The diagnostic threshold for gestational diabetes: Should it be lowered to improve pregnancy outcomes?

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Abstract

Background: Gestational diabetes mellitus (GDM) is one of the most frequent complications of pregnancy. Hyperglycemia during pregnancy confers an increased risk of adverse pregnancy outcomes for mother and offspring, and studies indicate that adequate maternal glycemic control improves these outcomes. However, there is no consensus regarding the best GDM diagnostic test or optimal cut-points to identify women who will most benefit from treatment.

The Diabetes Canada 2018 guidelines suggest use of either of two approaches for the diagnosis of GDM: 1) Preferred two-step approach; 2) Alternative one-step approach. Both methods include a fasting 75-gram oral glucose tolerance test (OGTT) but with higher and lower cut-points for diagnosis, respectively. Our study focused on women with OGTT results between these two sets of thresholds, which we considered "grey zone" results, as it is unclear whether diagnosing and treating these women for GDM improves pregnancy outcomes.

Objectives: The general objective of this study was to assess the association of higher versus lower cut-points in the second step of the OGTT with adverse maternal and neonatal outcomes. **Aim:** Examine the risk of large for gestational age (LGA) and secondary outcomes (including other birthweight-related outcomes [macrosomia, infant birthweight, small for gestational age], as well as maternal hypertensive disorder of pregnancy, induction of labour, primary caesarean section, length of hospital stay and a composite infant adverse outcome including preterm birth, shoulder dystocia, low Apgar score, stillbirth and neonatal death), (1) among women with GDM screening test results in the grey zone who were not diagnosed and treated for GDM with (a) women who also had grey zone results but received a GDM diagnosis and intervention (primary objective) and with (b) all women who were diagnosed with and treated for GDM, and (2) among all women who were diagnosed and treated for GDM, comparing across the two cut-point alternatives.

Methods: We conducted a retrospective cohort study of pregnant women undergoing GDM screening tests between September 01, 2013, and February 29, 2020, at two Montreal-area university hospitals (the Jewish General Hospital [JGH] and McGill University Hospital Centre [MUHC]). Both follow the Diabetes Canada preferred two-step diagnostic approach. However, the JGH uses the Diabetes Canada thresholds with higher cut-points for the OGTT, whereas the MUHC uses lower cut-points. We applied logistic regression models to evaluate associations with

LGA and binary secondary outcomes. For analyses of birthweight and length of hospital stay, we used linear and Poisson regression, respectively. Primary analyses were adjusted for maternal age and parity. Models for secondary outcomes were adjusted for additional potential confounders where applicable, including gestational age at delivery, neonatal sex, GDM treatment type (medication vs. lifestyle), mode of delivery (C-section vs. vaginal) and/or previous C-section.

Results: Of 4407 pregnancies evaluated, 836 met inclusion criteria. At JGH, n=252 women were classified as GDM and an additional n=73 women with grey zone results who were not classified as GDM were included in the grey zone group. At MUHC, n=511 women were classified as GDM, including n=80 women with grey zone results. Untreated women in the grey zone were less likely to have induction of labour compared with those with similar test results who were treated (OR 0.27, 95% CI 0.1, 0.64), and though inconclusive, had an increased OR point estimate for LGA (OR 2.14, 95% CI 0.86, 5.61). Women with a grey zone result who were not treated had a statistically significantly increased odds of an LGA infant, macrosomia, and higher birthweight compared with all women who were diagnosed with GDM using either the higher or lower cut-points, and they had lower odds of induction of labour compared with women who were diagnosed with GDM using the lower cut-points. Also, compared with women diagnosed with GDM by applying the lower cut-points, women diagnosed with GDM using the higher cut-points had a longer hospital stay for the mother and lower odds of induction of labour.

Conclusion: Women with mild hyperglycemia during pregnancy who are not currently diagnosed with or treated for GDM may benefit from intervention to reduce the risk of fetal overgrowth, and they are less likely to have induction of labour compared with women with mild hyperglycemia who are diagnosed with GDM. Further research with a larger study population and a randomized controlled trial design is needed to determine whether lower diagnostic thresholds can improve pregnancy outcomes.

RÉSUMÉ

Contexte : Le diabète gestationnel (DG) constitue l'une des complications les plus fréquentes de la grossesse. L'hyperglycémie pendant la grossesse confère en effet un risque accru d'issues défavorables pour la mère et la progéniture. Par ailleurs, des études indiquent qu'un contrôle glycémique maternel adéquat améliore ces résultats. Or il n'existe pas actuellement de consensus quant au meilleur test diagnostic pour le DG ou quant aux seuils optimaux à atteindre pour identifier de façon optimale les femmes qui bénéficieraient le plus d'un traitement.

Les directives de Diabète Canada formulées en 2018 suggèrent l'utilisation de l'une des deux approches suivantes pour un diagnostic de DG : 1) une approche privilégiée en deux étapes; 2) une approche alternative en une seule étape. Les deux méthodes incluent un test de tolérance au glucose (TTG) par voie orale de 75 grammes à jeun, mais avec des seuil respectivement supérieurs et inférieurs pour l'établissement d'un diagnostic. Notre étude s'est concentrée sur les femmes avec des résultats de TTG par voie orale se trouvant entre ces deux ensembles de seuils, que nous avons considérés comme des résultats de « zone grise » - puisqu'il n'est pas clair si le diagnostic et le traitement du DG améliorent effectivement les issues de grossesse.

Objectifs: L'objectif général de cette étude était d'évaluer l'association des seuils supérieurs et des seuils inférieurs dans la deuxième étape de TTG avec des issues maternelles et néonatales indésirables.

But: Examiner le risque de nourrissons présentant une taille grosse pour l'âge gestationnel (GAG) ainsi que les issus secondaires (les critères liés au poids à la naissance: macrosomie, poids du nourrisson à la naissance, une taille petite pour l'âge gestationnel; et autres critères des issus secondaires: trouble hypertensif maternelle de la grossesse, accouchement provoqué, césarienne primaire, durée du séjour à l'hôpital de la mère et résultats indésirables composites pour le nourrisson, dont la naissance prématurée, la dystocie des épaules, l'indice au taux Apgar faible, la mortinaissance et le décès néonatal), (1) chez les femmes ayant des résultats de test de dépistage du DG dans la zone grise n'ayant pas été diagnostiquées et traitées pour le DG avec (a) les femmes ayant également des résultats dans la zone grise mais qui ont reçu un diagnostic et une intervention de DG (objectif primaire); et avec (b) toutes les femmes qui ont été diagnostiquées et traitées pour

le DG; et (2) chez toutes les femmes qui ont été diagnostiquées et traitées pour le DG en utilisant les deux ensembles distincts de seuils.

Méthodes : Nous avons mené une étude de cohorte rétrospective de femmes enceintes subissant des tests de dépistage du DG du 1 septembre 2013 au 29 février 2020 dans deux hôpitaux universitaires de la région de Montréal : l'Hôpital général juif (HGJ) et le Centre universitaire de santé McGill (CUSM). Les deux centres suivent l'approche diagnostique bipartite privilégiée par Diabète Canada; cependant, l'HGJ utilise les seuils de Diabète Canada avec les seuils les plus élevés pour l'HGPO tandis que le CUSM utilise les seuils avec les seuils les plus bas. Nous avons appliqué des modèles de régression logistique pour évaluer les associations avec GAG et les issus secondaires binaires. Pour les analyses du poids à la naissance et de la durée du séjour à l'hôpital, nous avons utilisé respectivement la régression linéaire et la régression de Poisson. Les analyses primaires ont été ajustées en fonction de l'âge et de la parité de la mère. Les modèles pour les critères des issus secondaires ont été ajustés pour d'autres facteurs de confusion potentiels, le cas échéant, y compris l'âge gestationnel à l'accouchement, le sexe néonatal, le type de traitement (médicaments ou régime alimentaire), le mode d'accouchement (césarienne ou vaginale) et/ou une césarienne antérieure.

Résultats : Sur 4407 grossesses évaluées, 836 répondaient aux critères d'inclusion. À l'HGJ, n = 252 femmes ont été classées comme DG et n = 73 femmes supplémentaires avec des résultats de zone grise qui n'étaient pas classées comme DG ont été incluses dans le groupe de la zone grise. Au CUSM, n = 511 femmes ont été classées comme DG, dont n = 80 femmes avec des résultats de zone grise. Les femmes non traitées dans la zone grise étaient moins susceptibles d'avoir un déclenchement du travail par rapport à celles avec des résultats de test similaires qui ont été traitées (OR 0,27, IC à 95 % 0,1, 0,64), et bien que non concluantes, elles avaient une estimation ponctuelle de l'OR accrue pour GAG (OR 2,14, IC à 95 % 0,86, 5,61). Les femmes avec un résultat de zone grise qui n'ont pas été traitées avaient une probabilité statistiquement significativement accrue d'avoir un bébé GAG, une macrosomie et un poids de naissance plus élevé par rapport à toutes les femmes qui ont reçu un diagnostic de DG en utilisant les seuils supérieurs ou inférieurs, et elles avaient des probabilités plus faibles du déclenchement du travail par rapport aux femmes qui ont reçu un diagnostic de DG en utilisant les seuils inférieurs. De plus, par rapport aux femmes

diagnostiquées avec un DG en appliquant les seuils inférieurs, les femmes diagnostiquées avec un DG en utilisant les seuils supérieurs avaient un séjour à l'hôpital plus long pour la mère et une probabilité plus faible de déclenchement du travail.

Conclusion : Les femmes présentant une légère hyperglycémie pendant la grossesse qui ne sont pas actuellement diagnostiquées ou traitées pour le DG peuvent donc bénéficier d'une intervention visant à réduire le risque d'avoir une croissance fœtale excessive. Les femmes qui ont été diagnostiquées pour le DG sont plus susceptibles d'avoir un accouchement provoqué que les femmes atteintes d'hyperglycémie légère qui ne sont pas diagnostiquées pour le DG. Des recherches supplémentaires avec une population d'étude plus large et une conception d'essais contrôlés randomisés sont nécessaires pour déterminer si des seuils de diagnostic plus bas peuvent effectivement améliorer les issues de grossesse.

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I would not have made it this far without you all by my side, and with you, I will start the next chapter of my life…

PREFACE AND CONTRIBUTION OF AUTHORS

The main goal of the project constituting this Master thesis was to assess the association of applying lower cut-points introduced by the IADPSG approach in the second step of the OGTT with adverse perinatal outcomes compared with applying higher cut-points recommended by the Diabetes Canada preferred approach for the diagnosis of GDM. This thesis is presented in the traditional format following the Graduate and Postdoctoral Studies' guidelines and general requirements of a Master's thesis at McGill University. This thesis is organized into eight chapters:

Chapter 1 introduces the topic, the thesis rationale, the hypothesis, and the objectives of the project;

Chapter 2 provides a comprehensive literature review on gestational diabetes mellitus, epidemiology, risk factors, complications, pathophysiology and treatment as well as diagnosis test and the effect of distinct cut-points;

Chapter 3 explains the study design, data collection and statistical methods;

Chapter 4 presents the results, findings and related tables;

Chapter 5 discusses the overall findings and provides the future research directions;

Chapter 6 expresses the conclusions;

Chapter 7 provides the complete reference list; and

Chapter 8 contains supplementary material.

All chapters were written and completed by Sanaz Azizi. Dr. Tricia Peters (supervisor) and Dr. Kaberi Dasgupta (co-supervisor) reviewed and edited the text in this thesis and provided constructive feedback to improve it.

Dr. Tricia Peters was involved in all stages of the research from the conception and design of the research project, revising the electronic data capture form, implementation of the work to the analysis, active discussion of the results and provided critical ideas, constructive comments, constant support and revisions.

Sanaz Azizi contributed to the original concept of the project, prepared the electronic data capture form and several revisions of this form, reviewed the patients' documents in both sites, prepared a

Standard Operating Procedures for Data Entry in the Gestational Diabetes Platform for each site separately, led the team of data entry, completed the majority of data entry in both sites, performed data extraction, was involved in the statistical analyses, and interpreted the results.

Abolfazl Dehghan on the JGH site, Rebecca Lozano-Franco on the MUHC site and Hajar Iraqi, Nahal Siraj Fansia and Tania Morin on both sites were involved in data entry in the Gestational Diabetes Platform.

Dr. Tricia Peters, Dr. Kaberi Dasgupta, Dr. Agnieszka Majdan, Dr. Rachel Talia Bond, Dr. Natasha Garfield, Dr. Sara Meltzer and Dr. Shaun Eintracht were involved in the conception and design of the research project and provided helpful feedbacks during the project. Diane Gaudreau from Information Management Service (IMS) assisted in the development of the electronic Gestational Diabetes Platform. Julia Ma and Kathryn Morrison performed the statistical analyses.

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CHAPTER 1: INTRODUCTION AND OBJECTIVES

1.1 Introduction and Rationale

Gestational diabetes mellitus (GDM) and hyperglycemia during pregnancy can lead to adverse pregnancy outcomes for both mother and infant[1]. However, there is not enough evidence to determine the best glucose cut-points at which a pregnant woman should be diagnosed and therefore treated for GDM in order to prevent harmful maternal and fetal outcomes[2,3].

In the past, the glycemic cut-points used for diagnosis of GDM were defined based on identifying women at future risk of developing type 2 diabetes[4]. However, more recent studies showing that treatment of GDM reduces adverse perinatal outcomes such as macrosomia and caesarean section, suggested that the diagnosis of GDM should be based on the association with risk of both perinatal and maternal morbidities[5–7]. Specifically, in 2008, a large multi-centre prospective study called the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study showed that elevated maternal glucose during pregnancy has a linear association with adverse perinatal outcomes including large for gestational age (LGA) status, cord-blood serum C-peptide level above the 90th percentile (i.e., indicating increased fetal insulin production), primary caesarean delivery, and neonatal hypoglycaemia[8]. This observational study could not establish the level of hyperglycemia at which pregnant women and offspring would most benefit from interventions[2].

In 2010, the International Association Diabetes in Pregnancy Study Group (IADPSG), based on extensive analyses and review of the data from the HAPO study, arrived at a consensus-based recommendation for a one-step fasting 75-gram oral glucose tolerance test (OGTT) with lower cut-point values for GDM diagnosis in comparison with previously recommended diagnostic tests [9]. The recommendation marked the first time that the glucose cut-points were defined by the risk of adverse perinatal outcomes. However, the IADPSG suggestion was based on consensus after review of the HAPO study and was not based on the best evidence such as multiple high quality studies and randomized controlled trials (RCTs).

After applying IADPSG thresholds, studies started to compare the risk of adverse perinatal outcomes in women who were diagnosed with GDM using IADPSG thresholds with women who were diagnosed with GDM using other thresholds. However, these studies – as opposed to evaluating various thresholds using the same diagnostic test method – primarily compared the one-

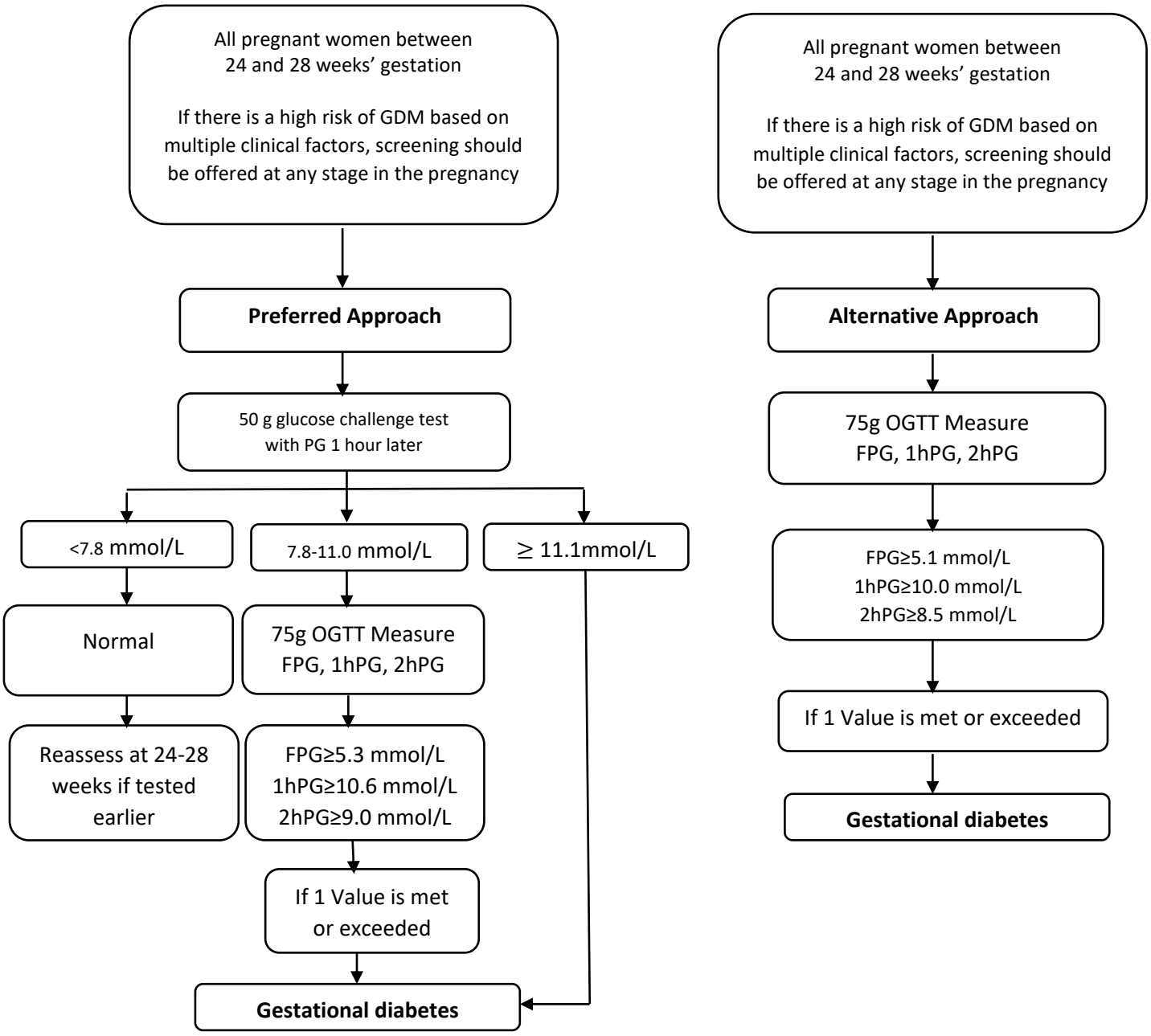
step IADPSG test versus two-step approaches, wherein women undergo an initial non-fasting screening test followed by a fasting diagnostic test if the first step result is in an "intermediate" range[10,11]. In fact, few directly compared the cut-points for the 75-gram OGTT. Also, only three relevant studies to our knowledge (which will be discussed in detail below) evaluated differences in maternal and neonatal outcomes associated with the diverse cut-points used for the 75-gram OGTT to evaluate the benefit of applying lower diagnostic criteria as recommended by IADPSG[12–14], and we have a critical knowledge gap related to this issue.

Despite over 10 years since the HAPO study and IADPSG recommendations, the best diagnostic approach for GDM remains controversial. Although the purpose of IADPSG was to introduce an international uniformity for the diagnosis of GDM, this approach has not been accepted universally. One important reason is that by using IADPSG criteria, GDM incidence increases without enough evidence of benefits for maternal and neonatal outcomes[2,15]. For example, in 2013, the US National Institutes of Health stated that "…the adoption of new criteria that would increase the prevalence of GDM, and the corresponding costs and interventions, without a clear demonstration of improvements in the most clinically important health and patient-centred outcomes," [2]and nearly ten years later this statement remains relevant.

Therefore, several separate guidelines and criteria for diagnosing GDM are recommended internationally. Furthermore, within Canada alone, the Diabetes Canada 2018 guidelines suggest two distinct approaches for the diagnosis of GDM: preferred two-step approach or alternative one-step approach (Figure 1).

In both approaches, GDM is diagnosed if ≥1 glucose value is above established cut-points[16]. Of note, the alternative approach applies the same thresholds suggested by IADPSG for the OGTT test[16].

Figure 1: Diabetes Canada 2018 Guidelines for the Diagnosis of Gestational Diabetes



1hPG: 1-hour plasma glucose; 2hPG: 2-hour plasma glucose; FPG: fasting plasma glucose; GDM: gestational diabetes mellitus; OGTT: oral glucose tolerance test; PG: plasma glucose.

The various GDM screening tests and cut-points used in different institutions - even in one city like Montreal - lead to confusion for clinicians and possibly also for patients who may be diagnosed with GDM in one institution but who would not be considered as having GDM in another. Also, the use of different diagnostic tests with various thresholds leads to a wide range of incidence and

prevalence for GDM in distinct populations. In addition, applying diagnostic tests with higher thresholds could result in failing to diagnose some of the pregnant women with clinical hyperglycemia who may experience adverse short- and long-term complications, which could potentially be prevented with effective diagnosis and treatment. This highlights the importance of achieving a global agreement on the best threshold for diagnosing GDM, which has been frequently expressed by experts[17].

On the other hand, it might be appropriate to have different methods in distinct clinical scenarios globally. For example, a one-step test may be preferred in developing countries or rural locations where returning for two tests would be difficult and/or pregnant women may not have a reliable follow-up or financially it is not feasible for them or the healthcare system. Moreover, recent studies show that the optimal criteria may vary by population[18], which could be a reason that there is as yet no consensus regarding the optimal GDM diagnostic criteria. Thus, an examination of GDM diagnostic criteria among our local population is further interesting and necessary to determine how distinct cut-points may affect maternal and neonatal outcomes in our own patients because it has direct and indirect effects on the healthcare system resources as well as short and long-term health consequences for mother and offspring. The details will be further explored in the next chapters.

As will be described below, we are uniquely positioned to conduct a direct comparison of pregnancy outcomes associated with higher and lower thresholds for the 75g OGTT. This is due to the fact that the two McGill University hospital centres employ distinct approaches to a two-step method for GDM screening.

1.2 Central hypothesis

Using lower (IADPSG) glucose thresholds in the second step of the preferred approach for GDM screening and diagnosis compared to use of higher values (Diabetes Canada preferred approach), leads to increased identification and intervention and results in lower risk of LGA and other adverse pregnancy outcomes.

1.3 Objectives

1.3.1 General objective

To assess the association of lower cut-points in the second step of the OGTT with adverse maternal and neonatal outcomes compared with applying higher cut-points recommended by the Diabetes Canada preferred approach for the diagnosis of GDM. Our study focused on women with mild hyperglycemia who had intermediate results at the 50g glucose challenge test (GCT) and then underwent a 75g OGTT. The two institutions where the study was conducted had different glucose thresholds at the second stage. We defined values between these thresholds as "grey zone" results. Those with "grey zone" results were diagnosed and treated for GDM at one institution and not considered GDM at the other. This was an opportunity for a comparison of resulting outcomes.

1.3.2 Specific objectives (Figure 2)

i) Primary objective: Compare the risk of LGA among women with GDM diagnostic test results in the grey zone between those who were diagnosed and treated for GDM vs. those who were not.

