OULU 2021
D 1597

ACTA UNIVERSITATIS OULUENSIS

Sanna Eteläinen

GESTATIONAL DIABETES

SCREENING, DIAGNOSIS AND CONSEQUENCES

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
FACULTY OF MEDICINE;
FACULTY OF SCIENCE;
MEDICAL RESEARCH CENTER;
OULU UNIVERSITY HOSPITAL;
FINNISH INSTITUTE FOR HEALTH AND WELFARE

ACTA UNIVERSITATIS OULUENSIS
D Medica 1597

SANNA ETELÄINEN

GESTATIONAL DIABETES

Screening, diagnosis and consequences

Academic dissertation to be presented with the assent of the Doctoral Training Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium 4 of Oulu University Hospital on 29 January 2021, at 12 noon

UNIVERSITY OF OULU, OULU 2021

Acta Univ. Oul. D 1597, 2021

Supervised by
Docent Marja Vääräsmäki
Professor Eero Kajantie

Reviewed by
Docent Riitta Luoto
Docent Saila Koivusalo

Opponent
Docent Helena Fadl

ISBN 978-952-62-2816-7 (Paperback)
ISBN 978-952-62-2817-4 (PDF)

ISSN 0355-3221 (Printed)
ISSN 1796-2234 (Online)

Cover Design
Raimo Ahonen

PUNAMUSTA
TAMPERE 2021

Eteläinen, Sanna, Gestational diabetes. Screening, diagnosis and consequences
University of Oulu Graduate School; University of Oulu, Faculty of Medicine, Faculty of Science; Medical Research Center; Oulu University Hospital; Finnish Institute for Health and Welfare
Acta Univ. Oul. D 1597, 2021
University of Oulu, P.O. Box 8000, FI-90014 University of Oulu, Finland

Abstract

Gestational diabetes mellitus (GDM) is defined as hyperglycaemia with onset or first recognition in pregnancy. Besides adverse maternal and neonatal perinatal outcomes, it is also associated with long-term consequences, such as type II diabetes, metabolic disturbances and cardiovascular diseases. Although the impact of GDM on maternal and foetal health is well known, there is no consensus concerning its screening policy and diagnostic criteria.

In Finland, risk factor-¬based GDM screening was changed to comprehensive screening in 2008 by Finnish Current Care Guidelines (CCGs). The aim of these guidelines was to standardise the screening method, diagnosis, treatment and also prevention of GDM, as well as of type II diabetes mellitus and obesity.

The aim of the present study was to evaluate the effect of the shift from risk factor-¬based to comprehensive screening on the prevalence and maternal and neonatal outcomes of GDM pregnancies in Finland, as well as to compare pregnancy outcomes according to International Association of Diabetes and Pregnancy Study Group (IADPSG) and National Institute for Health and Care Excellence (NICE) GDM criteria. We also explored the relationship between the number of abnormal values in the oral glucose tolerance test (OGTT) and pregnancy and perinatal complications.

The shift from risk factor-¬based to comprehensive GDM screening led to a significant increase in women with mild GDM who were more often primiparous, had a lower BMI and were less often treated with insulin. Comprehensive GDM screening led to decreased birth weight and macrosomia rates among newborns. Although the prevalence of neonatal hypoglycaemia increased, newborns required care in a neonatal ward less often due to their mild form of hypoglycaemia.

When comparing the IADPSG and NICE criteria, GDM prevalence was 2.4-fold higher according to the IADPSG criteria compared with the NICE criteria, but the macrosomia rate did not differ. Birth weight and the caesarean section rate increased already with mild, untreated hyperglycaemia. In the last study, which examined the significance of the number of abnormal OGTT values to pregnancy and perinatal outcomes, all women with GDM had an increased risk of delivery induction, regardless of the number of abnormal values, but the risk of caesarean section or macrosomia increased only after two or three abnormal values.

Keywords: diagnosis, gestational diabetes mellitus, oral glucose tolerance test, screening

Eteläinen, Sanna, Raskausdiabetes. Seulonta, diagnosointi ja seuraukset
Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta, Luonnontieteellinen tiedekunta; Medical Research Center; Oulun yliopistollinen sairaala; Terveyden ja hyvinvoinnin laitos
Acta Univ. Oul. D 1597, 2021
Oulun yliopisto, PL 8000, 90014 Oulun yliopisto

Tiivistelmä

Raskausdiabetes on sokeriaineenvaihdunnan häiriö, joka todetaan ensimmäisen kerran raskauden aikana. Siihen liittyy lisääntynyt raskauskomplikaatioiden riski sekä äidin ja lapsen vaara sairastua myöhemmin tyypin 2 diabetekseen, metaboliseen oireyhtymään sekä sydän- ja verisuonitauteihin. Vaikka raskausdiabeteksen hoidon hyödyt äidille ja lapselle on tunnettu jo pitkään, kansainvälistä yksimielisyyttä sen seulonnasta tai diagnoosikriteereistä ei ole.

Suomessa julkaistiin vuonna 2008 raskausdiabeteksen Käypä hoito -suositus, jossa aiemman riskitekijäpohjaisen seulonnan tilalle suositellaan yleistä seulontaa. Suosituksen tavoitteena on yhtenäistää seulonta- ja diagnoosikriteerit sekä hoito, turvata lapsen ja äidin hyvinvointi sekä ehkäistä raskausdiabeteksen toistumista, lihavuutta ja tyypin 2 diabeteksen kehittymistä.

Väitöskirjatutkimuksen tarkoituksena oli selvittää Käypä hoito -suosituksen vaikutusta raskausdiabeteksen yleisyyteen sekä äitien ja lasten terveyteen. Syntyneiden lasten rekisterin ja laboratoriotulosten avulla selvitettiin International Association of Diabetes and Pregnancy Study Group (IADPSG) ja National Institute for Health and Care Excellence (NICE) -seulontamenetelmien sekä sokerirasitustestin poikkeavien arvojen lukumäärän vaikutusta raskausdiabeteksen yleisyyteen sekä naisten ja vastasyntyneiden terveyteen.

