Health Board. Data saturation was established from midwives and dietitians on conclusion of data collection, however, data saturation from the perspective of obstetricians and endocrinologists specifically was not established due to low participant numbers represented.

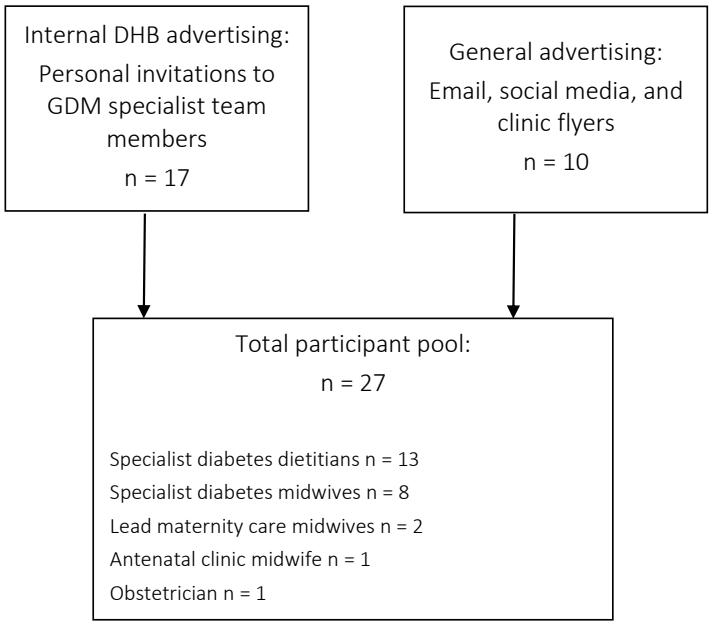


Figure 13 Sampling strategy and included participants.
DHB: District Health Board

The inductive thematic analysis identified three key domains: 1) *Social and Cultural Barriers to Care*; 2) *Service Provision* (enablers and challenges); and 2) *Nutrition Advice* (enablers and challenges). Key domains and corresponding themes are shown in Table 19. Examples of supporting quotations for specific codes used are included in Appendix C, Supplementary Table 6.

Within the domain "*Social and Cultural Barriers to Care*", central themes included "*Accessibility*", "*Cultural Barriers*", and "*Mental and Emotional Challenges*". Participants described various barriers affecting access and engagement with clinical services. Having appointments only offered on a certain day of the week were thought to potentially conflict with the women's personal commitments. Specifically, taking time off work or seeking childcare could incur additional costs. Secondly, transportation limitations and the cost of parking at clinical centres were physical accessibility barriers, especially for women travelling from outside of main city centres (Appendix C).

"*Social Issues*" were acknowledged to affect women's access to services and resources needed to implement lifestyle advice. This included socioeconomic barriers such as not being able to access nutrient-dense foods due to cost, transport to shopping centres, and lacking the cooking skills required to prepare healthy meals within a limited budget. Participants also described frequently advising women with family violence, addiction, homelessness, and mental health concerns. In these situations where a woman's safety was a greater concern, dietary advice was considered a low priority and not emphasised as strongly (Appendix C).

Participants described "*Cultural Barriers*", particularly among first- or second-generation immigrants to New Zealand, including refugee populations. These groups were believed to be more likely to experience inequity in nutrition care because of language and cultural barriers

> "[Deidentified city] is a refugee centre, so that's another group of people that often are very difficult to engage with. Not only language barriers, but email doesn't seem to cut it. They don't often speak English and can't converse, so it's not safe to adjust insulin or metformin, or anything over email, but then getting them on the phone is really hard." Dietitian 10

Table 19. Central themes identified through inductive thematic analysis

Domain	Themes
Social and cultural barriers to care	
	Accessibility • Geographical inequity • Transport • Health literacy challenges • Social issues • Food environment • Unidentified non-engagement Cultural barriers • Community disconnect Mental and emotional challenges • Shame, diabetes stigma, isolation
Service provision	
Enablers	Professional collaboration Innovation • Online, telehealth consultation, non-personal communication • Community Health Worker role
Challenges	Overwhelmed service • Unwelcoming clinic environment • Time limitations • Health professional burden • Nutrition needs across the continuum of care • Primary care gap
Nutrition advice	
Enablers	Creating trusting supportive environments • Autonomy • Personalisation Nutrition education and health literacy
Challenges	Nutrition resource gaps • Cultural relevance of existing resources • Nutrition guideline specificity Fragmentation and conflicting information • Distrust • Misinformation • Food beliefs and cultural trends • Over restriction

A disconnect within communities was also recognised as being a barrier (Appendix C). Lack of connection between community members was seen as having a negative impact on the way women access health information and services. Community lead maternity carer midwives identified that some women would engage with services late in their pregnancy, resulting in delayed care.

Mental and emotional challenges for women were also commonly recognised throughout the GDM care process. Examples included shame and stigma associated with the GDM diagnosis, which could negatively impact women's ability to adhere to the advice provided. Women were sometimes seen as being isolated or unsupported by family, or may disengage from care due to feeling as if they had "failed".

> "Often it's quite an isolating experience for them when they get that diagnosis and they feel like they've failed on some level. For some woman of certain ethnicities [they perceive] that inevitability of getting it [GDM]." Antenatal Clinical Midwife

Themes under the "*Service provision domain*" included "*Professional Collaboration*", "*Innovation*", and "*Overwhelmed Service*". The theme "*Professional Collaboration*" identified working within a multidisciplinary team environment as an enabler. Lifestyle advice was viewed as a collaborative therapy, alongside glucose monitoring and medication. Providing consistent nutrition messages from all health professionals was crucial to building trust with the women and overcoming misinformation.

> "Rather than trying to teach against each other, the consistent message is a big part of it. Once we are consistent, people know that we are consistent, then people start listening to us." Dietitian 12

Participants identified innovative strategies to address systemic challenges. In response to the Covid-19 pandemic, many participants offered online consultations, which improved their ability to engage women who experience access barriers to hospital-based services. Participants from Counties Manukau District Health Board, one of New Zealand's largest District Health Boards serving a large proportion of Māori and Pasifika peoples, described reliance on Community Health Workers to support engagement, facilitate group nutrition education, and address health literacy gaps.

> "Sometimes it feels daunting to come to the clinic every single time. Sometimes we can do a phone consult. We are doing phone consults and virtual reviews. That is why we have a Community Health Worker to bring their relationship together, and then at the same time we've also worked with other [non-governmental organisations]…So our messages are the same." Dietitian 12

> "This Community Health Worker will go into the family and make the recipe together to tap into those hard-to-reach areas. A lot of time, they don't need a dietitian because they just need basic [information and] to be able to cook." Dietitian 12

Participants described service provision challenges resulting from an "*Overwhelmed Service*" and clinical resourcing limitations. Specialist midwives and physicians experienced time pressures when meeting with women, which meant diet was a secondary priority amidst several pieces of information provided.

> "We're time-poor. We don't have enough staff. We gloss over the food, and it's almost like we go straight on to medication. Even though we know that diet and exercise are the number one way of treating things. We do have resources like little books and things that we could give the women, but it's almost like we miss that step now because we don't have the time or the inclination, or the woman's busy, so she can't actually listen to the information that we're giving. If we had more staff, we could definitely go more into depth with diet and exercise." Specialist midwife 6

Clinical capacity limitations meant some services could not offer all women an individual appointment with a dietitian. GDM services used group education and written resources to supplement these gaps or combined dietitian appointments with another specialist consultation (midwife or endocrinologist). Among dietitians who had capacity to see every woman for an initial one-on-one consultation, the inability to follow-up women for subsequent visits hindered their ability to personalise advice. Although follow-up appointments could be offered, there was concern that additional appointments would impede on time required to see higher priority newly diagnosed patients. This experience also portrayed job dissatisfaction among dietitians due to feeling ineffective and not being able to follow up with their patients.

> "We can't give follow-on advice effectively. Unless it's by phone or email, which again, goes into our unfunded time. That doesn't work well. There is a lack of job satisfaction because we can't follow up the women. We don't know what our interventions are doing. Because it's one appointment, as dietitians, we sound like broken records. We're giving the same information over and over again, which is just basic [information]." Dietitian 4

Recognising the positive impact of nutrition input across the continuum of care, interviewees described a desire for women to receive nutrition advice more frequently as well as including post-partum input to support long-term healthy lifestyle choices.

> "If I had more time with these ladies, I don't know whether some of them we could either delay or prevent them having to go on to other medications and insulin. Obviously, the key is to get tight control, so I appreciate why the diabetes nurses are like "We'll start you on some insulin," but I do wonder

> whether sometimes they actually just need a little bit more time to look diet first." Dietitian 3

The sub-theme "*Primary Care Gap"* recognised a deficit in resources required to address antenatal nutrition and lifestyle advice for women at risk of GDM, such as women with prediabetes or familial risk factors.

> "I don't think Primary Health services do well by dietary information for women who are at risk. I do not believe that for one minute. I think that pre-diabetic women or women who are at risk of diabetes are not managed well. It's pretty much ignored. I do not think that Primary Health, [that] the GP, in 15 minutes, can address the issues. I don't think they know where to refer to. I just don't think it's done well. I think it's a huge sector of the population that just aren't managed." Specialist Midwife 4

Participants also described that a disconnect between service providers and communities meant women and whānau ("family / extended family") may not seek help from health professionals due to feeling unsafe or uncomfortable in clinical settings such as the hospital. Existing community services were described as non-collaborative and lacking practical support to address health literacy and community needs.

> "You can't just sit at your office. So what is it about? It should be about connecting the community. It should be about bringing groups to do their community gardens. This is how you grow your kai ("food"). It's exactly the same as growing your pēpi ("infant"). You have to nurture them. Workshops in marae ("meeting place"). Working with Hapu ("communities"). Working with Iwi ("tribe")." Community Midwife 1

Within the *"Nutrition Advice Domain"* central themes included *"Creating Trusting, Supportive Environments", "Nutrition Education and Health Literacy", "Nutrition Resource Gaps",* and *"Fragmentation and Conflicting Information".* Participants described the significance of "*Creating Trusting, Supportive Environments*" to suggest that positive interactions were those that inspired autonomy, were personalised, and built women's health knowledge and understanding of their GDM management. Women were encouraged to be included in decision making and empowered by what was within their capacity to implement. Providing women with education to develop their understanding of GDM and the combined role of diet and medication was seen as an essential part of delivering a patient-centred service. Some participants emphasised the role of the dietitian to personalise dietary advice.

> "I try to explain to them what's happening with their body because I think if they can understand what's happening with their body, that can help them decide how they can help themselves." Specialist Midwife 2

Further barriers included gaps in the existing tools and resources available to participants. Often advising a high proportion of women from varying cultural backgrounds, nutrition information resources were deemed culturally irrelevant for some individuals. This was particularly relevant in District Health Boards serving a high proportion of refugee communities (Appendix C).

Discourse around the nutrition guidelines informing the content of resources provided was a further challenge described by dietitians. Non-specificity contributed to challenges when advising women with lower-normal body mass indices and from varying cultures who typically wouldn't consume the recommended 175 grams of carbohydrate per day before pregnancy. Inability for dietitians to follow up with women meant diets could not be personalised based on changes throughout gestation.

> "Ultimately, there's no real guidelines as to how much carbohydrates. What's the safety around ketones in pregnancy? The research has definitely changed. We've gone away from the prescriptive amount, but then we're left with "Ok, what do we guide?" I think the guidelines aren't there. The recommendations aren't there. So really, we're even sort of doubting our advice that we're giving." Dietitian 4

The theme *"Fragmentation and Conflicting Information"* described challenges experienced by women leading to misinformation and distrust of health care providers. Dietitians expressed concerns for when women would source nutrition advice from unverified sources, often contradicting recommendations. One community midwife interviewed justified her experience providing dietary recommendations to women after observing that the provided pamphlets included outdated advice (e.g. "to only eat three eggs per week") and directed women to online resources before meeting with the GDM service. The degree of fragmentation within the GDM service is unknown. Since dietitians could not see most women for further sessions, they expressed that having their advice followed up by other clinical team members may increase the risk of inconsistent messaging (Appendix C).

Participants also highlighted challenges originating from women's pre-conceived nutrition ideas being at odds with recommendations. Nutrition trends toward carbohydrate restriction for weight loss and management of Type 1 and Type 2 diabetes could explain the high prevalence of women over-restricting carbohydrates during pregnancy. Over-restricting food commonly resulted from misinformation. In some instances, women may over-restrict food to avoid medical treatment under the perception that prescribed medications are dangerous to the foetus.

> "I get quite a lot of women from a range of the different cultures where they will cut out carbohydrate entirely. [They] will have seen me. There's no way

> I would have said to cut out all carbohydrates. But then they come back, and they've cut out all carbohydrates. The baby's growth had dropped off, and the obstetrician was really concerned." Dietitian 2

6.5 Discussion

Dietary and lifestyle factors are unequivocally an important part in the management of GDM and are well-recognised by the New Zealand Ministry of Health clinical practice guidelines and by various governing bodies internationally (Duarte-Gardea et al., 2018; Ministry of Health, 2014; Tsirou et al., 2019). This study highlights health professional perspectives on various challenges that affect the way nutrition advice is delivered to women with GDM in New Zealand. Inductive thematic analysis used in this study defined three interconnected domains. These included the "Social and Cultural Barriers to Care Domain"; "Service Provision Domain"; and "Nutrition Advice Domain".

Findings from our study illustrate a clear gap in primary care support for women and whānau ("family / extended family") who develop GDM in New Zealand. This primary care gap parallels a systemic deficit known to perpetuate intergenerational disparities in diabetes-related ill-health between Māori, Pasifika, and European New Zealanders that have been known for over half a century (Jansen, Sundborn, Cutfield, Yu, & Simmons, 2020), and more recently, among new immigrant communities. Health disparities have been linked to multiple socioeconomic, accessibility, cultural, and environmental barriers to care described by participants in our study and reported elsewhere (Jatrana & Crampton, 2009, 2020). A paucity of primary antenatal initiatives that emphasise diabetes prevention means that being referred to secondary-level GDM services in New Zealand could be a woman's first encounter with diabetes and dietary information during pregnancy. Thus, it is not surprising that participants described encounters where women were prone to engaging in misinformation or may have exceeded gestational weight gain targets at the time of referral, thus increasing the risk of further medical monitoring and interventions later in gestation (Institute of Medicine & National Research Council, 2013). Our results are consistent with findings from a survey taken among general practitioners in New Zealand; primary care doctors reported it was uncommon for nutrition and weight management to be discussed with newly pregnant women due to limited time and knowledge of weight gain guidelines (Fieldwick, Smith, & Paterson, 2019). Considering many women seen in secondary care GDM services would have initially presented to a primary care provider with identifiable risk factors, a dearth of nutrition and lifestyle support available to women pre-conception and in their first trimester of pregnancy is a blatant missed opportunity.

Internationally, evidence from intervention studies point to the potential for dietary changes introduced early in pregnancy to reduce GDM occurrence (Griffith et al., 2020; Shepherd et al., 2017). However, the lack of lifestyle guidance for New Zealand pregnant women at risk of GDM in primary care represents a wider deficit in the structures guiding New Zealand's health system. The case to improve opportunities for dietetic involvement in primary care settings was recently endorsed in a report by the New Zealand Institute of Economic Research (Hogan & Tuaño, 2021). Authors highlighted an urgent need for dietetic positions to support an array of challenges faced by primary health and disability services. Guidance in pregnancy and GDM was one of several roles which, by improving dietary behaviours, could save $210 million per year in cardiovascular disease and diabetes care. Internationally, there have also been various initiatives exemplifying a shift toward integrative primary care services that include dietary and lifestyle education (Conca et al., 2018; Coppell et al., 2017; Gucciardi, Espin, Morganti, & Dorado, 2016; Utz et al., 2018; Wranik et al., 2019). Better access to nutrition professionals in primary care has the potential to ease the burden from other registered health professionals such as nurse practitioners, general practitioners, and midwives who act as a first point of contact for women in need of dietary advice (Mitchell, MacDonald-Wicks, & Capra, 2011).

Health coaches have also recently been upheld in primary care settings to perform various health educational roles and facilitate behaviour change (ProCare, Auckland District Health Board, Counties Manukau Health, Waitemata District Health Board, & Awi Ora, 2019; Te Pou, 2021). A supporting health coach role ("Community Health Worker") was also described by participants from Counties Manukau District Health Board, who serves the largest population of women with diabetes in pregnancy nationally. Community Health Workers from Counties Manukau District Health Board's GDM service perform various roles such as leading initial nutrition education groups and acting as a community liaison to women and whānau ("family / extended family") for health literacy and accessibility support. Experiences from Counties Manukau District Health Board show how health coaches or similar professionals could be embedded within primary care to bridge a gap between community members and health care providers. With the potential to overcome accessibility, health literacy, and time constraint barriers, such integrated services could enhance the quality of care from secondary specialist GDM professionals including dietitians, midwives, nurses, endocrinologists, and obstetricians.

Although often working beyond full clinical capacity, health professionals interviewed aimed to demonstrate empathy in clinical practice to build trust and create supportive environments for women. These themes are consistent with the philosophies from New Zealand's National Health strategy that strives toward high-trust systems that work together with people and their whānau ("family / extended family") at the centre of care (Minister of Health, 2016). Failure to

personalise advice was also believed to increase the risk of disengagement or distrust. Participants found this particularly concerning, knowing that it is common for patients to engage in alternative advice from online forums and are more likely to be led by misinformation if they do not trust health providers (O'Key & Hugh-Jones, 2010). Although personalising advice to meet women's individual needs was described in an overall positive light, these experiences were overshadowed by funding and staffing constraints which limited dietetic involvement for all women referred to the service. That is to say, health professionals from our study suggested that not every woman with GDM in New Zealand may receive the opportunity for a one-on-one dietitian consultation, and among those who do, a follow-up consultation was uncommon. Experiences describing limited clinical dietitian capacity are at odds with international guidelines recommending at least three visits with a dietitian to assist women with GDM to meet their nutrition goals (Duarte-Gardea et al., 2018). As such, the overall clinical impact of limited specialist nutrition input in varying settings across New Zealand should be investigated further.

In response to capacity constraints, a unique initiative from Counties Manukau District Health Board was to have group sessions run by a Community Health Worker, thus allowing clinical capacity for women with higher needs to be seen one-on-one with the specialist dietitian. Initiatives to provide primary nutrition advice in a lay group setting exemplify how antenatal nutrition and diabetes education could be provided by non-specialist health professionals in primary care. Community-based nutrition guidance has the potential to overcome accessibility barriers, meaning greater bandwidth for sustainable lifestyle changes. Results from 19 intervention trials (6633 women) have shown that combined diet and exercise interventions during early pregnancy could reduce GDM occurrence when compared to standard antenatal care (relative risk 0.85, 95% CI 0.71 to 1.01; moderate-quality evidence) (Griffith et al., 2020; Shepherd et al., 2017). For women who develop GDM later in pregnancy, providing lifestyle guidance sooner could also enhance specialist interventions, meaning that women would be referred to GDM services with pre-existing nutrition knowledge, thus allowing further personalised recommendations.