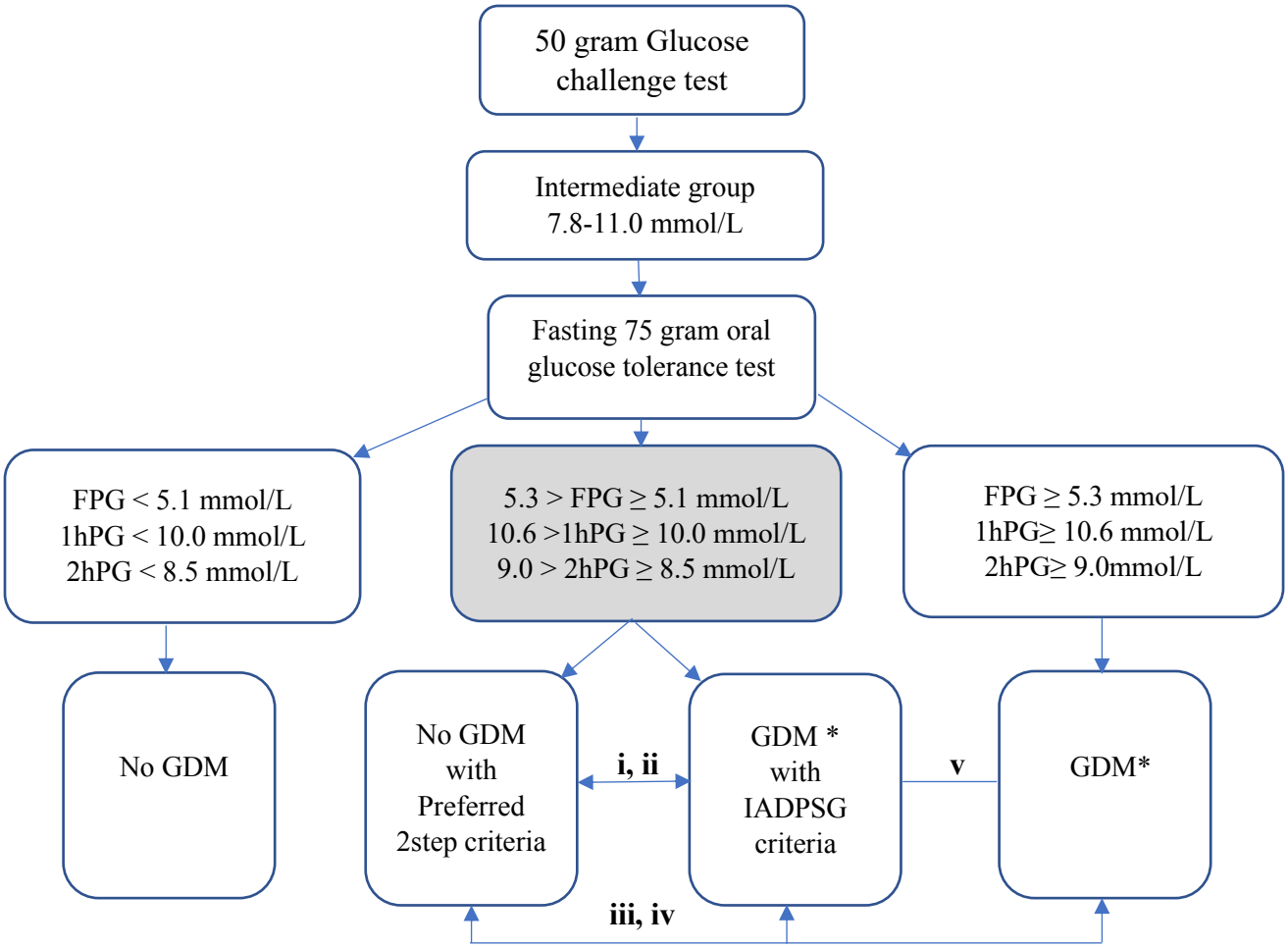
ii) Compare the risk of secondary outcomes (birthweight related outcomes: macrosomia, birthweight, small for gestational age (SGA) and other secondary outcomes: maternal hypertensive disorder of pregnancy, induction of labour, primary C-section, length of mother's hospital stay and a composite infant adverse outcome including preterm birth, shoulder dystocia, low Apgar score, neonatal death and stillbirth) of "untreated" grey zone with "treated" grey zone women.

iii) Compare the risk of LGA in the "untreated" grey zone group with all women who were treated for GDM.

iv) Compare the risk of the above secondary outcomes in the "untreated" grey zone group with all women who were "treated" for GDM.

v) Among all women diagnosed and treated for GDM, compare those who were diagnosed at higher cut-points against those diagnosed at lower cut-points in terms of (a) LGA and (b) secondary outcomes noted above.

Figure 2: Specific objectives



* The group received treatment

CHAPTER 2: LITERATURE REVIEW

2.1 Background

From a historical perspective, the observation of onset of diabetes in pregnancy with resolution after delivery dates to the 19th century. In 1823, Heinrich Gottlieb Bennewitz for the first time described a case of a woman who had symptoms of severe hyperglycemia which developed during pregnancy, delivered a macrosomic and stillborn baby, and the mother's symptoms resolved after delivery[19].

In 1909, the first diagnostic criteria for diabetes that occurs in pregnancy was described by Williams, who offered thresholds for "transient glycosuria in pregnancy"[20]. In 1950, Hoet and his colleagues explained the fetal and obstetric adverse outcomes of hyperglycemia in pregnancy[21]. They reported that the internal maternal environment during fetal life was related to the characteristics of the newborn, and this environment put the child at risk of obesity, hyperglycemia and eventually diabetes. Also, they emphasized the importance of treatment by correcting this hyperglycemia with insulin to prevent complications in the mother and infant.

In 1952, Jorgen Pedersen introduced the hyperglycemia-hyperinsulinemia hypothesis or the "Pedersen hypothesis"[22]. According to this hypothesis, maternal hyperglycemia raises the fetal blood glucose level and leads to hypertrophy in fetal pancreatic islet cells, which elevates insulin secretion, and as a result, increases glucose utilisation by the fetus. Pedersen identified fetal insulin as a main factor in intrauterine growth. Therefore, fetal hyperinsulinism explains the fetal overgrowth or macrosomic baby delivered by a mother with hyperglycemia[22,23]. In 1957, the term "gestational diabetes" was first used by Carrington,[24] but it obtained major recognition only after the publications in 1961 and 1964 by John O'Sullivan when he and his colleagues for the first time introduced specific criteria for diagnosing gestational diabetes[25,4].

2.2 Definition of gestational diabetes mellitus

The traditional definition of GDM is a mother's hyperglycemia with onset or first detection during pregnancy[26,27]. This definition contains both hyperglycemia which resolves after delivery as well

as diabetes mellitus which was undiagnosed before and recognised during pregnancy, such as type 1 and type 2 diabetes mellitus and monogenic diabetes.

Recently, the American Diabetes Association provided a clearer definition of GDM which is "diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation"[28]. According to this definition, the hyperglycemia diagnosed in the first trimester, which is assumed to be pre-existing diabetes, is excluded from the definition of GDM.

2.3 Epidemiology of gestational diabetes mellitus

GDM is one of the most common complications of pregnancy. In Canada, GDM is the most prevalent endocrine disorder in pregnancy, affecting over 5% of pregnancies[29].

GDM prevalence varies around the world, it is practically nonexistent in some places and in contrast, it is highly prevalent in some populations, involving close to half of the pregnancies[30–32]. This difference in reported prevalence depends on the characteristics of the underlying population, such as ethnic and genetic variability[33–36], with a GDM prevalence that is higher in pregnant women from Africa, Spain, India and Asia than for Caucasian pregnant women[28,37]. Also, applying various diagnostic criteria with different thresholds has a key role in this diversity in prevalence[31,38–40]. In addition, over the past 20 years, the prevalence of GDM worldwide has increased in parallel with the obesity epidemic and is expected to continue to rise with the increase in pre-pregnancy obesity and obesity in pregnant women[41].

2.4 Risk factors for gestational diabetes mellitus

GDM is the result of a combination of environmental, genetic, and epigenetic factors. Therefore, the cause of GDM is multifactorial and is not completely clear yet. However, there are some well-known risk factors implicated in the development of GDM[42]. They include obesity or being overweight, advanced maternal age, ethnicity, having a previous macrosomic baby, previous GDM, family history of diabetes in first-degree relatives, history of stillbirth, polycystic ovary syndrome, history of abortion and history of preterm delivery[42–45].

Also, several studies show low-grade, chronic inflammation is associated with insulin resistance and a higher risk of type 2 diabetes (T2DM) and GDM[46,47]. Some cross-sectional studies showed women with GDM and their babies have a higher level of inflammatory mediators than pregnant women without GDM, which suggests that chronic inflammation with the secretion of cytokines and chemokines may have a role in the development of GDM[48–50]. Moreover, a study on women who participated in the HAPO study found an association of genes for inflammatory cytokines including TNFα, RETN, IL6, and IL8 with higher glucose levels during pregnancy[47].

Moreover, some pre-pregnancy and during-pregnancy dietary factors also affect the onset of GDM. Among many dietary factors studied, a meta-analysis of the associations of diet and physical activity with risk for GDM showed, for instance, that Mediterranean diet (high amounts of fruits, vegetables, legumes, nuts, whole grains and unprocessed grains, extra virgin olive oil, moderate fish and wine, and low meat, eggs and animal fat consumption) was associated with a 15–38% lower relative risk of GDM. In contrast, the consumption of high amounts of red or processed meat, potato, and protein derived from animal sources was associated with a higher risk of GDM[51]. In addition, an association of higher levels of pre-pregnancy and early pregnancy physical activity with a lower risk of GDM has been observed[51–54], with more time spent active and higher intensity of activities enhancing this protective association[55].

In addition, several candidate genes have been identified that may be involved in the aetiology of GDM[56,57]. Specifically, some of the genetic factors that are associated with the risk of GDM include variants or single nucleotide polymorphisms in genes such as CDKAL1 (affecting β-cell survival), MTNR1B (associated with high fasting plasma glucose and insulin levels), KCNQ1 (altering β-cell function), insulin receptor substrate 1 (IRS-1) (impairing insulin secretion), GCK (associated with high glucose level) and TCF7L2, KCNQ1, KCNJ11, SLC30A8 (all involved in the regulation of insulin secretion)[58–64]. The interesting point is that most of these genes are also associated with a higher risk of developing T2DM which provides evidence that T2DM and GDM share a similar genetic background. It may a key reason that pregnant women with GDM have a higher risk of developing T2DM in the future[59,65,66].

Epigenetic changes like DNA methylation, histone modifications, and messenger RNA (mRNA) binding by microRNAs (miRNAs which are small non-coding RNA with the role of regulating gene expression and different cell functions) are other risk mediators for the onset of GDM. For

instance, Wu and colleagues, for the first time, identified a series of differentially methylated genes including COPS8 (regulating multiple signalling pathways), PIK3R5 (involved in cell growth, proliferation, differentiation, motility, survival and intracellular trafficking.), HAAO (catalyzing an excitotoxin that has a role in the pathogenesis of neurologic and inflammatory disorders) and CCDC124 (involved in cell cycle and divisions) which changes in pregnant women's blood before the onset of GDM[66,67]. Recent studies show miRNA-375 is associated with decreased insulin secretion and increased insulin resistance as well as inflammation[68]. Later studies in this field showed miR-29a, miR-132 and miR-222 were expressed less in pregnant women at 16-19 gestational weeks who were diagnosed with GDM at 24-28 gestational weeks in comparison with the control group without GDM[69]. Moreover, miR155-5p, miR16-5p, miR17-5p, and miR20a-5p are some of the miRNAs which have an association with GDM. These factors are proposed as potential biomarkers that may identify mothers who are at risk of GDM earlier during pregnancy[70,71].

2.5 Complications of gestational diabetes mellitus

Uncontrolled hyperglycemia is associated with an increased risk of short- and long-term adverse health outcomes for both the mother and her baby. Langer, *et al*., demonstrated that each 17 mmol/L elevation in fasting plasma glucose (FPG) is associated with a 15% rise in both maternal and neonatal adverse outcomes[72]. Furthermore, as described above, the HAPO study, a large multinational cohort study of 23,316 women, demonstrated that maternal hyperglycemia increased the risk of LGA offspring, primary caesarean delivery, shoulder dystocia, preterm delivery, neonatal hypoglycemia and admission to a neonatal intensive care unit (NICU)[8]. The odds ratios (ORs) from the HAPO study for these important adverse outcomes are presented below:

Table 2.1 Associations between maternal glycemia as a continuous variable and adverse perinatal outcomes (Adapted from Ref. 8)			
Outcome	Adjusted odds ratio (95% confidence interval) *		
	Fasting	At 1 hour	At 2 hours
Large for gestational age	1.38 (1.32, 1.44)	1.46 (1.39, 1.53)	1.38 (1.32, 1.44)
Primary caesarean delivery	1.11 (1.06, 1.15)	1.10 (1.06, 1.15)	1.08 (1.03, 1.12)
Shoulder dystocia	1.18 (1.04, 1.33)	1.23 (1.09, 1.38)	1.22 (1.09, 1.37)
Preterm delivery	1.05 (0.99, 1.11)	1.18 (1.12, 1.25)	1.16 (1.10, 1.23)

*Adjusted for: field centre, age, body-mass index, height, smoking status, alcohol use, presence or absence of a family history of diabetes, gestational age at oral glucose tolerance test, infant's sex, presence or absence of hospitalization before delivery, mean arterial pressure (in all models), parity (0, 1, or ≥2; not included in the model for primary caesarean delivery.

The main perinatal concern in GDM is excessive fetal growth and LGA, as this has implications for other short-term adverse pregnancy outcomes, such as birth trauma, shoulder dystocia, low Apgar score, preterm delivery, caesarean delivery, neonatal hypoglycemia, NICU admission and in some cases stillbirth and neonatal death[1,8,73,74]. It is worth mentioning that LGA refers to birth weight larger than the 90th percentile for that gestational age[75]. However, macrosomia is a birth weight higher than a specified threshold (≥ 4000g or sometimes ≥ 4500g) irrespective of gestational age[76]. Women with GDM also have a higher risk of serious perinatal complications including hypertensive disorders of pregnancy and primary caesarean delivery which is mentioned above[8,74].

In addition to short-term outcomes, there are also long-term consequences of maternal hyperglycemia for the mother and the newborn. Studies have shown that exposure to maternal hyperglycemia during pregnancy increases the risk of obesity and diabetes in young adulthood[77–79]. While the mechanisms for this impact on long-term outcomes are unclear, it is suggested that intrauterine hyperglycemia has an effect on β-cell programming in the fetus and impaired insulin secretion in the future for offspring[80–82]. Furthermore, maternal hyperglycemia has long-term complications for mothers include recurrent GDM, and risks of future type 2 diabetes and cardiovascular disease[77,83,84].

Importantly, identification and treatment of women with hyperglycemia during pregnancy is shown to improve outcomes[85,86]. We will discuss this in more detail in the "treatment of gestational diabetes mellitus" section.

2.6 Gestational diabetes mellitus pathophysiology

For a better understanding of the pathophysiology of GDM, we should first explain the normal physiology of pregnancy. During a healthy pregnancy, several physiological changes occur in the mother's body to meet the needs of the developing fetus. Insulin sensitivity is one of these adaptations, which varies depending on the needs of the pregnancy[87,88].

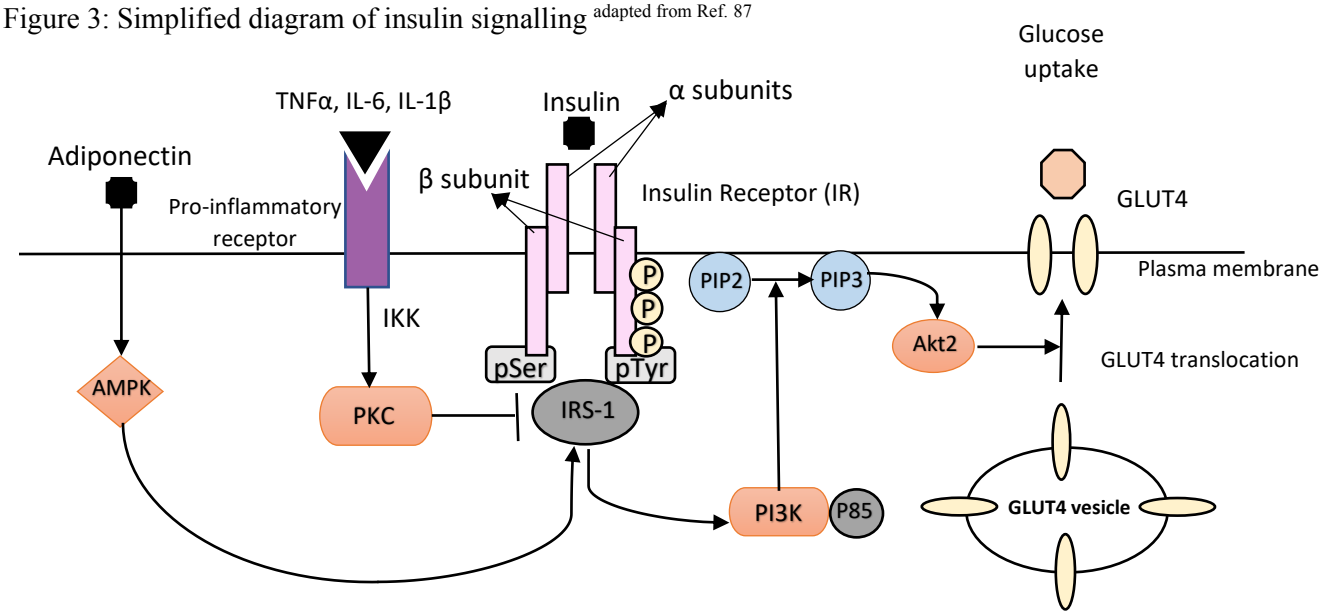
Insulin is secreted from the β-cells which are located near the centre of the Langerhans islets in the pancreas. In the physiologic situation, rising blood glucose after ingestion of carbohydrates stimulates the β-cells to produce insulin from proinsulin and secrete it. The three main target organs for insulin are the liver, skeletal muscle, and adipose tissue which the secreted insulin will connect to the insulin receptors in these organs to show its tissue-specific effects such as suppressing glucose production in the liver, promoting glucose and fatty acid uptake in skeletal muscles and inhibiting lipolysis as well as stimulating lipid biosynthesis in adipose tissues[89,90].

At the cellular level, the binding of insulin to the α subunits of the insulin receptors (IR), translates interaction to the β subunit of IR which have tyrosine kinase domains. Activation of IR leads to phosphorylation of its tyrosine kinase which leads to the activation of IRS-1. IRS-1 is a signalling adapter protein that plays a key role in transmitting insulin signals via intracellular pathways[91,92]. IRS-1 activates phosphatidylinositol-3-kinase (PI3K), which phosphorylates phosphatidylinositol-4, 5-bisphosphate (PIP2). Phosphatidylinositol-3, 4, 5-phosphate (PIP3), as a result of this phosphorylation, activates Akt2, and Akt2 promotes translocation of glucose transporter 4 (GLUT4) to the plasma membrane of target cells, the result of which is uptake of glucose into the cells[87] (Figure 3).

During early gestation, insulin sensitivity is normal if not higher than normal. After oral ingestion of glucose, glucose is taken up from blood into target cells to prepare a source for the energy demands of the fetus during the later phase of pregnancy. Despite the increased insulin sensitivity

and this effort to decrease blood glucose, there is still enough glucose in maternal circulation to provide adequate energy and lead to normal growth for the fetus in the first trimester[88].

Figure 3: Simplified diagram of insulin signalling adapted from Ref. 87



Insulin demand physiologically increases during pregnancy because of increased maternal caloric intake as well as maternal weight gain[93]. In response to this increasing demand, insulin secretion rises with the progression of pregnancy due to an increase in the secretion of insulin after oral glucose ingestion[94]. Moreover, insulin sensitivity decreases during later pregnancy as much as 60 to 80%[95], and the result of that is shifting excess glucose from the mother to the fetus in order to aid the growth of the fetus[88,96].

Furthermore, in the second and early third trimester, an increase in placental hormones such as estrogen, progesterone, cortisol, leptin, human placental lactogen and growth hormone occurs which together lead to physiological insulin resistance[87,97]. Insulin resistance is defined as a decline in the target tissues' ability to respond to insulin concentrations for glucose uptake[98]. This decrease in glucose consumption by the target cells leads to using more lipid units instead of carbohydrate units to provide energy for the mother's body. The result of this switch is preparing the glucose supply and more carbohydrates for fetal growth[88,96].

The molecular reason for this insulin resistance during normal pregnancy is the reduction of the post-receptor insulin signalling cascade, in particular the reduction of tyrosine phosphorylation of IRS-1[98]. As mentioned above, tyrosine autophosphorylation is the first step of the insulin signalling cascade and leads to active the other units like IRS-1 and PI3K which lead to translocation of GLUT4 to the cell membrane and rising glucose uptake to the cells [3,87].

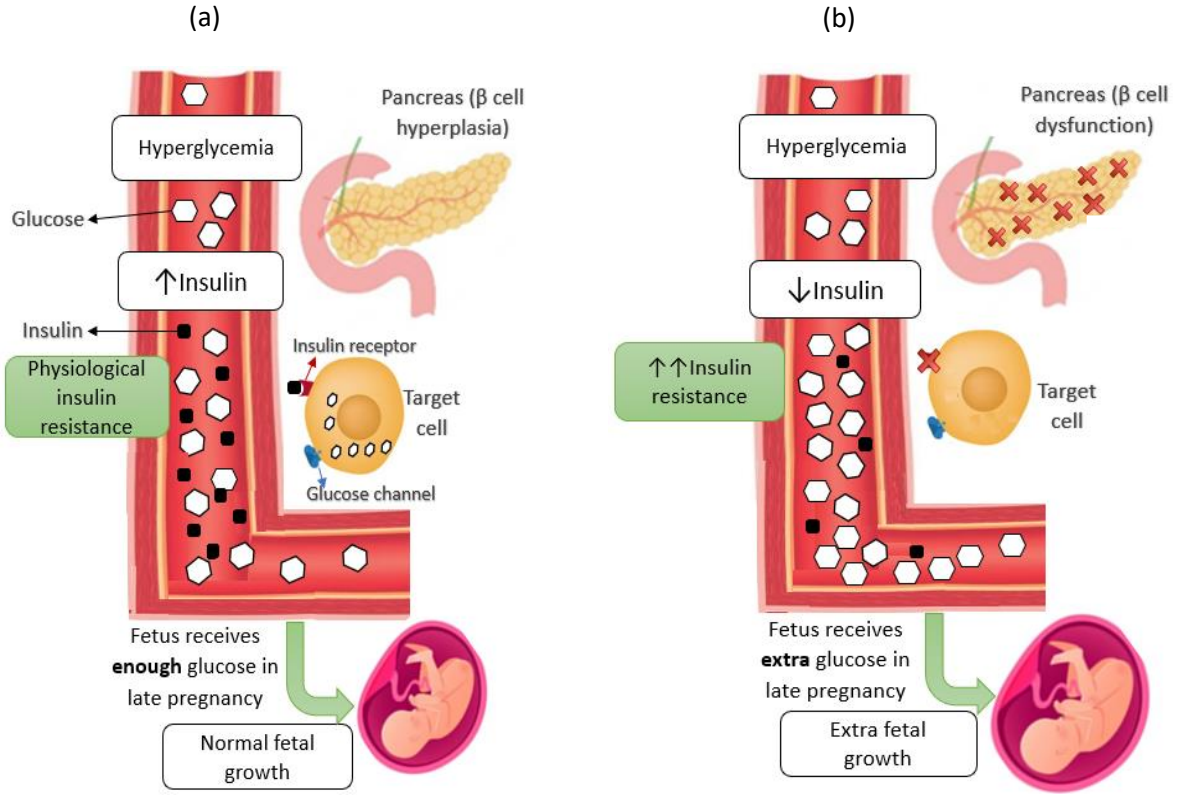
In response to insulin resistance, the pancreas in a healthy pregnant body increases insulin secretion by β-cell hyperplasia and hypertrophy that lead to a compensatory rise in insulin secretion to meet the metabolic needs of pregnancy[99]. As insulin resistance and compensatory hyperinsulinemia progress, in some pregnant women, β-cell dysfunction leads to not producing and releasing enough insulin and the result of that is hyperglycemia and GDM[94,100]. Pancreatic β-cell dysfunction occurs when the β-cell role of storing and releasing insulin in response to blood glucose levels is disrupted and is thus unable to detect correct blood glucose levels or secrete enough insulin. This can happen in any stage of insulin processing, such as pro-insulin synthesis, granule storage, etc[87]. In many cases, this β-cell defect exists before pregnancy, but is manifested as a result of increased insulin resistance in pregnancy and leads to hyperglycemia and the diagnosis of GDM[99].