Seulontamuutoksen myötä raskausdiabeteksen esiintyvyys Suomessa nousi 24% vuosina 2006-2010. Yleisellä seulonnalla diagnosoidut raskausdiabeetikot olivat useammin normaalipainoisia, ensisynnyttäjiä ja tarvitsivat harvemmin insuliinihoitoa. Lasten syntymäpainot olivat pienemmät kuin riskitekijäpohjaisen seulonnan aikana. Vastasyntyneillä todettiin enemmän hypoglykemiaa, mutta heidät pystyttiin useammin hoitamaan vierihoito-osastolla.

Käypä Hoito -suositusta tiukemmilla, maailmalla laajalti käytetyillä IADPSG-kriteereillä diagnosoidun raskausdiabeteksen esiintyvyys oli 2,4-kertainen NICE-kriteerien mukaan diagnosoitujen määrään verrattuna. Lasten syntymäpaino ja keisarileikkausten määrä olivat keskimääräistä suurempia jo Suomessa käytettäviä raja-arvoja matalammilla glukoositasoilla.

Niillä naisilla, joilla sokerirasituskokeessa oli yksi poikkeava glukoosiarvo, ainoastaan synnytyksen käynnistämisen riski oli muita naisia suurempi. Kun poikkeavia arvoja oli kaksi tai kolme, myös sikiön makrosomian ja keisarileikkauksen riski oli suurentunut.

Asiasanat: diagnoosi, raskausdiabetes, seulonta, sokerirasitustesti

To Lauri and Kaarlo

Acknowledgements

This thesis study was carried out in 2009–2020 at the Department of Obstetrics and Gynecology, Oulu University Hospital, PEDEGO Research Unit, MRC Oulu, University of Oulu, and Public Health Promotion Unit, National Institute for Health and Welfare. I wish to express my gratitude to the former and current academic heads of the Department of Obstetrics and Gynecology at Oulu University Hospital, Professor Juha Tapanainen, Professor Ulla Puistola, Professor Hannu Martikainen and Professor Terhi Piltonen, and the Head of Division of Children and Women, Adjunct Professor Eila Suvanto and Head of Department, Kati Ojala, MD, PhD, for their positive attitude toward my research and for providing an academically motivating environment in which to work.

My deepest gratitude goes first to my supervisors: "The Mother of the FinnGeDi study" Adjunct Professor Marja Vääräsmäki, for sharing your wisdom with me during our many conversations and for being the voice of reason in my most difficult moments concerning my research or my personal life and, most importantly, for believing and trusting me; and Professor Eero Kajantie, for sharing your knowledge and extensive experience with me.

Furthermore, I owe my sincere gratitude to Adjunct Professors Saila Koivusalo and Riitta Luoto, the official reviewers of my thesis. Your detailed comments, both constructive and critical, and insightful suggestions significantly improved this work. I would further like to express my gratitude to Adjunct Professor Helena Fadl for agreeing to be my opponent.

During the last years, I have had the wonderful experience of collaborating with many talented people, each of whom I wish to sincerely thank for their substantial contributions to this thesis: Hilkka Ijäs, MD, PhD and Elina Keikkala, MD, PhD, for their friendship, mentoring and sincerity; biostatistician Aini Bloigu, for sharing her experience and advice in statistics; Adjunct Professor Tuija Männistö, for enthusiastically sharing her experience and some of her best but also hardest moments as a doctoral candidate; Sanna Mustaniemi, MD, Marjaana Tikanmäki, MD, PhD, Marika Sipola, MD, PhD, Jenni Kinnunen, MD, and Matti Viljakainen, MD. I also warmly thank and acknowledge the expertise and contributions of all my co-authors: Professor Johan Eriksson, Professor Risto Kaaja, Professor Mika Gissler, Adjunct Professor Anneli Pouta and Professor Hannele Laivuori.

I want to express my gratitude to Adjunct Professor Tytti Raudaskoski and Professor Matti Uhari for joining my thesis follow-up group and for providing

important, constructive and encouraging insights and advice over these years. Matti, you are the reason I became so excited about research 15 years ago when I was a medical student!

I owe my warmest thanks to all my colleagues and friends at the Department of Obstetrics and Gynaecology. I feel very privileged to have a such wonderful work community. I want to thank my colleagues in gynaecological oncology; Marja Simojoki, Päivi Vuolo-Merilä, Marianne Hinkula, Jaana Männistö, Suvi Turunen and Elina Urpilainen, without your support this all would have been very much harder. I especially want to thank my long-term friends Iita Inget, Hanna Malinen, Maria-Elina Mosorin, Liisa Laatio, Outi Uimari, Tuomas Kauppinen, Henna Rossi, Minna Jokelainen, Heljä Mäklin, Anni Mäkinen, Pia Vittaniemi, Tanja Länsman, Kirsi Mäenalanen, Leena Liukkonen, and Elli Kansanniva.

I would not be here without my parents, Irene and Sulo, and my brother, Jani. Your love and especially your encouragement gave me the foundation on which to pursue my goals. To my parents, I am forever thankful for your amazing support and invaluable help with my children. Your never-ending love and support have made all of this possible – you have made me who I am today.

Above all, my deepest love and gratitude go to my family: my beloved sons, Lauri and Kaarlo. Thank you all for your patience and understanding, for always being loving and supportive while I worked to complete my thesis. Without your support, it would have been immensely difficult to keep my priorities straight throughout this process. I also want to thank my children-in-law, Unna, Elle, Jussa and Aku, for supportive and endurance with this thesis project.

And last but definitely not least, to my husband, Juha: I am deeply thankful for all your support and help, without which it would have been immeasurably more difficult to devote the innumerable hours needed during the last year to completing my thesis. Juha, you have taught me to love, to be confident, to be brave, to be persistent, to look at the world in a whole new way.