Our study identified professionals who viewed nutrition guidelines as being generalised and outdated. Constraints arose from the lack of specificity concerning quantities of nutrients (carbohydrate) to advise women with varying body sizes. A lack of ongoing monitoring after women receive initial dietary advice meant dietitians felt limited in their capacity to personalise beyond generalised recommendations. This finding is consistent with earlier survey results conducted among New Zealand dietitians, which highlighted a need for New Zealand -specific evidence-based practice guidelines (Lawrence et al., 2017). Lawrence et al. (2017) acknowledged important gaps in current standards of care including carbohydrate intake

recommendations, ethnic-specific considerations, guidance on appropriate gestational weight gain, and recommendations on the frequency of dietetic input. It is plausible these constraints identified from the "Nutrition Advice Domain" in our study contribute to a climate where women encounter fragmented nutrition advice which, due to conflicting messages or misinformation, is distrusted. These findings are also in line with a qualitative survey which showed that inconsistent information from health professionals was a barrier for women with GDM (Martis, Brown, & Crowther, 2017). To address this gap, collaborative initiatives are needed to improve specificity in dietary guidelines to be made suitable for heterogeneous populations of women with GDM, thus improving advice consistency.

A limitation of this study is that participants were invited by convenience sampling and respondents more likely to include individuals interested in the nutritional management of GDM. The majority interviewed were dietitians, which may have resulted in biases advocating for the profession. The high proportion of dietitians included reflected their overall role as exclusively providing nutrition advice, compared to the other professionals with varying clinical priorities. Secondly, an important limitation is that not all District Health Boards in New Zealand were represented, which could mean that service discrepancies from other regions were not captured entirely. Notably, health professionals from rural communities were underrepresented. Further, having only included health professions limits interpretation since we cannot provide a balanced perspective from the views of the women described. Only two endocrinologists and one obstetrician were interviewed, and data saturation was not achieved for this specific group due to small participant numbers. Although it was not an aim of the methodology, data saturation was reached among specialist diabetes dietitians and specialist diabetes midwives, indicated by recurring themes. Remote video interviews were a necessity at many points during this study and could have limited the level on non-verbal communication which is typically observed face-to-face. Video interviews allowed for a broader scope of participants to be recruited nationwide and prevented interruptions resulting from Covid-19 social restrictions at the time.

This study described enablers and barriers experienced by health professionals providing nutrition advice for women with GDM. Although presented as three distinct domains, we recognise that themes were interconnected, existing within the broader socioeconomic and political landscape that has influenced health care delivery in New Zealand for over a century. This study identified that limited clinical capacity, nutrition resource gaps, and a deficit in primary care guidance were significant challenges affecting dietary advice delivery, which could contribute to excessive distrust and fragmentation observed by providers. It is plausible that fragmented, generalised, or culturally inappropriate nutrition guidance could lead to

misinformation, emotional stress, or disengagement, putting mother and foetus at risk of potentially avoidable complications in pregnancy. As a result, the expectation for women to achieve nutrition goals based on one initial dietitian consultation or group education session with supporting printed resources is misguided and potentially costly. Thus, this study suggests that systemic changes are needed for services to address well-established equity gaps in GDM care and align appropriately with New Zealand's National Health Strategy (Minister of Health, 2016).

Future initiatives must consider restructuring health care delivery to address a significant gap in primary care and various broader social determinants such as accessibility and health literacy. Reorientation of health services to provide access to dietary and lifestyle advice sooner may be both cost-effective and more efficient, meaning secondary care health professionals such as dietitians could be better utilised as specialists. Further development of New Zealand-specific practice guidelines for the nutritional management of women with GDM is required to ensure consistent nutrition messages and equitable services are provided across all platforms.

Chapter 7. Discussion and conclusions

The increasing prevalence of obesity, delayed age of motherhood, and other medical conditions related to insulin-resistance such as PCOS are just some of the factors contributing to rising rates of GDM (McIntyre et al., 2019). However, not all women with pre-existing insulin resistance will develop GDM. Additionally, adverse outcomes which appear to be associated with pre-existing insulin resistance such as foetal overgrowth, gestational hypertension, and preeclampsia also occur in non-GDM pregnancies. Overall, this research explored insulin response patterns during pregnancy and the dietary implications for the prevention and management of GDM. Collectively, this work contributes to these concepts in the four key areas. First, findings presented across Chapters 4 and 5 demonstrated that a spectrum of *metabolic phenotypes* during pregnancy are under-recognised and, as a result, inadequately managed. The under-recognition of hyperinsulinaemia across a spectrum of insulin resistance during pregnancy potentially points to both gaps in the diagnostics and management of GDM. Secondly, it can be suggested that further understanding of the heterogeneity of maternal insulin secretory and sensitivity patterns could have significant implications to advance GDM management. Third, between Chapters 2, 3, and 6, it was shown that despite a healthy diet and lifestyle being important for pregnancy, there is no consensus on an optimal diet for pregnant women who carry metabolic risk factors for GDM or other adverse outcomes. Although this gap in dietary advice is well-recognised, findings from Chapters 4 and 5 point to how further understanding of metabolic phenotypes according to insulin response patterns and insulin sensitivity could be used as a tool to tailor dietary recommendations for more personalised care. Finally, Chapters 2, 5, and 6 have shown that dietary advice available in New Zealand for pregnant women with metabolic risk factors is highly variable and can be attributed to multi-layered gaps in primary health care services, diagnostic and referral algorithms, and management guidelines. Together, by looking through a lens which recognises a spectrum of metabolic phenotypes among pregnant women, this thesis presents avenues for further research that could improve screening of women at risk of metabolic decompensation during pregnancy. Furthermore, improved understanding of heterogenic insulin response responses may contribute to the improvement of lifestyle advice for pregnant women for better outcomes. The following discussion will cover these four key areas to which this thesis has contributed.

7.1 Recognising the impact of pre-existing hyperinsulinaemia on pregnancy

In pregnancy literature, hyperinsulinaemia is most frequently discussed in relation to foetal hyperinsulinaemia, which occurs when a developing foetus is exposed to overnutrition in the context of maternal hyperglycaemia and/or obesity (Corrales et al., 2021; McCance, 2011). The consequences of foetal hyperinsulinaemia are catastrophic. As the pivotal HAPO study showed, there was a continuous and linear relationship between maternal glycaemia, foetal hyperinsulinaemia, and adverse perinatal and neonatal outcomes (HAPO Study Cooperative Research Group et al., 2008). Thus, identifying maternal hyperglycaemia during pregnancy is unequivocally important to prevent foetal hyperinsulinaemia and to support maternal and offspring health (Crowther et al., 2005). However, a central argument of this thesis is that examining maternal glucose levels to prevent foetal hyperinsulinaemia only describes one part of the story. Maternal compensatory hyperinsulinaemia, in an exaggerated sense when physiological changes associated with pregnancy are superimposed on pre-existing metabolism, may be an under-recognised clinical characteristic that is just as significant for maternal and infant health. According to The Kraft Model of Hyperinsulinaemia, there is potentially a critical missed opportunity in care for pregnant women with normal glycaemia but excessive insulin resistance, hyperinsulinaemia, and associated metabolic derangements such as hyperlipaemia and low-grade inflammation. Without early gestation screening tools, this perturbed metabolic state could progress during several months of pregnancy before an elevated risk of adverse perinatal outcomes becomes apparent later in gestation (i.e., the manifestation of excess GWG or maternal hyperglycaemia).

In Chapter 2, literature was reviewed describing how insulin resistance and hyperinsulinaemia are recognised public health issues in a broader context relating to development of cardiometabolic diseases. Recognising that an increasing proportion of women may enter pregnancy with pre-existing insulin resistance and hyperinsulinaemia, the effect of pregnancy-related changes when combined with pre-existing issues was explored. From this literature, it was suggested that these further changes in maternal insulin metabolism (i.e. exaggerated hyperinsulinaemia and resistance) may present across various adverse pregnancy conditions, including blood pressure disorders, placental vascular disturbances (i.e. preeclampsia), excess GWG, and foetal overgrowth.

A link between maternal compensatory hyperinsulinaemia (i.e. as a pre-existing issue, when pregnancy changes are superimposed) and adverse neonatal outcomes is supported by mechanistic evidence. An interplay between excessive insulin concentrations circulating to the

liver and insulin resistance of adipose tissue leads to increased circulating maternal lipids, which have been proposed as being an important driver of foetal overgrowth (Barbour & Hernandez, 2018a). Excessive maternal insulin exposure at the placenta can alter foetal development by increasing fatty acid transport, reducing delivery of essential fatty acids (e.g. DHA), and altering the composition and/or function of lipoproteins in fetoplacental circulation (Hebert & Myatt, 2021; Sobrevia et al., 2016). Furthermore, the developmental origins hypothesis argues that foetal exposure to overnutrition leads to an increased risk of metabolic diseases later in life (Gaillard et al., 2019), an association that is well-established among infants born to pregnancies affected by preeclampsia, GDM, obesity, and excess GWG (Benagiano, Mancuso, Brosens, & Benagiano, 2021; Boney et al., 2005; Hrolfsdottir et al., 2015; M. Hu et al., 2021; Nehring et al., 2013). Thus, this body of work highlights that recognising hyperinsulinaemia during pregnancy could aid in identifying women and their offspring at risk of adverse outcomes. Identifying metabolic derangements before the development of hyperglycaemia could also alter the landscape of obstetric management in a way that is more proactive and personalised.

Combined findings from Chapters 4 and 5 demonstrated potential research and clinical significance of The Kraft Model of Hyperinsulinaemia in the context of pregnancy. Data presented from Dr Kraft's original work showed that nearly a third (31%) of women with normal glucose tolerance in pregnancy had Kraft Pattern III Hyperinsulinaemia. Although these data came with many limitations (i.e unknown demographic information and concerns surrounding insulin assay precision from the time), this work demonstrates the potential to explore whether there may be a connection between these insulin response patterns and adverse perinatal and/or neonatal outcomes. Recently, there has only been one cohort study that has demonstrated such an association between a similar insulin response pattern during mid-to-late gestation and adverse perinatal and neonatal outcomes (N.-J. Zhang et al., 2020), therefore pointing to an important area for further research.

Outside of pregnancy, elevated fasting and/or two-hour post glucose load (75-gram glucose) plasma insulin has been shown to precede the development of type 2 diabetes by up to two decades (Dankner et al., 2009; Hayashi et al., 2013). As such, it has been suggested that hyperinsulinaemia, identified with either a fasting or post-glucose load plasma insulin level, may be an important risk marker for cardiometabolic diseases (Crofts et al., 2015). This could therefore be used as a clinical care point to intervene with minimally invasive lifestyle-based strategies and alter an individual's trajectory toward chronic metabolic disease (Cooper, Brookler, Kyriakidou, et al., 2021).

Applying these concepts in a pregnancy context comes with great difficulty. Increased insulin secretion and resistance are recognised natural phenomena of pregnancy (Butte, 2000). Therefore, there are no criteria to determine at which point "normal" pregnancy-related elevations in insulin secretion begin to reflect an exaggerated state augmented due to pre-existing physiology. Drawing on observations between maternal glycaemia and adverse pregnancy outcomes (Bardugo et al., 2023; HAPO Study Cooperative Research Group et al., 2008), it is also likely that changes in insulin secretion and resistance occur across a biological continuum, rather than there being a threshold of absolutes. This is important in an early management context because it could suggest that as women move up a biological continuum of increased risk, there may be greater weighting placed on lifestyle-based strategies to mitigate or prevent adverse outcomes.

Findings presented in Chapters 5 and 6 indicated room to improve the early management of pregnancy to identify those at risk of adverse outcomes sooner in the gestational period. That is to say, a means to identify women with hyperinsulinaemia at the beginning of pregnancy has important implications for improving outcomes. The potential to introduce lifestyle strategies sooner is especially significant given that diet and lifestyle interventions can reduce incidences of excess GWG, maternal hypertension, caesarean delivery, and large-for-gestational age infants (Bain et al., 2015; Cantor et al., 2021; International Weight Management in Pregnancy (i-WIP) Collaborative Group, 2017; Lamminpää et al., 2018; Mohsenzadeh-Ledari et al., 2019; Muktabhant et al., 2015; Shepherd et al., 2017; Teede et al., 2022).

First trimester plasma insulin measurement – such as that described in Chapters 2, 4, and 5 – provides a promising template to identify women who may be at higher risk of metabolic perturbations later in pregnancy. However, three key concerns limit the clinical application of this method. First, there currently are no standard reference intervals to define a dysfunctional insulin response pattern during pregnancy, let alone in wider non-pregnant populations. Large population-based studies, such as that by N.-J. Zhang et al. (2020) would be required to determine thresholds at which the fasting and/or post glucose load insulin response increases the risk for perinatal and neonatal outcomes. For example, criteria could be developed using a similar methodology as what was applied to develop the IADPSG criteria for diagnosing GDM based on infant outcomes (large-for-gestational age) observed in the HAPO study findings (HAPO Study Cooperative Research Group et al., 2008; International Association of Diabetes Pregnancy Study Groups Consensus Panel, 2010).

Since changes to insulin metabolism occur rapidly across the gestational period, a standardised time window for measuring maternal insulin levels is also important. During the first trimester,

insulin sensitivity improves or is unchanged, resulting in reduced insulin requirements (Armistead et al., 2020). From placentation, insulin resistance and beta-cell hypertrophy lead to the progressive physiological hyperinsulinaemia of pregnancy. This means testing insulin patterns earlier in gestation (i.e. earlier than weeks 8-10, before placental formation) would model more closely to the pre-pregnancy state (Butte, 2000). Insulin resistance and secretion progressively increase from around gestational week 10 (Armistead et al., 2020); therefore, measuring insulin response patterns too late in gestation could lead to misclassifying more women with a dysfunctional hyperinsulinaemia pattern who, in reality, have an otherwise healthy insulin response. Pathologising women comes with the risk of over-medicalising pregnancy. Large population-based validation studies would be required to first identify an acceptable normal insulin response pattern in a healthy pregnancy for a defined time period (i.e. gestational age window). From these data, thresholds for defining dysfunctional insulin response patterns in pregnancy could be determined.

In practice, barriers are also anticipated around implementing any form of early-pregnancy testing. As identified from interviews with lead maternity care midwives in Chapter 6, some women engage in care relatively late in their pregnancy. Since an insulin assay is time-sensitive, a certain proportion of women could miss this point in care entirely.

The third key barrier to developing an algorithm to define hyperinsulinaemia during pregnancy is logistic. A reliable insulin assay taken during an OGTT is a clinically awkward test. Although OGTTs are standard practice during pregnancy to diagnose GDM, not all screening and diagnostic criteria call for universal testing with the complete fasting, two-hour protocol. One of the arguments for using the widely accepted two-step diagnostic criteria is that it is less invasive; based on the initial *non*-fasting glucose challenge (50-gram glucose load), only a certain proportion of women require the full two-hour diagnostic fasted OGTT (Chapter 2). The insulin assay test proposed in Chapter 5 used a modified Kraft algorithm for a two-hour fasted OGTT with a 75-gram oral glucose load. The burden of fasting and waiting two hours for a test, particularly during a time when women are more likely to feel unwell or nauseated due to first trimester pregnancy symptoms, means that the Kraft diagnostic protocol is likely inappropriate for wider clinical use. Moreover, the Kraft protocol requires a minimum of four samples (0-, 30-, 60-, and 120-min) during the OGTT to determine the insulin peak point, which comes at an additional cost to the standard 2-hour OGTT protocol for diagnosing GDM (0 and 120-min). Technical challenges with insulin measurement due to lack of assay standardisation and variable reproducibility also creates a challenge for determining clear diagnostic thresholds. To overcome these practical barriers, surrogate markers could be considered to develop screening algorithms that are more clinically applicable during usual antenatal screening.

There has been considerable effort from other research groups to develop personalised risk assessment models for pregnancy so that timely interventions could be delivered to mitigate negative outcomes (Thong et al., 2022). In general practice, cardiovascular screening algorithms are frequently used to guide preventative medical treatment (Ministry of Health, 2018). Applying the same thought around pregnancy as a metabolic "stress test", there is scope to suggest that similar screening algorithms to those used in general practice could be applied in the first trimester of pregnancy. Based on previously established clinical risk factors and biochemical markers (described in Chapter 2), parameters for insulin resistance and hyperinsulinaemia could include, but not necessarily be limited to: maternal age; ethnicity; BMI; smoking; alcohol and/or drug use; medical and obstetric history, including pre-existing hypertension, PCOS, prior GDM, previous small- or large-for-gestational age infant; first degree family history of type 2 diabetes; systolic blood pressure; glycaemic markers; blood or urinary ketones; lipid markers, including triglycerides and HDL cholesterol; sex hormone binding globulin; and liver enzymes. Other potential markers not currently used in standard clinical assessments could include adipokines, insulin, c-peptide, osteocalcin, and IGF axis biomarkers. Drawing on a range of parameters, a "pregnancy metabolic risk assessment" may provide a solution as a simple and cost-effective tool for universal screening as a part of usual antenatal assessments. Similar to the five-year cardiovascular risk prediction score for general adults (Ministry of Health, 2018), a pregnancy metabolic risk score could enhance communication around the significance of lifestyle-based strategies and monitoring for metabolic changes as pregnancy progresses.

7.2 Implications of metabolic phenotyping for the management of GDM

Current GDM treatment arguably follows a one-size-fits all system, with treatment goals focused on meeting glycaemic targets using either diet, exogenous insulin therapy, and/or oral hypoglycaemic agents (Tsakiridis et al., 2021). Findings from this body of work propose a modern approach to the management of GDM, which acknowledges a spectrum of metabolic phenotypes according to women's insulin resistance and insulin secretory patterns. In Chapter 4, our findings suggested that a large proportion of women with GDM and women with borderline/sub-clinical hyperglycaemia in pregnancy also have superimposed hyperinsulinaemia. With ours, and previous research (Immanuel et al., 2021; Y. Liu et al., 2018; Powe et al., 2016), beginning to recognise the heterogeneity of insulin secretory patterns in GDM – and, as suggested, other maternal and neonatal pathologies – defining varying metabolic sub-types has important implications for the future clinical treatment of GDM. Our studies in Chapters 4 and 5 suggest insulin assay using The Kraft Model of Hyperinsulinaemia could provide a means to sub-type women across a heterogeneous clinical spectrum, which with further work

could allow for personalised and precision care. Although we recognise limitations of the OGTT insulin test to identify high-risk women with hyperinsulinaemia, future research could build on the protocol described in our pilot study (Chapter 5) to develop further refined screening algorithms as a way to characterise plasma insulin responses of pregnant women.