Women with GDM experience insulin resistance beyond the physiological insulin resistance of pregnancy, which results in part from a decrease in IRS-1 tyrosine phosphorylation. This reduction in phosphorylation is in addition to the phosphorylation decrease that happens physiologically in pregnancy. As we mentioned above insulin by binding to the IR actives phosphorylation of tyrosine kinase. A series of experiments on biopsy samples of rectus abdominis muscles of women with or without GDM at the time of caesarean section reported that in women with GDM, the maximum effect of insulin for tyrosine phosphorylation on IRs is 37% lower compared with normal women[98]. This extra insulin resistance impairs the uptake of glucose by insulin-sensitive tissues and raises hepatic glucose output, which both lead to hyperglycemia[101].

At the cellular level, the decrease in IRS-1 tyrosine phosphorylation occurs due to decreasing tyrosine or increasing serine/threonine phosphorylation of the insulin receptor, which reduces intracellular insulin signalling. Moreover, human studies showed that in GDM there exists altered expression and/or phosphorylation of downstream regulators of insulin signalling, such as IRS-1, PI3K, and GLUT4[87,98]. All of these factors can result in excess insulin resistance in GDM women.

Another factor implicated in the pathogenesis of insulin resistance in GDM is neurohormonal dysfunction such as adiponectin dysfunction. One of the roles of adiponectin is modulating insulin sensitivity[101]. At the cellular level, IRS-1 is promoted by adiponectin through AMP-activated protein kinase (AMPK). In contrast, IRS-1 is inhibited by pro-inflammatory factors containing TNFα, IL-6 and IL-1β through activating protein kinase C (PKC) (Figure 3). Therefore, a decrease in adiponectin or an increase in pro-inflammatory factors by the effect on this intracellular pathway is associated with GDM development[87,102].

Figure 4: Glucose regulation in the third trimester of (a) healthy pregnancy, (b) women with GDM



2.7 Diagnosis of gestational diabetes mellitus

The aim of GDM screening tests is to recognize GDM in pregnant women because GDM is usually asymptomatic, and interventions that improve glucose control can prevent short- and

long-term adverse outcomes for both mother and baby[103]. However, as it is mentioned before, there is no consensus on the best screening and diagnostic GDM test currently.

Our study evaluates specifically the association of adverse pregnancy outcomes with distinct cut-points for the OGTT. However, to understand better how these thresholds evolved and why GDM diagnostic criteria are still debated we must first review the history of diagnosis of GDM.

O'Sullivan and Mahan in 1964 understood the measurable effects of pregnancy on carbohydrate metabolism and for the first time introduced a two-step method following a 3-hour 100 g oral OGTT for diagnosis GDM[4]. The major issue of this criterion was that the glycaemic cut-points were validated against the future risk of developing diabetes in mothers instead of perinatal outcomes[104]. Also, a few years after that, in 1973, a 50 g GCT was suggested by O'Sullivan, *et al*., for GDM screening in order to improve GDM diagnosis in pregnant women without the need to do 100g GCT for all of them[105,106].

In 1979 the National Diabetes Data Group (NDDG) suggested using plasma instead of whole blood for glucose analysis. Due to higher concentrations of glucose in plasma, the glycaemic cut-points increased (approximately 14% higher) and NDDG introduced a new guideline for GDM diagnosis[107]. However, very soon in 1982, by replacing the calorimetric assays with specific enzyme assays by using glucose oxidase and hexokinase, Carpenter and Coustan suggested lower cut-points which we apply currently as a 'two-step approach", and the Carpenter-Coustan criteria emerged (fasting: 5.3 mmol/l, 1-hour: 10.1 mmol/l, 2-hour: 8.7 mmol/l, and 3-hour: 7.8 mmol/l) [108].

The American Congress of Obstetricians and Gynecologists in 1986, recommended performing GDM screening tests only for high-risk women such as women over 25 years old, with body mass index (BMI) > 25 kg/m^2 or with an existing history of type 2 diabetes in first degree relatives[109]. However, performing the screening test just for high-risk pregnant women was inadequate, as many studies have shown that nearly half of women with GDM do not have these risk factors[104,110,111]. Therefore, screening for all pregnant women was suggested[112].

As mentioned before, the HAPO study demonstrated that maternal glucose levels have positive and continuous associations with adverse perinatal outcomes such as primary caesarean delivery and increased birthweight[8]. However, there were not any obvious thresholds for GDM diagnosis.

Hence, following from the HAPO study results, the IADPSG recommended OGTT cut-points based on glucose values with an adjusted OR of 1.75 for LGA, cord-blood serum C-peptide level above the 90th percentile and percent body fat over 90th percentile. However, the diagnostic thresholds used in the second step of the preferred Diabetes Canada approach are based on glucose values that correspond to an OR of 2.0 for the same adverse perinatal outcomes[9,113]. We will further describe this distinction below. Of note, the models were adjusted for age, height, BMI, field center, smoking, use of alcohol, family history of diabetes, gestational age at OGTT, baby's sex, parity, hospitalization before delivery and mean arterial blood pressure[9].

In light of the HAPO study result, various guidelines with distinct methods and cut-points exist globally, with heated debate on appropriate thresholds. These tests differ in the number of testing steps, the amount of glucose load consumed for the screening and diagnostic tests, and/or the number of criteria that must be met for diagnosis of GDM. Table 2.2 shows a selection of some of these current diagnostic tests and their thresholds.

Table 2.2 Cut-points of distinct GDM screening and diagnostic tests

Glucose Value mmol/L	Two-step test: First step: one-hour, 50 g GCT screening. If the GCT is 7.8–11.0 mmol/L, then apply OGTT as the second step.			One-step test 75 g OGTT	
	Diabetes Canada*#	**American Diabetes Association †#**	**New Zealand***	**WHO ***	**IADPSG***
Fasting	≥ 5.1	≥ 5.3	≥ 5.5	≥ 5.1	≥ 5.1
1-hour	≥ 10.0	≥ 10.0	Not required	≥ 10.0	≥ 10.0
2-hour	≥ 8.5	≥ 8.6	≥ 9.0	≥ 8.5	≥ 8.5
3-hour	Not required	≥ 7.8	Not required	Not required	Not required

* If ≥1 thresholds are met on OGTT considered as GDM

† If ≥2 thresholds are met on OGTT considered as GDM

Considered IADPSG suggestion as the second approach

2.7.1 One-step vs. two-step approaches

Current guidelines for GDM screening in pregnant women use either a one-step or a two-step approach. As mentioned above, the one-step approach is a diagnostic test applied for all pregnant women and the two-step includes a GCT screening step that will be followed by an OGTT diagnostic test for women with an intermediate GCT result. Each approach has advantages and disadvantages. By applying the one-step approach, screening and diagnosis can be completed in a single visit, but all women have to fast overnight for the test and allocate time for a 2-hour visit. On the other hand, by applying the two-step approach, for the first step 1-hour GCT screening test there is no need to be fasting, which makes it easily a part of the scheduled prenatal visit, and 70-80% of women will not need to proceed to do the fasting diagnostic OGTT test. However, around 20% of pregnant women must return on another day for a fasting OGTT test if they have intermediate results on the first screening test[2,103,114,115].

As mentioned before, a 50 g 1-hour GCT was introduced as the GDM screening test by O'Sullivan, *et al.,* in 1973. Their analysis showed that a ≥7.2 mmol/L cut-point by applying the Nelson–Somogyi method for the GCT had 79% sensitivity and 87% specificity for the diagnosis of GDM in pregnant women, and a subsequent systematic review indicated that the GCT is acceptable as a screening test. By considering a 100 g, 3-hour OGTT with Carpenter-Coustan cut-points as the gold standard, the sensitivity and specificity of the GCT cut-point of 7.2 mmol/L were respectively, 99% and 77%[116].

Clinical controversy exists as to whether a one-step approach leads to the overtreatment of GDM, in contrast to whether a two-step approach is missing some pregnant women with GDM who need treatment[113]. Two recent RCTs that compared the one-step and two-step approaches showed applying the one-step approach leads to more diagnosis of GDM, but without significant difference in the risk of perinatal outcomes including LGA and caesarean section between the two groups[117,118] (Table 2.3). Although this issue is not what we are investigating, it is also of great interest considering the various screening methods used globally.

Table 2.3 Risk of specific outcomes comparing the one-step vs. two-step test in two recent RCTs		
	Hillier, et al.[117]	Davis, et al.[118]
GDM diagnosis (one-step vs. two-step)	16.5% vs. 8.5%	14.4% vs. 4.5%
	Relative risk (97.5% CI)	Relative risk (95% CI)
Large for gestational age (LGA)	0.95 (0.87, 1.05)	0.90 (0.53, 1.52)
Caesarean section	0.98 (0.93, 1.02)	1.05 (0.85, 1.29)
Macrosomia (weight ≥ 4000 gm)	0.99 (0.91, 1.06)	0.94 (0.57, 1.55)
Small for gestational age (SGA)	1.05 (0.96, 1.14)	0.93 (0.65, 1.33)
Gestational hypertension	1.00 (0.93, 1.08)	0.99 (0.74, 1.31) †

† Composite outcome including other maternal outcomes (3rd or 4th degree vaginal laceration and Postpartum hemorrhage)

2.7.2. Diabetes Canada guidelines

As mentioned in Chapter 1, two approaches are suggested by the Diabetes Canada 2018 guidelines for the diagnosis of GDM: preferred two-step approach and alternative one-step approach (Figure 1).

In the preferred two-step approach, the first step is the non-fasting 50g 1-hour GCT performed for all pregnant women between 24 and 28 weeks' gestation, and women with intermediate results (1-hour glucose ≥7.8 to <11.0 mmol/L) will return another day for a fasting 75-gram OGTT with specific diagnostic glucose thresholds (fasting glucose ≥5.3 mmol/L, 1-hour glucose ≥10.6 mmol/L, 2-hour glucose ≥9.0 mmol/L)[16]. In the alternative approach, one-step fasting 75-gram OGTT is performed with lower glucose thresholds (fasting glucose ≥5.1 mmol/L, 1-hour glucose ≥10.0 mmol/L, 2-hour glucose ≥8.5 mmol/L). In fact, the alternative approach is the same approach with the same thresholds suggested by IADPSG[16]. In both approaches, GDM is diagnosed if ≥1 glucose value is above established cut-points[16].

Of note, pregnant women are usually screened for GDM at 24-28 weeks of gestation, as during the second trimester insulin resistance increases and as previously mentioned, in women who are

unable to produce enough insulin to accommodate this resistance, glucose levels rise. One of the factors that increase insulin resistance and contribute to GDM is placental hormones. Hence, earlier screening may not be helpful as there is not yet a rise in placental hormones, and later screening may miss the opportunity for interventions to improve adverse outcomes[119]. Therefore, 24-28 weeks of gestation is currently recommended as an optimal time period for screening.

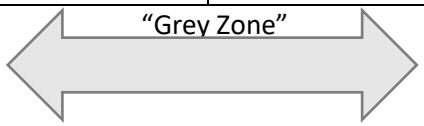
2.7.3 The reason for differences between thresholds

The difference between the thresholds in these two approaches (preferred two-step approach and alternative one-step approach) is the difference in the population to which the thresholds are applied as the two-step OGTT thresholds only apply to women with the intermediate result on the first step who have mild hyperglycemia. Another difference between these thresholds corresponds to OR for the neonatal outcomes as assessed in the HAPO study[8,9].

As mentioned above, the diagnostic thresholds in the preferred two-step approach were based on glucose values corresponding to an OR of 2.0 in the HAPO study for the risk of birth weight over 90th percentile (LGA), percent body fat over 90th centile and cord serum C-peptide over 90th centile. In fact, the calculation of this OR was based on the frequency of these HAPO study outcomes in the entire glucose concentration distribution in comparison with the lowest glucose concentration range as the reference. However, the IADPSG suggestion is the threshold that corresponds to an OR of 1.75 for the same adverse outcomes. Calculation of this OR was based on the frequency of the same outcomes associated with the mean values of plasma glucose concentrations for the OGTT results for the entire HAPO study population as the reference (instead of the lower glucose concentration, which was used for the OR of 2.0)[8,9].

In our study, if the result of the OGTT is a glucose value between the preferred approach thresholds as higher cut-points and the alternative approach thresholds as lower cut-points, we considered that result as a “grey zone” result (Table 2.4).

Table 2.4 Diagnostic thresholds of two approaches suggested by the 2018 Diabetes Canada guideline		
	OR 1.75	**OR 2.0**
Glucose (mmol/L)	The thresholds of OGTT in Alternative approach (IADPSG)	The thresholds of OGTT in Preferred approach
Fasting	5.1	5.3
1-hour	10.0	10.6
2-hour	8.5	9.0



2.7.4 Diagnostic cut-points and effects on diagnosis of GDM

Screening tests are generally used by clinicians to detect conditions for which early diagnosis and intervention may improve disease outcomes. For understanding and interpretation of the results of a test, we should first know the value of the test and how well it predicts known disease. Screening and diagnostic tests do not always have the "correct" result, so it is a key question how valid a special test is. Sensitivity and specificity are used to determine the validity of a screening test[120,121].

Sensitivity is the probability that a person with a disease will be correctly identified as "diseased", and her test result is positive. Specificity is the probability that a real person without the disease will be correctly identified as "non-diseased" and her test result is negative. The best sensitivity and specificity for a test is near 100%, but in reality, it is difficult to have both high sensitivity and specificity[120,121].

Table 2.5 Test sensitivity and specificity		
	True Disease	True non-diseased
Positive test result	Correctly Positive **a**	False Negative **b**
Negative test result	False Positive **c**	Correctly Negative **d**

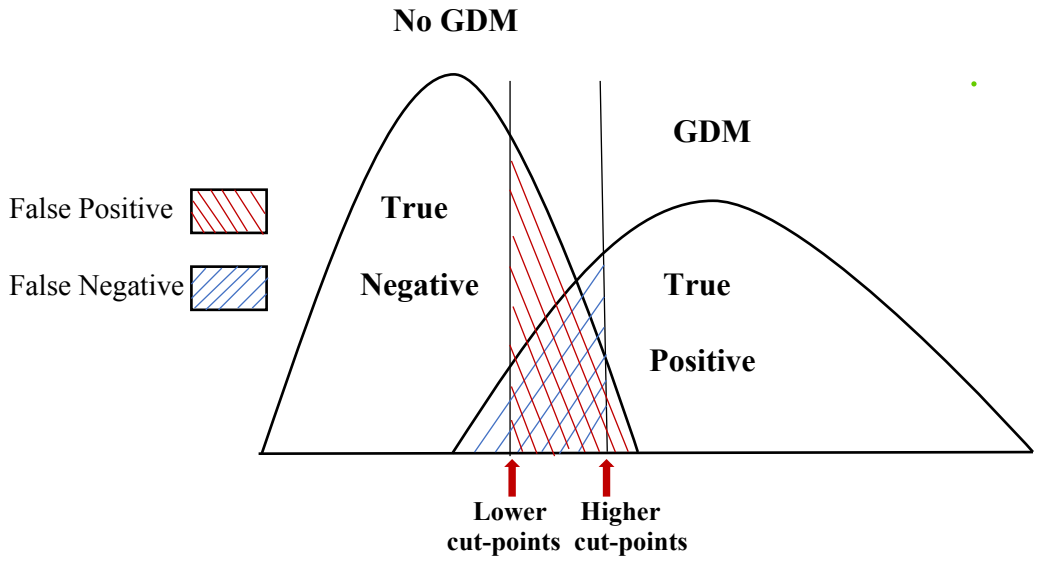
$$\text{Sensitivity} = \frac{a}{a+c} \times 100 \qquad \text{Specificity} = \frac{d}{b+d} \times 100$$

The sensitivity and specificity of a test can be modified by changing the cut-points[121]. Therefore, using different cut-points for the 75g OGTT leads to different sensitivity and specificity and as a result, affect which women will be labeled as having GDM.

Figure 5 shows the effect of applying lower and higher cut-points on false positive and false negative GDM diagnosis test results[121]. By applying lower cut-points such as the cut-points in IADPSG criteria for OGTT tests, it will improve the sensitivity and decrease the specificity. Therefore, in the case of the GDM diagnostic test, by applying IADPSG cut-points we classify more non-GDM individuals as GDM, and these will increase false positives. Also, we will label fewer GDM individuals as not having GDM, and this will decrease false negatives. In consequence, there will be higher sensitivity and lower specificity and, in the result, the test will diagnose more women with GDM.

In contrast, by applying higher cut-points we classify fewer non-GDM individuals as GDM, and these will decrease false positives. Also, we will label higher real GDM individuals as normal, and these will be rise false negatives. Therefore, the result of applying a higher cut-point is lower sensitivity and higher specificity of the test and misses some pregnant women with GDM.
Unnecessary treatment of GDM by applying IADPSG criteria and diagnosing more women with GDM versus not treating the real GDM women by applying a higher threshold and missing some GDM pregnant women is exactly the clinical controversy that we discussed before.

Figure 5: The effect of applying higher and lower cut-points on sensitivity and specificity of GDM screening test



For example, with respect to the fasting and one-hour plasma glucose levels for the 75g OGTT (applying the IADPSG cut-points and using the WHO criteria as the gold standard) showed 87.16% sensitivity and 96.08% specificity for fasting criteria (>5.1 mmol/L) and 85.74% sensitivity and 99.68% specificity for one-hour criteria (>10.0 mmol/L)[122]. Also, a systematic review of diagnostic tests showed 76% sensitivity and 92% specificity for FPG ≥ 5.1 and 54% sensitivity and 93% specificity for FPG ≥ 5.3[116].

2.8 Treatment of gestational diabetes mellitus

The aim of treating women with GDM is glycemic control to reduce the risk of relevant adverse outcomes. Studies show standard treatment decreases the risk of LGA and most of the other adverse outcomes including primary caesarean delivery, preterm delivery, shoulder dystocia and NICU admissions. A systematic review of 8 RCTs and 1 nonrandomized study indicated that treatment is associated with a lower risk of adverse perinatal outcomes[85]. Table 2.6 presents some of these outcomes and their relative risks. The women with GDM who are treated have approximately similar outcomes in comparison with the general pregnant population[85,123–125].

Table 2.6 Impact of intervention for GDM on pregnant women (Adapted from Ref. 85)[85]				
OUTCOME	No. of trials	No. of women with treatment	No. of women without treatment	Relative risk (95% CI)
Large for gestational age (LGA)	7	174/1654 (10.5%)	322/1675 (19.2%)	0.56 (0.47, 0.66)
Macrosomia (>4000 g)	8	164/1805 (9.1%)	330/1839 (17.9%)	0.53 (0.41, 0.68)
Primary caesarean delivery	3	81/561 (14.4%)	113/553 (20.4%)	0.70 (0.54, 0.91)
Induction of labour	5	338/1373 (24.6%)	285/1410 (20.2%)	1.18 (0.92, 1.52)
Preterm delivery	4	69/965 (7.2%)	92/968 (9.5%)	0.75 (0.56, 1.01)
Shoulder dystocia	3	15/1017 (1.5%)	36/1027 (3.5%)	0.42 (0.23, 0.77)
Hypertensive disorders in pregnancy	3	126/1305 (9.7%)	171/1326 (12.9%)	0.85 (0.50, 1.43)
NICU admissions	5	63/809 (7.8%)	84/791 (10.6%)	0.73 (0.53, 0.99)

Standard treatment of GDM includes lifestyle modification in the form of a specialized diet and increasing physical activity, with the addition of pharmacologic therapy if indicated. Lifestyle modification alone, as the first-line treatment in women with GDM, can control blood glucose in 70-85% of cases[126]. How the diet should be formulated for women with GDM is a complex issue and has not yet been fully resolved. Optimal weight gain and energy requirements for each woman, daily carbohydrate intake (should contain starchy foods with naturally high dietary fibre content), shifting protein intake from red and processed meat to plants, lean meat and fish and shifting fat intake from saturated fat to n-3 fatty acids are some of the points which should be considered for preparing a suitable diet for women with GDM[127]. Physical activity in combination with nutritional intervention is effective for the management of GDM, with benefits on both fasting and particularly postprandial blood glucose levels. The effects of physical exercise on adverse outcomes have not been fully investigated as most studies have combined physical activity with other lifestyle modifications[127]. Moreover, the best recommendation for this intervention in terms of the type, intensity, frequency and duration of a successful physical program remains uncleart[16,128].

Women with more pronounced hyperglycemia or those who fail lifestyle intervention to control glucose levels may require pharmacologic therapy. Insulin is considered the first line of pharmacological treatment for GDM by Diabetes Canada guidelines[16,129]. Studies demonstrated the use of insulin for achieving glycemic targets decrease fetal and maternal harmful outcomes. However, insulin usually requires constant adjustment to achieve glycemic goals. It is tailored to a woman's glycemic profile, wherein a woman with elevated fasting glucose levels would require basal or intermediate insulin, women with elevated postprandial values would require bolus insulin, and women with both anomalies may require basal/bolus treatment[16]. On the other hand, some RCTs indicated efficacy of oral diabetes medications like metformin and glyburide to control glucose levels in pregnant women with GDM. However, oral medications are not used as the first line of pharmacological treatment since these medicines are known to cross through the placenta and the long-term impacts of intrauterine exposure to them for children is a concern[129]. Moreover, some studies showed treatment with glyburide compared with use of metformin increase the risk of macrosomia and neonatal hypoglycemia[16].

2.9 Study Rationale

On the basis of this background, the importance of diagnosing and treating women with GDM in order to decrease adverse perinatal outcomes has been demonstrated. However, there is concern that women with mild hyperglycemia who might benefit from treatment could be missed by the current thresholds used in the second step of the Diabetes Canada guidelines.

Few studies have evaluated the risk of adverse pregnancy outcomes using distinct cut-points for the OGTT to diagnose women with GDM. In our search, we found only two observational studies that evaluated the same cut-points as our study[12,13]. These studies observed differences in the risk of LGA and induction of labour, in addition to other adverse pregnancy outcomes between groups, as described below. Also, during the progression of our study, the first RCT on this topic was published, although the cut-points were not exactly the same as those we assessed and the main objective did not focus on the grey-zone group like our study[14]. A subgroup analysis of women whose OGTT results fell between the lower and higher glycemic thresholds on the OGTT and either did or did not receive treatment for GDM also showed that treatment of these women resulted in better pregnancy outcomes.