Oulu, December 2020 *Sanna Eteläinen*

Abbreviations

ACOG	The American College of Obstetricians and Gynecologists
ADA	American Diabetes Association
BMI	Body mass index
BW	Birth weight
CCGs	Current Care Guidelines
CI	Confidence interval
FIGO	The International Federation of Gynecology and Obstetrics
GCT	Glucose challenge test
GDM	Gestational diabetes mellitus
GHT	Gestational hypertension
HAPO	Hyperglycaemia and Adverse Pregnancy Outcome study
HbA1c	Glycated haemoglobin
IADPSG	International Association of Diabetes and Pregnancy Study Group
LGA	Large for gestational age
NICE	National Institute for Health and Care Excellence
OGTT	Oral glucose tolerance test
OR	Odds ratio
SCOPE	Screening for Pregnancy Endpoints study
SD	Standard deviation
WHO	World Health Organization

List of original publications

This thesis is based on the following original publications, which are referred to throughout the text by their Roman numerals:

I Koivunen, S., Kajantie, E., Torkki, A., Bloigu, A., Gissler, M., Pouta, A., & Vaarasmaki, M. (2015). The changing face of gestational diabetes: the effect of the shift from risk factor-based to comprehensive screening. *European Journal of Endocrinology / European Federation of Endocrine Societies, 173*(5), 623–632. https://doi.org/10.1530/EJE-15-0294

II Koivunen, S.*, Torkki, A.*, Bloigu, A., Gissler, M., Pouta, A., Kajantie, E., & Vääräsmäki, M. (2017). Towards national comprehensive gestational diabetes screening -consequences for neonatal outcome and care. *Acta Obstet Gynecol Scand., 96*(1), 106–113. https://doi.org/10.1111/aogs.13030

III Koivunen, S., Viljakainen, M., Männistö, T., Gissler, M., Pouta, A., Kaaja, R., Eriksson, J., Laivuori, H., Kajantie, E., & Vääräsmäki, M. (2020). Pregnancy outcomes according to the definition of gestational diabetes. *PLoS One, 15*(3), e0229496. https://doi.org/10.1371/journal.pone.0229496

IV Eteläinen, S., Viljakainen, M., Männistö, T., Gissler, M., Pouta, A., Kaaja, R., Eriksson, J., Laivuori, H., Kajantie, E., & Vääräsmäki, M. The number of abnormal values in oral glucose tolerance test: the significance to pregnancy and perinatal outcomes. Submitted.

*Equal contribution.

Table of contents

1 Introduction

Gestational diabetes mellitus (GDM) is a common pregnancy-related disorder that, depending on screening policies, diagnostic cut-offs and study populations, affects 1–40% of pregnancies (Behboudi-Gandevani, Amiri, Bidhendi Yarandi, & Ramezani Tehrani, 2019; Hildén, Magnuson, Hanson, Simmons, & Fadl, 2020; McIntyre et al., 2018). GDM can predispose women to several complications during pregnancy and delivery – for example, hypertensive disorders, preterm delivery, delivery induction, vaginal tears and increased rate of caesarean sections (Catalano et al., 2012). For newborns, exposure to maternal hyperglycaemia in utero increases the risk for macrosomia, hypoglycaemia, hyperbilirubinemia, birth traumas, asphyxia and respiratory distress syndrome (Billionnet et al., 2017). Detection and treatment of GDM offers benefits to both the mother and her offspring during and shortly after pregnancy (Crowther et al., 2005; Landon et al., 2009).

In the long term, GDM is strongly associated with increased risk for type II diabetes, cardiovascular diseases and other metabolic disturbances (Di Cianni, Lacaria, Lencioni, & Resi, 2018; Kramer, Campbell, & Retnakaran, 2019). In addition, offspring exposed to maternal GDM also have a higher risk for the same conditions (Kaseva et al., 2018; Kaseva et al., 2019; Kawasaki et al., 2018; Pirkola, Pouta, Bloigu, Hartikainen, et al., 2010). It can be said that GDM represents the first warning of imminent type II diabetes. While these associations have been widely documented, the challenge is to prevent or postpone diabetes and its complications, and especially to identify the risk group, women with GDM, in a timely fashion.

Although the adverse effects of hyperglycaemia during pregnancy have been known for decades, until now no consensus over its screening and diagnosis has been reached. Basically, the diagnostic criteria of GDM were set according to their ability to identify mothers at risk of subsequent diabetes (O'Sullivan & Mahan, 1964). In 2008, the Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study showed that adverse pregnancy outcomes were associated with mild hyperglycaemia as a continuous relationship (Metzger et al., 2008). This study was the first to focus on the adverse perinatal outcome, not on the later risk, of type II diabetes for mothers. After the HAPO study, the International Association of Diabetes and Pregnancy Study Group (IADPSG) suggested universal screening and uniform diagnostic criteria. The ability to predict neonatal outcomes was first

employed by the IADPSG to define the diagnostic criteria for hyperglycaemia (Metzger et al., 2010).

The IADPSG made their GDM screening recommendations in 2010, and these criteria are still under debate (Meltzer, Snyder, Penrod, Nudi, & Morin, 2010). The World Health Organization (WHO), the American Diabetes Association (ADA) and the Endocrine Society have accepted these IADPSG guidelines, but they have not been adopted by the American College of Obstetricians and Gynecologists (ACOG), the UK National Institute of Clinical Excellence (NICE) or the US National Institute of Health (NIH) (ACOG, 2018; ADA, 2019; Blumer et al., 2013; Colagiuri et al., 2014; Vandorsten et al., 2013).

The criteria for the comprehensive screening and diagnosis of GDM used by the IADPSG, which include a lower threshold of the 75-g oral glucose tolerance test (OGTT) than previously globally used, have led to concerns about potential over-diagnosis of GDM, increased health care costs and even medicalisation of otherwise healthy pregnancies (Cundy, Ackermann, & Ryan, 2014; Meek, 2017). Hence, in 2015, the NICE proposed substantially different criteria for the diagnosis of GDM, with a higher fasting glucose value and a lower, two-hour value in the OGTT (NICE, 2015). According to these guidelines, GDM is diagnosed after one abnormal glucose concentration. However, its clinical significance for pregnancy outcomes remains unclear.

In Finland, GDM screening was limited to women with risk factors until 2008. However, up to one-half of women with GDM have been found to have no risk factors and thus go undiagnosed during risk factor-based screening (Pöyhönen-Alho, Teramo, Kaaja, & Hiilesmaa, 2005). When new Finnish Current Care Guidelines (CCGs) for screening and diagnosing GDM with different glucose thresholds in the OGTT were introduced in Finland in 2008, it was recommended, unlike previous policy, that all women except those with a very low GDM risk should be tested via a 75-g OGTT (Kaaja, 2013). This policy was known to increase the number of both screened women and women diagnosed with GDM, which was expected to present a challenge to the health care system.