Findings from this work suggest further knowledge around varying GDM insulin secretion phenotypes could alter treatment approaches. From examining our and previous data, there may be at least two distinct sub-groups of women with GDM: the insulin-sensitive with reduced insulin secretion and the insulin-insensitive with hyperinsulinaemia (insulin-resistant defined as HOMA-IR above the median for the normal glucose tolerant group) (Figure 14A and Figure 14B, each respectively). Immanuel et al. (2021) proposed that GDM women with reduced insulin secretion ("GDM-S", 15.7% in their cohort, as calculated using the Stumvoll first-phase index formula) may represent a sub-group that could benefit from insulin treatment early in gestation to compensate for an apparent insulin secretory inadequacy. When compared to the Kraft data analysed in Chapter 4 (Figure 7A), insulin response patterns from the "GDM-S" and "GDM-B" groups with "reduced" insulin secretion have a similar presentation as Kraft Patterns I and IIA ("Normal and "Borderline" insulin patterns). Both of these patterns display normal fasting plasma insulin (<20 μU/mL) and an insulin peak within two hours, characteristics of a normal plasma insulin response pattern. When these patterns are viewed in contrast to the "GDM-R" group, which map more closely to Kraft Pattern IIB and III (Figure 14B), it is not surprising that women with lower insulin secretion (Figure 14A) had a reduced risk of adverse outcomes, to a similar degree as women in the study with normal glucose tolerance.

To suggest that an insulin response pattern similar to Kraft I and/or IIA leads to better overall outcomes than women in the "GDM-R" group is consistent with the hypothesis presented in Chapter 4 and our case series from Chapter 5. This sub-group of GDM women with lower, or "healthier", early pregnancy insulin response patterns may have greater metabolic capacity to respond to lifestyle change and exogenous insulin treatments, leading to better outcomes. Lower circulating plasma insulin and better insulin sensitivity may mean that smaller doses of exogenous insulin are required to maintain glycaemia. Having better responsiveness to treatments could also explain reduced adverse outcomes such as large-for-gestational age infants, as observed in the "GDM-S" group described by Immanuel et al. (2021).

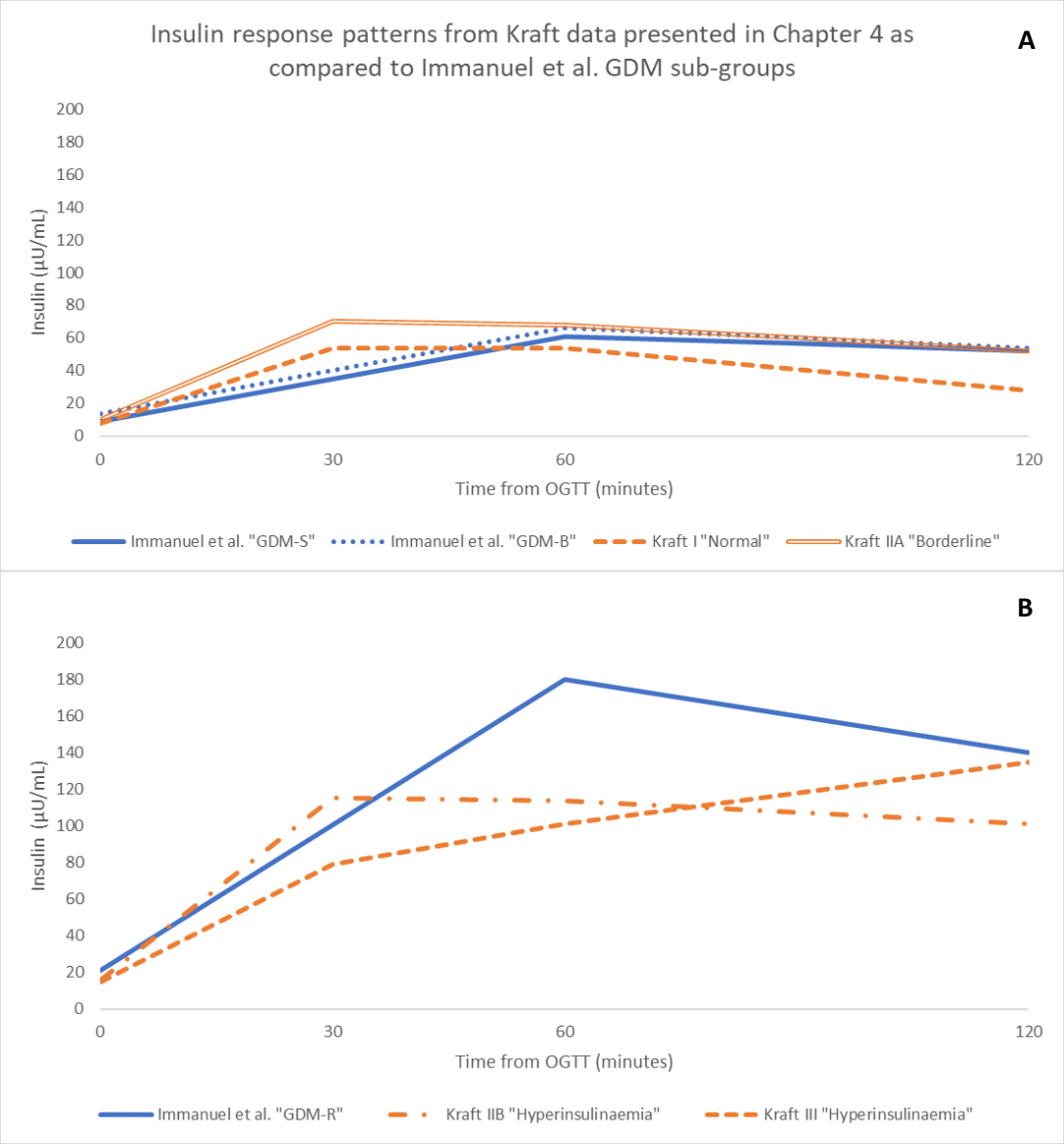


Figure 14. Insulin response patterns as reported by Immanuel et al. in three sub-groups compared to insulin response patterns from Kraft dataset analysis.

Patterns by Immanuel et al. (2020) were derived from assays collected from a 120-minute OGTT (75-gram glucose) before 20 weeks' gestation among women who were later diagnosed with GDM (samples taken at 0-, 60-, and 120-minutes). Kraft patterns were derived from data presented in Chapter 4, which includes frequencies of each Kraft pattern according to glucose tolerance groups GDM (samples taken at 0-, 30-, 60-, and 120-minutes). *Figure 14A:* "GDM-S" determined by a Stumvoll first-phase index ($1194 + 4.724 \times Ins_{0(pmol/l)} - 117.0 \times Gluc_{60(mmol/l)} + 1.414 \times Ins_{60(pmol/l)}$) <1590 and HOMA-IR <2.5; "GDM-B" included a combination of both HOMA-IR and Stumvoll indices ≥2.5 and <1590, respectively; Kraft I represents a "normal" insulin pattern and Kraft IIA is "borderline hyperinsulinaemia." *Figure 14B:* "GDM-R" determined by a HOMA-IR ≥2.5 and Stumvoll index ≥1590; Kraft patterns IIB and III show hyperinsulinaemia.

Values are reported as medians. OGTT: Oral glucose tolerance test.

The majority of women with GDM in our and previous studies were described as having insulin resistance with superimposed hyperinsulinaemia (i.e. increased insulin secretion post oral glucose load during an OGTT) (Immanuel et al., 2021; Y. Liu et al., 2018; North et al., 2021; Powe et al., 2016) (Figure 14). By demonstrating that hyperinsulinaemia over the life-course is a key process in the pathophysiology of insulin resistance and hyperglycaemia (Cooper, Brookler, Kyriakidou, et al., 2021), this metabolic phenotype may benefit from more intensive holistic lifestyle advice to improve the underlying metabolic inflexibility and inflammatory issues (Tinius et al., 2020).

An early screening protocol to identify hyperinsulinaemia before hyperglycaemia develops could allow lifestyle strategies to be introduced sooner among the women who need it most. In this instance, contextualised therapeutic dietary interventions may allow for targeted dietary modification to optimise GWG, glycaemia, foetal growth, and insulin sensitivity. There is additional room for lifestyle approaches such as targeted exercise (Cremona et al., 2018), improved sleep (Q. Lu et al., 2021; Tiwari et al., 2021), and stress management to improve insulin sensitivity alongside a therapeutic dietary approach (Fiskin & Sahin, 2021).

Decisions around medical treatment may also beg the question as to whether insulin therapy among these women has the potential to add to further metabolic dysfunction. Increased circulating plasma insulin may have multiple undesirable effects on tissues throughout the body, such as stimulating hepatic de novo lipogenesis, enhancing lipid and amino acid transport across the placenta (Barbour & Hernandez, 2018a; Jansson et al., 2013), and leading to further desensitisation of the insulin receptor (A. M. Y. Zhang et al., 2021). It is plausible that exaggerated hyperinsulinaemia from insulin treatment could worsen insulin resistance, with potential long-term negative effects. Despite metformin therapy being controversial due to concerns around placental transfer and lack of long-term safety data, this hyperinsulinaemic, insulin-resistant sub-group of GDM women may be the one who benefit the most from the insulin sensitising effects of the drug.

From a mechanistic standpoint, the metabolic implications of recommending exogenous insulin therapy to women with GDM when there is already an exaggerated insulin secretory response warrants further exploration. Outside of pregnancy, insulin treatment in individuals with advanced type 2 diabetes is associated with increased weight gain, further exacerbating insulin resistance (Prasathkumar, Becky, Anisha, Dhrisya, & Sadhasivam, 2022). Compared to those who are treated with diet and lifestyle alone, women with GDM who require insulin therapy tend to be more insulin resistant (Benhalima et al., 2015; Y.-Y. Sun et al., 2020), have a higher HbA1c in early gestation, and higher glycaemic markers during diagnosis (Bakiner, Bozkirli, Ozsahin,

Sariturk, & Ertorer, 2013; Ducarme et al., 2019; Ito et al., 2016; Tang, Xu, Li, & Li, 2019; Wong & Jalaludin, 2011); therefore, reflecting a higher risk phenotype. Women requiring insulin therapy often undergo induction of labour and have higher rates of caesarean delivery (J. Brown et al., 2017a). Their infants are also more likely to be born heavier or large-for-gestational age and/or require intensive care unit admission on delivery to treat neonatal hypoglycaemia (Benhalima et al., 2015; Delia Bogdanet et al., 2018; Crowther et al., 2005; Wong & Jalaludin, 2011). Those with higher insulin requirements also demonstrate poorer glycaemic control and outcomes compared to women on lower insulin doses (R. Koren, Hochman, Koren, Ziv-Baran, & Wiener, 2022). Long term, women treated with insulin encounter an increased risk of type 2 diabetes compared to women treated with nutrition and lifestyle strategies alone (Chodick et al., 2010; Dalfra et al., 2001; A. J. Lee, Hiscock, Wein, Walker, & Permezel, 2007).

An elevated risk for adverse outcomes among women treated with exogenous insulin to maintain glycaemic control almost certainly reflects a population with more advanced metabolic dysfunction, rather than saying it is the effect of treatment alone (Benhalima et al., 2015). However, since even the most minimally invasive treatments come with caveats, perhaps the risk of adverse outcomes, such as those that appear more frequently among insulin-treated GDM pregnancies, needs to be examined more closely. After all, the aim of treatment should be to minimise adverse outcomes. Initiation of treatment must outweigh the potential costs of higher GWG and further exacerbated hyperinsulinaemia for the merit of overcoming glucotoxicity – just as risks and benefits are considered for initiating oral hypoglycaemics which lack long term safety data. Advancing knowledge on metabolic subtypes affected by GDM could provide grounds to explore responses to different treatment modalities and develop better understanding of which women are suited for insulin treatment.

7.3 Lifestyle advice for pregnant women

Although a healthy diet is hailed as essential to promote positive maternal and offspring outcomes, the optimal diet to prevent metabolic conditions such as GDM, hypertensive disorders of pregnancy, and foetal overgrowth remains elusive (Hernandez & Brand-Miller, 2018; Mierzyński et al., 2021; Parrettini et al., 2020). Despite the well-recognised importance of healthy lifestyle choices during pregnancy, experiences from health professionals described in Chapter 6 indicated various challenges when providing dietary advice. These challenges were attributed to fragmentation, conflicting information, and inadequacy in the dietary guidelines. Combined evidence from this body of work points to a modern perspective for GDM management which may be important to address the discourse around dietary guidance.

Looking at dysglycaemia in the context of a woman's insulin sensitivity and secretory response profile could provide a licence to alter dietary advice in a way that is more personalised and nuanced. The growing body of knowledge around type 2 diabetes management informs this perspective. It has now been demonstrated that type 2 diabetes remission can be achieved through diet, independently of weight loss; growing evidence shows that insulin resistance and insulin secretory dysfunction, in a chronic disease context, can be improved by manipulating specific dietary components (Guess, 2022). Strategies that improve metabolic health independently of energy restriction have promising implications for maternal and infant health, especially since diets that emphasise weight loss are generally not recommended in pregnancy.

Outside of pregnancy, carbohydrate-restricted dietary patterns have been shown to be an effective strategy for improving glycaemic control and/or lipid profiles (increased HDL and lower triglycerides), and reducing the need for medication in individuals with type 2 diabetes (Evert et al., 2019; Feinman et al., 2015). Mechanistically, carbohydrate consumption also stimulates physiological insulin release, which in individuals with defective insulin secretion and sensitivity may manifest as hyperinsulinaemia, with or without hyperglycaemia (Cooper, Brookler, Kyriakidou, et al., 2021; Crofts et al., 2016). Healthy dietary patterns which include carbohydrate-restriction are, therefore, proposed as a strategy to mitigate this postprandial hyperinsulinaemia (Feinman et al., 2015; Wheatley et al., 2021). In the context of type 2 diabetes, carbohydrate-restricted diets have been shown to be beneficial for improving various metabolic risk markers including reduced glycaemia, reduced triglyceride levels, and visceral adipose tissue (Wheatley et al., 2021). However, a beneficial effect of carbohydrate restriction on insulin sensitivity is controversial; some authors have suggested carbohydrate restriction may increase muscle-specific insulin resistance (Guess, 2022; Kirk et al., 2009), although these observations are limited to acute feeding experiments, therefore not reflecting long-term cardiovascular risk. Contrary to arguments that carbohydrate-restriction carries an increased cardiometabolic risk, evidence from various clinical trials have demonstrated overall improvements in cardiovascular risk factors such as lower triglycerides, increased HDL cholesterol, reduced blood pressure, and reduced inflammatory markers following low carbohydrate dietary interventions (Athinarayanan et al., 2019; Athinarayanan et al., 2020; Ebbeling et al., 2022; Forsythe et al., 2008; Hyde et al., 2019; Santos, Esteves, da Costa Pereira, Yancy, & Nunes, 2012; Volek et al., 2009).

There is rationale to suggest that dietary protocols tested outside of pregnancy for individuals with insulin resistance could be a way forward for optimising metabolic health among women who enter pregnancy with pre-existing metabolic issues. However, varying degrees of carbohydrate-restricted dietary approaches have not been well-studied in pregnancy, therefore

limiting current application and clinical practice guidelines (Sweeting et al., 2021). Moderate carbohydrate restriction can be defined as 26% to 45% of dietary energy from carbohydrate, while a low carbohydrate diet may provide less than 26% dietary energy or under 130 grams per day (Chapter 2). It should be noted that these are distinctly different from very-low-carbohydrate or ketogenic diets providing 20 to 50 grams of carbohydrate per day which equates to less than 10% of dietary energy (Feinman et al., 2015; Wheatley et al., 2021).

On reviewing current literature (Chapter 2), trials investigating carbohydrate-restricted or low GI diets for women with GDM provided approximately 40-55% of energy from dietary carbohydrate (Cypryk et al., 2007; S. Han et al., 2017; Mijatovic et al., 2020; Moreno-Castilla et al., 2013), which is both within and outside of the upper range of moderate carbohydrate restriction. With the exception of early anecdotes by Jovanovic-Peterson and Peterson (1990) and randomised trials from Hernandez (2014; 2023) (which compared the conventional reduced-carbohydrate diet to a more liberal higher carbohydrate diet, ~214 g/g vs. 316 g/day) which were discussed Chapter 2, there is limited literature examining the effect of carbohydrate-restriction in the realm of 25% to 30% energy from carbohydrates.

In a recent review of the current evidence base for carbohydrate guidelines during pregnancy, Sweeting et al. (2021) demonstrated a dearth of literature exploring lower carbohydrate intake below 175 grams per day or under 40% of dietary energy during pregnancy. Only one RCT to date (n = 46 women) compared a modestly low carbohydrate intervention below 175 grams of carbohydrate per day (Mijatovic et al., 2020). Carbohydrate intake in the intervention group at the end of the study was 165 grams per day, and 190 grams per day in the control ($p = 0.04$). While no differences in primary outcomes were observed (blood ketone concentrations), the study sparked interest due to the infants of women in the intervention group being born with smaller head circumferences, which supports the current understanding of the importance of glucose for foetal brain development (Sweeting et al., 2021). The diets of mothers in the intervention group may have also provided inadequate micronutrients (iron and iodine). The clinical significance of these marginal differences must be explored further in larger trials, especially since only 32 women were considered in the final analysis.

The lack of studies examining further carbohydrate-restricted approaches during pregnancy (i.e. 26% to 40% of dietary energy) is largely attributed to the IOM carbohydrate recommendations for pregnant women to consume a minimum of 175 grams of carbohydrate per day (Institute of Medicine, 2002/2005). This minimum carbohydrate threshold is also specifically cited in several clinical practice guidelines for the management of GDM (American Diabetes Association, 2021b; American Diabetes Association Professional Practice Committee, 2021b; Duarte-Gardea et al.,

2018; Feig et al., 2018; Hod et al., 2015; Ministry of Health, 2014). The IOM guideline was historically developed from estimated adult brain requirements, plus an additional 35 grams for the foetal brain. However, within the background document, authors acknowledge uncertainties at the time, including limited knowledge of the proportion non-carbohydrate fuels, such as fatty acids and ketone bodies, metabolised by the foetal brain (Institute of Medicine, 2002/2005). Although estimates for foetal glucose needs were taken from animal models to develop the IOM guidelines, recent *in vivo* data using a four-vessel sampling model (uterine and umbilical arterial and venous blood) supports the estimated requirement for 35 grams of maternal glucose per day (Michelsen et al., 2019). More recently, the availability of evidence demonstrating the rate and quantity of human placental glucose consumption (as an additional 35 grams per day) prompted Hernandez and Rozance (2023) to propose a revised Recommended Daily Allowance for maternal carbohydrate intake of 220 grams per day. This was suggested particularly in the context of rising rates of maternal obesity, where the existing Recommended Daily Allowance for carbohydrate during pregnancy would provide less than 28% of daily energy based on an energy requirement of 2500 kcal/day. To date, lower and upper thresholds for carbohydrate intake during pregnancy remain to be determined.