Two observational studies in Canada compared adverse pregnancy outcomes in women diagnosed with GDM by the two-step approach with women not diagnosed or treated for GDM who would have received a GDM diagnosis if we consider the lower thresholds (IADPSG cut-points). The first was a retrospective study of healthcare databases in Ontario that evaluated the risk of adverse pregnancy outcomes among 90,140 women who all underwent a 75g OGTT as the second step after completing a 50g GCT[12]. This study divided participants into 3 groups based on OGTT results in the second step of the GDM diagnostic test: women without GDM by either criteria; women who could be considered GDM by applying lower thresholds (thresholds of one-step IADPSG) but did not receive GDM diagnosis and treatment by considering higher cut-points as OGTT thresholds (preferred approach criteria) and women who were considered GDM by applying higher cut-points and received treatment.

Compared with women who met the lower criteria but were not treated due to the application of higher diagnostic thresholds, women who were diagnosed with GDM using the higher thresholds and treated for GDM had a lower risk of LGA infants (RR 0.87, 95% CI 0.82, 0.91) and less shoulder dystocia (RR 0.80, 95% CI 0.71, 0.90) but experienced a higher risk of NICU admission (RR 1.21, 95% CI 1.14, 1.28) and preterm delivery (RR 1.25, 95% CI 1.15, 1.36). Also, this comparison showed an increased risk for primary caesarean section (RR 1.07, 95% CI 1.03, 1.12) in women who were diagnosed and treated for GDM, whereas the risk of hypertensive disorders of pregnancy was similar between groups (RR 0.99, 95% CI 0.91, 1.07) and the authors concluded that the knowledge of GDM diagnosis may affect clinical practice.

Another retrospective study using data from a provincial perinatal database evaluated the risk of adverse pregnancy outcomes among 178,527 pregnancies in Alberta screened for GDM using a two-step approach[13]. Five groups were considered in this study: women with normal 50 g screen, women with normal 75 g OGTT, women with abnormal OGTT at glucose thresholds suggested by IADPSG (lower thresholds, “HAPO 1.75”); women with abnormal OGTT at glucose thresholds suggested in the second step of preferred approach with one abnormal glucose values (higher thresholds, “HAPO 2-1”); women with abnormal OGTT at glucose thresholds suggested in the second step of preferred approach with two or more abnormal glucose values (higher thresholds, “HAPO 2-2”). Women with abnormal OGTT results by considering lower thresholds who were not diagnosed with GDM (“HAPO 1.75”) had a statistically significantly higher rate of LGA

compared with women who had one abnormal OGTT value by considering higher thresholds ("HAPO 2-1") and more were diagnosed with and treated for GDM (14.2% vs. 11.8%). Also, women in "HAPO 2-1" group (higher thresholds) had a higher rate of induction of labour compared with women in the "HAPO 1.75" group (lower thresholds) (38.2% vs. 29.6%). However, the frequencies of hypertensive disorders of pregnancy (9.6% and 9.1%) and caesarean delivery (36.8% and 36.2%) were similar in both groups.

In contrast, some studies have shown that the risk of adverse maternal and neonatal outcomes is similar using various GDM diagnostic criteria. For instance, a RCT recently showed the risk of LGA was similar between lower and higher glycemic criteria groups in a one-step 75g OGTT test (8.8% and 8.9%, respectively)[14]. This RCT randomly assigned 4061 pregnant women who completed a 75g OGTT at 24 to 32 gestation weeks into two groups: one group was evaluated for GDM by using lower thresholds (IADPSG criteria); the other group was evaluated for GDM by applying higher thresholds suggested by the current New Zealand guideline (FPG ≥ 5.5 mmol/L or 2hPG ≥ 9.0 mmol/L). Note that in this RCT they did a one-step test with different thresholds for the groups in comparison with our study, which focused on women who completed the two-step approach and were classified according to different thresholds for the second step. Therefore, we looked at the even more intermediate risk women who passed the first step. The primary outcome of this RCT was LGA, and secondary outcomes were related to maternal and infant health. The comparison between the two groups which were considered as GDM by applying lower and higher thresholds did not show any differences in maternal and neonatal adverse outcomes except more detected and treated hypoglycemia (10.7% vs. 8.4%) by applying lower thresholds due to a higher percentage of women receiving a diagnosis of GDM. The rates of LGA as the primary outcome were 8.8% versus 8.9% in the lower glycemic criteria group compared with the higher glycemic criteria group, respectively (RR 0.98, 95% CI 0.80, 1.19).

As part of this RCT, a subgroup analysis was performed which focused on the 195 and 178 women whose OGTT results fell between the lower and higher glycemic thresholds and either did or did not receive treatment for GDM, respectively. Importantly, this subgroup analysis indicated less LGA (6.2% vs. 18.0%) and macrosomia (4.1% vs. 16.3%) in women with the intermediate results between two thresholds who received GDM diagnosis and treatment compared with women with the same results who were not considered as GDM and were not treated. Also, subgroup analyses

in this RCT showed women with OGTT results between these two thresholds who were diagnosed as GDM had higher rates of induction of labour (56.9% vs. 30.3%) and neonatal hypoglycemia (27.2% vs. 9.0%) than women with OGTT results between these two thresholds who were not diagnosed and treated as GDM.

Taken together, these three prior studies showed that women with grey zone results who did not receive treatment have a higher risk of having a LGA infant compared with women who are diagnosed with and treated for GDM. On the other hand, women diagnosed with GDM may have more interventions (C-section, induction of labour) and health service utilization (NICU admission, detection of neonatal hypoglycemia) compared with women with grey zone results who did not receive treatment.

As the above studies have shown, there is concern about failing to identify women who could benefit from intervention but were not diagnosed with GDM due to applying higher cut-points. However, this must be balanced against the unnecessary treatment of pregnant women by applying lower cut-points without evidence of benefits in adverse pregnancy outcomes or potentially even causing harm such as NICU admission, neonatal hypoglycemia, or influencing the mode and timing of delivery. Our study aimed to focus on this issue among our local population and to serve as the basis to inform a future multi-centre prospective study or RCT to compare the effect of these distinct GDM diagnostic thresholds on maternal and neonatal outcomes.

CHAPTER 3: RESEARCH DESIGN AND METHODS

3.1 Study design

This retrospective cohort study was performed using data from a chart review of women undergoing GDM screening tests at two Montreal-area university hospitals (the Jewish General Hospital [JGH] and McGill University Health Centre [MUHC]). Both centres follow the Diabetes Canada preferred two-step diagnostic approach. However, JGH uses the Diabetes Canada preferred thresholds with the higher cut-points for the second step, whereas MUHC uses the IADPSG thresholds with lower cut-points.

Importantly, prior to data collection, we confirmed the ability of the glucose assay to discriminate between the two different thresholds and were informed that the coefficient of variation of the assay is around 1% (at 5.1mmol/L the 95% confidence interval is 5.0 to 5.2 and at 5.3mmol/L the 95% confidence is 5.2 to 5.4; verbal communication, Dr. Shaun Eintracht).

A Standard Operating Procedure (SOP) for data entry in each site was developed to coordinate data entry (see Appendix 1 and 2). To prepare the SOP, we reviewed in detail the documents of 40 patients in each site to determine the best places to find each item. Preparing these detailed SOP was a time-consuming process but proved invaluable to standardising data entry and to increase the speed of data entry and decreasing the time of filling each form from 3 hours to less than 20 minutes.

An Electronic Data Capture system was developed in collaboration with Information Management Service at the Lady Davis Institute for secure electronic data entry (Appendix 3). It has a password-protected login and a web server for saving and securing data. For preparing the form, we consulted with endocrinologists and obstetricians. We revised the electronic form sixteen times to achieve the ideal version after experiencing repeated technical issues including saving the dates and issues in calculating gestational age and gestational weight gain that required my direct involvement in troubleshooting and achieving solutions. Also, we trained a team of four additional members to assist with data entry. Ethical approval for both centres was obtained from their respective institutional review boards (Appendix 4).

3.1.1 Study population

Pregnant women undergoing GDM screening tests from September 01, 2013, until February 29, 2020 (n=4407 pregnancies), were assessed for study inclusion criteria.

Of note, the initial population assessed included data from 2010, but following changes in GDM diagnostic criteria that were differentially adopted by certain providers between 2010-2013, it was decided to limit inclusion to after 2013 when both institutions followed new Diabetes Canada diagnostic criteria.

3.1.2 Inclusion criteria

i) Delivery at JGH or MUHC

ii) Completed both the first and second steps of the GDM screening test

iii) First step was completed between 24-28 weeks of gestation

iv) Singleton pregnancy

v) Women without pre-existing diabetes such as type 1 or 2 diabetes

vi) Pregnancy without assisted reproduction such as intrauterine insemination (IUI) or in vitro fertilization (IVF).

3.2 Data collection

We used an electronic data collection form to record study information as described above. We reviewed inpatient and outpatient medical charts step by step according to the SOPs as explained above. Clinical information for mother and baby was extracted from the mothers' charts, including demographic data (maternal age at delivery, maternal date of birth, parity, date of delivery, neonatal sex), GDM screening test data (date, type of test, results of the test), GDM treatment type (diet and lifestyle, oral medication, insulin, combination), length of mother's hospital stay, previous caesarean, gestational weight gain, adverse maternal outcomes (hypertensive disorders of pregnancy including chronic hypertension, gestational hypertension, preeclampsia, pre-eclampsia superimposed on chronic hypertension, eclampsia, postpartum hypertension prior to

discharge from hospital; mode of delivery including spontaneous, induced, operative vaginal delivery, C-section, or a combination) as well as neonatal outcomes including birthweight, preterm birth, Apgar score, shoulder dystocia, stillbirth and neonatal death.

In Table 3.1 you will find the definitions of the primary and secondary outcomes in this study.

Table 3.1 Definitions of select adverse pregnancy outcomes associated with GDM

Perinatal Adverse Outcome	**Definition**[75]
Large for gestational age (LGA)	Birthweight above the 90th percentile for gestational age
Macrosomia	Birthweight ≥ 4000 g
Small for gestational age (SGA)	Birthweight lower than the 10th percentile for gestational age
Preterm birth	Birth at <37 weeks gestational age
Low Apgar score	Any score lower than 7[130]
Shoulder dystocia	Labour requires additional obstetric manoeuvres following the failure of gentle downward traction on the fetal head to affect the delivery of the shoulders[131,132]
Neonatal death	In our study we considered death of a live baby following delivery and before discharge from hospital
Stillbirth	Delivery of a fetus that does not show any signs of life at 20 weeks of pregnancy or more.
Hypertensive disorders of pregnancy	Including: • Chronic hypertension: hypertension known before or during first 20 weeks of pregnancy • Gestational hypertension: A systolic blood pressure ≥ 140 mmHg and/or a diastolic BP ≥ 90 mmHg appearing after gestational week 20 • Pre-eclampsia: hypertension after gestational week 20 and ≥1 new onset conditions: proteinuria; other

	maternal organ dysfunction (renal, hepatic, neurologic, hematologic) • Pre-eclampsia superimposed on chronic hypertension: Occurring features of pre-eclampsia in women with known chronic hypertension[133] • Eclampsia: New onset of generalized tonic-clonic seizures in a woman with preeclampsia[134] • Postpartum hypertension: Develop hypertension in the postpartum time frame (6 weeks)[135].

3.3 Statistical Methods

Sample size estimation showed a population of at least N=480 (240 per group) would be required to have 80% power to compare these distinct GDM diagnostic cut-points at a significance level of alpha=0.05 to detect a between-group difference of LGA as demonstrated in the literature (9.9% vs 18.6% risk for LGA among women diagnosed and treated for GDM versus those not treated, respectively, as reported in a systematic review and meta-analysis of 3,881 patients from 10 RCTs)[136]. Schoenfeld derived asymptotic formulas and sensitivity analyses were used to estimate the required sample size in our study.

For achieving our objectives, we performed eight analyses. The first and second analyses as our primary analyses compared respectively the risk of LGA (as the primary outcome) and the risk of secondary outcomes (birthweight-related outcomes including macrosomia, SGA and birthweight and other secondary outcomes: maternal hypertensive disorder of pregnancy, induction of labour, primary C-section, length of mother's hospital stay and a composite infant adverse outcome including preterm birth, shoulder dystocia, low Apgar score, neonatal death and stillbirth) between women with OGTT results in the grey zone who were not diagnosed with GDM at JGH with women who were diagnosed with GDM and received intervention at MUHC.

We performed other analyses as secondary analyses. The third and forth analyses compared the risk of LGA of women in the grey zone at JGH with women who were diagnosed with GDM and

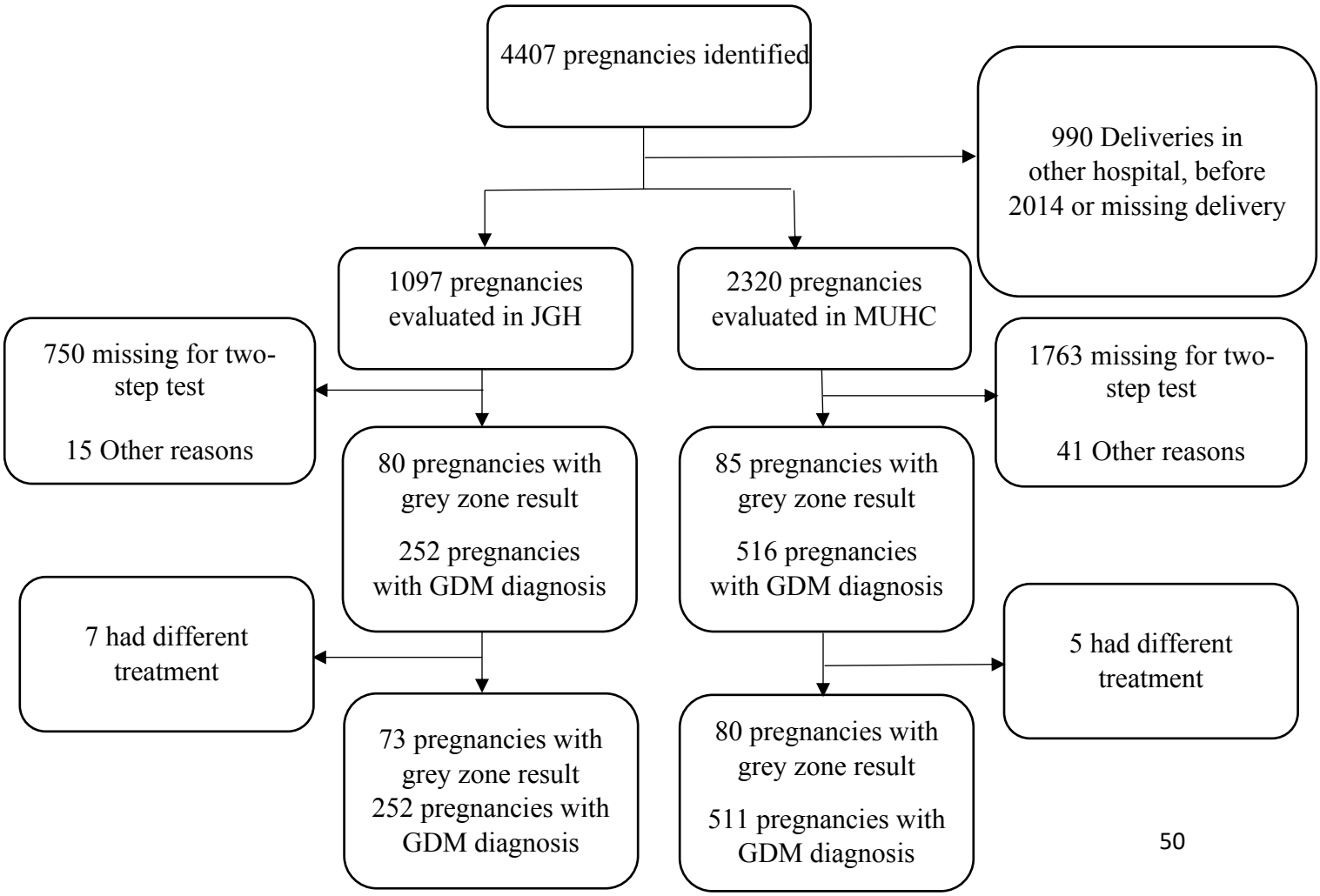
received intervention at MUHC and JGH, respectively. The fifth analyses compared the risk of LGA of women who were diagnosed with GDM and received intervention at JGH with the same group at MUHC. The remaining analyses compared the risk of birthweight-related outcomes and the other secondary outcomes as mentioned above in the same comparison groups of analyses three to five, respectively.

Descriptive data were reported using means and standard deviations for continuous variables or counts and proportions for categorical variables. We constructed a logistic regression model to evaluate LGA as our primary outcome as well as other binary outcomes including macrosomia, induction of labour, primary C-section, SGA, maternal hypertensive disorder of pregnancy, and a composite infant adverse outcome including preterm birth, shoulder dystocia, low Apgar score, stillbirth, and neonatal death. In addition, linear regression was used for birthweight (continuous outcome) and Poisson regression was used for length of mother's hospital stay (non-normal distribution), respectively. Data analyses were conducted using R version 4.0.2.

CHAPTER 4: RESULTS

We evaluated data from 4407 pregnancies. Of these, 3559 (80.75%) pregnancies were excluded (22.4% for delivery before 2014 with different criteria, in other hospitals or missing delivery, 57.02% for missing doing both steps of the test and 1.27% for other reasons such as assisted reproduction and not GCT results in the intermediate zone). Among the remaining 848 pregnancies, 165 had grey zone findings (JGH, n=80 and MUHC, n=85). The 80 pregnancies with grey zone results at the JGH were not diagnosed with or treated for GDM; there were 252 women treated for GDM at JGH. The 85 pregnancies with grey zone results at the MUHC were among the 516 there treated for GDM. Of note, seven women in the grey zone at the JGH were actually treated for GDM, contrary to their institutional approach, while five women at the MUHC who should have been treated for GDM as per their institutional policy were not treated; we excluded these 12 women. Thus, there were ultimately 73 grey zone women at JGH and 80 pregnancies at MUHC (Figure 6).

Figure 6: Diagram of patient selection



Women were classified into the following groups for comparison:

- **Grey zone - JGH (n = 73)**: Women at JGH with an intermediate result for the first step of the GDM screening test (i.e. glucose value 7.8-11.0 mmol/L on 1-hour 50-gram non-fasting GCT) and "passed" the second step (75-gram OGTT) using the higher cut-points, but who would have been classified as having GDM using the lower cut-points.
- **Grey Zone - MUHC (n = 80)**: Women at MUHC with an intermediate result for step 1 and "passed" the second step using the higher cut-points, but who were diagnosed and treated for GDM due to use of the lower thresholds at this centre.
- **GDM – JGH (n = 252)**: Women at JGH with an intermediate result for the first step and failed the second step according to the higher thresholds.
- **GDM – MUHC (n = 511)**: Women at MUHC with an intermediate result for the first step and failed the second step according to the lower thresholds.

In the MUHC, women were on average one year older than the women at JGH (mean 35.0 ±3.83 and 34.5±4.47 years in the two MUHC groups versus mean 33.5±4.01 and 33.6±4.78 years in the two JGH groups). The grey zone group at JGH had a lower percentage of primiparous (34.2%) compared with other groups, and grey zone women in JGH and MUHC had a higher proportion of prior caesarean section (30.1% and 25.0%, respectively). Moreover, fewer women in the grey zone group at JGH had prior GDM (5.5%). The women with grey zone results at JGH had lower fasting glucose values (4.40±0.48 vs 4.84±0.33) and higher 2-hour values (7.92±1.11 vs. 7.74±1.05) compared to the group of grey zone women in MUHC. There were expected differences between groups for treatment, although interestingly, a higher proportion of women with grey zone result at the MUHC were treated pharmacologically compared to even the women who were considered GDM by applying higher cut-points at JGH centre (38.8% vs. 21%). Moreover, the women with grey zone result in MUHC had higher percentage of babies with female sex (61.3%) compared with other groups. The untreated grey zone women at JGH had higher gestational weight gain (13.5±5.78 kg) compared with the other groups.

Table 4.1 Characteristics of Study Participants

Characteristic	Total	Grey zone in JGH	Grey zone in MUHC	GDM in JGH	GDM in MUHC
Number of women	836	73	80	252	511
Maternal age at delivery, years (Mean, SD)	34.1 (4.53)	33.5 (4.01)	35.0 (3.83)	33.6 (4.78)	34.5 (4.47)
Primiparous (N, %)	353 (42.2)	25 (34.2)	34 (42.5)	102 (40.5)	226 (44.2)
Prior Caesarean (N, %)	184 (22.1)	22 (30.1)	20 (25.0)	51 (20.2)	111 (21.9)
Prior GDM (N, %) ¶	87 (10.4)	4 (5.5)	11 (13.8)	25 (9.9)	58 (11.4)
GCT result, mmol/L (Mean, SD) *					
1-hour	9.13 (0.89)	8.75 (0.78)	8.85 (0.77)	9.22 (0.90)	9.14 (0.89)
OGTT result, mmol/L (Mean, SD) †					
Fasting	4.90 (0.69)	4.40 (0.48)	4.84 (0.33)	4.74 (0.78)	5.05 (0.61)
1-hour	10.73 (1.29)	9.79 (0.82)	9.83 (0.78)	10.88 (1.16)	10.79 (1.35)
2-hour	8.76 (1.60)	7.92 (1.11)	7.74 (1.05)	9.14 (1.68)	8.68 (1.57)
Gestational age at time of GCT, weeks (Mean, SD)	26.0 (1.04)	25.8 (1.17)	25.9 (1.03)	25.8 (1.13)	26.1 (0.95)
Treatment (N, %)					
Lifestyle	446 (59.8)	0	49 (61.3)	188 (79.0)	258 (50.8)
Pharmacologic treatment ‡	299 (40.2)	0	31 (38.8)	50 (21.0)	250 (49.2)
Fetal sex Female (N, %)	425 (50.8)	36 (49.3)	49 (61.3)	145 (57.5)	244 (47.7)
Gestational weight gain, kg (Mean, SD) ‡‡	12.3 (5.69)	13.5 (5.78)	12.7 (6.08)	12.30 (5.53)	12.20 (5.76)

JGH: Jewish General Hospital; MUHC: McGill University Hospital Centre

* GCT: Glucose challenge test

† OGTT: Oral glucose tolerance test

¶ Among women with prior pregnancy

‡ Pharmacologic treatment contains insulin and/or medication

‡‡ N= 43 in grey zone group in JGH, N=77 in grey zone group in MUHC, N=218 in group with GDM in JGH and N=476 in the group with GDM in MUHC

Untreated (JGH) vs. treated (MUHC) grey zone Women with GDM screening test results in the grey zone who were not diagnosed and treated for GDM (grey zone in JGH) had a higher percentage of LGA compared with offspring of women who had grey zone results but received a GDM diagnosis and intervention (grey zone in MUHC) (21.9% vs. 11.4%; Table 4.2). A lower proportion of women in the untreated grey zone group (in JGH) underwent induction of labour (13.7% vs 36.2%). However, there were similar rates of macrosomia, preterm birth, shoulder dystocia, stillbirth, neonatal death, maternal hypertensive disorder, birthweight, Apgar score and length of mother's hospital stay in both groups (Table 4.2).

Untreated grey zone (JGH) vs. treated GDM (JGH) The frequency of LGA and macrosomia was higher among women with grey zone results without GDM diagnosis (grey zone in JGH) compared with women at the same centre who received GDM diagnosis and intervention (GDM in JGH) (21.9% vs. 8.3% for LGA and 15.1% vs. 5.2%, for macrosomia; Table 4.2). Moreover, shoulder dystocia was more frequent (6.8% vs. 2.0%) and birthweight higher (3422.7±489.3 vs. 3230.4±539.7 grams) in the group of grey zone women without treatment (grey zone in JGH) compared with women at the same centre who were diagnosed with GDM (GDM in JGH). Interestingly, women treated for GDM at the MUHC had the highest rates of SGA. Results were similar between these two groups for other secondary outcomes (Table 4.2).