The aim of the present study was to evaluate the effect of the shift from risk factor-based to comprehensive screening on the prevalence and maternal and neonatal outcomes of GDM pregnancies in Finland, and to compare pregnancy outcomes according to IADPSG and NICE GDM criteria. We also explored the relationship between the number of abnormal values in the OGTT and pregnancy and perinatal complications.

2 Review of the literature

2.1 Definition of GDM

In 1882, Duncan published an article about puerperal diabetes (Duncan, 1882). At the time, maternal mortality was as high as 60% among these pregnant women, and perinatal mortality was 47%. The diagnosis of diabetes was in those days mainly based on glucosuria (Hadden, 1998). The discovery of insulin in 1921 served as the cornerstone of diabetes treatment and also improved maternal survival.

The term ‘gestational diabetes’ was first used in 1957 by Carrington and colleagues (Carrington, Shuman, & Reardon, 1957). In 1964, O´Sullivan and Mahan created the classification of GDM (Hadden, 1998), which was based on blood glucose values in the three-hour, 100-g OGTT and predicted the future risk of developing diabetes; obstetric complications, however, did not receive any attention (O`Sullivan & Mahan, 1964). Later, it was shown that GDM was also associated with an increased rate of macrosomia and perinatal mortality (O'Sullivan, Charles, Mahan, & Dandrow, 1973; O'Sullivan, Gellis, Dandrow, & Tenney, 1966).

GDM was defined for the first time as ‘glucose intolerance with recognition of onset during pregnancy’ in the International Workshop-Conference on Gestational Diabetes in the 1980s (ADA, 1980). Carpenter and Coustan mathematically converted the original Somogyi-Nelson method-derived thresholds to glucose oxidase-derived plasma values and created new criteria for GDM (Carpenter & Coustan, 1982). The Fourth International Workshop-Conference on Gestational Diabetes applied the Carpenter-Coustan Criteria (CCC) to both three-hour, 100-g and two-hour, 75-g OGTTs (Metzger et al., 1998).

GDM has been further defined as any carbohydrate intolerance and/or hyperglycaemia with onset or first recognition during pregnancy (Metzger & Coustan, 1998). Currently, GDM has been described by the ADA as diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation (ADA, 2019).

2.2 Pathophysiology of GDM

2.2.1 Glucose metabolism in normoglycemic pregnancy

Hormones regulate metabolic changes in normal pregnancy to prepare the mother for pregnancy, labour and lactation, and to ensure the adequate transfer of nutrients to the foetus. It is normal that mothers' insulin resistance increases throughout pregnancy, and that gluconeogenesis from the liver enables the control of adequate fasting glucose levels (Catalano, Huston, Amini, & Kalhan, 1999). During normal early pregnancy, maternal fasting glucose levels decrease and then stabilise or begin to increase after 28 gestational weeks (Lain & Catalano, 2007). By the end of the third trimester, insulin sensitivity decreases by 50% and hepatic glucose production increases by 30% (Catalano et al., 1999). These changes are related to increasing insulin secretion by 200%. Other hormones are also responsible for pregnancy-related metabolic changes, like oestrogen, progesterone, cortisol, prolactin and glucagon (Di Cianni, Miccoli, Volpe, Lencioni, & Del Prato, 2003).

2.2.2 Glucose metabolism in GDM

GDM develops when the metabolic changes in normal pregnancy fail to offset increased insulin resistance and/or the defective function of pancreatic beta cells, resulting in hyperglycaemia. Women who develop GDM are already more insulin-resistant before pregnancy compared with normoglycemic pregnant women (Buchanan, Xiang, Kjos, & Watanabe, 2007; Catalano, Avallone, Drago, & Amini, 1993; Catalano et al., 1999).

Inadequate insulin secretion is most easily demonstrated in late pregnancy, when insulin requirements are uniformly high and differ only slightly between normal women and women with GDM (Buchanan et al., 2007). β-cell dysfunction seems to play a role in the development of hyperglycaemia during pregnancy compared to a non-pregnant state (Catalano et al., 1999). During pregnancy, hyperglycaemia appears when β-cells become too exhausted to produce enough insulin to overcome increasing insulin resistance caused by mainly placental hormones and adipose tissue.

Usually, GDM women are considered together, as a single group. However, GDM is a heterogenous disease, with hyperglycaemia resulting from either decreased insulin sensitivity (51%) or decreased insulin secretion (30%), or an overlap between these conditions (18%) (Powe et al., 2016). GDM women with

insulin sensitivity as the main problem appear to be at high risk for foetal macrosomia and GDM-associated adverse outcomes (Powe et al., 2016). Insufficient β-cell function in pregnancy can be a consequence of the same condition that results in hyperglycaemia in general: autoimmune diseases, monogenic causes and chronic insulin resistance due to various causes (Buchanan et al., 2007).

2.3 Screening and diagnosing GDM

2.3.1 Principles of disease screening

In 1968, the WHO published the book, *Principles and Practice of Screening for Disease*, the screening guidelines of which (Table 1) are still applied today (Wilson & Jungner, 1968).

Table 1. Wilson and Jungner criteria for disease screening.

No	Criteria
1	The condition should be an important health problem.
2	There should be a treatment for the condition.
3	Facilities for diagnosis and treatment should be available.
4	There should be a latent stage of the disease.
5	There should be a test or examination for the condition.
6	The test should be acceptable to the population.
7	The natural history of the disease should be adequately understood.
8	There should be an agreed policy on whom to treat.
9	The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole.
10	Case-finding should be a continuous process, not just a “once and for all” project.

Screenings to promote health have a long tradition in Finland, including breast and cervical cancer screening, and prenatal screening of chromosomal and structural abnormalities. Implementing a new national screening test demands a lot of preparatory work and the continuous evaluation of the health benefits, costs and societal impacts of screening. Some screenings, such as GDM screening, have been initiated by health care professionals without particular steering and evaluation. In these cases, the effectiveness of screening has also been assessed afterwards. There must be a balance between the advantages and disadvantages of the screenings, and

the implementation of and participation in them and, above all, their effectiveness at the population level must be shown (Sauni, 2014).