The Estimated Average Requirement and Recommended Daily Allowance for carbohydrate during pregnancy is based on placental glucose exchange rate and foetal brain glucose requirements. Thus, the rationale provided as the basis for the IOM guidelines is based on an assumption that glucose needs must be sourced from maternal dietary intake without taking into consideration the capacity for maternal gluconeogenesis and other lipid-based fuel metabolism (Institute of Medicine, 2002/2005). However, authors of the IOM guideline also recognise that ketone bodies may contribute as much at 30% of foetal brain energy needs since ketogenesis is a common tendency in the fasted state during pregnancy (Denne & Kalhan, 1986; C. J. Homko, Sivan, Reece, & Boden, 1999; M. S. Patel, Johnson, Rajan, & Owen, 1975). Research into carbohydrate-restricted diets has certainly demonstrated that not only it is feasible for non-pregnant adults to consume below the IOM recommended carbohydrate targets, but it may also be therapeutic for some individuals with metabolic dysfunction. As work in this area progresses, there is scope to explore the efficacy of such approaches in pregnancies with pathological insulin resistance and hyperinsulinaemia.

In practice, pregnant women might frequently eat less than the IOM Recommended Daily Allowance of 175 grams of carbohydrate per day. In our qualitative study, diabetes specialist dietitians interviewed referred to the 175-gram minimum intake guideline as “outdated,” “ancient history,” and infrequently referred to them specifically when advising women with GDM. Participants discussed how they were often challenged when meeting smaller-bodied

women with GDM whose usual dietary intakes were below the "recommended" amount; therefore, advising women to eat *more* carbohydrate than their usual intake to achieve glycaemic control appeared to be at odds with the goals of treatment. Challenges around the lack of specificity in current carbohydrate recommendations have been described in other studies (Lawrence et al., 2017; Mustafa et al., 2021; Tsirou et al., 2019). As it has been indicated in Chapters Two, Four, and Five, heterogeneity among maternal insulin resistance and secretory responses means there is likely no one-size-fits-all approach when it comes to dietary carbohydrate modification. Future studies may look toward tailored dietary approaches according to insulin resistance and secretory response phenotypes. Emerging technologies using flash- and continuous-glucose-monitoring systems may provide a strategy to observe individual responses to varying types and loads of carbohydrate more closely, as they have been shown to improve clinical outcomes (lower HbA1c, caesarean section rate, neonatal birth weight) in pregnant women with diabetes (combined outcomes from trials including women with GDM and pre-existing type 2 and type 2 diabetes) (Chang, Tan, Ang, & Lau, 2022).

7.4 Multi-layered gaps in care for pregnant women

Combined findings presented in this body of work reveal gaps in care for women who enter pregnancy with pre-existing hyperinsulinaemia and insulin resistance, which may lead to a greater risk of adverse outcomes during pregnancy and later life. The current model that involves screening for GDM during mid-late gestation and monitoring weight and blood pressure changes as they present means there could be a major missed opportunity the first half of pregnancy when dysfunctional metabolic changes in begin to manifest. Although HbA1c is used to identify women with possible undiagnosed type 2 diabetes or pre-diabetes, beyond glycaemic markers there is no clear clinical pathway to identify women with pre-existing hyperinsulinaemia and insulin resistance from the early stages of pregnancy. A gap in specific dietary advice and treatment available for women in these higher risk categories, therefore, means women could continue throughout the first half of pregnancy with suboptimal lifestyle behaviours.

One common and well-recognised adverse outcomes associated with unhealthy nutrition and lifestyle behaviours during pregnancy is excess GWG, which is linked to further adverse metabolic changes including increased inflammation and circulating lipids (Corrales et al., 2021). Despite good evidence that lifestyle changes improve pregnancy outcomes (Bain et al., 2015; D'Arcy, Rayner, Hodge, Ross, & Schoenaker, 2020; Gaillard et al., 2019), preventative interventions fail to translate into meaningful public health strategy, as evidenced by the global rise of women and offspring affected by maternal obesity and GDM, fuelling the futile cycle of

diabetes begetting diabetes (C. Chen et al., 2018; Dabelea et al., 2005; Egan et al., 2017; Feig et al., 2014; Ferrara, 2007; Ferrara et al., 2004; Schwartz et al., 2015; Zhu & Zhang, 2016)

In Chapter 6, findings from our qualitative study demonstrated a "primary care gap" as a theme that was consistently raised by health professionals; a lack of primary care initiatives constrained their effort to provide dietary advice to women once diagnosed with GDM. It was acknowledged that women with GDM may only first encounter dietary advice during mid-to-late gestation, after having already exceeded their recommended GWG. After accounting for the time taken to introduce dietary changes, several weeks could pass when their foetus is exposed to a perturbed metabolic state (Corrales et al., 2021). Due to a lack of clear clinical guidance for primary care practitioners, the type of advice women receive while in "diagnostic limbo" during the early stages of pregnancy appears to be a matter of clinical judgement, subject to the health professionals' knowledge, time, and/or capacity.

Health care discrepancies were suggested in the case studies presented in Chapter 5. We presented one woman (Case #3) with obesity and Kraft Patter IIB Hyperinsulinaemia in early pregnancy who pursued healthy lifestyle changes and successively achieved a total GWG that was below the IOM guidelines (Institute of Medicine & National Research Council, 2013). She reported that her interest in dietary change was initiated following advice from her midwife, who had acknowledged her increased risk of excess GWG and GDM. In contrast, Case #1, also with Kraft Pattern IIB Hyperinsulinaemia in early pregnancy, reported higher consumption of ultra-processed foods and exceeded GWG goals. Due to the perceived risks, she was recommended an induction of labour which was followed by further difficulties during delivery. Although these two women were individual cases, not necessarily indicating a specific cause and effect, their experiences demonstrate the potential role of primary care providers during early pregnancy to advise on the significance of diet and to facilitate healthy lifestyle choices. However, it is disheartening to observe that one woman can receive strong advice from her midwife to consider her nutrition behaviours while another with similar metabolic risk factors does not. This is an important gap and area for future research that has implications for clinical practice. It does make one ponder how many women are being given a disservice and the resulting inequity from such a gap in primary care guidance.

As shown in Chapter 6, health professionals face many barriers to providing dietary advice to pregnant women, including those in the GDM services. These practical limitations carried into health professionals' experiences; a sense of distrust, misinformation, and dietary over-restriction were commonly observed among the women. We suggested that these challenges were linked to the shortcomings of current dietary guidelines and logistic barriers in

the current health delivery model which meant limited professional time to provide personalised nutrition advice. Indeed, addressing health care gaps requires more than simply revised and updated dietary guidelines for pregnant women and those planning pregnancy; it requires a paradigm shift in health care delivery. To truly optimise metabolic health for future pregnancies and generations to come, health care needs to be future-looking, proactive, and personalised – and with fewer reactive, treatment-based approaches for managing conditions, such as GDM, as they present.

Beyond concerns around specific nutrient recommendations, the wider and most significant nutrition challenge for pregnant women and those planning pregnancy is the sub-optimal "Westernised" nutrition and lifestyle environment. That is the modern-day environment characterised by a noisy, busy, stressful, sleep-deprived, and technology-driven lifestyle, and the continual onslaught of hormone-disrupting chemicals and ultra-processed foods (P. Hanson et al., 2020). From the late 20th century, high income countries have become increasingly burdened with a pandemic of type 2 diabetes and obesity (Cannon & Leitzmann, 2022). Changes in the food environment are largely attributed to this public health crisis; the most important changes to the dietary environment over the last century is the growing availability of low-cost, energy-rich, nutrient-poor, ultra-processed foods, which are undoubtably damaging to human health (Monteiro et al., 2018). Chapter 2 discussed literature highlighting how sub-optimal dietary patterns and other lifestyle behaviours are knowingly associated with the increased risk of adverse pregnancy outcomes such as excess GWG, GDM, and hypertensive disorders. Further findings from intervention studies demonstrate that many women consuming sub-optimal diets could benefit from *any* type of lifestyle intervention to improve health behaviours (Bain et al., 2015; Cantor et al., 2021; International Weight Management in Pregnancy (i-WIP) Collaborative Group, 2017; Lamminpää et al., 2018; Mohsenzadeh-Ledari et al., 2019; Muktabhant et al., 2015; Shepherd et al., 2017; Teede et al., 2022). That means that finding the "best" diet for optimising metabolic heath may not be as pertinent as finding ways to improve dietary and lifestyle behaviours on a wider population level.

Moreover, from a public policy perspective, healthy eating guidance has failed to effectively encourage preventative healthy dietary behaviours. This means that nutrition challenges experienced by pregnant women reflect issues existing at a broader population level. In a recent commentary article, Cannon and Leitzmann (2022) argue that the greatest failure in current dietary guidelines is the biochemical paradigm of nutrition science on which they are based. By reducing foods into separate chemical constituents that emphasise eating less "unhealthy" food components such as saturated fat, the Dietary Guidelines for Americans neglect traditional food practices, ways of eating, and the wider societal and environmental impact of reductionist views.

The dietary guidelines have also too easily been exploited by the food industry to market ultra-processed foods under the guise of nutrition claims to suggest they are health-promoting (e.g. ultra-processed breakfast cereals may be marketed as a "good source of fibre" and confectionary may be marketed as "low in fat"). The failure has meant that despite public health efforts to encourage healthy dietary behaviours according to dietary guidelines, there has been little or no progress on the obesity and diabetes crisis over the last two decades.

Pregnancy provides a unique and important opportunity during which women take their health seriously. For example, smoking cessation is more likely to occur during pregnancy than any other time in a woman's life (Best Practice Journal, 2013). It is also common practice for pregnant women to reduce or eliminate their alcohol use (Sellman & Connor, 2009), take nutritional supplements, and receive vaccinations for the health of their developing baby. However, it is clear from research presented in across this body of work and the wider consensus (B. Hill et al., 2020), that dietary and lifestyle guidance is inadequately executed.

7.5 Strengths and limitations

The central strength of this body of work is the novel contribution provided through identifying concepts that are recognised from the wider field of type 2 diabetes and exploring these in a pregnancy context. The Kraft Model of Hyperinsulinaemia recognises that elevated fasting and/or post-glucose load plasma insulin may be used as a risk marker for later-life cardiometabolic diseases. This model has not previously been applied in a pregnancy context to identify women who may enter pregnancy with pre-existing hyperinsulinaemia. When the Model was applied in Chapters 4 and 5, potential methodologies for examining insulin response patterns during pregnancy were demonstrated. While these criteria have not been validated against other standardised measures, the protocol demonstrated in Chapter 5 provides a framework for further research in this area.

A further strength of this work is the New Zealand context that is examined in Chapters 5 and 6. This context, therefore, has potential clinical practice and policy implications for improving dietary management during pregnancy to improve outcomes and costs to our society. Choosing a New Zealand context as a delimitation of this research could also be viewed as a limitation since practice-based findings may not necessarily translate across international systems.

As a whole, further limitations of this body of work are as follows: Firstly, a central premise of this research was that pre-existing hyperinsulinaemia and insulin resistance are likely undesirable when superimposed into a pregnancy context as they may lead to unfavourable metabolic changes. Literature presented in Chapter 2 provided rationale to suggest that this is

an important area for further research. However, throughout this work, in particular Chapters 4 and 5, The Kraft Model of Hyperinsulinaemia was applied in ways that have only been explored to a limited degree in a pregnancy context. Although the role of insulin resistance and low-grade inflammation is recognised in the pathophysiology of obesity, GDM, and type 2 diabetes, metabolic changes occurring over the acute gestational period certainly differ from chronic metabolic diseases. Indeed, insulin resistance and hyperinsulinaemia are expected phenomena during pregnancy. This research explored possible screening strategies for future management of women at risk of adverse outcomes; however, further research is needed to substantiate and progress findings. Therefore, the baseline definition of a "normal" or "healthy" insulin response pattern is one that may continue to change as this field develops.

Second, the potential for OGTT with an insulin assay to define hyperinsulinaemia and metabolic sub-types comes with several barriers. This type of testing is likely limited to the research setting due to practical barriers associated with the OGTT. Although commonly used to diagnose GDM, the OGTT is heavily criticised for being an artificial simulation of metabolic responses and not a true reflection of a person's usual eating and lifestyle (D. Bogdanet, O'Shea, Lyons, Shafat, & Dunne, 2020). Even when used to diagnose GDM, some women may be hesitant to undertake an OGTT due to concerns about the effects of consuming a large amount of glucose in the testing drink. As an isolated glucose test, the OGTT misses the effect of other food components such as fibre, fat, and protein that typically mitigate postprandial glucose and insulin responses. The effect of other lifestyle factors such as eating frequency and exercise are also not taken into account. This means that based on diet and lifestyle behaviours, two individuals classified as having a hyperinsulinaemia response pattern could have vastly different insulin and glucose profiles over a 24-hour period. Especially since pregnancy is a highly dynamic state; some women may experience more adverse effects on their sleep, stress, and exercise capacity than others. Therefore, a different methodology that accounts for real-world insulin and glucose patterns should be explored.

Finally, the lack of standardisation for plasma insulin measurement is a significant challenge when it comes to interpreting assays. Some of these factors addressed in Chapter 2 include variable precision among assay techniques, particularly RIA, and challenges surrounding conversion to Système International units. Additionally, basal plasma insulin has an oscillatory release pattern, further complicating interpretation of fasting plasma insulin assays. Without standardisation, insulin measures cannot be compared across populations. This presents as a major barrier to developing criteria to define normal and dysfunctional insulin response patterns. Standardisation of insulin measurement techniques is needed in order to progress this work.

7.6 Future research, policy, and practice

As a whole, this research identified many gaps which could inform future research, policy, and practice. To address challenges ahead for maternal health and the health of future generations, the following recommendations are proposed.

7.6.1 Recommendations for research

The wider research field involving insulin measurement and describing metabolic sub-types according to insulin response patterns is riddled with inconsistencies. Standardised criteria are first needed to define hyperinsulinaemia in a wider non-pregnant context. Once a clear reference standard is established, similar thought can be applied to develop criteria specific for pregnant populations. Since insulin resistance and insulin secretion increase rapidly over the gestational period, such criteria must also define gestational age-specific parameters to avoid misclassification.

An important area for further research is the relationship between different insulin response pattern sub-types and perinatal and neonatal outcomes. Relationships to long-term maternal and offspring outcomes could also be explored. As shown in Chapter 2, there is limited population-based data linking "dysfunctional" insulin response patterns in pregnancy to an increased risk of adverse outcomes. Large population-based cohort studies would be required to determine clinical thresholds associated with adverse outcomes. In practice, such thresholds may also be used to inform how women should be screened for hyperinsulinaemia to initiate early lifestyle management.

Practical limitations of an OGTT insulin test have been described. In additional to the impracticalities of requiring multiple measures to ascertain a post-glucose load insulin response, insulin assays are expensive tests (especially when compared to plasma glucose). Therefore, the development of low-cost and simple ways to identify women with an elevated risk of adverse outcomes is important for more proactive preventative management. Future work may seek to validate surrogate markers for hyperinsulinaemia that are more widely applicable for clinical practice. Surrogate biochemical markers could be combined with other clinical parameters such as BMI, medical history, family history, age, and obstetric history to develop a pregnancy metabolic risk screening algorithm, similar to the cardiovascular risk assessment used in general practice. Furthermore, the more recent development of technologies that allow for even simpler point-of-care testing using capillary blood (i.e. with a finger prick) and continuous glucose monitoring may also provide a way forward for screening in primary care (Chang et al., 2022; Soffe, Nock, & Chase, 2019). Research is being progressed by the supervisory team from this

research into the clinical utility of mixed meal tolerance tests which could also be applicable for this demographic. A mixed meal approach as an alternative to the OGTT could be a strategy to personalise testing according to body size and prior dietary patterns, therefore overcoming some of the practical limitations of the fasted OGTT. Further research into these less invasive approaches holds potential to enhance primary care services and reduce patient burden.

Future dietary studies among pregnant women at risk of adverse outcomes should look to varying degrees of carbohydrate modification based on individual insulin and glycaemic responses. Since evidence from previous dietary research shows that varying types of dietary interventions can improve overall hard clinical outcomes, studies should include sensitive, sub-clinical outcomes measures reflective of overall maternal metabolic health. Outcome markers for future research may include (but not be limited to) glycaemic measures, including glucose time-in-range from continuous glucose monitoring devices, lipids, insulin response, and surrogate markers of insulin sensitivity (e.g. irisin and adiponectin). Measures could also be extended to include neonatal metabolic responses using cord blood c-peptide, adiponectin, leptin, and adiposity.

Finally, to suggest that future dietary research could explore varying degrees of carbohydrate restriction among women with Kraft Pattern Hyperinsulinaemia is likely to be met with hesitation from the wider GDM research community. The carbohydrate content of diets for women with GDM has been an ongoing source of controversy in recent years. This academic controversy has also occurred in parallel with cultural shifts toward the increasing popularity of carbohydrate-restricted dietary approaches. Inevitably, there are likely many women who have observed the benefit of carbohydrate-restriction prior to pregnancy and continued a version of this type of eating into pregnancy, as evidenced by social media groups (Low-Carb/Keto Pregnancy & Breastfeeding Support Group, n.d.). Future research around carbohydrate modification during pregnancy could explore experiences from women who have voluntarily limited their carbohydrate intake prior, during, and/or after pregnancy to inform intervention studies.

7.6.2 Recommendations for policy and practice

From a clinical practice perspective, there is a need to better recognise women who present with pre-existing insulin resistance and hyperinsulinaemia before and during the early stages of pregnancy. This could include women accessing fertility assistance services; women with an obstetric history of miscarriage, small- or large-for-gestational age infants, GDM, or hypertensive disorders; women with medical or sub-clinical medical conditions such as PCOS,

thyroid conditions, dyslipidaemia, mildly elevated HbA1c, or obesity before pregnancy, and those with a first degree relative with type 2 diabetes. That is not to say women with risk factors should be warned away from pregnancy; it means that a better understanding of the risks could allow women to be supported and more conscious of lifestyle behaviours that may mitigate their risk.

Furthermore, access to dietary advice for women in high-risk categories for pregnancy complications such as GDM and preeclampsia could be improved. In order to achieve efficient and effective referral pathways, there is a need to support dietitian/nutritionist services in primary health care organisations with suitable funding and training pathways.

Training support on nutrition in pregnancy could be provided to upskill lead maternity carers and other relevant health professionals who frequently engage with pregnant women. Guidance could also be offered on how to engage in helpful conversations with women to facilitate healthy lifestyle changes. Open-ended questions around nutrition behaviours could also help to identify women/families with food insecurity or other social risk factors to initiate additional support. Unanimous simple messages reflective of healthy dietary patterns could include the following principles:

- choose whole, unprocessed foods;
- choose water to drink;
- limit the use of ultra-processed foods, particularly those containing sugar and refined carbohydrates;
- prefer fresh food and meals made from minimally-processed ingredients and develop food preparation skills to suit family life.