Of note, grey zone women at the JGH had the highest proportion of LGA (21.9%) across groups, followed by grey zone women at MUHC (11.4%), who were treated for GDM. Furthermore, women at JGH with grey zone results had the highest proportion of macrosomia (15.1%), shoulder dystocia (6.8%) and caesarean section (41.1%), and lowest proportion of induction of labour (13.7%) and also the rates of SGA were among the lowest (5.5%) (Table 4.2).

Table 4.2 Frequency of adverse pregnancy outcomes for mother and infant					
Outcome	**Total**	**Grey zone in JGH**	**Grey zone in MUHC**	**GDM in JGH**	**GDM in MUHC**
Number of women	836	73	80	252	511
Large for gestational age (N, %)	74 (8.9)	16 (21.9)	9 (11.4)	21 (8.3)	37 (7.3)
Birthweight, gram (Mean, SD)	3272.5 (512.1)	3422.7 (489.3)	3312.2 (521.6)	3230.4 (539.7)	3271.9 (498.1)
Macrosomia (N, %)	52 (6.2)	11 (15.1)	7 (8.9)	13 (5.2)	28 (5.5)
Small for gestational age (N, %)	71 (8.5)	4 (5.5)	4 (5.1)	19 (7.5)	48 (9.4)
Preterm birth (N, %)	87 (10.4)	7 (9.6)	8 (10.0)	33 (13.1)	47 (9.2)
Shoulder dystocia (N, %)	29 (3.5)	5 (6.8)	3 (3.8)	5 (2.0)	19 (3.8)
Apgar score (Mean, SD)	8.39 (1.46)	8.49 (1.13)	8.26 (1.72)	8.33 (1.54)	8.40 (1.47)
Stillbirth (N, %)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Neonatal death (N, %)	2 (0.3)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.2)
Mode of delivery (N, %)					
Spontaneous vaginal	247 (29.5)	25 (34.2)	21 (26.2)	90 (35.7)	132 (25.8)
Induced vaginal	221 (26.4)	10 (13.7)	29 (36.2)	50 (19.8)	161 (31.5)
Operative vaginal	53 (6.3)	8 (11.0)	4 (5.0)	18 (7.1)	27 (5.3)
Caesarean	315 (37.7)	30 (41.1)	26 (32.5)	94 (37.3)	191 (37.4)
Maternal hypertensive disorder (N, %)	82 (9.8)	6 (8.2)	9 (11.2)	19 (7.5)	57 (11.2)
Length of mother's hospital stay, days (Mean, SD)	2.67 (2.86)	2.40 (1.20)	2.46 (2.24)	3.06 (4.40)	2.51 (1.88)

JGH: Jewish General Hospital; MUHC: McGill University Hospital Centre

4.1 Primary Analysis

Multivariate models for LGA Untreated grey zone women (in JGH) had more than double the odds of having an LGA infant compared with treated grey zone women, but this finding was inconclusive (OR 2.14, 95% CI 0.86, 5.61) (Table 4.3).

Multivariate models for secondary outcomes The women with grey zone results who did not receive intervention due to higher diagnostic cut-points (grey zone in JGH) had statistically significantly lower odds of induction of labour compared with women with grey zone results who received intervention by considering lower cut-points (grey zone in MUHC) (OR 0.27, 95% CI 0.1, 0.64). The results for other outcomes were inconclusive (Table 4.4).

4.2 Secondary Analyses

Multivariate models for LGA The women with grey zone results who were not treated (in JGH) had conclusively higher odds of LGA compared to women diagnosed with and treated for GDM at the JGH (OR 3.05, 95% CI 1.47, 6.26) (Table 4.3). They also had higher odds of LGA compared to women treated for GDM at the MUHC (OR 3.71, 95% CI 1.86, 7.17) (Table 4.3). LGA odds did not differ conclusively between women treated for GDM at the JGH and women treated for GDM at the MUHC, despite differences in diagnostic thresholds (OR 1.18, 95% CI 0.62, 2.17). The odds of LGA were similar with and without adjustment for relevant potential confounders (Table 4.3).

Table 4.3 Regression results for the association of 75g oral glucose tolerance test results with large for gestational age and birthweight-related outcomes.

	Grey zone in JGH vs. Grey zone in MUHC		Grey zone in JGH vs. GDM in JGH		Grey zone in JGH vs. GDM in MUHC		GDM in JGH vs. GDM in MUHC	
	Unadjusted Odds Ratio (95% CI)	**Adjusted Odds Ratio (95% CI)**	**Unadjusted Odds Ratio (95% CI)**	**Adjusted Odds Ratio (95% CI)**	**Unadjusted Odds Ratio (95% CI)**	**Adjusted Odds Ratio (95% CI)**	**Unadjusted Odds Ratio (95% CI)**	**Adjusted Odds Ratio (95% CI)**
Primary outcome: Large for gestational age*	2.18 (0.91, 5.51)	2.14 (0.86, 5.61)	3.09 (1.5, 6.28)	3.05 (1.47, 6.26)	3.57 (1.83, 6.74)	3.71 (1.86, 7.17)	1.16 (0.65, 2)	1.18 (0.62, 2.17) †
Birthweight-related outcomes								
Macrosomia‡	1.82 (0.68, 5.23)	1.48 (0.51, 4.49)	3.26 (1.37, 7.65)	2.87 (1.17, 6.94)	3.04 (1.39, 6.26)	2.61 (1.14, 5.64)	0.93 (0.46, 1.8)	0.95 (0.46, 1.87)
Small for gestational age*	1.09 (0.25, 4.76)	0.97 (0.21, 4.53)	0.71 (0.2, 1.97)	0.82 (0.23, 2.31)	0.56 (0.16, 1.42)	0.69 (0.2, 1.8)	0.78 (0.44, 1.34)	0.67 (0.36, 1.18) †
	Unadjusted Beta (95% CI)	**Adjusted Beta (95% CI)**	**Unadjusted Beta (95% CI)**	**Adjusted Beta (95% CI)**	**Unadjusted Beta (95% CI)**	**Adjusted Beta (95% CI)**	**Unadjusted Beta (95% CI)**	**Adjusted Beta (95% CI)**
Infant birthweight‡	110.5 (-50.6, 271.6)	83.7 (-65.8, 233.2)	192.3 (54.6, 330.1)	117.7 (10.3, 225.2)	150.6 (28.7, 272.4)	121.6 (18.5, 224.8)	-41.4 (-118.8, 35.9)	-1.2 (-61.6, 59.2)

JGH: Jewish General Hospital; MUHC: McGill University Hospital Centre

* Adjusted for maternal age, parity

†Adjusted for maternal age, parity, and GDM treatment type (medication vs. lifestyle)

‡ Adjusted for maternal age, parity, gestational age at delivery, neonatal sex

Table 4.4 Regression results for the association of 75g oral glucose tolerance test results with other secondary outcomes.

	Grey zone in JGH vs. Grey zone in MUHC		Grey zone in JGH vs. GDM in JGH		Grey zone in JGH vs. GDM in MUHC		GDM in JGH vs. GDM in MUHC	
	Unadjusted Odds Ratio (95% CI)	**Adjusted Odds Ratio (95% CI)**	**Unadjusted Odds Ratio (95% CI)**	**Adjusted Odds Ratio (95% CI)**	**Unadjusted Odds Ratio (95% CI)**	**Adjusted Odds Ratio (95% CI)**	**Unadjusted Odds Ratio (95% CI)**	**Adjusted Odds Ratio (95% CI)**
Composite infant adverse outcome* †	0.82 (0.37, 1.78)	1.11 (0.44, 2.82)	0.97 (0.49, 1.81)	1.3 (0.6, 2.74)	1.12 (0.59, 2.02)	1.58 (0.72, 3.27)	1.16 (0.79, 1.69)	1.03 (0.64, 1.64)
Induction of labour ‡	0.28 (0.12, 0.61)	0.27 (0.1, 0.64)	0.64 (0.29, 1.29)	0.66 (0.29, 1.38)	0.35 (0.16, 0.66)	0.27 (0.12, 0.54)	0.54 (0.37, 0.77)	0.47 (0.32, 0.69)
Primary Caesarean-section†	1.71 (0.68, 4.41)	2.32 (0.84, 6.62)	1.06 (0.51, 2.11)	1.24 (0.57, 2.61)	0.99 (0.49, 1.89)	1.31 (0.63, 2.6)	0.93 (0.63, 1.38)	1.02 (0.67, 1.53)
Maternal hypertensive disorder†	0.71 (0.23, 2.07)	0.81 (0.24, 2.59)	1.1 (0.39, 2.72)	1.2 (0.41, 3.06)	0.71 (0.27, 1.59)	0.73 (0.27, 1.69)	0.65 (0.37, 1.1)	0.63 (0.35, 1.08)
	Unadjusted Risk Ratio (95% CI)	**Adjusted Risk Ratio (95% CI)**	**Unadjusted Risk Ratio (95% CI)**	**Adjusted Risk Ratio (95% CI)**	**Unadjusted Risk Ratio (95% CI)**	**Adjusted Risk Ratio (95% CI)**	**Unadjusted Risk Ratio (95% CI)**	**Adjusted Risk Ratio (95% CI)**
Length of mother's hospital stay ¶ §	0.97 (0.77, 1.22)	0.98 (0.8, 1.2)	0.78 (0.64, 0.96)	0.85 (0.69, 1.03)	0.95 (0.84, 1.09)	0.98 (0.85, 1.14)	1.22 (1.09, 1.35)	1.19 (1.08, 1.32)

JGH: Jewish General Hospital; MUHC: McGill University Hospital Centre

* Including preterm birth, shoulder dystocia, low Apgar score, stillbirth and neonatal death

† Adjusted for maternal age, parity, gestational age at delivery

‡ Adjusted for maternal age, parity, gestational age at delivery, previous C-section

¶ Used Poisson regression

§ Adjusted for maternal age, parity, gestational age at delivery, mode of delivery (C-section vs. vaginal)

Multivariate models for secondary outcomes Women with grey zone result who were not treated (grey zone in JGH) with women who were treated for GDM at the JGH showed increased odds of macrosomia (OR 2.87, 95% CI 1.17, 6.94) and higher birthweight (beta 117.7 g, 95% CI 10.3, 225.2). Also, the comparison of women with grey zone result who were not treated (grey zone in JGH) with women who were diagnosed and treated for GDM by applying lower diagnostic cut-points (GDM in MUHC) showed statistically significantly higher odds of macrosomia (OR 2.61, 95% CI 1.14, 5.64) and higher birthweights (beta 121.6 g, 95% CI 18.5, 224.8). Analyses of macrosomia and birthweight in other comparison groups and the odds of SGA for all comparison groups were inconclusive (Table 4.3). The results of birthweight-related outcomes were similar in unadjusted and adjusted analyses (Table 4.3).

The women with grey zone results who were not treated (grey zone in JGH) had statistically significantly lower odds of induction of labour compared with women in MUHC who were diagnosed with GDM by applying lower cut-points (GDM in MUHC) (OR 0.27, 95% CI 0.12, 0.54; Table 4.4). Also, women who were treated for GDM at JGH had statistically significantly lower odds of induction of labour compared with women treated for GDM in MUHC (OR 0.47, 95% CI 0.32, 0.69; Table 4.4). However, the odds of induction of labour for women with untreated grey zone results (grey zone in JGH) compared with women who were diagnosed with GDM by applying the same cut-points (GDM JGH) was inconclusive. Also, the women who were diagnosed with and treated for GDM by applying the higher cut-points (GDM in JGH) had significantly longer hospital stay for the mother compared with women who were treated for GDM by applying the lower cut-points (GDM in MUHC) (RR 1.19, 95% CI 1.08, 1.32). Results were similar for unadjusted and adjusted analyses, except for the length of the mother's hospital stay, which in the comparison of untreated women with grey zone result (grey zone in JGH) with women at the same centre who were considered to have GDM by applying the higher thresholds (GDM in JGH) the unadjusted length of hospital stay was statistically significantly shorter (RR 0.78, 95% CI 0.64, 0.96). Results for other secondary outcomes were underpowered for all comparisons.

CHAPTER 5: DISCUSSION

We evaluated the association of applying higher versus lower thresholds for the diagnosis of GDM with the risk of adverse pregnancy outcomes in 836 pregnancies. Our main comparison was of women with OGTT results that fell in between the higher and lower cut-points ("grey zone" results) on the second step OGTT of a two-step approach for GDM diagnosis; we compared women at two centres with distinct diagnostic thresholds, which resulted in women with similar test results either having a diagnosis and intervention for GDM or receiving routine care. Our results suggested that women with grey zone results who were not diagnosed and treated for GDM may be more likely to have an LGA infant and had lower odds of induction of labour at the time of delivery compared with women who also had grey zone results but were diagnosed with and treated for GDM. Although the difference in the risk of LGA was not statistically significant between these two groups, still the suggestion of increased frequency of LGA and the result of less induction of labour are important and indicate that further research with a larger study population and prospective design is warranted to better evaluate the benefits and risks of diagnosis and treatment of these women with mild hyperglycemia during pregnancy.

To our knowledge, only one RCT based in New Zealand evaluated the risk of adverse pregnancy outcomes due to distinct cut-points for the OGTT. This RCT was published during the progression of our study, and a subgroup analysis of this trial including 373 women whose OGTT results fell between the higher and lower glycemic thresholds found that treatment decreased the risk of LGA infants compared with women who did not receive treatment (6.2% vs. 18.0%, respectively)[14]. This result is similar to the result of our study, which showed a lower frequency of LGA with treatment of women who had OGTT results in the grey zone compared with those who did not (11.4% vs. 21.9%, respectively). However, our study focused on women with even more mild hyperglycemia who had intermediate results in the first GDM screening step and underwent two-step GDM screening, whereas the RCT was based on a one-step 75g OGTT. Moreover, as mentioned previously, the RCT assessed slightly different diagnostic thresholds than our study.

In our study, the women with grey zone results - who did not receive intervention due to applying higher cut-points - had an increased frequency of LGA infants (21.9%) compared with women who received a GDM diagnosis using either these same cut-points (8.3%) or by applying lower cut-points (7.3%). Similar to our results, a retrospective study that used data from a provincial

perinatal database in Alberta observed that women who met the lower criteria (IADPSG criteria) on the 75g OGTT of a two-step test but who were not likely diagnosed with GDM had a significantly higher rate of LGA compared with women who had one abnormal value by considering higher thresholds and were thus probably diagnosed with and treated for GDM (14.2% vs. 11.8%)[13]. It is noteworthy that in this study they did not have access to clinical data to confirm the groups were appropriately assigned, as they collected maternal and delivery information from a provincial database and collected laboratory results from a unit of Alberta Health Services[13], whereas we had the clinical data and confirmation of whether GDM treatment was received for each woman. Another retrospective study in Ontario similarly showed a higher frequency of LGA (16.5% vs. 14.3%) for women with grey zone results who did not receive treatment compared with women who were diagnosed with and treated for GDM by applying higher cut-points on the 75g OGTT in the second step of the two-step approach[12]. Of note, in our study we also compared the two groups of all women who were diagnosed with GDM by applying higher and lower cut-points, respectively, and observed similar risk of LGA in both groups (8.3% vs.7.3%). These results are consistent with the RCT result for the same comparison groups, which also indicated similar rates of LGA for women diagnosed with GDM using the higher or lower thresholds on the 75g OGTT (8.9% vs. 8.8%)[14].

Moreover, women with grey zone results who have not received the intervention had a higher frequency of macrosomia compared with women with grey zone results who received treatment (15% vs. 8.9%), although this difference was not significant in our study (possibly due to the small sample size). Similarly, the comparison of women with intermediate results in the RCT revealed a higher rate of macrosomia among women who did not receive treatment compared with women who received treatment (16.3% vs. 4.1%, RR 0.25, 95% CI 0.12, 0.54). Also, compared with women who were diagnosed with and treated for GDM by applying higher and lower cut-points, the women with grey zone results who were not diagnosed with GDM and were not treated were more likely to have a baby with macrosomia in our study (15.1% for untreated grey zone women vs. 5.2% for the GDM with higher cut-points and 5.5% for the GDM with lower cut-points). In the Alberta study, the women whose test results fell between the two thresholds and probably did not receive intervention had a higher frequency of macrosomia compared with women with one abnormal value who likely received treatment (13.5% vs. 10.0%)[13]. However, comparison of macrosomia between the two groups of women who were considered as GDM by applying higher

and lower thresholds showed similar frequency in our study (5.2% vs. 5.5%) as well as in the RCT (12.3% vs. 11.8%)[14]. This difference can reflect the beneficial effect of treatment for these women with mild hyperglycemia.

Our results, in combination with the above study results, reveal the importance of considering intervention for the women with OGTT results between the higher and lower thresholds to improve at least LGA and macrosomia as two main perinatal adverse outcomes. However, in contrast with the two retrospective studies, our study compared treated and untreated women with mild hyperglycemia at intermediate risk of GDM complications, which made our study unique in this aspect.

Furthermore, we also found that compared with women with grey zone results who were not diagnosed with GDM, women with grey zone results who were diagnosed with and treated for GDM had a significantly higher rates of induction of labour (36.2% vs. 13.7%). Similarly, the subgroup analyses in the RCT showed that women with OGTT results between the two diagnostic thresholds who were diagnosed with GDM had higher rates of induction of labour than women with OGTT results between these two thresholds who were not diagnosed with GDM (56.9% vs. 30.3%)[14], and women in the Alberta study who had only one abnormal value by applying higher cut-points and were likely considered to have GDM had a higher rate of induction of labour compared with women who met lower cut-points but probably were not considered as GDM (38.2% vs 29.6%)[13]. In our study, a comparison of women with grey zone results who did not receive GDM diagnosis and treatment with women at the same centre who were diagnosed with GDM by applying higher cut-points and received treatment did not show any significant difference in induction of labour (13.7% vs. 19.8%), but showed lower rates of induction of labour compared with women who were diagnosed with GDM at another centre which used lower cut-points (13.7% vs. 31.5%). Also, in our study we observed that among women diagnosed with GDM by the distinct thresholds, the women who were considered as GDM by applying higher cut-points has statistically lower odds of induction of labour compared with women who were considered GDM by applying higher cut-points (19.8% vs. 31.5%). Our results are similar to the RCT results which showed a lower risk of induction of women in the group considered as GDM by applying higher cut-points compared with the women considered as GDM by applying lower cut-points (30.2% vs. 33.7%)[14].

The reason for the difference in induction of labour could be that labelling these women as GDM leads to an increase in intervention during labour, as for example, Diabetes Canada guidelines suggest delivery before 40 weeks in women with GDM to balance the benefits of decreasing preventable stillbirth and caesarean rates against the potential increase in neonatal complications such as hyperbilirubinemia[16]. Alternatively, another hypothesis for more induction of labour in women with mild hyperglycemia who received treatment could be that unnecessary treatment of this group may have led to maternal hypoglycemia and consequent fetal distress. Also, according to the baseline characteristics in our study, in the untreated grey zone group we had higher previous caesarean section rates, and as women with prior caesarean section would be less likely to have induction of labour this could also contribute to differences in induction of labour between groups. Moreover, in our study, these distinct GDM diagnostic thresholds were applied in two separate centres, and differences in clinical practice between centres could play role in the difference regarding clinical decision-making for induction of labour.

Also, in the Ontario study, the women with grey zone results who were not treated had a significantly higher risk of shoulder dystocia (3.8% vs. 3.0%; RR 0.80, 95% CI 0.71, 0.90) compared with women who received GDM diagnosis with higher cut-points and were treated[12]. In our study, shoulder dystocia was more frequent in the group of women with grey zone results without GDM treatment compared with women who were considered as GDM by applying higher cut-points (6.8% vs. 2.0%). The comparison of women with intermediate results in the RCT showed that women who were not treated for GDM had higher frequency of shoulder dystocia compared with women who received treatment (3.9% vs. 0.5%). In our study, similarly, frequency of shoulder dystocia was higher among the women with grey zone results who did not receive intervention compared with women with grey zone results who were treated for GDM (6.8% vs. 3.8%) although the number of events was limited due to small sample size. In both the RCT and our study, the risk of shoulder dystocia was evaluated as a composite outcome (due to low number of events), and there were no significant differences in the composite adverse outcomes in either study. As shoulder dystocia is related to fetal overgrowth and can be associated with severe nerve injury of the newborn, post-partum hemorrhage and/or vaginal lacerations for the mother[137], this difference reveals the importance of GDM treatment to potentially reduce adverse outcomes in women with grey zone results and should be further explored in larger studies.

Moreover, in the Ontario study, women who were considered as GDM by applying higher cut-points had a higher risk of NICU admission (14.8% vs. 12.2%) and preterm delivery (8.1% vs. 6.5%) compared with women with grey zone results who were not considered as GDM[12], and in the RCT, the offspring of women with treated mild hyperglycemia had greater frequency of neonatal hypoglycemia compared with those with untreated mild hyperglycemia (27.2% vs. 9.0%)[14]. These results suggest that diagnosis of GDM may affect clinical practice. Of note, higher rates of neonatal hypoglycemia may be due to routine screening of newborns of women with a diagnosis of GDM, which permits more identification and treatment of neonatal hypoglycemia; thus, it is possible that infants of women with grey zone results may have mild neonatal hypoglycemia that remains unidentified. These risks and benefits will be important to clarify, although our study was not able to obtain sufficient information regarding the rates of neonatal hypoglycemia across GDM diagnostic criteria groups. Furthermore, due to the limited number of events, our study investigated the risk of some outcomes including preterm delivery in combination with other adverse outcomes and did not observe a significant difference for this composite neonatal outcome between groups.

In addition, in our study the women who were considered as GDM by applying higher cut-points had a longer hospital stay for the mother compared with women who were diagnosed with GDM by applying the lower cut-points (3.06±4.40 vs. 2.51±1.88 days), although there were no differences in length of stay for comparisons including the untreated grey zone women, and the comparison of postnatal stay for women in the RCT who were diagnosed with GDM using higher and lower cut-points did not show significant difference (3.0±2.1 vs. 3.0±2.1 days). This difference in our study is interesting and could reflect distinct practices for each centre or may be a result of more complications in the women with GDM at the JGH that leads to a more prolonged stay, although identification of a specific cause for this was outside the scope of our current study.

Taken together, our results, in the context of previous observational studies and a recent RCT, reveal the importance of developing larger, better quality studies that will determine whether treatment decreases adverse outcomes among the group of women with mild hyperglycemia who are not currently diagnosed with GDM in Canada due to the recommendation of higher diagnostic thresholds - without incurring excess risk or expense. For instance, induction of labour in women for whom this delivery method may not be truly warranted incurs extra expenses related to

medications, monitoring, and possible longer hospital stay, and may also increase the risk of adverse perinatal outcomes such as hyperbilirubinemia[138,139]. Also, detection of more neonatal hypoglycemia is important for preventing adverse neonatal events, but routine screening among women with GDM may also detect mild subclinical hypoglycemia and result in excess interventions and NICU admission.

It is important to also mention that in addition to a higher risk of adverse perinatal outcomes in these women with grey zone results, this group of women with mild hyperglycemia is probably also at risk of developing T2D in the future; as these women are not considered to have GDM, they are not recommended to have routine follow-up for the development of T2D as are their counterparts who receive a GDM diagnosis. Moreover, the offspring of a mother with OGTT results between the higher and lower thresholds may display increased long-term risks of obesity and T2D similar to the babies born from mothers with GDM. Therefore, identification and treatment of these mothers with mild hyperglycemia may benefit their own future health as well as that of their offspring.