The purpose of screening is to identify asymptomatic individuals with a high probability of having or developing a specific disease. A diagnostic test can be administered to all individuals as a one-step process or a two-step process, in which the first step identifies individuals at increased risk for the disease so that, in step two, diagnostic testing can be limited to high-risk populations. The ideal screening test should have a high detection rate and a low false positive rate (Jørgensen, Hedley, Gjerris, & Christiansen, 2014). The benefits of the screening include decreasing harms that can be performed of missing the diagnoses of the screened disease or condition. For GDM, its diagnosis followed by appropriate counselling and therapy can decrease maternal and foetal morbidity, particularly macrosomia, shoulder dystocia and pre-eclampsia.

2.3.2 Screening of GDM

Although there is increasing awareness of the impact of GDM on maternal and foetal health, there is no global consensus concerning its screening policy and diagnostic criteria. In 1964, the diagnostic criteria of GDM were set according to their ability to identify mothers at risk of subsequent diabetes (O'Sullivan & Mahan, 1964). A two-step method for GDM screening was developed, which consisted of a 50-g glucose challenge test (GCT) followed by the measurement of the glucose level one hour later. If the glucose level exceeded a threshold level of 7.2 mmol/l, a second step involving a three-hour, 100-g OGTT was undertaken. The diagnostic cut-off values of the 100-g OGTT were 5.0, 9.1, 8.0 and 6.9 mmol/l at fasting, one hour, two hours and three hours, respectively. At least two abnormal values were needed to diagnosis GDM. During that time, whole venous blood was used instead of the venous plasma typically used today. These criteria aimed to identify women at risk of subsequent type II diabetes, as women with GDM had a 22.6% risk of developing type II diabetes in the eight years following pregnancy. The prevalence of GDM was around 2% at that time.

Glycated haemoglobin (HbA1c) in the second or third trimester has also been studied as a screening test for GDM in risk factor-based and universal screening. In three different studies, HbA1c thresholds of 5.0, 5.3, 5.5 and 7.5% were evaluated using different diagnostic criteria for GDM with no clear relationship between HbA1c level and GDM (Agarwal, Dhatt, Punnose, & Koster, 2005;

Agarwal, Hughes, Punnose, Ezimokhai, & Thomas, 2001; Rajput, Yogesh, Rajput, & Nanda, 2012).

In 2008, the multinational HAPO study examined associations between maternal glucose tolerance and neonatal outcomes in an unprecedentedly large sample of over 23 000 women (Metzger et al., 2008). The study showed a continuous relationship of maternal glucose to birth weight and macrosomia. As maternal glucose concentrations rise, the risk of macrosomia and other complications increases.

Based on the results of the HAPO study, the IADPSG published their guidelines in 2010 (Metzger et al., 2010). In their recommendations, the IADPSG set cut-off points for GDM whereby the key outcomes of the HAPO study (birth weight, cord C-peptide level, percent body fat above the 90th percentile) were increased by 1.75-fold compared to women with mean glucose concentrations for the population. For the first time, glucose thresholds for the diagnosis of GDM were based upon adverse perinatal outcome instead of future risk of type II diabetes.

After publishing the IADPSG criteria, many organisations' guidelines, including those of the ADA, the WHO and The International Federation of Gynecology and Obstetrics (FIGO), adopted these criteria in the screening and diagnosis of GDM (ADA, 2019; Metzger et al., 2010; WHO, 2014). However, several organisations, including the NICE, the ACOG Bulletin, the NIH and the Society of Obstetricians and Gynaecologists of Canada (SOCG), did not support the IADPSG criteria because of the alleged major increase in health care costs and resource allocation (ACOG, 2018; Berger et al., 2016; NICE, 2015; NIH, 2013). For example, the NICE proposed alternative criteria for the diagnosis of GDM, with a higher fasting glucose value and a lower, two-hour value than the values specified by the IADPSG (NICE, 2015).

2.3.3 Risk factor-based or universal screening?

GDM screening methods can involve a one-step approach with a two-hour, 75-g risk factor-based (NICE, 2015) or universal (IADPSG) (Metzger et al., 2010) OGTT. In risk-factor based screening, the most common risk factors are maternal age, overweightness or obesity, prior GDM, previous macrosomic offspring, multiparity, family history of diabetes, and high-risk ethnicity (Farrar, Simmonds, Bryant, Lawlor, et al., 2017; Pöyhönen-Alho et al., 2005; Saeedi, Hanson, Simmons, & Fadl, 2018).

Risk factor-based screening for GDM has been found to be poorly predictive of GDM (Pöyhönen-Alho et al., 2005; Saeedi et al., 2018). It has been shown that up to 40% of GDM cases would remain undiagnosed with risk factor-based screening compared to universal screening. In the Screening for Pregnancy Endpoints (SCOPE) retrospective study, 2 428 healthy nulliparous women with singleton pregnancies were recruited from Ireland and the UK (Murphy et al., 2016). Compliance with risk factor-based screening for GDM was assessed in terms of the prevalence of risk factors and GDM among the study participants. The results showed poor compliance with risk factor-based screening for GDM. According to NICE guidelines, 27% (650) of the women had one or more identifiable risk factors as defined by the NICE, yet only 60.8% of these women were actually screened. Additionally, 261 (14.6%) women had no risk factors but were still screened for GDM. Of those who did not have any risk factor, 7.7% (20) were diagnosed with GDM. In conclusion, risk factor-based screening is currently described in the literature as controversial, inadequate and inconsistent (Avalos, Owens, & Dunne, 2013; Dahanayaka et al., 2012; Murphy et al., 2016; Reece, Leguizamón, & Wiznitzer, 2009).

Screening guidelines vary globally from no routine to universal screening, in which all pregnant women undergo screening. In Finland, GDM screening was limited to women with risk factors until 2008. However, up to one-half of women with GDM have been/were found to have no risk factors and to thus go undiagnosed during risk factor-based screening (Pöyhönen-Alho et al., 2005). When new CCGs to screen and diagnose GDM were introduced in Finland in 2008 (and updated in 2013), it was recommended, in contrast to previous policy, that all women except those with a very low GDM risk should be tested via a 75-g OGTT (Kaaja, 2013).