Providing clinicians with the capacity to take the required time with women to discuss wider lifestyle determinants in their pregnancy could be pivotal for improving lifestyle behaviours and saving health care costs. Work conditions and remuneration for midwives, in particular, lead maternity care community midwives who often act as the first point of contact for newly pregnant women could be improved. In order to address gaps in primary care, the New Zealand government could be made aware of the lack of investment in midwifery, including pay inequity, a disproportionate reduction in funded clinical hours relative to an increasing population, and limited career opportunities (Midwifery Employee Representation & Advisory Service, 2022). Certainly, discussion around policy and health care delivery is a complex issue. With only limited financial resources, investing in any particular service needs to come at an overall net benefit which outweighs the proposed cost. Reorienting services to invest in preventative care for better

outcomes for women and future generations has the potential to save many-fold health care costs for chronic metabolic diseases.

7.7 Conclusion

This multiple-methods research aimed to explore insulin response patterns during pregnancy and the implications for dietary advice provided to women at risk of adverse outcomes. Throughout, this body of work provided a specific focus on implications for GDM management. Over the previous six chapters, evidence was presented linking Kraft Pattern Hyperinsulinaemia to adverse pregnancy outcomes to suggest that identifying metabolic dysfunction early in pregnancy could provide a means to introduce interventions to mitigate this risk. Further, several gaps in care were described around the dietary management of women during early gestation at risk of GDM and those later in pregnancy once diagnosed.

As a whole, this body of work has demonstrated the potential clinical significance of recognising hyperinsulinaemia during pregnancy. That is, in the context of it being a dysfunctional process superimposed on normal pregnancy physiology. Further knowledge of parameters to define hyperinsulinaemia may aid in developing screening tools. Furthermore, a growing understanding of the heterogeneity of insulin response patterns among pregnant women, especially among those with GDM, could inform further research into therapeutic diet and lifestyle interventions. This could mean that, in practice, advice may be more tailored for individual metabolic sub-types.

Finally, this research has highlighted many gaps in the management of women who enter pregnancy with a prior risk of adverse outcomes related to insulin resistance and metabolic maladaptation. These gaps in preventative lifestyle guidance for pregnant women and those planning pregnancy are arguably a missed opportunity in care. Further work to improve early screening and dietary advice is essential to obstruct the intergenerational cycle of obesity begetting obesity and diabetes begetting diabetes.

Pregnancy is a crucial life stage characterised by major metabolic changes and, as discussed, vulnerabilities. Since women are the portal for future generations, lifestyle choices during pregnancy can profoundly impact a woman's own health trajectory and that of her offspring. That is to say, guiding and supporting women and their families to follow healthy lifestyles from conception could be the most important time to positively impact the future health of women, their families, and future generations.

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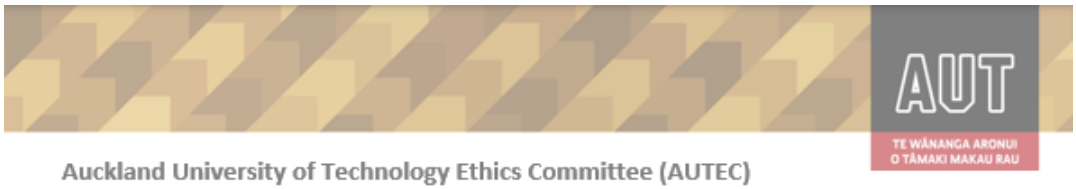
Appendices

Appendix A. Ethics approval letters

Chapter 4. Auckland University of Technology Ethics Committee, 19/404, 23 October 2019



Auckland University of Technology Ethics Committee (AUTEC)

Auckland University of Technology
D-88, Private Bag 92006, Auckland 1142, NZ
T: +64 9 921 9999 ext. 8316
E: ethics@aut.ac.nz
www.aut.ac.nz/researchethics

23 October 2019

Caryn Zinn
Faculty of Health and Environmental Sciences

Dear Caryn

Ethics Application: 19/404 **An exploration of insulin and glucose response curves among pregnant women from the historical Kraft dataset**

I wish to advise you that a subcommittee of the Auckland University of Technology Ethics Committee (AUTEC) has **approved** your ethics application.

This approval is for three years, expiring 23 October 2022.

Standard Conditions of Approval

1. The research is to be undertaken in accordance with the Auckland University of Technology Code of Conduct for Research and as approved by AUTEC in this application.
2. A progress report is due annually on the anniversary of the approval date, using the EA2 form.
3. A final report is due at the expiration of the approval period, or, upon completion of project, using the EA3 form.
4. Any amendments to the project must be approved by AUTEC prior to being implemented. Amendments can be requested using the EA2 form.
5. Any serious or unexpected adverse events must be reported to AUTEC Secretariat as a matter of priority.
6. Any unforeseen events that might affect continued ethical acceptability of the project should also be reported to the AUTEC Secretariat as a matter of priority.
7. It is your responsibility to ensure that the spelling and grammar of documents being provided to participants or external organisations is of a high standard.

AUTEC grants ethical approval only. You are responsible for obtaining management approval for access for your research from any institution or organisation at which your research is being conducted. When the research is undertaken outside New Zealand, you need to meet all ethical, legal, and locality obligations or requirements for those jurisdictions.

Please quote the application number and title on all future correspondence related to this project.

For any enquiries please contact ethics@aut.ac.nz. The forms mentioned above are available online through http://www.aut.ac.nz/research/researchethics

Yours sincerely,

Kate O'Connor
Executive Manager
Auckland University of Technology Ethics Committee

Cc: sylvia.north@aut.ac.nz; ccrofts@aut.ac.nz

Auckland University of Technology Ethics Committee (AUTEC)

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www.aut.ac.nz/researchethics

22 July 2020

Caryn Zinn
Faculty of Health and Environmental Sciences

Dear Caryn

Re Ethics Application: **20/216 Early pregnancy hyperinsulinaemina and later gestation effects, a pilot study**

Thank you for providing evidence as requested, which satisfies the points raised by the Auckland University of Technology Ethics Committee (AUTEC).

Your ethics application has been approved for three years until 22 July 2023.

Standard Conditions of Approval

1. The research is to be undertaken in accordance with the Auckland University of Technology Code of Conduct for Research and as approved by AUTEC in this application.
2. A progress report is due annually on the anniversary of the approval date, using the EA2 form.
3. A final report is due at the expiration of the approval period, or, upon completion of project, using the EA3 form.
4. Any amendments to the project must be approved by AUTEC prior to being implemented. Amendments can be requested using the EA2 form.
5. Any serious or unexpected adverse events must be reported to AUTEC Secretariat as a matter of priority.
6. Any unforeseen events that might affect continued ethical acceptability of the project should also be reported to the AUTEC Secretariat as a matter of priority.
7. It is your responsibility to ensure that the spelling and grammar of documents being provided to participants or external organisations is of a high standard and that all the dates on the documents are updated.

AUTEC grants ethical approval only. You are responsible for obtaining management approval for access for your research from any institution or organisation at which your research is being conducted and you need to meet all ethical, legal, public health, and locality obligations or requirements for the jurisdictions in which the research is being undertaken.

Please quote the application number and title on all future correspondence related to this project.

For any enquiries please contact ethics@aut.ac.nz. The forms mentioned above are available online through http://www.aut.ac.nz/research/researchethics

(This is a computer-generated letter for which no signature is required)

The AUTEC Secretariat
Auckland University of Technology Ethics Committee

Cc: sylvia.north@aut.ac.nz; ccrofts@aut.ac.nz

Health and Disability Ethics Committees

Health and Disability Ethics Committees
Ministry of Health
133 Molesworth Street
PO Box 5013
Wellington
6011

0800 4 ETHICS
hdecs@health.govt.nz

19 June 2020

Miss Sylvia North
Human Potential Centre
AUT Millennium Institute
Private Bag 92006
Auckland 1142

Dear Miss North

Re:	Ethics ref:	19/NTA/124/AM01
	Study title:	Study 1: Exploring hyperinsulinaemia in pregnancy: A sub-analysis of the historical Kraft database of insulin- and glucose-response patterns.Study 2: Exploring insulin patterns in pregnancy: A pilot study.

I write to advise that this amendment has been *approved* by the Northern A Health and Disability Ethics Committee. This decision was made through the HDEC Expedited Review pathway.

Please ensure all documents that are updated for HDEC review are clearly tracked with the changes made. The replacement Participant Information Sheet received on 10 June 2020 was not.

Non-standard conditions:

1. The inclusion of COVID-19 related considerations to the Protocol is noted; it might be helpful to put this into the Participant Information Sheet (PIS) also so participants are reassured as well as knowing what to expect upon attending for face to face visits.
2. The Protocol does not have a data governance plan, please amend this.
3. The PIS does describe where data will be held and that only the Coordinating Investigator has access to identifiable data. However, the Protocol should carry this information, including detail of how it is de-identified, how any linking data is held separately, who has access to de-identified data etc. Please refer to Ch 12 of the National Ethical Standards (Dec 2019) - https://ethics.health.govt.nz/ **under the Quick Links option**.
4. The PIS allows participants to withdraw at any time. Please consider a timeframe on this so as not to lose data that is essential to completion of the PhD and ensure both the PIS and Protocol cover this information.
5. 4. In the bullet points in the PIS a 3-hour test is referred to; elsewhere this has been changed to 2 hours. Please correct this difference.
6. Please amend the PIS to reflect the amended glucose tolerance testing.

Non-standard conditions must be completed before commencing any changes as a result of this amendment, however they do not need to be submitted to or reviewed by HDEC.

If you would like an acknowledgement of completion of your non-standard conditions you may submit a post approval form amendment through Online Forms. Please clearly

identify in the amendment form that the changes relate to non-standard conditions and ensure that supporting documents (if requested) are tracked/highlighted with changes.

For information on non-standard conditions please see section 128 and 129 of the *Standard Operating Procedures for Health and Disability Ethics Committees* (available on www.ethics.health.govt.nz)

Please don't hesitate to contact the HDEC secretariat for further information. We wish you all the best for your study.

Yours sincerely,

Mrs Kate O'Connor
Acting Chairperson
Northern A Health and Disability Ethics Committee

Encl: appendix A: documents submitted
appendix B: statement of compliance and list of members

Auckland University of Technology Ethics Committee (AUTEC)

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www.aut.ac.nz/researchethics

16 September 2020

Caryn Zinn
Faculty of Health and Environmental Sciences

Dear Caryn

Re: Ethics Application: **19/405 Exploring dietary advice in Gestational Diabetes Mellitus (GDM): Perspectives from health professionals in Auckland, New Zealand**

Thank you for sending through your responses to the conditions for the amendment to your ethics application.

The amendment to the recruitment and data collection protocols (recruitment via Facebook and focus groups via teleconference) has been approved.

Non-Standard Conditions of Approval

1. Inclusion in the Information Sheet that the video recording will be deleted immediately after the focus group/straight after transcription has occurred.
2. Inclusion of the following additional bullet point in the Consent Form: 'I understand that the identity of my fellow participants and our discussions in the focus group are confidential to the group and I agree to keep this information confidential'

Non-standard conditions must be completed before commencing your study. Non-standard conditions do not need to be submitted to or reviewed by AUTEC before commencing your study.

I remind you of the **Standard Conditions of Approval**.

1. The research is to be undertaken in accordance with the Auckland University of Technology Code of Conduct for Research and as approved by AUTEC in this application.
2. A progress report is due annually on the anniversary of the approval date, using the EA2 form.
3. A final report is due at the expiration of the approval period, or, upon completion of project, using the EA3 form.
4. Any amendments to the project must be approved by AUTEC prior to being implemented. Amendments can be requested using the EA2 form.
5. Any serious or unexpected adverse events must be reported to AUTEC Secretariat as a matter of priority.
6. Any unforeseen events that might affect continued ethical acceptability of the project should also be reported to the AUTEC Secretariat as a matter of priority.
7. It is your responsibility to ensure that the spelling and grammar of documents being provided to participants or external organisations is of a high standard.

AUTEC grants ethical approval only. You are responsible for obtaining management approval for access for your research from any institution or organisation at which your research is being conducted. When the research is undertaken outside New Zealand, you need to meet all ethical, legal, and locality obligations or requirements for those jurisdictions.

Please quote the application number and title on all future correspondence related to this project.

For any enquiries please contact ethics@aut.ac.nz. The forms mentioned above are available online through http://www.aut.ac.nz/research/researchethics

(This is a computer-generated letter for which no signature is required)

The AUTEC Secretariat
Auckland University of Technology Ethics Committee

Cc: , sylvia.north@aut.ac.nz; ccrofts@aut.ac.nz

Appendix B. Tools from conducted studies

Chapter 5. Participant information sheet and consent form

Participant Information Sheet

Study title:	**Exploring insulin patterns in pregnancy: A pilot study.**	
Locality:	Auckland University of Technology	Ethics committee ref.: 19/NTA/124
Lead investigator:	Sylvia North, PhD Candidate	Contact phone number: 0210349245

You are invited to take part in a study looking at how insulin patterns in early pregnancy and later gestation effects. You can choose to be involved or not. If you don't want to take part, you don't have to give a reason, and it won't affect the care you receive. If you do want to take part now, but change your mind later, you can pull out of the study at any time.

This information will help you decide if you'd like to take part. It sets out why we are doing the study, what you will be doing, what the benefits and risks to you might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. You do not have to decide today whether you will participate in this study. Before you decide you may want to talk about the study with other people, such as family, whānau, friends, or your midwife or doctor. Feel free to do this.

If you agree to take part in this study, you will be asked to sign the Consent Form on the last page of this document. You will be given a copy of both of these forms to keep.

This document is 9 pages long, including the Consent Form. Please make sure you have read and understood all the pages.

What is the purpose of the study?

In this study, we aim to look at how insulin patterns change during your pregnancy. Changes in insulin patterns can cause problems in pregnancy such as high blood pressure and diabetes in pregnancy (also called gestational diabetes). This work will help us understand more about the patterns of insulin during different stages of pregnancy. This could also help us understand more about how diet and lifestyle can help with managing the changes in insulin levels in pregnancy.

This is a small study which is one of four studies that form part of Sylvia North's PhD thesis with Auckland University of Technology (AUT). Funding for this study has been provided from AUT. The findings of this research may be used for publishing in journals and academic presentations.

The main contact for this study is Sylvia North who can answer any questions you might have by email (sylvia.north@aut.ac.nz) or phone (+64210349245).

This study was approved by the Auckland Health and Disability Ethics Committee (19/NTA/124).

What will my participation in the study involve?

You have been invited to participate in this study because you met the criteria in an advertisement.

Please read the following carefully to identify whether you meet the complete selection criteria.

We are looking for…

- Healthy newly pregnant women with no pre-existing routine medications or medical conditions before pregnancy.
- Between the ages of 25 and 35 years.
- Naturally conceived singleton pregnancy at less than 14 weeks gestation.
- Currently, or intending to be, under the care of a midwife or lead maternity carer (LMC) and prepared to permit access to information from your LMC about your pregnancy.
- Pre-pregnancy body mass index (BMI) between 25-35 kg/m^2
  OR previous blood pressure problems in pregnancy
  OR previous baby weighing over 4.5 kg
- Auckland-living and planning to stay in Auckland for the pregnancy and delivery.
- Willing and able to attend a 2-hour oral glucose tolerance test in a clinical setting in Auckland between week 12-16 gestation.
- Prepared to take 14 days of home capillary fasting glucose levels via finger prick, seven between week 24-26, and seven between week 35-37 gestation.
- Prepared to answer questions on diet and exercise.
- Current diet pattern contains a minimum of 150 g of carbohydrates per day (equivalent of approximately 2 slices of bread, 2 pieces of fruit, 1 cup of milk, 1 medium potato, and 1 cup of rice)
- NO history of pre-existing diabetes or pre-diabetes (HbA1c ≥40 mmol/mol measured in the previous 24 months).
- NO history of cancer other than non-melanoma skin cancer.
- You will be excluded on the event of complications requiring medical supervision or miscarriage.

How do I agree to participate in this research?

If you decide to take part in this study, please respond to me (Sylvia North) directly to arrange a suitable time for your first 2-hour appointment at local public lab (LabTests). This appointment will be in the morning as you will need to be fasted to complete the oral glucose tolerance test. **You will need to complete the consent form which was sent alongside this information sheet.**

Your participation in this research is voluntary (it is your choice) and whether you choose to participate will neither advantage nor disadvantage you. You can withdraw from the study at any time. If you choose to withdraw from the study, you will be offered the choice between having any data that is identifiable as belonging to you removed or allowing it to continue to be used in a manner where you cannot be personally identified. However, once the findings have been produced, removal of your data may not be possible.

What will happen in this research?

Clinical visit (week 12-16 gestation):

You will be asked to first attend a 2-hour clinic appointment at a community lab (LabTests, Auckland) to participate in an oral glucose tolerance test. This appointment will be scheduled on a morning between 12-16 weeks gestation.

You will be asked to attend the clinic after a 12-hour overnight fast (nothing to eat or drink other than plain water).

A qualified phlebotomist will take venous blood samples for this test. You will be asked to consume a 75-gram glucose drink. A total of four samples will be taken for this test: 0 minutes (fasted), and 30, 60, and 120 minutes after consuming the glucose drink.

You will have the opportunity to have any blood samples returned to you once analysed. Other small amounts of blood on medical supplies will be disposed of with medical waste.

While you wait for this test, your weight and height will be examined. I will also ask you some questions about your diet and exercise. I will also then explain the second part of the study, which will involve recording your own fasting glucose levels at home later in pregnancy.

Assessments will be conducted in a private clinic room. Wifi will be available for you to use while you wait for the test to be completed.

After completing the 2-hour oral glucose tolerance test, you will be provided with a light breakfast.

Home glucose monitoring (week 24-26 and 35-37 gestation):

For the second part of this study, you will be asked to record your fasting glucose levels for one seven days between weeks 24-26 and weeks 35-37 gestation. Before the week of testing, you will be provided with a home glucose monitoring kit containing a glucose monitor, testing strips, and lancets (14 days of supplies). You will be given either a written or online log sheet to record your information at home. You will be shown how to correctly draw a finger-prick glucose sample during your first clinical visit.

The log sheet will also include some questions about your diet, exercise, and changes during pregnancy to complete at the end of your week of testing.

After completing the study, you will receive an $80 Pak 'n' Save voucher and a voucher for two-hours of dietitian consultations with Sylvia North (NZRD) valued at $265, to be redeemed within 8 months after study conclusion.

This is not a clinical intervention study. You will remain under the care of your LMC. You will be provided with your blood test results and a clinical interpretation (where appropriate) once you have completed all four assessments.

Your data will be de-identified before analysis and stored in a password-protected external drive kept at an AUT location for 10 years. I will be the only person who has access to the identifiable results while you are involved in the study

This is not a clinical trial. You will remain under the care of your Lead Maternity Carer. You will be provided with your blood test results and a written explanation of these results once you have completed all four assessments.

Sylvia North, Primary Investigator, will be the only person to have access to your identifiable data and consent forms during the process of collection and analysis. All hard-copy information (consent forms, participant questionnaires) will be scanned into digital format and physical copies destroyed. Digital information will be stored on a password-protected external drive and kept at an AUT location, accessible only to Sylvia North.

Your personal information will be deidentified and given an ID code, for which only Sylvia North will have the ID key. Once the study is complete, you will receive a two-page summary of the key findings from the study, including your personal results. The primary investigator (Sylvia North) will be the only person who has access to the identifiable results while you are involved in the study.