One of the difficulties in determining optimal cut-points for screening and diagnostic tests is choosing cut-points with both high sensitivity and specificity. Also, as the HAPO study showed, glucose level and associated adverse outcomes have a linear association and thus, it is difficult to determine at which level of hyperglycemia the pregnant women should be considered as having GDM and will most benefit from interventions. Therefore, the current thresholds were determined by consensus instead of optimal experimental evidence. It is important to note that using lower cut-points and identifying more women with GDM means more direct and indirect effects on the healthcare system (costs, clinic visits, glycemic monitoring, potential increased induction of labour and C-section), as well as adverse effects like time burden, anxiety and psychosocial stress for pregnant women associated with a GDM diagnosis[140–143]. Hence, it is essential to assess carefully whether the increased diagnosis would be beneficial enough to prevent adverse maternal and neonatal outcomes.

5.1 Strengths and limitations

Our study has several strengths. First, we focused on women who had OGTT results between the higher and lower diagnostic thresholds and compared women who received intervention with those who did not; this allowed us to evaluate the benefits and risks of GDM diagnosis and treatment among the important group of women at intermediate risk of GDM complications for whom the implications of intervention are less clear. Our study was unique in that it explored pregnancy outcomes among women with mild hyperglycemia; all of the women had an intermediate result on the 50g GCT and completed both steps of the GDM screening test, which permitted us to focus on the impact of intervention for the grey zone group.

The study of this group is clinically important because evidence is starting to show that by treating this group of women, the probability of short-term adverse outcomes for mother and baby will decrease, and with more directed follow-up, it is also possible that the risk of long-term complications such as type 2 diabetes – with its heavy burden on health systems – may also be reduced. On the other hand, with more specific studies on this group, if it becomes clear that they are unnecessarily treated, it will be an additional burden on the health system. Therefore, focused study of this particular group of women with mild hyperglycemia has been recently very much considered, as evidenced by the subgroup analysis of the recent RCT and the ensuing letters to the editor, many of which support conducting a large-scale RCT dedicated to this "grey zone" group[14].

Another strength of our study was the use of patient data from our local population of women at risk of GDM, allowing a focus on clinical outcomes in relation to our own current practices. This also permitted confirmation of treatment status for women in each group and allowed for collection of patient-level data on multiple potential confounding factors.

However, the design of our study also has certain limitations. The biggest limitation of our study was the small sample size due to unexpected limitations in the number of eligible women, which led our analyses to have insufficient power to detect group differences. Prior to conducting the study, we assessed 10 years of GDM screening data at JGH and observed participants with grey zone results. However, we encountered an unexpectedly high proportion of exclusions due to the type of tests doctors prescribed to screen women for GDM, with many women not completing both steps of preferred two-step approach. Specifically, 2513 of 4407 pregnancies (57.02%) were excluded for the reason of not completing both of the steps of the screening test. For sufficient

power to compare these distinct GDM diagnostic cut-points in order to detect a pre-determined difference of LGA between the two groups of women with grey zone results, we would have needed 240 women per group, whereas we were only able to obtain data on 73 and 80 pregnant women with grey zone results at the two centres, respectively. Therefore, the lack of statistically significant differences between the groups for our primary comparison may reflect an insufficient sample size rather than a true lack of a difference.

Furthermore, as a retrospective chart review, our study was limited by the quality of data entry, incomplete documentation and unrecorded or unrecoverable information. For example, we were unable to collect reliable offspring data for neonatal hypoglycemia and hyperbilirubinemia, and we confronted a higher proportion of missing values for gestational weight gain among women with grey zone results without GDM (41% missing) compared with women who were diagnosed with GDM (4%), as the untreated grey zone women were not followed as closely in the clinic prepartum as those with GDM. Therefore, we could not consider gestational weight gain as a potential confounder to include in adjusted models. Also, we did not have information on ethnicity, exercise, diet, or smoking, each of which could serve as a potential confounder and affect the association of glucose level on the OGTT with adverse perinatal outcomes. For instance, if women with grey zone results who were not treated for GDM were systematically more likely than the treated comparison groups to exercise and follow a healthy diet during pregnancy, the association of the exposure (glucose level on the OGTT) with adverse pregnancy outcomes may be weakened. As we did not have data on these potential confounders, residual confounding may be present.

Also, certain baseline characteristics differed across groups; while these were not statistically different and we were able to adjust our analyses for some potential confounders which may affect the association of glucose level on the OGTT with adverse perinatal outcomes such as maternal age, parity, neonatal sex, gestational age at delivery, GDM treatment type, mode of delivery and previous C-section where they were suitable, these differences could impact results. For example, in comparison with women who were considered as GDM in JGH, more women with GDM were treated pharmacologically at the MUHC. This is likely the result of distinct treatment targets and different clinical approaches in these two centres: the JGH uses the Diabetes Canada targets (FPG <5.3, 1-hour postprandial target < 7.8 mmol/L)[16], whereas the MUHC uses stricter targets (FPG < 4.7, 1-hour postprandial target < 7.2). This can affect the comparison of pregnancy outcomes for

women who were diagnosed with GDM in JGH versus MUHC, as more intensive treatment at MUHC may have resulted in less risk of adverse pregnancy outcomes. Furthermore, the use of more pharmacological treatment among women with GDM in MUHC could contribute to the higher rates of SGA and less LGA in this group. It is also important to note that all of the untreated grey zone women received their routine perinatal care at one centre (JGH) whereas all treated grey zone women were followed at another centre (MUHC). Therefore, the observed differences in outcomes between these two main comparison groups could be due in part to distinct obstetrical practices at each centre, rather than solely the result of diagnosing and treating for GDM.

Our study was unable to calculate the incidence of GDM resulting from the application of the two different sets of diagnostic cut-points because we did not have the overall number of women who underwent a two-step diagnostic test in each centre during the period of our study. The reason of that is in the JGH, the women were identified based on screening test results, whereas in the MUHC, this data could not be made available and thus women were identified by clinic visits. The difference in incidence for each set of cut-points would be important to assess in future studies since the potential observation of a significant increase in the incidence of GDM by applying lower cut-points without any difference in pregnancy outcomes would indicate that lower thresholds are over-identifying and treating women for GDM. Furthermore, our study was focused on the short-term outcomes, while assessment of long-term complications for the mother and offspring for these groups of women will also be important considering that women with grey zone results may have a higher risk of future T2D and their offspring may have a higher risk of obesity and diabetes.

Finally, these results are generalizable to women in the Canadian health system who complete GDM screening tests with the thresholds suggested by Diabetes Canada and who delivered at the two included hospital centres. Our results are applicable to women who undergo two-step GDM screening, with a result on the first step test that falls between the lower and higher diagnostic thresholds. As mentioned before, other countries and health systems may have different cut-points and diagnostic approaches due to economic or practical reasons, thus limiting the external validity of our study for other health systems and populations.

5.2 Future Research Directions

Considering the high prevalence of GDM and the potential of short- and long-term health complications for both mother and offspring, further studies focused on whether to intervene for women with grey zone results are warranted. Specifically, well-powered studies using a randomized controlled design will be most important to determine the potential risks and benefits due to distinct diagnostic thresholds, to evaluate GDM incidence by applying certain cut-points, and to assess cost-effectiveness of different approaches.

Moreover, in spite of more than ten years of research since the HAPO study and IADPSG recommendations, few RCTs have evaluated GDM diagnostic methods and cut-points. The RCT design limits bias and confounding and its prospective nature improves data collection compared with retrospective studies like ours. The recent RCT is an important step forward in evaluating the risk of short-term adverse pregnancy outcomes associated with distinct GDM diagnostic cut-points. Considering our results and the results of the subgroup analysis from this trial, where women with OGTT results between the lower and higher glycemic thresholds who were treated had reduced risk of LGA and macrosomia, but increased risk of induction of labour and neonatal hypoglycemia, compared with those who were not treated, conducting a properly powered RCT which focuses on this group of women is important and feasible. However, this aim will require a multicentre and potentially multinational collaboration to achieve a sufficient sample size. For instance, after five years of recruitment in the recent RCT, over 5000 women were assessed for eligibility and 4061 were randomized; however, the subgroup analyses of women with grey zone results who were treated and untreated, included only 195 and 178 women per group.

CHAPTER 6: CONCLUSION

Gestational diabetes mellitus is an increasingly common complication of pregnancy, and failure to properly diagnose and treat GDM can lead to adverse maternal and neonatal outcomes. However, there remains no global consensus on the best diagnostic criteria for GDM.

Our study suggests that women with mild hyperglycemia in pregnancy who are not diagnosed or treated for GDM using the diagnostic thresholds of the "preferred approach" currently recommended by Diabetes Canada may benefit from intervention to reduce the risk of LGA and macrosomia, although there is some concern about increasing interventions like induction of labour that was observed due to applying lower thresholds. However, our conclusions were limited by the insufficient sample size and the potential for bias and residual confounding. Therefore, further research with a larger study population and a randomized controlled trial design is needed to determine whether applying lower diagnostic thresholds for GDM can improve pregnancy outcomes and if the level of increased intervention is acceptable.

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CHAPTER 8: APPENDICES

8.1. Standard Operating Procedures (SOP) for Data Entry in the Gestational Diabetes Platform (Jewish General Hospital)

Description: This document describes the steps to take when entering data from ChartMaxx into the Gestational Diabetes Platform. This SOP indicates the electronic database(s) and the specific document(s) where each data point can be found, as well as the order in which these should be searched when entering data.

1. **MRN** – already populated.

2. **Child No** – already populated.
   - Will automatically change according to the number of pregnancies in the grey zone or GDM for each individual. (If there was another pregnancy with the grey zone result or GDM and you answer "yes" to the question in **step #41**, this number will be changed.)

*****Step #1: BEFORE ENTERING ANY DATA***

- Go to "ChartMaxx main menu"→click on "Navigator" → type the MRN in the MR# box (the MRN is in the top of the data entry form) → click "Search" → click "Basic Search:…" to highlight all available documents for the patient → Click "Retrieve" → Then, click on "View" and select "Longitudinal" to sort documents → click on "LONGITUDINAL" in "JGH Chart Order" menu to display the folders.

- Check "Summaries" → "Summary Sheet" and "Delivery Summary" for dates of deliveries.
  - If there is no "Summary Sheet" or "Delivery Summary", the delivery was likely in another hospital, which is an exclusion criterion
    - In this situation, please find EDC according to step #3 or tick the "EDC-not available" checkbox if there is not any ultrasound
    - In the "Inclusion criteria" section, select "Other" for the "Hospital of delivery" item.
    - Then, for the question of "Is patient eligible?" select "NO" and submit the form.
  - If you find several pregnancies between January 1, 2014, and January 1, 2020, first skip to #5 and #7 to find the date of pregnancies with the grey zone results or first GDM between 2014 and 2020 and then return to Step #3 and find the EDC related to those pregnancies.

    - Grey Zone Result:

FBS	5.1-5.2
1h glucose result	10.0-10.5
2h glucose result	8.5 - 8.9

- GDM:

FBS	≥5.3
1h glucose result	≥10.6
2h glucose result	≥9.0

- NB: For using all the **calendar boxes** in the platform, please consider these points:
  - EITHER type the date into the box OR select the date using the calendar (do not try to use both methods of data entry for the same date, or an error will occur).
  - To select a date using the calendar, follow this process:
    - click on the YEAR to change, then click on the MONTH to change (or click on the < or > to change the month), then click on the DAY.
  - If you entered an incorrect date and you try to correct it, please consider these points and confirm correct data entry:
    - If you change the date while the platform is saving, the system will return to the date previously saved.
    - If you touch the turning arrow on the date field, it will revert to a previous date entered.

3. **EDC (Estimated Date of Confinement)**:
   1) ChartMaxx: "Other Investigations" → "Obstetrical Ultrasound Report"
      - Confirm the date of ultrasound is consistent with the current pregnancy.
      - Use "Best Overall Assessment": "EDC" for the date
   2) ChartMaxx: "History & Physical" → "Obstetrical File 1" → EDC
   3) ChartMaxx: "Summaries" → "Delivery Summary" → "EDD" at top of page

4. **EDC- not available**:
   If you cannot find EDC in the documents, please check this box.

5. **Date of first test**:
   - "Labs New" → Double click "Lab Results Query" → Enter "MRN" → Select "Date Range": January 1, 2014, to January 1, 2020 → Click "Query" on bottom right → Select "GT50" and "GTP" → Find the test results related to current pregnancy→ Enter the test results and dates.

6. **Calculated gestational age (GA) at first test** _The platform calculates automatically (using EDC).

7. **Date of Second test:**
   - "Labs New" → Double click "Lab Results Query" → Enter "MRN" → Select "Date Range": January 1, 2014, to January 1, 2020 → Click "Query" on bottom right → Select "GT50" and "GTP" → Find the test results related to current pregnancy→ Enter the test results and dates.

➢ Inclusion Criteria

8. Hospital of delivery:

1) ChartMaxx: "Summaries" → "Delivery Summary" and "Summary Sheet"
    - If there is no "Summary Sheet" or "Delivery Summary", the delivery was likely in another hospital → Please select "Other".

9. First and Second test results available

- If in Steps #5 and #7 you find both the screening and diagnostic tests select "Yes", and if not, select "No".

10. First step test between 24-28 weeks:

- If the result of GA at the time of the first test that is calculated by the platform is between 24 and 28weeks, please select "Yes".
- If GA is not between this period, please select "No".

11. Is patient eligible?

- If in Step #8, "Other" was selected, or for Steps #9 or #10, "No" was selected, please select "No" → jump to Step #41 and after that submit the form.
- If in Step #8, "Other" was not selected and for both Steps #9 and #10 "Yes" was selected, please select "Yes". By selecting "Yes", the next part of the form will appear.

<u>If the patient is eligible:</u>

➢ Exclusion criteria:

12. Pregnancy Type (Singleton, Multiple - exclude Multiple):

1) ChartMaxx: "Summaries" → "Delivery Summary" and "Summary Sheet"
2) ChartMaxx: "Nursing Documents" → "Nursing Assessment"

13. Prior GDM (exclude prior GDM): (Please check at least step 1 plus one of the other 2 steps to confirm)

1) ChartMaxx: "History & Physical" → "Obstetrical File 1" → "Particularities" → Mother
    - Confirm the date of the "Obstetrical File" is consistent with the current pregnancy and check the information about prior pregnancies in this document.
    - Check this document to find prior pregnancies in or out of JGH.
2) ChartMaxx: "Nursing Documents" → "Nursing Assessment" for prior pregnancies→ health history section.
3) ChartMaxx: "Summaries" → "Summary Sheet"→ Check prior pregnancies to find if there are any prior pregnancies with GDM

14. Existing diabetes (exclude pre-existing, *i.*e., type 1 or type 2 diabetes):
(Please check at least 2 steps to confirm)

1) ChartMaxx: "History & Physical" → "Obstetrical File 1"
    - Confirm the date of the obstetrical file is consistent with the current pregnancy.
2) ChartMaxx: "Nursing Documents" → "Nursing Assessment"→ health history section.
    - Confirm the date of the obstetrical file is consistent with the current pregnancy.
3) ChartMaxx: "Summaries" → "Summary Sheet"

15. Assisted reproduction (IUI or IVF, etc.) (exclude assisted reproduction):
(Please check at least 2 steps to confirm)

1) ChartMaxx: "Summaries" → "Summary Sheet"
2) ChartMaxx: "History & Physical" → "Obstetrical File 1"
    - Confirm the date of the obstetrical file is consistent with the current pregnancy.
3) ChartMaxx: "Other Investigations" → "Obstetrical Ultrasound Report" (sometimes mentioned).
    - Confirm the date of ultrasound is consistent with the current pregnancy.
4) ChartMaxx: "Ambulatory Services" → read the "Ambulatory Services" documents (sometimes mentioned).

- If assisted reproduction is not mentioned in the documents, select "No".

16. Is the patient excluded from the study?

- If yes, skip to Step #41
- If more than two items in exclusion criteria were "not available" exclude the patient and skip to #41.
- If two or less items were "not available" → save as a draft for more discussion and decision.
- If the patient is not excluded from the study, select "No" and the next part of the form will appear.

<u>If the patient is not excluded</u>:

➢ Screen #1 and Screen #2

- "Date of test" and "Calculated gestational age" fill automatically according to prior data entered.

For other items ("Type", "Fasting glucose result", "1h glucose result", "2h glucose result":

- Oacis
    - Double click "Lab" → Click "Show All" on bottom right → Click Magnifying Glass (below "Plan" on menu bar)
    - Type "50"→ Select "Pregnancy GTT 50g Screen" and click ">"
    - Type "75"→ Select "Pregnancy GTT 75g" and click ">"
    - Type "glucose" → Shift and select all "glucose" values and click ">"

- Click “Apply” on bottom right
- Confirm that the date of these results corresponds to the current pregnancy

- “Labs New”
  - Double click “Lab Results Query”
  - Enter “MRN”
  - Select “Date Range”: January 1, 2014, to January 1, 2020
  - Click “Query” on bottom right
  - Select “GT50” and “GTP” and enter results
  - Confirm that the date of these results corresponds to the current pregnancy.

17. **Length of hospital stay** (<u>for mother</u>):
    - Calculate that according to this calculation:
      “Calculation: discharge date - admission date”
      - Discharge date: “Summaries” → “Summary Sheet”
      - Date of admission: “Summaries” → “Delivery Summary”→ upper part of the page
    - If the mother was admitted in one month and discharged in the next month, please pay attention to the number of days in each month and calculate the length of hospital stay like this:
      eg. Date of admission: Feb 27, discharge date: Mar 2 ➔ Length of hospital stay: **3**

18. **Maternal date of birth**:
    1) ChartMaxx: “Summaries”→ “Delivery Summary” → upper part of the page
    2) ChartMaxx: “Administrative Documents” → “Patient Information"

19. **Date of delivery:**
    1) ChartMaxx: “Summaries”→ “Delivery Summery” → page 4
    2) ChartMaxx: “Nursing Documents” → “Care Map”→ Post-delivery section

20. **Maternal age at delivery _** The platform calculates automatically.

21. **Calculated gestational age (GA) at delivery** _ The platform will calculate automatically (based on EDC).

22. **Preterm birth:**
    1) Check gestational age at the date of delivery as entered in the form.
       - For birth at <37 weeks gestational age → Select “Yes”
       - For birth at ≥37 weeks gestational age → Select “No”
    2) ChartMaxx: “Nursing Documents” → “Care Map” → “Post-Delivery” section.

23. Previous caesarean

1) ChartMaxx: "Summaries"→ check the method of delivery in previous "Summary Sheets"→ "Medical, surgical, obstetrical treatment"
    - Also, check step #2 to find if prior delivery at another hospital / in another country
2) ChartMaxx: "History & Physical" → "Obstetrical File 1" → "Previous Pregnancies" → "Method of delivery"
    - Confirm the date of the "Obstetrical File 1" is consistent with the current pregnancy.
3) ChartMaxx: "Nursing documents" → "Nursing Assessment" → Page 1→ "OBS history" → "Past Pregnancies"
    - Confirm the date of the "Nursing Assessment" is consistent with the current pregnancy.

24. Maternal parity :(consider parity before the current pregnancy, *e.g.*, If a woman is G1 P0 in this pregnancy, maternal parity is 0)

1) ChartMaxx: "Summaries"→ "Delivery Summery" → upper part of the page (e.g., G6P1…)
2) ChartMaxx: "History & Physical" → "Obstetrical File 1"
3) ChartMaxx: "Nursing Documents" → "Nursing Assessment"

25. Neonatal sex:

1) ChartMaxx: "Summaries" → "Delivery Summary" → page 4
2) ChartMaxx: "Nursing Documents" → "Care Map" → "Post-Delivery" section.

26. Birth weight:

1) ChartMaxx: "Summaries" → "Delivery Summery" → page 4
2) ChartMaxx: "Nursing Documents" → "Care Map" Post-Delivery section

27. Large for gestational age → Do not enter.

28. Weight percentile → Do not enter.

29. Apgar Score: (Record the Apgar Score reported at <u>1 minute</u>)

1) ChartMaxx: "Summaries"→ "Delivery Summary" → page 4
2) ChartMaxx: "Progress Notes" → "Progress Notes" for current pregnancy

30. Apgar Score - Not available:

- If you cannot find the Apgar score checkmark this selection.
- In the case of "stillbirth" please select "Apgar Score-Not available".

31. Shoulder dystocia: (Check both steps to confirm)

1) ChartMaxx: "Summaries" → "Summary Sheet" and "Delivery Summary"→ complications.
2) ChartMaxx: "Progress Notes" → "Progress Notes" for current pregnancy→ Check the delivery note.
    - If C-section, select "No" for this item unless it is documented that the reason for C-section was emergency C-section due to shoulder dystocia.

32. Stillbirth:

1) ChartMaxx: "Perinatal death" → "Perinatal loss summary sheet"
    - If there was a stillbirth, there will be an additional tab that shows up in ChartMaxx in grey called "Perinatal Death".
    - If there was a perinatal death, there will be an additional tab that shows up in ChartMaxx in grey called "Perinatal Death".
2) ChartMaxx: "Summaries" →"Delivery Sheet" and "Delivery Summary" → page 4 → Newborn assessment section.
3) ChartMaxx: "Nursing Documents" → "Care Map"

33. Neonatal hypoglycemia:

1) ChartMaxx: "Nursing Documents" → "Care Map" → "Post-Delivery" section → Check whether baby was in "Main" or "NICU" (see checkbox on right side of page 1)

2) ChartMaxx: "Summary" → "Summary Sheet" → "Discharge medication and dosage" section and ChartMaxx: "Nursing Documents" → "Care Map"→ Page 12
    - Check whether it is documented that mother discharged with baby.
    - If baby was in "Main" and it is documented that mother was discharged with baby → select "Not available" for neonatal hypoglycemia.
    - If it was not documented that mother was discharged with baby → select "Not available" for neonatal hypoglycemia.
    - If documented that baby was in NICU or mother was discharged without baby → Search the documents:
        - If the reason is "hypoglycemia" → select "Yes"
        - If other reason(s) → select "No"
        - If no reason is documented → select "Not available"
    - In cases of "stillbirth" please select "No"

34. Hyperbilirubinemia:

1) ChartMaxx: “Nursing Documents” → “Care Map” → “Post-Delivery” section → Please check that baby was in “Main” or “NICU” (checkbox on right side of page 1)

2) ChartMaxx: “Summary” → “Summary Sheet” → “Discharge medication and dosage” section and ChartMaxx: “Nursing Documents” → “Care Map”→ Page 12
   - Check whether it is documented that mother was discharged with baby.

   - If baby was in “Main” and it is documented that mother was discharged with baby → select “Not available” for neonatal hyperbilirubinemia.
   - If it is not documented that mother was discharged with baby → select “Not available” for neonatal hyperbilirubinemia.
   - If it is documented that baby was in NICU or mother was discharged without baby → Search the documents:
     - If the reason is “hyperbilirubinemia” → select “Yes”
     - If other reason(s) → select “No”
     - If no reason is documented → select “Not available”

   - In cases of “stillbirth” please select "No"

35. Neonatal death:

1) ChartMaxx: “Perinatal death” → “Perinatal Loss Summary Sheet”
   - If there was a perinatal death, there will be an additional tab that shows up in ChartMaxx in grey called “Perinatal Death”.
2) ChartMaxx: “Summary” → “Summary Sheet” → “Discharge medication and dosage” section and ChartMaxx: “Nursing Documents” → “Care Map”→ Page 12
   - Check whether it is documented that mother was discharged with baby.