2.3.4 Glucose threshold for diagnosis of GDM

GDM represents one part of a continuum of maternal hyperglycaemia (Metzger et al., 2008). There are no unanimously accepted international criteria for diagnosis or screening, and existing guidelines may vary considerably even between high-income countries (Farrar, Simmonds, Bryant, Lawlor, et al., 2017). Glucose thresholds and test types are presented in Table 2. The risk of adverse pregnancy outcomes increases in tandem with increasing glucose values in OGTTs without any clear thresholds (Metzger et al., 2008).

Table 2. Plasma glucose thresholds for the diagnosis of GDM according to different guidelines.

Organisation	Year	Test	Fasting (mmol/l)	1-hour (mmol/l)	2-hour (mmol/l)	3-hour (mmol/l)
O´Sullivan[2]	1964	100-g OGTT	5.0[1]	9.2[1]	8.1[1]	6.9[1]
WHO[3]	1999	75-g OGTT	7.0	-	7.8	-
ADA[2]	2003	75-g OGTT	5.3	10.0	8.6	-
Finnish CCG[3]	2008	75-g OGTT	5.3	10.0	8.6	-
IADPSG[3]	2010	75-g OGTT	5.1	10.0	8.5	-
WHO[3]	2014	75-g OGTT	5.1	10.0	8.5	-
NICE[3]	2015	75-g OGTT	5.6	-	7.8	-

[1] Values measured in whole blood, [2] two or more values required for GDM diagnosis, [3] one value required for GDM diagnosis.

The one-step, two-hour, 75-g OGTT is widely used, even though the 100-g OGTT has been popular in the US for many years (Meek, 2017).

2.3.5 Number of abnormal values in the OGTT

Most of the screening guidelines for GDM require only one abnormal value in the OGTT for the diagnosis of GDM (Meek, 2017). However, some institutes, like the ACOG, confirm GDM diagnosis when at least two glucose values in the OGTT are abnormal (ACOG, 2018).

It has also been debated whether women with one abnormal value in the OGTT are at increased risk for adverse pregnancy outcomes (Roeckner, Sanchez-Ramos, Jijon-Knupp, & Kaunitz, 2016). In the meta-analysis of this issue, women with only one abnormal value in the two-step, three-hour, 100-g OGTT had a significantly increased risk for macrosomia, neonatal hypoglycaemia, caesarean section, pregnancy-induced hypertension, neonatal respiratory distress syndrome, neonatal intensive care submission and an Apgar score < 7 at five minutes. However, these women were not diagnosed with GDM and hence were not treated.

The HAPO study found a 17.8% prevalence of GDM, and approximately 70% of these women had only one abnormal value in the 75-g OGTT (Sacks et al., 2012). Despite this, the authors of the study found a linear relationship between maternal glucose concentrations and adverse pregnancy outcomes.

2.3.6 IADPSG

By using the data from the HAPO study (Metzger et al., 2008), the IADPSG was first employed to define diagnostic criteria to predict neonatal outcomes. The IADPSG's diagnostic cut-off values were calculated based on the HAPO results as the glucose values at which the odds for birth weight, primary caesarean section delivery, clinically defined neonatal hypoglycaemia, cord C-peptide and percent body fat of the newborn above the 90th percentile reached 1.75 times the estimated odds of these outcomes above the mean glucose values (Metzger et al., 2010; Metzger et al., 2008). However, these IADPSG guidelines do not take into account important clinical maternal outcomes, such as hypertensive disorders in pregnancy or the requirement for induction of delivery, which are the key clinical criteria of concern to clinicians.

The WHO and the ADA have adopted the IADPSG criteria for gestational diabetes, and a large number of other countries worldwide currently use these criteria (ADA, 2019; WHO, 2014). Several studies have shown that the use of IADPSG criteria is associated with increased GDM prevalence but also with improved pregnancy outcomes, presumably by permitting the treatment of a greater number of women at risk of pregnancy complications (Black, Sacks, Xiang, & Lawrence, 2010; Djelmis et al., 2016; Duran et al., 2014; Meek, Lewis, Patient, Murphy, & Simmons, 2015). The prevalence of gestational hypertension, prematurity and caesarean sections, as well as the prevalence of large for gestational age (LGA) and small for gestational age (SGA) infants, were reduced, and fewer newborns presented one-minute Apgar scores < 7.

Using the IADPG criteria, it is recommended that all pregnant women should be screened with a 75-g OGTT at 24–28 gestational weeks. The glucose thresholds for diagnosis of GDM are fasting ≥ 5.1 mmol/l, one-hour ≥ 10.0 mmol/l and two-hour ≥ 8.5 mmol/l.

2.3.7 NICE

The UK NICE proposed alternative criteria for the diagnosis of GDM in 2015 (NICE, 2015). Previous guidelines in 2008 recommended a fasting glucose threshold of 7.0 mmol/l. After the IADPSG criteria, the NICE recommended a new set of diagnostic criteria for GDM based upon cost-effectiveness measures and the standard costs of complications. According to 2015 NICE guidelines, the cut-off

values for GDM in the 75-g OGTT are fasting glucose ≥ 5.6 mmol/l and a two-hour value ≥ 7.8 mmol/l (one-hour value not included).

The NICE recommends a risk factor-based screening for GDM. Women with obesity, previous GDM, previous macrosomic offspring (> 4.5 kg), a first-degree relative with diabetes, or an ethnic origin associated with a high risk of diabetes should be tested with a 75-g OGTT as soon as possible, as well as a further OGTT at 24–28 gestational weeks if the results of the first OGTT are normal (NICE, 2015).

The NICE 2015 criteria have faced criticism because these thresholds were derived theoretically from a few studies reporting the cost-effectiveness of different approaches to the diagnosis and screening of GDM (Meek, 2017) In addition, important adverse outcomes, such as macrosomia or long-term risks, were not included in the analysis.