Once the study is complete, deidentified data and consent forms will be stored separately on two password-protected external drives kept at an AUT location for 10 years, accessible only to Dr Caryn Zinn.

There is no intended future use of these data beyond this pilot study.

What are the possible benefits and risks of this study?

What are the discomforts and risks?

The oral glucose tolerance test used in this study are assessments which are usually offered during pregnancy to diagnose gestational diabetes. Some people may experience some discomfort during an oral glucose tolerance test for the following reasons. Firstly, you will be required to attend the appointment after a 10-hour overnight fast. This means having nothing to eat or drink other than plain water until the 2-hour test is complete. Secondly, there is also the possibility that you may experience light-headedness during this test as your glucose levels lower. If this happens during the test, you will be provided with something to eat to relieve these symptoms. Third, some people may be uncomfortable with needles and blood draws. Each test will involve four blood draws, either through a an inserted cannular or individual needle-pricks.

You will also be asked some questions about your pregnancy. Pregnancy can be a sensitive time, and I appreciate that you may experience some discomfort describing your experiences with any complications or changes in diet.

How will these discomforts and risks be alleviated?

These assessments will be conducted in a private room. If you experience discomfort such as light-headedness, there will be a place for you to sit or lay down. You will be provided with water to drink. At the end of the 2-hour oral glucose tolerance test, you will be provided with a light breakfast.

You may choose to withdraw from the study at any time.

During the questionnaire/interview, you may also decline to answer a question at any time.

For the home glucose monitoring, you have the choice to opt-out of any of the 14 samples over two separate weeks.

The information you provide will be kept confidential. This study is observational, meaning you will receive no judgement and you will not be asked to change your diet or lifestyle in any way.

If you experience any distress related to participating in this study, AUT Health Counselling and Wellbeing offer three free sessions of confidential counselling support for adult participants in an AUT research project. These sessions are only available for issues that have arisen directly as a result of participation in the research and are not for other general counselling needs. To access these services, you will need to:

- drop into our centres at WB219 or AS104 or phone 921 9992 City Campus or 921 9998 North Shore campus to make an appointment. Appointments for South Campus can be made by calling 921 9992
- let the receptionist know that you are a research participant, and provide the title of my research and my name and contact details as given in this Information Sheet

You can find out more information about AUT counsellors and counselling on http://www.aut.ac.nz/being-a-student/current-postgraduates/your-health-and-wellbeing/counselling.

What are the benefits?

Benefits to you: At the end of this study, you will receive a summary of your personal information on glucose and insulin from your pregnancy. We will provide a clinical summary and interpretation of these results. However, as the insulin test is not used as a standard clinical assessment, the clinical interpretation of some insulin results may be limited.

You will receive an $80 Pak 'n' Save voucher and a voucher for two-hours of dietitian consultations with Sylvia North (NZRD), valued at $265, to be redeemed within 8 months after study conclusion.

Benefits to me (the researcher): This work will contribute to the completion of my PhD thesis. This will be one of four studies in a wider body of work exploring insulin patterns in pregnancy and gestational diabetes. This work will also help me develop professional networks and expertise in this area and improve my intellectual and professional practice.

Benefits to the wider community: This study will help us understand more about how insulin patterns early in pregnancy may be related to fasting glucose levels, blood pressure, gestational weight gain, and infant size. This research is important because excessive insulin levels and insulin resistance may play a role in many pregnancy complications, including gestational diabetes. Findings from this study may help to develop further research to understand the role in insulin levels in the dietary management and prevention of pregnancy complications such as gestational diabetes and blood pressure disorders. This has important implications for informing practice and developing strategic care to deliver the best outcomes for mothers and infants. Work aimed at improving the long term health of mothers and future generations affected by gestational diabetes has the potential to reduce downstream in health costs on a national and global level.

Who pays for the study?

This research is funded by AUT to support post-graduate research toward a PhD qualification.

This research will cost you nothing but your time. Including communication, travel time, the one clinic visit (involving a 2.5-hour assessment), and home testing, this will take up to 12 hours of your time across your entire pregnancy.

What if something goes wrong?

In the unlikely event of a physical injury as a result of your participation in this study, you would be eligible to apply for compensation from ACC just as you would be if you were injured in an accident at work or at home. This does not mean that your claim will automatically be accepted. You will have to lodge a claim with ACC, which may take some time to assess. If your claim is accepted, you will receive funding to assist in your recovery.

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

Covid-19

Appropriate social distancing will be applied relevant to the Alert Level status at the time of all interaction. This includes contact tracing at the time of lab assessments, one metre spacing throughout face-to-face assessments. We aim to uphold general good hygiene practices as standard practice for the AUT Millennium and community labs.

What are my rights?

Participation in the research is your choice. You are free to decline this invitation to participate or withdraw from this research at any time without experiencing any disadvantage.

If you would like to participate, please respond to this invitation within two weeks. Your first clinic appointment will be scheduled within four weeks.

Precautions will be taken to protect your privacy. All assessments will be conducted in a private room in a clinical setting. All data you provide will be de-identified both in my records and future publications to protect your privacy.

What happens after the study or if I change my mind?

Your involvement in this study is voluntary, meaning you have the right to change your mind if you choose to no longer participate.

Due to the small amount of blood used in this study, we are unable to store your blood samples. If at the time you choose not to keep your finger-prick blood samples, this small amount of blood will be disposed of with medical waste. Your information from participating will have your name removed from it and will be stored electronically at a secure AUT location for 10 years, after which these electronic files will be destroyed.

You have the right to access information about them collected as part of the study. At the end of the study, you will receive a 1 to 2-page summary of the main research findings. You will also be notified of any research publications produced from this research.

What do I do if I have concerns about this research?

Any concerns regarding the nature of this project should be notified in the first instance to the Project Supervisor, Dr Caryn Zinn (e: caryn.zinn@aut.ac.nz or ph: 09 921 9999 x 7842).

Please keep this information sheet and a copy of the consent form for your future reference. If you have any questions, concerns or complaints about the study at any stage, you can contact:

Researcher Contact Details:

Sylvia North (PhD candidate): e: sylvia.north@aut.ac.nz or ph: +64210349245

Project Supervisor Contact Details:

Dr Caryn Zinn: e: caryn.zinn@aut.ac.nz or ph: 09 921 9999 x 7842

Dr Catherine Crofts e: catherine.crofts@aut.ac.nz or ph: 09 921 9999 x 6030

If you want to talk to someone who isn't involved with the study, you can contact an independent health and disability advocate on:

Phone: 0800 555 050
Fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@advocacy.org.nz

For Maori health support please contact:

Stacey Gillard-Tito, midwife: e: staceygillard_04@hotmail.com or ph: 0275499916

You can also contact the health and disability ethics committee (HDEC) that approved this study on:

Phone: 0800 4 ETHICS
Email: hdecs@moh.govt.nz

Approved by the Northern Health and Disability Ethics Committee on the 9th of December, 2019, reference number 19/NTA/124, and Auckland University of Technology Ethics Committee on the 22nd of July, 2020, reference number 20/216.

Consent Form

Study title: **Exploring insulin patterns in pregnancy: A pilot study.**

Locality: Auckland University of Technology Ethics committee ref.: 19/NTA/124

Lead investigator: Sylvia North, PhD Candidate Contact phone number: 0210349245

- O I have read and understood the information provided about this research project in the Information Sheet dated 20 May, 2020.
- O I have had an opportunity to ask questions and to have them answered.
- O I have had the opportunity to use a legal representative, whanau/ family support or a friend to help me ask questions and understand the study.
- O I am satisfied with the answers I have been given regarding the study and I have a copy of this consent form and information sheet.
- O I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without being disadvantaged in any way.
- O I consent to the research staff collecting and processing my information, including information about my health.
- O I understand that if I withdraw from the study, then I will be offered the choice between having any data or tissue that is identifiable as belonging to me removed or allowing it to continue to be used. However, once the findings have been produced, removal of my data may not be possible.
- O I consent to my Lead Maternity Carer being informed about my participation in the study and of any significant abnormal results obtained during the study.
- O I agree to an approved auditor appointed by the New Zealand Health and Disability Ethics Committees, or any relevant regulatory authority or their approved representative reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study.
- O I have not been diagnosed with diabetes or another pre-existing medical condition treated with routine medications.
- O I have not had a significant injury, trauma, or surgery in the last 6 months.
- O I agree to provide the necessary blood samples (at least three) for an oral glucose tolerance test provided in this study. I understand that, at the time blood is collected, I will be provided the opportunity to keep disposable materials containing my blood samples.
- O I understand that my participation in this study is confidential and that no material, which could identify me personally, will be used in any reports on this study.
- O I understand the compensation provisions in case of injury during the study.
- O I know who to contact if I have any questions about the study in general.
- O I understand my responsibilities as a study participant.
- O I wish to receive a summary of the research findings (please tick one): YesO NoO

Participant's signature: .....

Participant's name: .....

Participant's ethnicity (optional) : .....

Participant's Contact Details:

.....

.....

Date:

Lead maternity carer's name:

.....

Lead maternity carer contact details:

.....

.....

Date:

Approved by the Northern Health and Disability Ethics Committee on the 9th of December, 2019, reference number 19/NTA/124, and Auckland University of Technology Ethics Committee on the 22nd of July, 2020, reference number 20/216.

Participant questionnaire

Early pregnancy hyperinsulinaemia and later gestation effects, a pilot study

This questionnaire is to be completed by the researcher during the first clinic visit ***between 12-16 weeks gestation***

Name:			
Date:			
Gestational age:		**Parity:**	
Pre-pregnancy weight (kg):	**Weight (kg):**	**Height (cm):**	**BMI (kg/cm²):**
Lead Maternity Career contact details:			
Clinical information: Please indicate any clinical issues from this pregnancy identified by your lead maternity carer. Please include diagnostic variables where possible. *...Blood pressure concerns?* *...Blood sugar concerns?* *...Thyroid problem?* *...Nutrition deficiency (e.g. Iron or B12)?* *...Weight gain/loss?* *...baby growth centiles?* *...scheduled labour or delivery?* *...other complications?*			
Prescribed mediation(s) or supplement(s):			
Blood tests (if available): HbA1c (include date):			

Dietary assessment:

Food Frequency Questionnaire: *Please indicate how often you consumed the following foods in the last three months*

	Never or less than once per month	1-3 per month	1-3 per week	4-6 per week	Daily or more
Non-starchy vegetables (fresh or frozen) e.g. broccoli, carrot, cauliflower, spinach, kale, tomato, cabbage					
Starchy vegetables e.g. potato, kumara, parsnip, taro, yam					
Fruit					
Whole grains e.g. oats, rice, quinoa, grainy bread					
Refined grain products e.g. pasta, breakfast cereals, white bread, crackers					
Beans, peas, legumes, chickpeas					
Processed meat e.g. commercial salami, ham, or sausage, chicken nuggets					
Meat, poultry, egg, and organ meat (i.e. liver)					
Fish and other seafood					
Full-fat milk, yoghurt, or cheese					
Low-fat or non-fat milk, yoghurt, or cheese					
Nuts, seeds, or unsweetened nut butter					
Baked goods: Biscuits, cakes, pastries, doughnuts					
Processed snack foods e.g. chips, popcorn, pretzels, muesli bars, fruit bars, bliss balls					
Chocolate or sweets					
Jam honey, syrups, or sweetened spreads					
Juice, coconut water, sugar-sweetened drinks					
Low-calorie sweetened drinks e.g. diet drinks					
Alcohol					

How many cups of tea do you drink per day?	
Do you add milk? Y / N	Do you add sugar? Y/N
How many cups of coffee do you drink per day?	
Do you add milk? Y / N	Do you add sugar? Y/N

What kind of fat or oil do you use in cooking? *Tick as many as needed*				
Butter or ghee	Margarine	Olive oil	Vegetable oil (canola, soy, sunflower rice bran, grapeseed, cotton seed, rapeseed)	Coconut oil
Other, please specify:				

Have you been on a special diet in the last three months?			
Paleo	Yes	No	Sometimes
Gluten-free	Yes	No	Sometimes
Dairy-free	Yes	No	Sometimes
Low-carbohydrate	Yes	No	Sometimes
Sugar-free	Yes	No	Sometimes
Vegetarian	Yes	No	Sometimes
Vegan	Yes	No	Sometimes
High-fibre, low glycaemic-index, low fat	Yes	No	Sometimes
Other, please specify			

24-hour food recall: *Please describe all food and drink you consumed in the last 24-hours*

Time:	Food / drink: *e.g. bread (2 slices, wholemeal), peanut butter (2 tablespoons, natural), natural muesli (1/2 cup), milk (1 cup, dark blue top), apple (1 medium)*
Time:	Food / drink:
Time:	Food / drink:
Time:	Food / drink:
Time:	Food / drink:
Please indicate any dietary supplements (include brand and frequency):	
Has your diet changed in the previous three months? If so, why?	

Activity Questions:

What types of exercise have you done in the last week? *"Exercise" could be any activity that moderately raises your heart rate.* *e.g. walking, housework, gardening, pilates, yoga, strength training, swimming*
How has your exercise been different in the two months? **Why have you recently changed your exercise regime?**

Participant questionnaire

Early pregnancy hyperinsulinaemia and later gestation effects, a pilot study

*This questionnaire is to be completed by the **participant at the end of gestational week 24-26 and 35-37.***

Name:	
Date:	
Gestational week:	**Current weight (kg):**
Clinical information: Please indicate any clinical issues from this pregnancy identified by your lead maternity carer. Please include as much detail as you can. *...Blood pressure concerns?* *...Blood sugar concerns?* *...Thyroid problem?* *...Nutrition deficiency (e.g. Iron or B12)?* *...Weight gain/loss?* *...baby growth centiles?* *...scheduled labour or delivery?* *...other complications?*	
Prescribed mediation(s) or supplement(s):	
Blood tests (if available): HbA1c (include date):	

Self-measured fasting glucose levels:
Remember when taking a finger-prick glucose reading:

- Use a new lancet needle each time
- Use clean hands, washed with warm soapy water (not sanitiser)
- Wipe away the first drop of blood before collecting the sample

Date:	Time recorded:	Glucose mmol/L:
#1		
#2		
#3		
#4		
#5		
#6		
#7		
Notes:		

Participant Information Sheet

Date Information Sheet Produced: 19 October 2019

Project Title: **Exploring dietary advice for gestational diabetes: Perspectives from health professionals in New Zealand.**

Researcher: Sylvia North (PhD candidate)

An Invitation

My name is Sylvia North and as a part of my PhD at Auckland University of Technology, I'm interested in exploring the nutritional management of gestational diabetes. This is an invitation to participate in a qualitative study with health professionals involved in the care of women with gestational diabetes.

You have been invited to participate in this study because you have been identified as a health professional involved with gestational diabetes, and you meet the selection criteria (outlined below). Please read this information sheet carefully before deciding whether to participate.

What is the purpose of this research?

The aim of this research is to explore the role of nutrition advice in the management of gestational diabetes in New Zealand from the perspective of health professionals who have been involved in gestational diabetes care (public or private sectors).

This study will explore the following research questions:

1. *How do health professionals perceive their role in supporting women with gestational diabetes to make healthy diet and lifestyle choices?*
2. *What are health professionals' perceptions of the significance (or impact) of nutrition and lifestyle advice provided during a gestational diabetes pregnancy?*
3. *What are health professionals' views, opinions, and experiences with offering nutrition advice to pregnant women with gestational diabetes?*
4. *What are the existing gaps (if any) in the current delivery of nutrition care which could be addressed to improve the success of nutrition interventions?*

The findings of this research may be used for academic publications and presentations.

How was I identified and why am I being invited to participate in this research?

You have been invited to participate in this study because you have self-identified as meeting the following inclusion criteria:

- **Are a New Zealand registered dietitian, diabetes physician, midwife, neonatal specialist, nurse, obstetrician, paediatrician, physiotherapist, nutritionist, or naturopath.**
- **Have been professionally involved in the care of women with gestational diabetes in the last 6 months.**
- **Are practising in either a public or private care setting.**
- **Are based in New Zealand.**

How do I agree to participate in this research?

If you decide to take part in this study, please respond to me (Sylvia North) directly. You will need to complete the consent form, which was sent alongside the information sheet. Please send the completed copy of this consent form to me by email to indicate your involvement in this study. After receiving your consent form, I will liaise with you to arrange a suitable time and location your focus group or interview.

Your participation in this research is voluntary (it is your choice) and whether choose to participate will neither advantage nor disadvantage you. You are able to withdraw from the study at any time. If you choose to withdraw from the study, then you will be offered the choice between having any data that is identifiable as belonging to you removed or allowing it to continue to be used. However, once the findings have been produced, the removal of your data may not be possible.

What will happen in this research?

I will be conducting a series of focus groups and interviews. Focus group sessions will last no longer that one hour in duration and involve no more than 8 participants. If you are involved in a focus group, this will be arranged with colleagues or peers from your profession (i.e. other midwives).

One-on-one interviews will be arranged if participation in a focus group is not possible. You also have the choice to be interviewed individually if you feel uncomfortable sharing your views in a group setting.

Focus groups or interviews will be either conducted face-to-face or via remote video call (Zoom). Sessions with be audio recorded (and video recorded for video calls) and transcribed. I will facilitate the sessions with questions around the following areas:

- *Your perspective on your clinical role and the role of nutrition advice for gestational diabetes.*
- *Your experiences with providing nutrition advice to women with gestational diabetes.*
- *Your perspectives on the impact of nutrition advice that's provided to women with gestational diabetes.*

Your data will be de-identified before analysis and stored in a password-protected AUT network drive for 6 years. After this period the data will be destroyed. I (Sylvia North) will be the only person who has access to the identifiable transcripts at the time of data analysis.

What are the discomforts and risks?

We anticipate no discomfort or risks from participating in this study. However, we understand there can be many opinions in nutrition which may sometimes be controversial. There is also a possibility that you could feel uncomfortable or at risk professionally if the discussion leads to participants sharing nutrition opinions which might sit outside practice guidelines. This is also a possibility of experiencing discomfort if some participants were to discuss negative views and opinions.

How will these discomforts and risks be alleviated?

As a part of the consent signing process, all participants will also be asked to agree to confidentiality within the group. To protect you professionally, we will ensure the information shared is de-identified and can no way be traced back to you.

You may decline to answer a question at any time during the study. You will also be giving the opportunity to clarify your responses over email or phone after the session has concluded if at the time you felt you didn't say something how you intended.

In the unlikely event that any issues arise as a result of participating in this research, AUT Health Counselling and Wellbeing is able to offer three free sessions of confidential counselling support for adult participants in an AUT research project. These sessions are only available for issues that have arisen directly as a result of participation in the research, and are not for other general counselling needs. To access these services, you will need to:

- drop into our centres at WB219 or AS104 or phone 921 9992 for City/South Campus or 921 9998 for North Shore campus to make an appointment.
- let the receptionist know that you are a research participant, and provide the title of my research and my name and contact details as given in this Information Sheet

You can find out more information about AUT counsellors and counselling on http://www.aut.ac.nz/being-a-student/current-postgraduates/your-health-and-wellbeing/counselling.