   - If it is documented that mother was discharged with baby → select “No” for neonatal death.
   - If it is not documented that mother was discharged with baby but no documentation of neonatal death is present → select “Not available” for neonatal death.

36. Day of death: If you find neonatal death in the above steps, select “Yes” for neonatal death, and record the date.

37. Mode of delivery:

1) ChartMaxx: “Summaries” → “Summary Sheet” and “Summaries” → “Delivery Summary” → Page 2
   - If spontaneous, must also check #2 to confirm no “Induction”
     - Induction may not be mentioned in the “Summaries”

- If "Summaries" mentioned just C-section without reason, to find the reason, check ChartMaxx→ "Operative Record" →"Operative Report"→ "Preoperative Note".
    - Also, determine whether C-section was emergency or elective

- **To determine "Induction of labour"**:

2) ChartMaxx: "Nursing Documents" → "Nursing Documents" → "Nursing Assessment" → "Reason of admission" to determine if mother admitted for "Induction of labour"
3) ChartMaxx: "Progress Notes" → Admission note and orders

- **To determine the "Reason for induction" or "Reason of operative delivery":**

4) ChartMaxx: "Summary" → "Delivery Summary" and "Summary Sheet".
    - If no reason for induction documented, leave the "Reason for induction" blank.
    - If no reason of operative delivery documented, leave the "Reason of operative delivery" blank.

    - **NB: it is possible that a caesarean section was done if labour did not progress after induction.
    - If there was induction AND use of operative delivery, select both in the form.
    - If there was induction AND C-section, select both in the form
        - In "Reasons of caesarean" box, document whether Emergency C-section as well as reason of C-section.

38. For maternal weight (Pre-gravid weight and Final gestational weight):

1) ChartMaxx: "Nursing Documents" → "Nursing Assessment"→ "OBS HISTORY" section → Weight before and current

2) ChartMaxx:
    a. For GDM patients: "Consultation" from perinatal clinic visit → For finding pre-gravid weight
        a. *NB: For women in the grey zone, will likely not be available unless followed for another reason*

3) ChartMaxx: "History & Physical" → "Obstetrical File 4"
    - You can find here the last weights recorded.
    - In the top of the weight column sometimes recorded the "weight before pregnancy".

4) ChartMaxx: "Ambulatory Services" → read the "Ambulatory Services" notes to observe if there is any recorded weight from the clinic.

- The weights can be recorded as either kilograms (kg) or pounds (lb), and the platform automatically calculates the other one.

- If no recorded weight in documents, select “Pre-gravid weight - Not available” and “Final gestational weight - Not available”.
- If just one of the weights is documented, for the other one select “Not available” and record the one available weight.
- If you use the “Obstetrical File 4” or “Ambulatory Services”, please pay attention that the time of the weight that is collecting for “Final gestational weight” be **less than one month** before the time of delivery. If there is no recorded weight near delivery time please choose "Final gestational weight - not available".

39. Hypertensive disorders of pregnancy: (Please check both steps)

1) ChartMaxx: “Summaries” →“Summary Sheet”
   - If the “Summary Sheet” does not mention hypertension (or “HTN”), check step 2.
2) ChartMaxx: “History & Physical” → “Obstetrical File 1”

- Please select “Yes” for hypertensive disorders if onset occurs before to hospital discharge following delivery. eg. For Post-partum hypertension select “Yes”.

40. GDM treatment type: (Please check all steps)

1) ChartMaxx: “History & Physical” → “Obstetrical File 1”
2) ChartMaxx: “Nursing Documents” → “Nursing Assessment” → “Health History” section.
3) ChartMaxx: “Ambulatory services”
   - If perinatal visits / glucose charts, select “Considered as GDM”.
   - If no perinatal clinic visits / no glucose charts, select “Not considered as GDM.”
4) ChartMaxx: “Prescriptions & Orders” – look for Discharge (outpatient) prescription of insulin or oral antihyperglycemic Rx for current pregnancy.
   - If the results of the second test show GDM (FPG≥5.3, 1hPG≥10.6, 2hPG≥9.0) but in the documents did not mention GDM and the type of treatment, please flag this part and explain the issue and save the form as a draft (without submit) for further discussion.

41. Did the patient have another pregnancy with GDM or glucose result in the grey zone?

1) Check “Summaries” → “Summary Sheet” and “Delivery Summary” for dates of deliveries.
2) Repeat Steps #5 and # 7 and “Screen 1 & Screen 2” to find whether that woman has any other pregnancies in the grey zone or GDM.
   - If in current pregnancy the woman had GDM, she will be excluded for her next pregnancy with grey zone result or GDM (as prior GDM is an exclusion criterion).
   - Thus, in cases like this, select “Yes” and another form will be created. After collecting the initial information for second pregnancy, it will be excluded.
3) If “Yes” is selected, the platform will add another form with the same “MRN” but different “Child No.” to the dashboard.

42. Any part for which you are hesitant, select a **red flag** and add your question there to review with the team.

43. If you do not fill a box with the red star, you are not able to submit the form directly. You will be asked to “Submit the forms with errors” or “Return to form and fix errors”. If you miss a box by mistake, please return to form and complete.

44. Final steps:

- “Save the form as draft” if you are not sure about some parts, OR
- “Submit” if you are certain that it is complete

Thank you!

8.2. Standard Operating Procedures (SOP) for Data Entry in the Gestational Diabetes Platform (McGill University Health Centre)

Description: This document describes the steps to take when entering data from Oacis into the Gestational Diabetes Platform. This SOP indicates the electronic database(s) and the specific document(s) where each data point can be found, as well as the order in which these should be searched when entering data.

1. **MRN** – already populated.
2. **Child No** – already populated.

    - Will automatically change according to the number of pregnancies in the grey zone or GDM for each individual. (If there was another pregnancy with a grey zone result or GDM and you answer "yes" to the question in step #41, this number will be changed.)

Step #1: BEFORE ENTERING ANY DATA;

1) Go to "Oacis" main menu→click on "Single Patient Lookup " → select "MRN" for "Search for patient by" → type the MRN in the "MRN (required)" box (the MRN is in the top of the data entry form) → In the "Registration system section" please select "RVH PCS" and remove the tick from the "Search all registration systems" → click "Search" → Click on the name of patient → Click on "Ok" → Click on the name of patient in the vOACIS to change the color from pink to blue→ Click on the icon "Document viewer" to see the list of visits and documents.
    - If the patient had visits in different hospitals, you see different folders in "Patient work list". Please click on "RVH-HRV" to see the documents in the "Royal Victoria Hospital".

2) Check "Patient work list"→ "RVH-HRV" → list of visits and "Obstetric|Inpatient" for dates of deliveries.
    - If there is no "Obstetric|Inpatient", the delivery was likely in another hospital.
        - In this situation, please find EDC according to step #3 or tick the "EDC-not available" checkbox if there is not any ultrasound.
        - In the "Inclusion criteria" section, select "Other" for the "Hospital of delivery" item.
        - Then, for the question of "Is patient eligible?" select "NO" and submit the form.

    - If you find several pregnancies between January 1, 2014, and January 1, 2020, first skip to #5 and #7 to find the date of pregnancies with the grey zone results or first GDM between 2014 and 2020 and then return to Step #3 and find the EDC related to those pregnancies.

- **Grey Zone Result:** FBS 5.1-5.2
  1h glucose result 10.0-10.5
  2h glucose result 8.5 - 8.9
- **GDM:** FBS ≥5.3
  1h glucose result ≥10.6
  2h glucose result ≥9.0
- NB: For using all the calendar boxes in the platform, please consider these points:
  - EITHER type the date into the box OR select the date using the calendar (do not try to use both methods of data entry for the same date, or an error will occur).
  - To select a date using the calendar, follow this process:
    - click on the YEAR to change, then click on the MONTH to change (or click on the < or > to change the month), then click on the DAY.
  - If you entered an incorrect date and you try to correct it, please consider these points and confirm correct data entry:
    ▪ If you change the date while the platform is saving, the system will return to the date previously saved.

    ▪ If you touch the turning arrow on the date field, it will revert to a previous date entered.

3. EDC (Estimated date of confinement):

1) Oacis: Select "Results" from top of the vOACIS → select "Image" → "OBS TAS > 16 WKS < 28WKS" → "Best overall assessment" (usually found in the third line of "Dating" section of ultrasounds)→ "EDC"
   - Confirm the date of ultrasound is consistent with the current pregnancy.
   - If there is not any "OBS TAS > 16 WKS < 28WKS", please look at any other ultrasound.
2) Oacis: "Patient Worklist" → "RVH-HRV" → "Obstetric | Inpatient" → "Postpartum Communication" → Page 1 → "EDC"
3) Oacis: "Patient Worklist" → "Obstetric|Inpatient" → "Admission history and physical" or "OBS Centricity" ("Resume/Transfer/Discharge") → "EDC"

4. EDC- not available:

If you cannot find EDC in the documents, please check this box.

5. **Date of first test**:

    1) Oacis: Select “Results” from top of the vOACIS → select “Laboratory” →click on “Show all” at the bottom right of Oacis for searching in all results → click “Filters” button → Select “GLU 0M” “GLU +60M” “GLU +120M” “ GLUCOSE FASTING ” “ GLUCOSE 1 HR PC ” “ GLUCOSE 2 HR PC ” “ GTTGluc0m ” “ GTTGlu +60 ” “ GTGlu +120 ” “ Glucose 0m GTT” “ Glucose +60m GTT” “ Glucose +120m GTT” from “Available Services” for “Filter Services” (you can save the filter and use that in the next searches)→ Find the test results related to current pregnancy→ You can see the result tests and the dates.
        - Also, by clicking on each test in the “Specimen Comment” you can see the amount of Glucose that was used (eg., 50gr → GCT/first test; 75 gr→ OGTT/second test)
    2) Oacis: “Patient Worklist” →“RVH-HRV” → “Evaluations/ Gestational diabetes/Nutrition”→ Current → Sometimes the test dates and results are mentioned.
    3) Oacis: “Patient Worklist” →“RVH-HRV” → Consults → Sometimes the test dates and results are mentioned
    4) Oacis: “Patient Worklist” →“RVH-HRV” → The first “Progress notes/ Diabetes-multidisiplinary F/U/ Obstetrics” for that pregnancy → Sometimes the test dates and results are mentioned.

6. **Calculated gestational age (GA) at first test** _The platform calculates automatically (using EDC).

7. **Date of Second test:**
    1) Oacis: Select “Results” from top of the vOACIS → select “Laboratory” →click on “Show all” at the bottom right of Oacis for searching in all results → click “Filters” button → Select “GLU 0M” “GLU +60M” “GLU +120M” “ GLUCOSE FASTING ” “ GLUCOSE 1 HR PC ” “ GLUCOSE 2 HR PC ” “ GTTGluc0m ” “ GTTGlu +60 ” “ GTGlu +120 ” “ Glucose 0m GTT” “ Glucose +60m GTT” “ Glucose +120m GTT” from “Available Services” for “Filter Services” → Find the test results related to current pregnancy→ You can see the result tests and the dates.
        - Also, by clicking on each test in the “Specimen Comment” you can see the amount of Glucose that was used (eg., 50gr → GCT/first test ; 75 gr→ OGTT/second test)

    2) Oacis: “Patient Worklist” → “RVH-HRV” → “Evaluations/ Gestational diabetes/Nutrition” → Current → Sometimes the test dates and results are mentioned.

    3) Oacis: “Patient Worklist” → “RVH-HRV” → Consults → Sometimes the test dates and results are mentioned

    4) Oacis: “Patient Worklist” → “RVH-HRV” → The first “Progress notes/ Diabetes-multidisciplinary F/U/ Obstetrics” for that pregnancy → Sometimes the test dates and results are mentioned.

➢ Inclusion Criteria

8. Hospital of delivery:

1) Oacis: "Patient Worklist" → "RVH-HRV" → "Obstetric | Inpatient" related to delivery
    - If there is not "Obstetric | Inpatient" for current pregnancy in the list, the delivery was likely in another hospital → Please select "Other".

9. First and Second test results available

- If in Steps #5 and #7 you find both the screening and diagnostic tests select "Yes" and if not, select "No".

10. First step test between 24-28 weeks:

- If the result of GA at the time of the first test that is calculated by the platform is between 24weeks and 28weeks, please select "Yes".
- If GA is not between this period, please select "No".

11. Is patient eligible?

- If in Step #8, "Other" was selected, or for Steps #9 or #10, "No" was selected, please select "No" → jump to Step #41 and after that submit the form.
- If in Step #8, "Other" was not selected and for both Steps #9 and #10 "Yes" was selected, please select "Yes". By selecting "Yes", the next part of the form will appear.

<u>If the patient is eligible:</u>

➢ Exclusion criteria:

12. Pregnancy Type (Singleton, Multiple - exclude Multiple):

1) Oacis: Select "Results" from top of the vOACIS → select "Image" → find related ultrasounds → the column "Exam" usually mentions the number of fetuses.
2) Oacis: "Patient Worklist" → "RVH-HRV" → "Obstetric | Inpatient"→ "Hospitalisation summary" → "Summary sheets"
3) Oacis: "Patient Worklist" → "RVH-HRV" → "Obstetric | Inpatient" → "Obstetrical (delivery) resume"

13. Prior GDM (exclude prior GDM): (Please check at least 2 steps to confirm)

1) Oacis: "Patient Worklist" →"RVH-HRV" → "Evaluations/ Gestational diabetes/Nutrition"→ Past medical history
2) Oacis: "Patient Worklist" →"RVH-HRV" → "Obstetric|Inpatient" → "Admission history and physical" or "OBS Centricity" ("Resume/Transfer/Discharge") → OB provider admission history and physical → "Pregnancy History" → "Previous Pregnancies"

3) Oacis: "Patient Worklist" → "RVH-HRV" →"Obstetric|Outpatient" with "Diabetes multidisciplinary F/U" before the current "Obstetric|Inpatient" → "Diabetes multidisciplinary F/U"
4) Oacis: "Patient Worklist"→ RVH-HRV → "Medical observation P1"/"Obstetrical chart" related to current pregnancy (Sometimes in "Document received from outside")
5) Oacis: "Patient Worklist"→ RVH-HRV → "Medical Consultation"

14. Existing diabetes (exclude pre-existing, *i.e.*, type 1 or type 2 diabetes): (Please check at least 2 steps to confirm)

1) Oacis: "Patient Worklist" →"RVH-HRV" → "Evaluations/ Gestational diabetes/Nutrition"→ Past medical history
2) Oacis: "Patient Worklist" → RVH-HRV → "Obstetric|Inpatient" → "Admission history and physical" or "OBS Centricity" ("Resume/Transfer/Discharge") → OB provider admission history and physical → "Pregnancy History" → "Previous Pregnancies"
3) Oacis: "Patient Worklist" → RVH-HRV →"Obstetric|Outpatient" with "Diabetes multidisciplinary F/U" before the current "Obstetric|Inpatient" → "Diabetes multidisciplinary F/U"
4) Oacis: "Patient Worklist" → RVH-HRV → "Obstetric|Inpatient" → Hospitalisation Summery (Summery sheet)
5) Oacis: "Patient Worklist"→ RVH-HRV → "Medical observation P1"/"Obstetrical chart" related to current pregnancy (Sometimes in "Document received from outside")

15. Assisted reproduction (IUI or IVF, etc.) (exclude assisted reproduction): (Please check at least 2 steps to confirm)

1) Oacis: "Patient Worklist" → RVH-HRV → "Obstetric|Inpatient" → Hospitalisation summary (Summary sheet)
2) Oacis: Select "results" from top of the vOACIS → select "Image" → find related ultrasounds → The sonography usually mentions assisted reproduction.
    a. Confirm the date of ultrasound is consistent with the current pregnancy.
3) Oacis: "Patient Worklist" →"RVH-HRV" → "Evaluations/ Gestational diabetes/Nutrition" → "Past medical history" and "Current"
4) Oacis: "Patient Worklist"→ RVH- HRV → "Medical Observation P1"/"Obstetrical Chart" related to current pregnancy (Sometimes in "Document received from outside")

- If assisted reproduction is not mentioned in the documents, select "No".

16. Is the patient excluded from the study?

- If yes, skip to Step #41.
- If more than two items in exclusion criteria were "not available", exclude the patient and skip to #41.
- If two or less were "not available" → save as a draft for more discussion and decision.

- If the patient is not excluded from the study, select "No" and the next part of the form will appear.

If the patient is not excluded:

➢ Screen #1 and Screen #2

- "Date of test" and "Calculated gestational age" fill automatically according to prior data entered.
- **For other items ("Type", "Fasting glucose result", "1h glucose result", "2h glucose result":**

1) Oacis: Select "Results" from top of the vOACIS → select "Laboratory" →click on "Show all" at the bottom right of Oacis → click "Filters" button Select "GLU 0M" "GLU +60M" "GLU +120M" " GLUCOSE FASTING " " GLUCOSE 1 HR PC " " GLUCOSE 2 HR PC " " GTTGluc0m " " GTTGlu +60 " " GTGlu +120 " " Glucose 0m GTT" " Glucose +60m GTT" " Glucose +120m GTT" from "Available Services" for "Filter Services" → Find the test results related to current pregnancy→ Enter result tests.
    - Also, by clicking on each test in the "Specimen Comment" you can see the amount of Glucose that was used (50gr → GCT / first test ; 75 gr→ OGTT / second test)
2) Oacis: "Patient Worklist" → "RVH-HRV" → "Evaluations/ Gestational diabetes/Nutrition" → Current → Sometimes the test dates and results are mentioned.
3) Oacis: "Patient Worklist" → "RVH-HRV" → Consults → Sometimes the test dates and results are mentioned
4) Oacis: "Patient Worklist" → "RVH-HRV" → The first "Progress notes/ Diabetes-multidisciplinary F/U/ Obstetrics" for that pregnancy → Sometimes the test dates and results are mentioned.

17. Length of hospital stay (<u>for mother</u>):

- Calculate according to this calculation:

  "Calculation: discharge date - admission date"

- To find these dates: Oacis: "Patient Worklist" → "RVH-HRV" →keep the mouse cursor on "Obstetric | Inpatient" → the admission and discharge date will appear!

18. Maternal date of birth:

1) Oacis: "Patient Worklist" → RVH- HRV → "Obstetric|Inpatient" → "Obstetrical (delivery) resume" ("Resume/Transfer/Discharge")→ upper part of the page → "DOB"

2) Oacis: “Patient Worklist” → RVH- HRV → “Obstetric|Inpatient” → “OBS Centricity” (“Resume/Transfer/Discharge”) → upper part of the page → “DOB”
3) Oacis : “Summary“ → “Patient Demographics“ → “DOB”

19. Date of delivery:

1) Oacis: “Patient Worklist” → RVH- HRV → “Obstetric|Inpatient” → “Obstetrical (delivery) resume” (“Resume/Transfer/Discharge”) → Page 2 → “Delivery information” → “Delivery date”
2) Oacis: “Patient Worklist” → RVH- HRV → “Obstetric|Inpatient” → “Postpartum Communication” → “Delivery information”

20. Maternal age at delivery _ The platform calculates automatically.

21. Calculated gestational age (GA) at delivery _ The platform will calculate automatically (based on EDC).

22. Preterm birth:

1) Check gestational age at the date of delivery as entered in the form.
    - For birth at <37 weeks gestational age → Select Yes.
    - For birth at ≥37 weeks gestational age → Select No

23. Previous caesarean

1) Oacis: “Patient Worklist” → RVH- HRV → “Obstetric|Inpatient” → “Admission history and physical” or “OBS Centricity” (“Resume/Transfer/Discharge”) → OB provider admission history and physical → “Pregnancy History” → “Previous Pregnancies”
2) Oacis: “Patient Worklist”→ RVH- HRV → “Medical Observation P1”/“Obstetrical Chart” related to current pregnancy (Sometimes in “Document received from outside”)

24. Maternal parity: (consider parity before the current pregnancy, *e.g*., If a woman is G1 P0 in this pregnancy, maternal parity is 0)

1) Oacis: “Patient Worklist” → RVH- HRV → “Obstetric/Inpatient” → “Obstetrical (delivery) resume” → “Resume/Transfer/Discharge” → Page 1 →upper part of the page (eg., G6P1…)
2) Oacis: “Patient Worklist” → RVH- HRV → “Obstetric|Inpatient” → “OBS Centricity” (“Resume/Transfer/Discharge”) → upper part of the page (eg. G/ 4 P/ 3…)
3) Oacis: “Patient Worklist” → RVH- HRV →“Obstetric|Outpatient” with “Diabetes multidisciplinary F/U” before the current “Obstetric|Inpatient” → “Diabetes multidisciplinary F/U”

25. Neonatal sex:

1) Oacis: "Patient Worklist" → RVH-HVR →"Obstetric| Inpatient" → "Obstetrical (delivery) resume" → "Resume/Transfer/Discharge" → Page 2 →"Baby information" → "Sex"

2) Oacis: "Patient Worklist" → RVH-HVR →"Patient Worklist" → "Obstetric|Inpatient" → "Postpartum Communication" → "Delivery Information"

26. Birth weight:

1) Oacis: "Patient Worklist" → RVH- HRV →"Obstetric| Inpatient" → "Obstetrical (delivery) resume" ("Resume/Transfer/Discharge") → Page 2 →"Baby information" → "Birth Weight"
2) Oacis: "Patient Worklist"→ RVH- HRV → "Obstetric|Inpatient" → "Postpartum Communication" → "Delivery information"

27. Large for gestational age → Do not enter.

28. Weight percentile → Do not enter.

29. Apgar Score: (Please record the Apgar Score reported at <u>1 minute</u>)

1) Oacis: "Patient Worklist" → RVH- HRV → "Obstetric| Inpatient" → "Obstetrical (delivery) resume" → "Resume/Transfer/Discharge" → Page 2 → 1 Min Apgar score
2) Oacis: "Patient Worklist" → RVH- HRV → "Patient Worklist" → "Obstetric|Inpatient" → "Postpartum Communication" → "Delivery Information" → 1 Min Apgar score

30. Apgar Score - Not available:

- If you cannot find the Apgar score checkmark this selection.

31. Shoulder dystocia:

1) Oacis: "Patient Worklist" → RVH- HRV → "Obstetric| Inpatient" → "Obstetrical (delivery) resume" ("Resume/Transfer/Discharge") → Page → "Delivery information" → "Shoulder dystocia"
2) Oacis: "Patient Worklist" → RVH- HRV → "Obstetric| Inpatient" → "Obstetrical (delivery) resume" ("Resume/Transfer/Discharge") → "Delivery comments" and "assessment"
3) Oacis: "Patient Worklist" → RVH- HRV → "Obstetric|Inpatient" → "Progress Notes-Inpatient" → Please check the delivery note.
    - If C-section, select "No" for this item unless it is documented that the reason for C-section was emergency C-section due to shoulder dystocia.

32. **Stillbirth:**
    1) Oacis: "Patient Worklist" → RVH- HRV → "Obstetric| Inpatient" → "Obstetrical (delivery) resume" → "Resume/Transfer/Discharge" → Page 2 → "Baby information" → "Outcome"
    2) Oacis: "Patient Worklist" → "RVH- HRV" → "Obstetric | Inpatient"→ "Hospitalisation summary" → "Summary sheets"
    3) Oacis: "Patient Worklist" → RVH- HRV → "Obstetric|Inpatient" → "Postpartum Communication" → "Delivery information"

33. **Neonatal hypoglycemia:** Select "Not available"

34. **Hyperbilirubinemia:** Select "Not available"

35. **Neonatal death:**

    - Please check whether they mentioned that mother was discharged with baby:

    - If it is documented that mother was discharged with baby → select "No" for neonatal death.
    - If it is not documented that mother was discharged with baby but no documentation of neonatal death is present → select "Not available" for neonatal death.
    - Also, you can check the consultations after the delivery (a few days or months after delivery) for follow-up GDM and there usually mentions some information about baby.