2.3.8 GDM screening in Finland

Until 2008, GDM risk factor-based screening was used in Finland (risk factors are shown in Table 3), and the diagnostic values and the number of abnormal values needed for diagnosis of GDM varied between hospital districts (Teramo, 2006). According to the national CCGs launched in 2008 and updated in 2013, it was recommended that all women except those with a very low risk of GDM be screened for GDM by comprehensive screening (Kaaja, 2013) (Table 3). Thereafter, for the first time, consistent national guidelines for the screening and treatment of women with GDM in both primary and special health care were implemented.

In both time periods, screening for GDM was performed and diagnosis was made via a standard two-hour, 75-g OGTT with samples obtained at baseline after overnight fasting and at one and two hours after the glucose load. The test was mainly performed between the 24th and 28th gestational week. In both screening policies, it was recommended that an OGTT be performed for the first time between the 12th and 16th gestational week for high-risk groups (before 2008: prior GDM; after 2008: prior GDM, BMI > 35, polycystic ovary syndrome with insulin resistance). If this test was normal, then it would be repeated between the 24th and 28th gestational week.

In both time periods, screening for GDM was performed and diagnosis was made via a standard two-hour, 75-g OGTT with samples obtained at baseline after overnight fasting and at one and two hours after the glucose load. The test was mainly performed between the 24th and 28th gestational week. In both screening policies, it was recommended that an OGTT be performed for the first time between

the 12th and 16th gestational week for high-risk groups (before 2008: prior GDM; after 2008: prior GDM, BMI > 35, polycystic ovary syndrome with insulin resistance). If this test was normal, then it would be repeated between the 24th and 28th gestational week.

Table 3. Finnish GDM screening guidelines.

Screening method	Indication for OGTT
Risk factor-based screening	Risk factor-based screening for those with: • Prior GDM • Overweight (BMI > 25 kg/m^2) • Age over 40 years • Previous macrosomic offspring (4 500 g or more) • Suspected macrosomia in the current pregnancy
Comprehensive screening	All women except those with very low GDM risk: • Primiparous: age < 25 years, BMI < 25 kg/m^2, no family history of diabetes • Multiparous: age < 40 years, BMI < 25 kg/m^2, no previous macrosomic offspring

The OGTT test is mainly performed between the 24th and 28th week of gestation. In both screening policies, an OGTT is recommended for the first time between the 12th and 16th gestational week for high-risk groups (before 2008: prior GDM; after 2008: prior GDM, BMI > 35, polycystic ovary syndrome with insulin resistance) and, if this test is normal, a repeat OGTT at 24–28 gestational weeks.

In both time periods, screening for GDM was performed and diagnosis was made via a standard two-hour, 75-g OGTT with samples obtained at baseline after overnight fasting and at one and two hours after the glucose load. The test was mainly performed between the 24th and 28th gestational week. In both screening policies, it was recommended that an OGTT be performed for the first time between the 12th and 16th gestational week for high-risk groups (before 2008: prior GDM; after 2008: prior GDM, BMI > 35, polycystic ovary syndrome with insulin resistance). If this test was normal, then it would be repeated between the 24th and 28th gestational week.

GDM was diagnosed during both screening periods if the venous plasma glucose concentration was 5.3 mmol/l or more at baseline, 10.0 mmol/l or more at one hour, or 8.6 mmol/l or more at two hours after the glucose load. During both periods, the diagnosis of GDM was based on one or more abnormal values in the OGTT.

According to the national guidelines, women with one or more abnormal OGTT values received individualised dietary and lifestyle counselling in maternal

welfare clinics and thereafter began glucose self-monitoring. Insulin therapy at the delivery hospital was considered if self-monitored plasma glucose concentrations repeatedly exceeded the target levels (< 5.5 mmol/l fasting < 7.8 mmol/l one-hour postprandial) despite the dietary intervention. The use of oral glycaemic agents was occasional and not primarily recommended by the guidelines (Kaaja, 2013).

2.4 Prevalence

The prevalence of GDM varies worldwide, ranging from 1% to 31.5% of all pregnant women (Zhu & Zhang, 2016). It recurs in 30–84% of women, and it is increasing in prevalence worldwide (Behboudi-Gandevani, Amiri, Bidhendi Yarandi, & Ramezani Tehrani, 2019; Eades, Cameron, & Evans, 2017; Hildén, Magnuson, Hanson, Simmons, & Fadl, 2020; McIntyre et al., 2018). When using the IADPSG criteria, the frequency of GDM has varied from 9% to 26% (Lapolla & Metzger, 2018). The prevalence of GDM also varies among racial and ethnic groups, with higher rates in African American, Hispanic American, Native American, Pacific Islander, and South or East Asian women than in white women (Ferrara, 2007; Yuen, Wong, & Simmons, 2018).

Prevalence is difficult to estimate as rates vary from study to study due to a lack of accepted diagnostic criteria and differences in screening procedures. An increase in prevalence has been found with increasing maternal age and depending on the year of data collection. Diagnostic criteria, country and gestational week at testing have also been found to have an effect on GDM prevalence (Eades et al., 2017).

The large variation in estimated GDM prevalence is due to different screening strategies, and direct comparisons between countries is also difficult because many countries do not perform systematic screening for GDM, and practices often diverge from guidelines. For example, among Nordic countries, Sweden has the most restrictive screening for GDM, resulting in a very low overall prevalence of 1% (Hildén et al., 2020).

In Finland, the number of deliveries has been in continuous decline since 2011; and in 2019, 45 265 children were born. After Finland's publication of CCGs in 2008, the number of OGTTs performed from year to year has increased. In addition, the prevalence of GDM is continuously rising, a trend which appears to be a global phenomenon.