What are the benefits?

Benefits to you: The main benefit you will receive for participating in this research is in the opportunity to share your professional opinions and challenges faced in your current role working with gestational diabetes. This may also be an opportunity to learn from your colleagues. Findings from this research aim to contribute to a body of evidence that will identify areas where your role can be better supported to improve patient outcomes.

You will receive a $30 Pak 'n' Save voucher for your time and contributions. We will also provide light refreshments during each focus group (for face-to-face only). You will also receive a brief report summarising the main findings of the project via mail or email after analysis has been completed.

Benefits to me (the researcher): This work will help develop my professional expertise as a New Zealand registered dietitian with a special interest in pregnancy and diabetes nutrition care. Leading this research and having direct contact with participants will help expand my professional networks. This work will contribute to the completion of my PhD thesis as one of four studies in a wider body of work exploring hyperinsulinemia in the nutritional management of gestational diabetes.

Benefits to the wider community: This study will benefit the wider diabetes research community by exploring gestational diabetes and its nutritional management from a local perspective. This study will explore experiences and attitudes around nutrition therapy for gestational diabetes. These findings will contribute to an improved understanding of the challenges faced by clinicians and patients when implementing nutrition advice.

How will my privacy be protected?

The interview or focus group will be conducted in a private room. The recordings, transcribed data, and future publications will be de-identified to protect your privacy. Video recording will be deleted immediately after the transcription has occurred. However, since there are few health professionals working with patients with gestational diabetes in New Zealand we acknowledge that there is a possibility you may be identified by colleagues or the public who are aware of your role.

What are the costs of participating in this research?

This research will cost you nothing apart from your time. We will communicate with you to find a time and location that works for you. If we cannot arrange the focus group/interview at your workplace, you may incur the cost of travel and parking at the meeting location. You will be notified of further details if this is the case.

Including communication and the one-hour focus group or interview, this will take up to 1.5 hours of your time.

What opportunity do I have to consider this invitation?

If you would like to participate, please respond to this invitation within two weeks. Your focus group or interview will be scheduled as soon as possible.

Will I receive feedback on the results of this research?

At the end of the study, you will receive a two-page summary of the main research findings. You will also be notified of any research publications produced from this research.

What do I do if I have concerns about this research?

Any concerns regarding the nature of this project should be notified in the first instance to the Project Supervisor, Dr Caryn Zinn (e: caryn.zinn@aut.ac.nz or ph: 09 921 9999 x 7842).

Concerns regarding the conduct of the research should be notified to the Executive Secretary of AUTEC, Dr Carina Meares, ethics@aut.ac.nz , 921 9999 ext 6038.

Whom do I contact for further information about this research?

Please keep this Information Sheet and a copy of the Consent Form for your future reference. You are also able to contact the research team as follows:

Researcher Contact Details:
Sylvia North (PhD candidate): e: sylvia.north@aut.ac.nz or ph: +64210349245

Project Supervisor Contact Details:
Dr Caryn Zinn: e: caryn.zinn@aut.ac.nz or ph: 09 921 9999 x 7842
Dr Catherine Crofts e: ccrofts@aut.ac.nz or ph: 09 921 9999 x 6030

Approved by the Auckland University of Technology Ethics Committee on 13th November 2019, AUTEC Reference number 19/405.

Consent form to participate in an interview or focus group

Project title: ***Exploring dietary advice for gestational diabetes: Perspectives from health professionals in New Zealand.***

Project Supervisors: ***Drs Caryn Zinn and Catherine Crofts***

Researcher: ***Sylvia North (PhD candidate)***

- ○ I have read and understood the information provided about this research project in the Information Sheet dated **19 October, 2019**
- ○ I have had an opportunity to ask questions and to have them answered.
- ○ I understand that it is my choice to participate in either a focus group or interview.
- ○ I understand that notes will be taken during the interview or focus group and that they will also be video (for remote calls only) and audio-taped and transcribed.
- ○ I understand that the identity of my fellow participants and our discussions in the focus group are confidential to the group and I agree to keep this information confidential.
- ○ I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without being disadvantaged in any way.
- ○ I understand that if I withdraw from the study then, while it may not be possible to destroy all records if I am a part of a focus group discussion, I will be offered the choice between having any data that is identifiable as belonging to me removed or allowing it to continue to be used in a deidentified format. However, once the findings have been produced, removal of my data may not be possible.
- ○ I agree to take part in this research.
- ○ I wish to receive a summary of the research findings (please tick one): Yes○ No○

Participant's signature: .....

Participant's name: .....

Participant's Contact Details:

.....

.....

.....

.....

Date:

Approved by the Auckland University of Technology Ethics Committee on 13th November 2019, AUTEC Reference number 19/405.

Appendix C. Supplementary material from published manuscripts

Supplementary material from Chapter 3

Supplementary Table 1. Search terms used for database searches.

1	pregnan* OR gestation* OR maternal
2	(large OR size OR adipos* OR fat) N4 (infant* OR neonat* OR offspring OR child* OR newborn*) OR (foetal OR fetal OR neonat* OR cord) N2 (hyperinsulinaemia OR hyperinsulinemia OR insulin OR glucose) OR (foetal OR fetal OR neonat*) N2 (hypoglycaemia OR hypoglycemia) OR “macrosomia” OR "c peptide" OR "c-peptide"
3	rct OR "random* control* trial*" OR "control* clinical trial*" OR "control* trial*"
4	(diet* OR nutri* OR food OR lifestyle) N4 (assess* OR intervention* OR analy* OR pattern* OR intake OR consum* OR adhere*) OR "calorie intake" OR "energy intake" OR "kilojoule intake" OR "calorie restriction*"
5	#1 AND #2 AND #3 AND #4

Supplementary Table 2. Risk of bias assessments for the included studies using the Cochrane Collaboration's bias risk assessment tool.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personal (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attention bias)	Selective reporting (reporting bias)	Other bias
Ferrara, 2020	+	+	-	+	+	+	+
Garmendia, 2020	+	+	?	+	+	+	-
Harreiter, 2019	+	+	-	+	+	+	?
Van Poppel, 2019	+	+	-	+	+	+	?
Kizirian, 2016	+	+	+	+	+	+	+
Mijatovic, 2020	+	+	+	+	+	+	-
Patel, 2017	+	+	-	+	+	+	+
Patel, 2018	+	+	-	+	+	?	+
Rae, 2000	+	+	+	?	-	+	-
Rhodes, 2010	+	+	?	+	+	+	-
Van Horn, 2018	+	+	-	+	+	+	+
Walsh, 2014	+	+	-	+	+	+	+
Donnelly, 2015	+	+	-	+	+	+	+
Horan, 2016	+	+	-	+	+	+	+
Zhang, 2019	+	+	+	+	+	+	?

Key: + Low risk of bias; - High risk of bias; ? Unclear risk of bias

Supplementary material from Chapter 4

Supplementary Table 3. Glucose and insulin values grouped by GDM diagnosis status.

	All	Normal	Borderline	GDM
n	925	616	123	186
Glucose 0 min (mmol/L)	4.53 ± 0.75	4.27 ± 0.45	4.75 ± 0.69	5.20 ± 1.04
Glucose 30 min (mmol/L)	8.16 ± 1.70	7.45 ± 1.18	8.97 ± 1.30	9.96 ± 1.81
Glucose 60 min (mmol/L)	8.43 ± 2.43	7.24 ± 1.57	9.60 ± 1.65	11.59 ± 1.95
Glucose 120 min (mmol/L)	7.11 ± 2.27	6.07 ± 1.22	7.52 ± 1.30	10.26 ± 2.46
Glucose 180 min (mmol/L)	5.58 ± 2.02	4.97 ± 1.28	5.57 ± 1.72	7.62 ± 2.74
Insulin 0 min (µU/mL)	17.12 ± 14.32	15.08 ± 12.24	19.39 ± 17.08	22.37 ± 16.99
Insulin 30 min (µU/mL)	101.55 ± 61.18	100.26 ± 61.75	108.17 ± 63.62	101.49 ± 57.6
Insulin 60 min (µU/mL)	117.94 ± 70.44	105.75 ± 65.71	138.54 ± 75.19	144.93 ± 72.13
Insulin 120 min (µU/mL)	119.71 ± 79.76	97.26 ± 67.12	138.16 ± 78.0	182.06 ± 83.60
Insulin 180 min (µU/mL)	80.12 ± 69.0	63.41 ± 55.08	84.85 ± 71.0	132.54 ± 81.75

Variables reported as mean ± SD, otherwise n (%).
GD diagnosis groups: "Normal" includes subjects with no abnormal glucose values from the oral glucose tolerance test using thresholds from the American Diabetes Association (2010); "Borderline" includes subjects with one abnormal glucose value; "GD" includes subjects with two or more abnormal glucose values.

Supplementary Table 4. Within-subject simple effects of time on each GDM diagnostic group for insulin.

	F[a]	p-value	DF	Effect size
Normal	6.10	<0.001	4, 175	0.12
Borderline	4.02	0.04	4, 113	0.12
GDM	6.53	<0.001	4, 595	0.42

GDM diagnosis groups: "Normal" includes subjects with no abnormal glucose values from the oral glucose tolerance test using thresholds from the American Diabetes Association (American Diabetes Association, 2010); "Borderline" includes subjects with one abnormal glucose value; "GDM" includes subjects with two or more abnormal glucose values.

$^{**}P < 0.001$

[a] Test statistic from the repeated measures ANOVA. Effect size reported as partial eta-squared.

DF: Degrees of freedom.

Supplementary material from Chapter 5

Supplementary Table 5. Dietary recall information

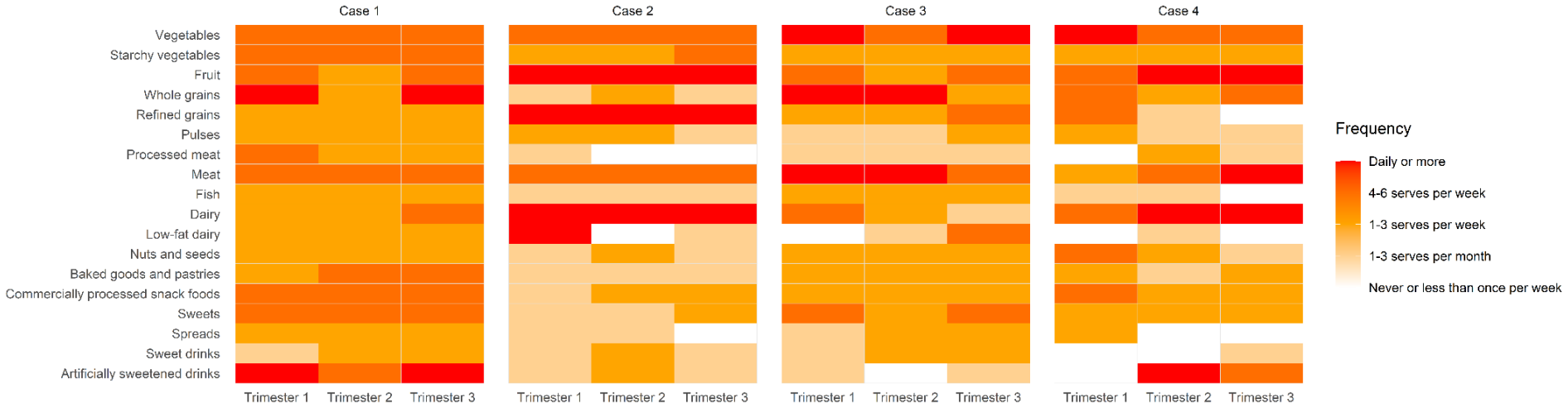
	Case Study 1	Case Study 2	Case Study 3	Case Study 4
Total energy (kJ)				
Trimester 1	9241.9	4231.1	7517.4	7284.2
Trimester 2	7201.1	3943.4	7715.5	10051.8
Trimester 3	10202.2	3741.4	9786.7	7060.1
Protein (g)				
Trimester 1	79.0	75.7	112.3	88.5
Trimester 2	90.8	56.4	80.3	100.2
Trimester 3	111.3	45.0	99.0	111.5
Total fat (g)				
Trimester 1	92.6	43.6	77.9	70.5
Trimester 2	85.5	25.8	59.9	122.4
Trimester 3	94.8	26.0	106.6	61.4
Carbohydrate (g)				
Trimester 1	258.6	72.3	150.2	166.7
Trimester 2	142.3	111.9	235.2	208.7
Trimester 3	270.5	110.1	243.7	159.4
Sugar (g)				
Trimester 1	137.1	40.4	52.9	82.5
Trimester 2	63.6	38.1	64.5	72.5
Trimester 3	115.3	34.7	126.8	91.2
Fibre (g)				
Trimester 1	33.7	11.7	20.7	45.2
Trimester 2	17.4	11.5	18.2	26.0
Trimester 3	24.8	14.3	14.3	23.4

24-hour dietary recall analysis performed using FoodWorks 10 (Xyris Software, 2021)

Supplementary Table 6. Medications and nutritional supplements

	Case Study 1	Case Study 2	Case Study 3	Case Study 4
Medications, pre-pregnancy	-	Sertraline (50 mg)	-	Citalopram (20 mg)
Medications, during pregnancy	Docusate sodium with senna (as required)	Iron infusion (30 wk)	-	-
Supplements, from 1st-3rd tri	Prenatal multi vitamin and mineral (Blackmores Pregnancy & Breast-Feeding Gold) Colecalciferol, 1.25 mg (monthly dose)	Folic acid, 800 mcg Potassium iodide, 50 mcg	Prenatal multi vitamin and mineral (Egle, Tresos Natal) Methyl-folate (Allergy Research, 833 mcgDFE) Zinc compound (Blackmores Bio Zinc) Magnesium compound (Ethical Nutrients MegaZorb Mega Magnesium) Fish oil, 1000 mg (Bloom's Health Products)	Folic acid, 800 mcg Potassium iodide, 50 mcg Colecalciferol, 1.25 mg (monthly)
Supplements from 2nd-3rd tri (additional)	Ferrous sulphate, 325mg	Ferrous sulphate, 325mg	-	Ferrous sulphate, 325mg, Magnesium, 500 mg (Go Healthy) Fish oil, 3000 mg (Sanderson)

Wk: weeks. Tri: Trimester



Supplementary Figure 1: Heat map representing change in the consumption frequency of certain types of foods.

Supplementary Table 7. Indicative questions for semi-structured interviews and focus groups

"Tell me about your clinical role in the continuum of care for women diagnosed with GDM" *Contextual probing questions:* • Clinical role, background, experience in GDM care. • Describe the service and your role in working with the women.
"Tell me about your experiences with providing nutrition advice…" *Contextual probing questions:* Positive: "What works well" • Positive experiences in your role. • The impact of dietary and lifestyle advice and how it effects outcomes for women. Negative: "What doesn't work so well?" • Challenges experienced in your role. • Negative consequences as a result of inadequate or inappropriate nutrition knowledge. • Barriers to access or implementing lifestyle changes.
"Comment on any gaps in the existing systems or resources available that could be improved to reduce the risk of acute and/or later-life complications in women affected by GDM." *Contextual probing questions:* • Suggestions that could improves the effectiveness of interventions. • Suggestions to improve women's participation in their care. • Suggestions to overcome some of the identified barriers or challenges discussed.

Supplementary Table 8. Coding framework defining individual codes used for thematic analysis.

Code	Description	Example
Social and Cultural Barriers to Care Domain		
Accessibility and Non-engagement	Describes accessibility challenges that either limit engagement or lead to non-engagement with the publicly funded GDM services. Includes challenges such as transport and geographical distance to clinic appointments.	"The ones that don't engage are often Pacific Islanders or Māori ethnicity. They often don't have a lot of money. Limited transport. They can't afford to pay for the parking at [our DHB's] hospital, or take time off work. They might have had other health issues their whole lives. If they're overweight, they might be under many services. They are sick of the health system. They don't want to engage. They're not used to using email, so they don't want to. They don't know how to use it and don't reply. People don't pick up their phone if it's got no caller ID on it." Dietitian 10 "The big thing is, especially for some of the low income women, is that we offer clinics only on Thursday morning. Some women can't afford to take work off because they will lose that day's income." Dietitian 8 "It's expensive [to drive to the clinic] as well, so if we can reduce that cost for them too." Dietitian 1
Community disconnect	Reference to challenges associated with a lack of connection within the community. Includes reference to challenges where services fail to meet the specific needs of their community.	"It's a lack of connection as well. A lack of that type of connection within their community. Within themselves. Their tangata whenua. Understanding what's important to them. What their whakapapa is….all that history. They think that they're the way that they are because they're just the way that they are. But actually, there's systems that have made you the way that you are." Community Midwife 1 "The thing is that I'm trying to say is that services can't problem solve for themselves, so they just give up. If she doesn't understand me, it's not her fault, it's actually our fault. I find it really frustrating because you see it everywhere." Community Midwife 1 "For example, I had one Pacific Island mother. She was the mother of eight [children]. She was in his 40s. [Spoke] very poor English. She didn't really understand anything I had said, but the reason why they got in contact with me was because I know her younger kids who go to the same play school as my kids. One of the careers at the

		centre said to me that I needed to take on this mum. She was ten weeks out of giving birth when I received her. She was overweight, so she was no longer able to have her baby here. She needed to be rushed over to Wellington to be able to have her baby. This was on a Friday that she found this out over the weekend. She was in absolute hysterics and didn't know what to do. She couldn't understand me. Then what I had to do was get back to the centre where the kids go to, talk to the career who was also Pacific Islander and have a three-way call to translate what was happening. The centre had to pay for the whānua to go over to Wellington and paid for their accommodation and transport. Then she had her baby because I was able to get a third party in that she trusted that she felt comfortable with and open up to ask for help. She wasn't going to ask for help. We were able to sort out and over the weekend she was able to pull herself together, and on Monday she went over [to Wellington Hospital]. There's all these barriers that whānau face. It's because of the lack of connection that whānau have that we can't support within the community." Community Midwife 1
Cultural needs and barriers	Describes cultural barriers to care including language and ethnicity.	"These women need to be communicated [to] with their partners. They need to be communicated to in a language that is appropriate to them." Dietitian 2 "You have interpreters, or you might have access to a Māori liaison, but it is still tricky to engage someone if someone doesn't want to be there in the first place. I'd say with our Māori population, they might be the most likely to come in and feel judged. They already feel [that way by] coming into a hospital. They're less likely to engage, and that's tricky because we are there to help. We're not there to be judgmental. If someone already got that idea before coming in from previous [experiences], that is really hard to overcome. At the same time, with it being pregnancy, most people do come because their baby is involved and so making sure that we're being as welcoming and caring as possible." Dietitian 11
Food environment	Describes environmental influences of food choices as determinant of unhealthy dietary behaviours.	"I had one lady said to me. It's just terrible. She said, "I step outside my front door and I can just smell all the takeaways" and she said [that] the temptation too high. It's heartbreaking, really." Specialist Midwife 5