36. **Day of death:** If you find neonatal death in the above steps, select "Yes" for neonatal death and record the date.

37. **Mode of delivery:**
    1) Oacis: "Patient Worklist" → RVH- HRV → "Obstetric|Inpatient" → "Obstetrical (delivery) resume" ("Resume/Transfer/Discharge") → Page 1 → "Maternal labor/Delivery information" and "Delivery comments"
        - If spontaneous, must also check #2 (below) to confirm no "Induction"
        - If in delivery information mentioned just C-section without reason, to find the reason, check Oacis: "Patient Worklist" → RVH-HRV→ "Obstetric|Inpatient" → "Operation Report"
            - Always start the reason of C-section by "**Elective**" or "**Emergency**" word!
            - We called the C/S "Emergency" when they must do C/S after failed progress of labour

- **To determine "Induction of labour"**: (Please check all the steps to find there used induction or not)

2) Oacis: "Patient Worklist" → RVH- HRV → "Obstetric|Inpatient" → "Current admission record" (evaluations) → "Current admission record"→ "Reason of admission" to determine if mother admitted for "Induction of labour"

3) Oacis: "Patient Worklist" → RVH- HRV → "Obstetric|Inpatient" → "Admission history and physical" or "OBS Centricity" ("Resume/Transfer/Discharge") → "Admission Note"→ "Chief complain" and "indication for induction" to determine if mother admitted for "Induction of labour"
4) Oacis: "Patient Worklist" → RVH- HRV → "Obstetric|Inpatient" → "Progress Notes-Inpatient"→ Admission notes and orders

- **To determine the "Reason for induction":**

5) Oacis: "Patient Worklist" → RVH- HRV → "Obstetric|Inpatient" → "Obstetrical (delivery) resume" ("Resume/Transfer/Discharge") → Page 1 → "Maternal labor/Delivery information" → "Reason for induction"
6) Oacis: "Patient Worklist" → RVH- HRV → "Obstetric|Inpatient" → "Current admission record" (evaluations) → "Current admission record"→ "Indication for induction"
7) Oacis: "Patient Worklist" → RVH- HRV → "Obstetric|Inpatient" → "Admission history and physical" or "OBS Centricity" ("Resume/Transfer/Discharge") → "Admission Note"→ "indication for induction"

- **To determine "Operative delivery" and "Reason of operative delivery":**

8) Oacis: "Patient Worklist" →"RVH-HRV" → "Obstetric|Inpatient" → "Obstetrical (delivery) resume" ("Resume/Transfer/Discharge") → Page 2 → "Delivery information" → Forceps/ Vaccume
9) Oacis: "Patient Worklist" →"RVH-HRV" → "Obstetric|Inpatient" → "Obstetrical (delivery) resume" ("Resume/Transfer/Discharge") → "Delivery comments" and "Assessment"

    - If no reason for induction documented, leave the "Reason for induction" blank.
    - If no reason of operative delivery documented, leave the "Reason of operative delivery" blank.

    - **NB: it is possible that a caesarean section was done if labour did not progress after induction.
    - If there was induction AND use of operative delivery, select both in the form.
    - If there was induction AND C-section, select both in the form
        - In "Reasons of caesarean" box, document whether Emergency C-section as well as reason of C-section.

38. **For maternal weight (Pre gravid weight and Final gestational weight):**

1) Oacis: "Patient Worklist" → "RVH-HRV" → "Evaluations/ Gestational diabetes/Nutrition" → Pre-Pregnancy Weight

2) Oacis: “Patient Worklist” → RVH-HVR → “Obstetric|Inpatient” → “Admission history and physical” or “OBS Centricity” (“Resume/Transfer/Discharge”) → “Admission Record” → Weight (pre-pregnancy)
3) Oacis: “Patient Worklist” → RVH-HVR → “Obstetric|Outpatient” with “Diabetes multidisciplinary F/U” before the current “Obstetric|Inpatient” →“Diabetes multidisciplinary F/U” → “Today’s Maternal Surveillance” → “Weight” for Final gestational weight
4) Oacis: “Patient Worklist” →First “Obstetric|Outpatient” with Diabetes multidisciplinary F/U → “Today’s Maternal Surveillance” → weight AND “Assessment and Plan” for finding the pre-gravid weight.
5) Oacis: “Patient Worklist”→ RVH-HVR →Click on “Document type” button → Select “Nutrition consult” from “Document Type” → Search in them for weights.
6) Oacis: “Patient Worklist”→ RVH-HVR → “Medical observation P4”/ “Obstetrical chart” related to current pregnancy (Sometimes in “Document received from outside”) → You can find here the final gestational weight recorded.

- The weights can be recorded as either kilograms (kg) or pounds (lb), and the platform automatically calculates the other one.
- If no recorded weight in documents, select “Pre-gravid weight - Not available” and “Final gestational weight - Not available”.

- If just one of the weights is documented, for the other one select “not available” and record the one available weight.

39. Hypertensive disorders of pregnancy:

1) Oacis: “Patient Worklist” → “RVH-HRV” → “Obstetric | Inpatient”→ “Hospitalisation summary” → “Summary sheet”
   - If in the “Summary Sheet” does not mention HTN please check step 2.
2) Oacis: “Patient Worklist” →“RVH-HRV” → →“Obstetric|Outpatient” with “Diabetes multidisciplinary F/U” before the current “Obstetric|Inpatient” →“Diabetes multidisciplinary F/U” → ”Diagnosis”
3) Oacis: “Patient Worklist” → “RVH-HRV” → “Obstetric | Inpatient” → “Postpartum Communication”→ “Medical/Surgical History”
4) Oacis: “Patient Worklist”→ “RVH-HRV” → “Obstetric|Inpatient” → “Admission history and physical” or “OBS Centricity” (“Resume/Transfer/Discharge”) → “Medical History” → “hypertension”

40. GDM treatment type: (Please check all steps)

1) Oacis: “Patient Worklist” →“RVH-HRV” → →“Obstetric|Outpatient” with “Diabetes multidisciplinary F/U” before the current “Obstetric|Inpatient” →”Insulin type/dose”
2) Oacis: “Patient Worklist” → “Obstetric|Inpatient” → “Admission history and physical” or “OBS Centricity” (“Resume/Transfer/Discharge”) →“Current medication”

3) Oacis: “Patient Worklist”→ “RVH-HRV” →Click on “Document type” button → Search in “Medical consultation” from “Document Type” to find type of treatment.
4) Oacis: “Patient Worklist”→ “RVH-HRV” → “Order & Prescriptions” category– look for discharge (outpatient) prescription of insulin of oral antihyperglycemic Rx for current pregnancy.
5) Oacis: “Patient Worklist”→ “RVH-HRV” → “Medical observation P1”/“Obstetrical chart” related to current pregnancy (Sometimes in “Document received from outside”)

41. Did the patient have another pregnancy with GDM or glucose result in the grey zone?

1) Check “Patient work list”→ “RVH-HRV” → list of visits and “Obstetric|Inpatient” for dates of deliveries.
2) Repeat Steps #5 and #7 and “Screen 1 & Screen 2” to find whether that woman has any other pregnancies in the grey zone or GDM.
    - If in current pregnancy the woman had GDM, she will be excluded for her next pregnancy with grey zone result or GDM (as prior GDM is an exclusion criterion).
    - Thus, in cases like this, select “Yes” and another form will be created. After collecting the initial information for second pregnancy, it will be excluded.
3) If “Yes” is selected, the platform will add another form with the same “MRN” but different “Child No.” to the dashboard.

42. Any part for which you are hesitant, select a **red flag** and add your question there to review with the team.

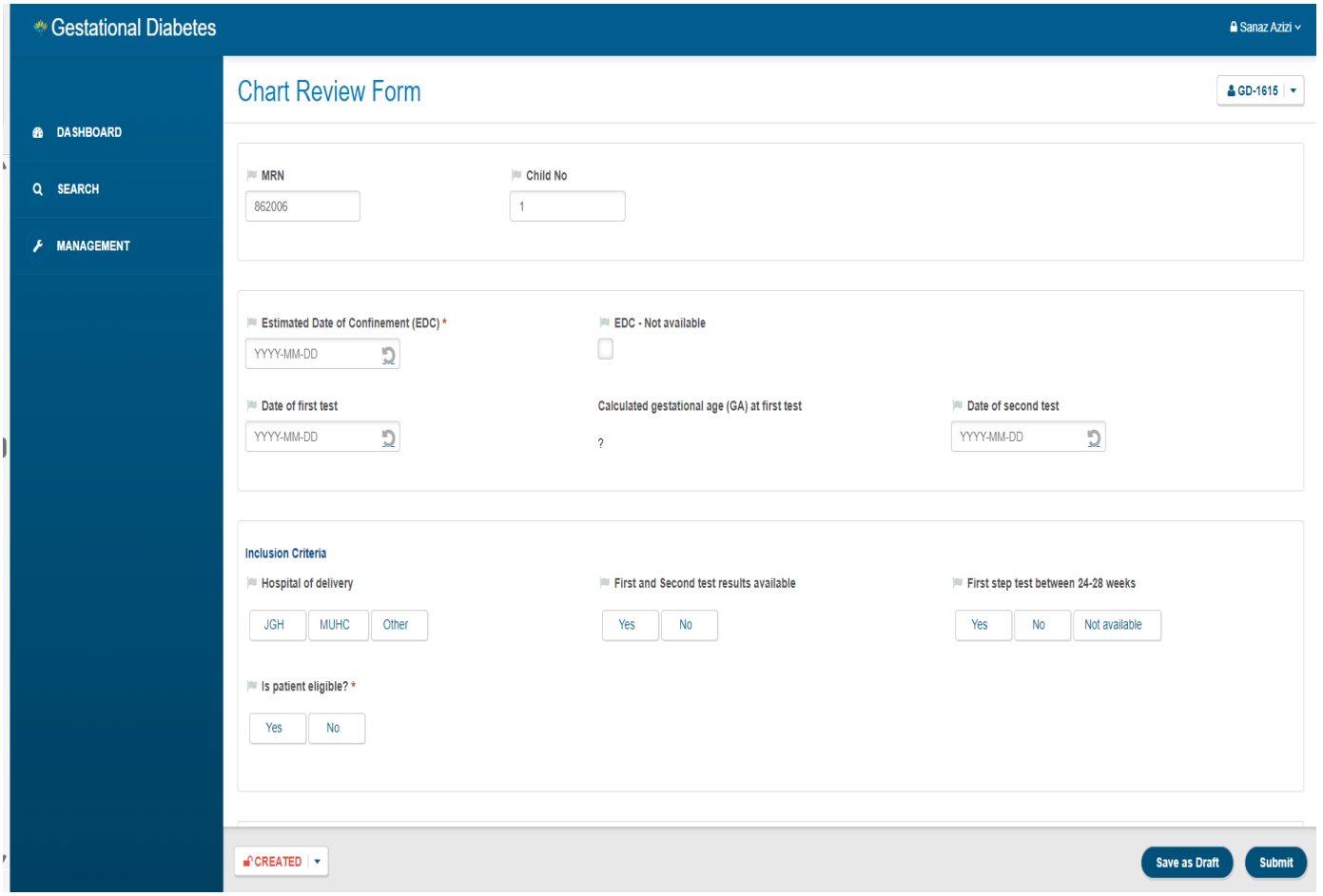
43. If you do not fill a box with the red star, you are not able to submit the form directly. You will be asked to “Submit the forms with errors” or “Return to form and fix errors”. If you miss a box by mistake, please return to form and complete.

44. Final steps:

- “Save the form as draft” if you are not sure about some parts, OR
- “Submit” if you are certain that it is complete

Thank you!

8.3 Data collection form



8.4 Research ethics approval

Centre intégré universitaire de santé et de services sociaux du Centre-Ouest-de-l'Île-de-Montréal
Québec

2020-07-22

Dr. Tricia Peters
c/o: Tricia Peters
email: tricia.peters@mcgill.ca

Object: Project 2021-2262 - Final Research ethics committee Approval of the Project Following Conditional Approval
The diagnostic threshold for gestational diabetes: Should it be lowered?

Dear Dr. Peters,

The Medical/Biomedical Research Ethics Committee (REC) of CIUSSS West-Central Montreal Research Ethics Board (REB) is pleased to inform you that the above-mentioned study received ethics approval.

A delegated review of the research project was provided by member(s) of the Medical/Biomedical . The responses and revisions submitted via an F20 form were reviewed and approved by the Chair on 2020-07-22.

Subsequent to the receipt and review of the above-mentioned chart review project, please be advised that your request for permission to review approximately 1000 medical charts at the CIUSSS West-Central Montreal as part of your project is granted.

It is our understanding that specific aims of this chart review are to determine whether diagnostic criteria for the two-step screening test for gestational diabetes mellitus (GDM) that is stricter than the criteria currently endorsed by Diabetes Canada would reduce the rate of macrosomia. In order to examine this, we will ascertain the number of macrosomic offspring among women not diagnosed with GDM by current thresholds, but whom would receive a GDM diagnosis if lower thresholds were adopted.

This retrospective chart review will be done by yourself and a resident. The data collected will be coded and kept on the LDI server for a period of 7 years. No contact will be made with patients at any time during this retrospective chart review.

This approval is for the period of one year at which point you must request permission once again. Please contact the Medical Records Department at 514-340-8222 ext. 28202 to arrange for consulting charts.

The following documents are granted final ethics approval by the Medical/Biomedical REC:

- Initial Submission Form (F11R-14617)
- REC Conditions & PI Responses Form(s) (F20-16945)
- - Document(s) approved by the REC (GDM proposal_DQ_final.docx)
  - Document(s) approved by the REC (Peters_Protocol.docx)
  - Document(s) approved by the REC (GDM Data Capture Form_20200610.xlsx

The responses and revisions will be reported to the Medical/Biomedical REC and will be entered accordingly into the minutes of the next meeting, to be held on 2020-08-21.

The Medical/Biomedical REC of CIUSSS West-Central Montreal REB had the necessary scientific expertise and carried out the scientific evaluation of the project. The Committee rendered a positive evaluation of the project.

The ethics approval is valid until 2021-07-22.

The COVID-19 pandemic and the state of emergency declared by the Province of Quebec create exceptional

circumstances, having impacts on research activities, in particular their evaluation and conduct. In this context, the conduct of this study must be aligned with the specific guidelines in effect at the CIUSSS du Center-Ouest-de-l'Île-de-Montréal and in each respective participating institution, if applicable.

The Research Ethics Board of the CIUSSS West-Central Montreal Board (Federalwide Assurance Number: 0796) is designated by the province (MSSS) and follow the published guidelines of the TCPS 2 - Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (2018), in compliance with the "Plan d'action ministériel en éthique de la recherche et en intégrité scientifique" (MSSS, 1998), and the membership requirements for Research Ethics Board defined in Part C Division 5 of the Food and Drugs Regulations; and acts in conformity with standards set forth in the United States Code of Federal Regulations governing human subjects research, and functions in a manner consistent with internationally accepted principles of good clinical practice.

Duties of Researchers
Ethics approval may be withdrawn if the following stipulations are not met:

- To obtain prior written approval from the REB for any substantive modification to the research, including changes to the study procedures, financial arrangements and/or resource utilization, before initiating the change; except where urgent action is required to eliminate an immediate hazard to a study participant;
- To maintain confidentially, the updated Research Participants Registry is to be retained for the length of time required by regulations, and in accordance with institutional policy;
- To comply with all relevant regulations and guidelines governing the conduct of research involving human subjects and the requirements of the REB;
- To comply with all REB requests to report study information, including prompt reporting of unexpected or serious adverse events (SAEs) or alarming trends in expected SAEs, according to the policies and procedures of each institution where the study is conducted;
- To advise the REB and all study subjects of new significant findings emerging during the course of the study;
- To comply with quality assurance assessment as defined by each institution's policy;
- To maintain study records according to regulatory requirements.

All research involving human participants requires review at recurring intervals. To comply with the regulation for continuing review of at least once per year, it is the responsibility of the investigator to submit an Annual Renewal Submission Form (F9) to the REB prior to expiry. The annual renewal form that will be available to you approximately 60 days prior to the expiry date of this letter. Please note that if the protocol approval expires before its renewal is granted, the data collected after the expiration date may not be considered valid. However, should the research conclude for any reason prior to approval expiry, you are required to submit a Completion (End of a Study) Report (F10) to the REB once the data analysis is complete to give an account of the study findings and publication status.

Furthermore, should any revision to the project or other development occur prior to the next continuing review, you must advise the REB without delay, by submitting an amendment form to the committee. Regulation does not permit initiation of a proposed study modification prior to its approval by the REB.

Please note that that the CIUSSS WCM *Quality Assurance Program* aims to support 10% of active research in our institution. In order to promote best practices in research ethics, our team may contact you to schedule an on-site visit during the course of the study.

Please be advised that you may only initiate the research project after all required reviews and decisions are received and documented.

Respectfully,

Dr. Vasiliki Bessy Bitzas, N, PhD, CHPCN(C)
Chair, Medical/Biomedical Research Ethics Committee

Centre universitaire de santé McGill | McGill University Health Centre

2021-03-10

Dr. Rachel Bond

email: rachel.bond@mail.mcgill.ca

Re: Authorisation to conduct your research study at the MUHC
Objet: Autorisation de réaliser votre projet de recherche au CUSM

Titre du projet: Le seuil diagnostic pour le diabète gestationnel: Faut-il le baisser?
Project Title: The diagnostic threshold for gestational diabetes: Should it be lowered?

Numéro de dossier du CER évaluateur / File Number of Reviewing REB: MP-05-2020-2263
CER évaluateur / Reviewing REB: CÉR de CIUSSS du Centre Ouest-de-l'Île-de Montréal
Date d'approbation éthique / REB Approval Date: 2020-07-22
Numéro de dossier CUSM / MUHC File Number: MEO-05-2021-6733

Personne contacte au CER CUSM / MUHC REB contact person:

Clinical Trials 2 (CT2) Panel
Sheldon Levy
sheldon.levy@muhc.mcgill.ca

***** La version française suit *****

Dr. Bond,

We are pleased to allow you to carry out the research project, identified above, under the auspices of the MUHC.

We are writing to confirm that the study mentioned above has received all required institutional approvals, namely:

- Contracts
- Use of adult resources
- Access to adult health records

This authorization allows you to perform research at the MUHC.

By granting this authorization, our institution recognizes the ethical review that was done by the REB mentioned above.

- This REB is the Reviewing REB for this project in accordance with the MSSS *Cadre de référence des établissements publics du RSSS pour l'autorisation d'une recherche menée dans plus d'un établissement* (le Cadre de référence) (the MSSS Framework);
- This REB confirmed on the date of REB approval, see above, the positive outcome of the

scientific and ethics reviews of the project; and
- This REB approved the network version of the consent form used in French and English for this research. If the Reviewing REB determines that changes to the network version of the consent form affect the ethical acceptability of the project it may suspend its ethical approval for the institution.

We acknowledge receipt of the consent form that you prepared for our institution from the network version and a copy of this authorization will be forwarded to Reviewing REB.

This authorization is given on condition that you commit to:

- Respecting the provisions of the MSSS framework relevant to your research project;
- Complying with the MUHC regulatory framework (April 2016) for research involving humans, including the identification of research participants;
- Using the version of the documents relating to the research approved by the Reviewing REB, to which only administrative changes have been made and communicated to the Reviewing REB; and
- Meeting the requirements set by the Reviewing REB for ongoing ethical oversight of research.

The authorization given to you to realize the research project under the auspices of our institution will be renewed without further proceedings on the date specified by the REB assessor's decision to renew its ethical approval for this research.

Please contact the MUHC REB coordinator mentioned above for any questions regarding this authorization or its renewal or about administrative changes that have been made to the version of the documents relating to the research approved by the Reviewing REB.

Please do not hesitate to contact me during the conduct of the study at our institution, if necessary. You can also seek the advice from our REB by contacting the MUHC REB Panel mentioned above to obtain the support needed.

Lastly, we ask you to refer to both study numbers assigned to your research project by our institution and by the Reviewing REB when discussing the study.

Sincerely,

Sheldon Levy (see signature below)
for:
Marie Hirtle, LL.B. LL.M.
Mandated Person
McGill University Health Centre

cc. Vasiliki Bitzas, Reviewing REB Chair
Tricia Peters, PI who submitted to Reviewing REB

Docteure Bond,

Il nous fait plaisir de vous autoriser à réaliser la recherche identifiée en titre et sous les auspices du CUSM.

Nous vous écrivons pour confirmer que l'étude susmentionnée a reçu toutes les approbations

institutionnelles requises, à savoir:

- Les contrats
- Utilisation des ressources adultes
- Accès aux dossiers de santé adultes

Cette autorisation vous permet de réaliser la recherche au CUSM.

Pour vous donner cette autorisation, notre établissement reconnaît l'examen éthique effectué par le CER évaluateur mentionné ci-haut.

- Ce CER agit comme CER évaluateur pour ce projet, conformément au *Cadre de référence des établissements publics du RSSS pour l'autorisation d'une recherche menée dans plus d'un établissement* (le Cadre de référence) ;
- Ce CER a confirmé le résultat positif de l'examen éthique et scientifique du projet à la date d'approbation éthique mentionnée ci-haut ; et
- Ce CER a approuvé la version réseau du formulaire de consentement en français et en anglais utilisé pour cette recherche.

Nous accusons réception du formulaire de consentement que vous avez préparé pour notre établissement à partir de la version réseau et nous le joindrons à la copie de cette autorisation qui sera transmise au CER évaluateur.

Cette autorisation vous est donnée à condition que vous vous engagiez à:

- Respecter les dispositions du Cadre de référence se rapportant à votre recherche;
- Respecter le cadre réglementaire de notre établissement sur les activités de recherche, notamment pour l'identification des participants à la recherche;
- Utiliser les versions des documents se rapportant à la recherche approuvées par le CER évaluateur, les seuls changements apportés, si c'est le cas, étant d'ordre administratif et identifiés de façon à ce que le CER évaluateur puisse en prendre connaissance ; et
- Respecter les exigences fixées par le CER évaluateur pour le suivi éthique de la recherche.

L'autorisation qui vous est donnée ici de réaliser la recherche sous les auspices du CUSM sera renouvelée sans autre procédure à la date indiquée par le CER évaluateur dans sa décision de renouveler son approbation éthique de cette recherche.

Pour toute question relative à cette autorisation ou à son renouvellement ou au sujet de changements d'ordre administratifs qui auraient été apportés à la version des documents se rapportant à la recherche approuvée par le CER évaluateur, veuillez communiquer avec le coordinateur de CER mentionné en rubrique.

Je vous invite à entrer en communication avec moi pendant le déroulement de cette recherche dans notre établissement, si besoin est. Vous pouvez aussi solliciter l'appui de notre CER en vous adressant au Panel du CER CUSM mentionné ci-haut pour obtenir les conseils et le soutien voulu.

En terminant, veuillez toujours mentionner dans votre correspondance au sujet de cette recherche le numéro attribué à votre demande par notre établissement ainsi que le numéro attribué au projet de recherche par le CER évaluateur.

En espérant le tout à votre entière satisfaction.

Cordialement,

Mandatée (SL) Personne
Sheldon Levy
for:
Marie Hirtle, LL.B. LL.M.
Personne Mandatée
Centre Universitaire de Santé McGill