		"The way society is and what they see. Especially when they go to school and they see their other colleagues having a pie and soda for breakfast. They think that's normal. I think peer pressure and whatever is going on around them impacts on what they want to do. They don't want to be denied it either. They think that's their right to have it." Specialist midwife 3
Health literacy challenges	Reference to gaps in education and skills people must acquire and prepare healthy food. Includes comments relating to a person's perception of GDM or type 2 diabetes risk and use of technology being a source of inequity.	"It's like everything that they perceive is meant to be healthy is actually unhealthy, [such as] doing a calorie deficit. [They say] "but I've seen on Facebook" and things like that. It's just a trend [and] lack of education that they continue to have that is intergenerational." Community Midwife 1 "A lot of our women don't know how to cook. They don't know how to use a knife to cut a potato, or a peeler. In our communities where money is quite tight, so we also introduce how to use lentils in the food. We use recipes and a video to go with it. We also have a Community Health Worker who is doing cooking sessions. For example, if we identify a particular family who don't know how to prepare a healthy recipe, we engage with them, talk about the healthy plate model and how to modify the recipes. This Community Health Worker will go into the family and make the recipe together [to] tap into those hard-to-reach areas. A lot of time, they don't need a dietitian because they just need basic [education and] to be able to cook." Dietitian 12
Mental and emotional distress: Shame, stigma, isolation	Reference to how women referred to the service experience shame as a result of their GDM diagnosis and the resulting mental/emotional impact on the women.	"At diagnosis, a lot of the time there's a lot of shame with it, and they don't want to talk to their family about it. There's a lot of shame. There's a stigma with diabetes in general, so that's probably where that comes from." Dietitian 10 "Often it's quite an isolating experience for them when they get that diagnosis. They feel like they've failed on some level. For some women of certain ethnicities [they perceive] that inevitability of getting it, especially when they've had a first-generation family member with it. It kind of feels like a self-fulfilling prophecy." Antenatal clinical midwife
Social issues	Person describes social and economic barriers to care and the impact on adherence to recommendations.	"For the younger mums as well, so they've got their own things going on. Transport…We don't want to be doing this, but sometimes we need to do it because whānau can't pay for their prescriptions and things like that…So it's money that they

	Includes reference to the cost of food and family structure/shared responsibilities.	don't have to be able to afford. I guess really being able to understand that eating healthy, minimising stresses, understanding and educating is hard for them when it's not a priority." Community Midwife 1 "A lot of the women are coming from a poor background. Money is a bit tighter. They may not be able to afford fruit and vegetables. There's a lot of takeaway shops in certain areas. They might be just having takeaways every night. Some of the women actually don't know how to chop vegetables. It can be really basic stuff. They don't know how to prepare food. They may not have enough money. They're worried about turning the power on for the oven, so they don't do any cooking. It's quicker and easier to go to the takeaway shop. Another person in the family is doing all the cooking. They might be living in a house where someone else is in control of the food and the budget. They just have to eat what's presented to them." Specialist Midwife 5
Service Provision Domain		
Enablers		
Professional collaboration	Describing the role of health professionals (dietitian, midwife, physician, obstetrician) and how health messages are reinforced within a multi-disciplinary team environment.	"I think it gives the message that it's very much the monitoring, the exercise, diet, the medication, the doctor *are all as a whole.* I feel like being there makes it seem like the food stuff is more important." Dietitian 8 "We need to be consistent, and we can't confuse people. One of the things to do is develop consistent messages. We can't keep on saying, "OK, you do this, you do that". I think it would be fabulous if eventually, we have a national group that focuses on diabetes in pregnancy so we can actually sit down and really talk about those topics. No carbs, low carb, keto. All those things and then have a common statement to say what the reason is behind our recommendations. Rather than trying to teach against each other, the consistent message is a big part of it. Once we are consistent, people know that we are consistent, then people start listening to us." Dietitian 12
Innovation	Reference to changes implemented to address systematic problems in the service. Include examples of specific	"Waiting was always the main thing. We cut that waiting a lot. Which means patients' satisfaction has improved. Sometimes they end up waiting, sometimes it's half an hour. But half an hour is vastly different from three hours…And walking away and never

	strategies to reduce the clinical burden and enhance efficiency.	coming again because they now have a negative experience of the clinic. We're setting them up to disengage" Physician 2 "We can close the gap by giving more training to the students and hopefully, eventually they can actually come out. I see that GDM is a primary care [role] and should come from a primary care service. It doesn't sit in the secondary care. Secondary care is more like type one, Type 2, or very high risk GDM, where we can do a lot more with specialist service. My dream is we need to train more dietitians to be able to take on the GDM role. Not just the GDM, also the post-natal gap. These two gaps should be filled by a dietitian but not by another professional. The reason is because we have the knowledge. A lot of time I have women who would come to me [saying] "I'm going to get a health trainer from Google who told me that I should cut out all the food" That's the message coming through. It's very generic. Then you have people saying "I don't know what else I can eat!" Dietitian 12 "The [dietitians] are very proactive. That's why we're trying to work through a separate pathway where [dietitians] can be empowered with delegated authority through a pathway where they start treatment. The pregestational diabetes patients, those with diabetes existing before pregnancy who are at higher risk upfront…What we've seen these days is that 70% of them need treatment upfront. Currently, what's working is the dietitian walk by and say "I think this woman is going to need treatment", so we make a decision upfront." Physician 2
Online and non-personal communication	Comments discussing the use on online media to provide advice. Includes remove video and telephone consultations, text messages, and email contact.	"We are doing a bit of telehealth now because of [the Covid-19 pandemic]. We have lots of people that have come to appointments from out of town, and that could be up to three and a half-hour drive for them to get you. It's quite good that [the Covid-19 pandemic] has changed access to telehealth for us. We're actually able to offer it in the hospital now." Dietitian 11
Challenges		
Overwhelmed service	Reference to resourcing or funding constraints affecting clinic or health professional capacity. Includes	"What doesn't work is that at [our] DHB we are only funded to see a single woman for 45 minutes and in one appointment. We have no follow-up. We can't see if our interventions are helpful. Unless we add them in as extras, which we don't have time

	constraints such as the number of appointments offered or time constraints.	for. With that, we can't give follow on advice effectively. Unless it's by phone or email, which again, goes into our unfunded time. So that doesn't work well." Dietitian 4 "We're time-poor. We don't have enough staff. We gloss over the food, and it's almost like we go straight on to medication. Even though we know that diet and exercise are the number one way of treating things. We do have resources like little books and things that we could give the women, but it's almost like we miss that step now because we don't have the time or the inclination, or the woman's busy so she can't actually listen to the information that we're giving. If we had more staff, we could definitely go more into depth with diet and exercise." Specialist midwife 6 "The women are allocated a room, and then the whole team goes to see the women in their room, so they stay where they are, and then we come to them. I think in some ways it works. It can be pretty crowded. You're waiting for notes sometimes for quite long periods, and other times you won't get the notes that you need." Dietitian 13 "Women could do with far more intensive input. I think that they could be seen two or three times minimum throughout their pregnancy. We only generally get to see women for one-to-one once, or twice if there's something going on. But ideally, we would catch them much more frequently. We just don't have the capacity." Dietitian 13
Health professional burden	Statement referring to personal mental or emotional stress or strain from the health professional perspective. Includes experiences with burn out and job dis-satisfaction.	"There is a lack of job satisfaction because we can't follow up the women, so we don't know what our interventions are doing." Dietitian 4 "It's really hard because we are very much expected to do so much. I've got women that come to me with huge mental health stuff. And they're sitting there in my room really divulging all their mental health stresses and anxieties and impacts on, you know, family violence, trauma history. Of course, I hear it, and I'm cognizant of it, and have to go to meetings to discuss women that are more high risk in that regard, in terms of the baby's well-being etc, but you've got to also know where you stop and someone else has to take over. Unfortunately, with the nutrition stuff, access to dietitians and nutritionists is really hard in a primary health space. It's just not funded for." Antenatal Clinical Midwife

Staffing challenges	Person describes staffing challenges relating to access to specialists or a multi-disciplinary team environment.	"To expand our service, we need to have more elasticity in staffing. Meaning, if somebody falls sick, where do we find the cover? Is it somebody else that needs to step in and do more? Even if they're registrars, we depend on them as a person and are part of the clinic. That is how we resource the clinic and how we plan the number of patients that can be seen. If they are sick or are on leave, automatically, that means no cover, and we'll have to work around that. That means we overall don't have sufficient cover or elasticity to take out the load or expand." Physician 2 "The physician's aren't always available. We don't have one! When the service was set up we had a purpose physician. We had three, actually. And now we don't. They seem to have withdrawn what service we've got. Which makes it hard for us because we're struggling…I would like a named physician for our service, and I would like more dietitian FTE [clinical hours]. We're very limited on our FTE. When they're on leave, which is perfectly acceptable, we're getting a backlog of women. Then we try to fit them all in at once. Because the service originally said that they would provide a dietitian appointment for every woman that comes through the service. Sometimes that doesn't happen." Specialist midwife 4
Nutrition across the continuum of care	Reference to the potential role of or a desire for nutrition input across the continuum of care. Includes reference to post-partum follow up as a gap in care in some regions.	"Maybe we say they need to be seen twice within the first 6-8 weeks. I don't really know what that looks like. Often, I find that we give nutrition information and we don't really have the capacity to follow up to say, "how did it go?" or "how did you find it?" To further individualised the information. If that's a week or four weeks. I don't know at some stage. We need to be able to follow up. I think we need to be able to follow up and check on how that went. You can't just give a recommendation and then believe that's going to be applicable to them for their [whole] pregnancy." Dietitian 13 "Often if I'm seeing them maybe a week down the track from the dietitian, they'll ask me things about diet. I've got a rudimentary understanding of [dietary requirements]. It's not my field. It would be much better if they had the chance to talk to the dietitian again with some women where we have had trouble with inconsistencies in their diet. There was one woman who was getting hypos after the [short-acting insulin] it was mainly that she didn't really understand the amount of carbohydrate that she wasn't having enough carbohydrate for the insulin to act on. She was getting a hypoglycaemia,

		but she was blaming it all on the insulin, but actually, it was, she just needed to adjust to diet. I often think that women need that first big appointment with the dietitian. Then see me. And then, if they do need to start on additional medication, they just need to follow up from the dietitian at that stage. That would be very helpful. I don't know if that can be built into the system, but it would certainly be very helpful." Physician 1
Unwelcoming clinic environment	Describing challenges with the clinic environment affecting service delivery and engagement.	"That whole hospital setting does definitely turn a lot of people off." Dietitian 11 "Our clinic space is a real issue. We're in tiny rooms that are not really clinic spaces. You know that room is supposed to have a bed in it and you're pushing chairs and trying to find some space. There's no air conditioning or anything like that. It's not welcoming at all for patients. We've had lots of complaints about and not had much back about what to do about that." Dietitian 11
Primary care gap	Person describes areas where primary care services could improve the efficacy of GDM services. Includes comments relating to health literacy, primary antenatal care, referral pathways, diabetes awareness and prevention.	"I don't think Primary Health services do well by dietary information for women who are at risk. I do not believe that for one minute. I think that pre-diabetic women or women who are at risk of diabetes and not managed well. It's pretty much ignored. I do not think that Primary Health, [that] the GP, in 15 minutes, can address the issues. I don't think they know where to refer to. I just don't think it's done well. I think it's a huge sector of the population that just aren't managed." Specialist Midwife 4 "Women always say "my midwife never spoke to me about how much weight I should gain," which I find that hard to believe. Weight gain in pregnancy is one of the biggest contributing factors to getting GDM. Then people are shocked when they come in at 26 weeks, and they've already gained 15 kilos and have got GDM. Maybe that needs to be emphasised." Dietitian 8
Nutrition Advice Domain		
Enablers		
Autonomy	Describes how health care providers aim to support women's autonomy in care by	"In midwifery, we were always taught to try and empower women to respect their bodies and that pregnancy is a process that is a key moment in time where they can

	maintaining their involvement in decision making.	influence their babies. If they're eating good quality food and looking after themselves, then hopefully they'll have a good outcome with a healthy baby." Specialist Midwife 2 "I think it's information. I think it's being kind and giving them access to information, including them. Giving them time to actually be part of what they think the solutions are." Antenatal clinical midwife
Nutrition education, health literacy	Person provides specific examples of how their clinical skills and experience informs advice provided to meet the individual needs of women in the service. Included examples of educating women on the physiology of GDM and the role of nutrition and medications.	"I try to explain to them what's happening with their body because I think if they can understand what's happening with their body, then that can help them decide how they can help themselves." Specialist Midwife 2 "You're reinforcing that advice. If they're struggling and treatment isn't doing well, they can ask, or they can be offered a follow-up dietitian advice later. I do encourage all women to see the dietitian because I think it's important they get the understanding that what they do can impact long-term health. Then it's not just about a nice day in labour or having a healthy baby. It's about the health of their whole whānau ["family"]. I try and get that across to our community midwives as well." Obstetrician
Personalisation	Person describes how clinical advice is personalised or patient-centred to ensure the intervention is appropriate and that women's needs are met.	"Sometimes for these women, I find that there are so many dietary changes that actually hard to know which one to start with. Where do you begin?! How I work with these women is by asking what it is they want to do? What is their priority? Sometimes their priority for the week is making sure they test four times per day and take insulin. It's actually really important to find out what's their priority." Dietitian 2 "You really have to work with that individual and work out with her what's the best that she can do. Because the best that she can do is going to be better than nothing. If you aim for something that's unreasonable or unrealistic for her, you won't achieve anything. I generally feel reasonably satisfied that we've done the best on an individual basis." Specialist midwife 7
Trust and supportive environments	Comments referring to how the health profession aims to build trust and rapport when providing dietary advice.	"I think a lot of people come in thinking that there's going to be judgment from the health professionals. We're trying to ensure that we're not coming across judgmental because we're there to help." Dietitian 11

	Include reference to meeting women's mental and emotional needs.	"It comes down to the relationship. That is a hard thing because it's people and it's time. But I think it does come down to the fact that people feel listened to and respected, and that there's been time to individualise their care. There are a lot of women who will either follow the advice or not be concerned about the relationship, but for these women that do have very entrenched habits and ideas. I think it they have to feel that you are really interested in them and that you are listening to them. It's everything else. Information isn't usually the thing that helps change views. It's a relationship." Obstetrician
Challenges		
Cultural appropriateness	Reference to cultural appropriateness of the service provided. Includes language barriers and written information provided.	"Having resources that are more culturally appropriate. And to be fair, we're getting better. There are some diabetes [resources] that cater to Indian [diets], which are really useful. But a lot of these minorities that we're getting, particularly through the refugees…We have nothing in their language that we can give them." Dietitian 10 "It's quite hard to present broadly. People glaze over if you start talking about taro and green banana or something if it's something they haven't even tried in their life… it's also not necessarily appropriate to silo people into their ethnic groups. There are groups of these women from specific ethnic groups with similar challenges that need to be supported. I don't want to be seen that I want to separate out all ethnicities. It's not quite like that. It's just that some of the issues are common within specific ethnic groups and I think parts of that is external cultural influences. It would be useful if those are more specifically addressed for certain groups." Dietitian 2
Distrust	Describes distrust of the health care providers that could negatively influence dietary management of GDM. Includes experiences where women purposefully withhold from engaging with services in a way that limits the professional's ability to perform their role.	"We sometimes wonder if we're harassing them because we are trying to talk to them so often. Some women avoid us because they're not doing the testing. They're not doing anything that we're advising them to do. Even though we say we won't tell off. It's about how we can encourage you and support you through this." Specialist Midwife 6 "I do also refer to the dietitian here in [deidentified town]. The local women don't actually like going to see them because they are so clinical. Because they've being here

		for a little while it's hard for them to see change when a lot of change doesn't actually come. So [women] find [the dietitian] quite abrupt." Antenatal clinical midwife
Fragmentation and conflicting information	Potential for fragmented or inconsistent health messages negatively impacting women. Comments around a missed opportunity for dietetic input or follow up nutrition advice being provided by other health professionals (or non-health professionals).	"At [deidentified DHB] it really feels like a tick in the box. You've seen the dietitian, done! That doesn't work. So now it's going back to that follow-up... who is actually following them up, it's the diabetes midwife. So that can then lead to misinformation of dietary recommendations. Which is concerning." Dietitian 4 "To build trust, we have to stop confusing people and that's it. I think a lot of time, people would say "I went to that person, and they told me to do this, and then another person tells me to do this. So what should I listen to?" Some women try very hard and keep changing [their diet] until they just give up. We need to be consistent, and we can't confuse people. One of the things to do is develop consistent messages." Dietitian 12
Nutrition guidelines discourse	Comments on specific dietary recommendations and how nutrition guidelines influence advice provided. Refers to discourse from non-specific carbohydrate prescription ("blanket guidelines") outlines in dietary guideline documents and challenges in dietetic practice.	"It seems a little bit archaic. As soon as you start to make it more… even though we want it to be more individualised, we have to also have the capacity to do that. At the moment, it's a blanket recommendation, but really it needs to be more individualised, but we can only do that if we have the funding and the capacity to offer those services." Dietitian 13 "I know the guideline also says to use it "as a guide". So not being prescriptive, but to use it as a guide. What I find a bit tricky is, trying to not fall back on [the Ministry of Health guideline] because that is a guide and it's not something we should be saying. It's not prescriptive. But then it was on the same token you've got patients who say "how much can I eat? What's safe? What's not safe?" Well, it's hard to know how to guide them on that because there is no follow up to see what their blood sugars are doing, what's their weight doing, what's baby's growth doing? That's what ultimately tells us and then it doesn't really take into account differences as well. Then we look at a Southeast Asian Lady and then [the prescribed amount of carbohydrate] would be too much. I often will say "look, that's only a guide. If you can, just eat as much as you would be able to and that will be fine." I know she's not going to ever going to get to 175 grams per day at all." Dietitian 5

Food beliefs and cultural trends	Comments describe women acting on incorrect or non-evidence based dietary advice. Includes reference to food beliefs, cultural trends that impact dietary behaviours, denial, misinformation, and over restriction.	“There's always going to be misinformation out there so if we can get in first with the information, then hopefully that will reduce the risk of that. But even after they watch the video, they’re still going to be looking online and joining groups and heading to other pregnant ladies.” Dietitian 3 “You can almost type the people as they come into our practice. This woman is going to starve herself. We just get that they get that impression. Often, it's people who are very healthy, and they take their health very seriously. I think the important thing, and I know our dieticians are absolutely on this page as well, is to enforce that it is just pregnancy. It's not something they should feel guilty about. That is a challenge. It's a whole modern approach to food. People are obsessed one way or another. They either can't stop eating or they're totally obsessed with quality and quantity. My heart sinks when a woman comes in and says, “I like ‘Clean Eating’” So what do you mean by that? Sometimes it’s just avoiding almost everything. I’m fine if ‘Clean Eating’ means no processed food, but if it means no dairy, no meat, no carbs. There are some quite unusual dietary opinions out there.” Obstetrician