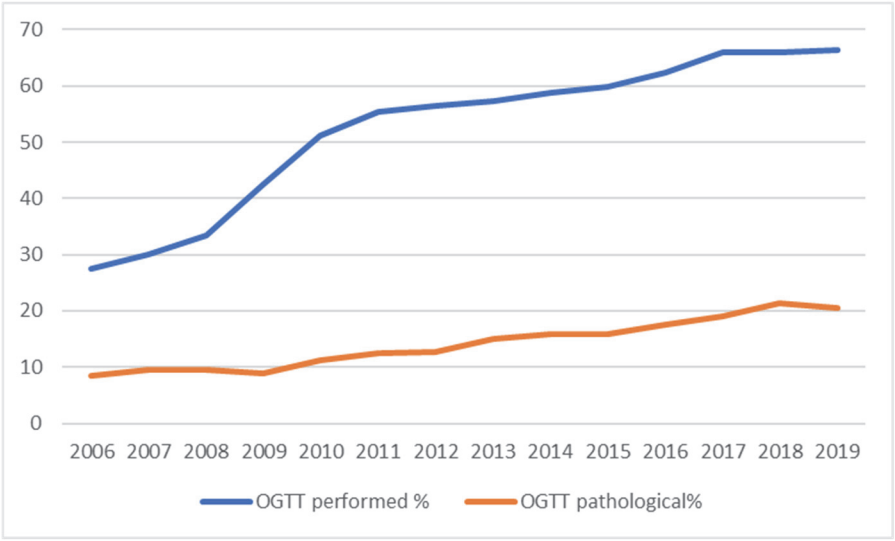

Fig. 1. The rate of performed OGTTs and pathological OGTTs in Finland in 2006 to 2019. Unpublished data from the Finnish Medical Birth Register, Finnish Institute for Health and Welfare (THL).

2.5 Risk factors of GDM

The aetiology of GDM is multifactorial. Several clear risk factors can combine to initiate the onset of GDM. Increasing age, overweightness or obesity, family history of diabetes, ethnicity and previous GDM are proposed major risk factors of GDM (Chen et al., 2015; McIntyre et al., 2019; Yuen et al., 2018; C. Zhang, Rawal, & Chong, 2016). The GDM risk increases 4% per unit of increase in BMI (Najafi et al., 2019). Gestational weight gain above the local recommendations has been associated with a lower risk of infants being small for gestational age and preterm birth, and a higher risk for macrosomia and caesarean section, but also with higher risk of adverse maternal and infant outcomes (Goldstein et al., 2017). Specific high-risk ethnicities include Hispanics, Africans, Native Americans, South and East Asians, Pacific Islanders and Indigenous Australians (Yuen et al., 2018). Also, physical inactivity and diet quality (frequent consumption of potatoes, meat/processed meats and protein derived from animal sources) are associated with an increased risk of GDM (Mijatovic-Vukas et al., 2018).

Genetic factors are also implicated in the aetiology of GDM. A number of candidate genes have been identified, but knowledge from genome-wide

association studies on genetic factors of GDM is still limited. Genetic predisposition to GDM overlaps at least partially with type II diabetes (Wu, Cui, Tam, Ma, & Wang, 2016). Maternal hypothyroidism is associated with several pregnancy and perinatal complications, including GDM (Turunen et al., 2019). Polycystic ovary syndrome (PCOS) has been considered to be a risk factor for GDM, but the relevant data are inconclusive. Pregnancies in those with PCOS are characterised by factors known to increase the prevalence of GDM, especially high BMI and fertility treatment; as such, PCOS, unlike obesity, may not be an individual risk factor for GDM (Mustaniemi et al., 2018; Palm et al., 2018). There may also be an association between low vitamin D levels in the blood and GDM, as low blood vitamin D increases GDM risk, whereas vitamin D supplementation may ameliorate glycaemic control in women with GDM, but the study results are slightly conflicting (Ojo, Weldon, Thompson, & Vargo, 2019; Y. Zhang, Gong, Xue, Xiong, & Cheng, 2018).

2.6 Treatment of GDM

The main goal of GDM treatment is to maintain normoglycemia and thereby reduce the adverse pregnancy outcomes of GDM. Traditionally, treatment of GDM has been based on diet and lifestyle interventions, such as exercising, but if normoglycemia is still not achieved, then medical treatment is offered. Self-monitoring of glucose levels helps to reach and maintain normoglycemia. The recommendations of target levels also vary between the guidelines (Table 4).

Table 4. Target glucose levels in GDM treatment according to the selected guidelines.

Guideline	Year	Capillary plasma glucose level (mmol/l)		
		Fasting	1-h postbrandial	2-h postbrandial
Finnish CCG[1]	2013	< 5.5	< 7.8	-
NICE[2]	2015	< 5.3	< 7.8	< 6.4
FIGO[3]	2015	< 5.3	< 7.8	< 6.8
ACOG[4]	2018	< 5.3	< 7.8	< 6.7
ADA[5]	2019	< 5.3	< 7.8	< 6.7

[1] Current Care Guidelines, [2] The National Institute for Health and Care Excellence (UK), [3] The International Federation of Gynecology and Obstetrics, [4] The American College of Obstetricians and Gynecologists, [5] American Diabetes Association.

2.6.1 Effect of GDM treatment on pregnancy outcome

The goal of GDM treatment is to normalise maternal glycaemic levels; an effective treatment is known to reduce adverse pregnancy outcomes (Crowther et al., 2005; Landon et al., 2009). Euglycemia reduces the need for pharmacotherapy and prevents excessive weight gain and adverse pregnancy outcomes, such as macrosomia of the foetus. In previous studies from Sweden of women with marked hyperglycaemia (a 75-g OGTT 9.0–11.0 mmol/l, two-hour level; capillary whole blood), the risk of LGA infants (> mean + 2 SD) was found to be four- to seven-fold (nontreated) (Fadl et al., 2015; Fadl, Ostlund, Magnuson, & Hanson, 2010; Ostlund et al., 2003). Hypoglycaemia of the mother during pregnancy is more typical when using stricter target glucose levels, but severe hypoglycaemia of the mother is a rare event (Fadl et al., 2015).

Two large intervention studies demonstrated that the treatment of even mild GDM reduces perinatal complications, such as macrosomia, caesarean section and neonatal hypoglycaemia (Crowther et al., 2005; Landon et al., 2009). In a multicentre randomised controlled trial (RCT), mild GDM was defined as a normal fasting glucose < 95 mg/dl/5.3 mmol/l but with two or more values exceeding the postbrandial thresholds of the Carpenter-Coustan criteria after a 100-g, three-hour OGTT, which is a commonly used metric in the US (Landon et al., 2009). Women were assigned to receive formal nutrition counselling, diet therapy and insulin if required (treatment group) or usual prenatal care (control group). The results showed that treating mild GDM resulted in reduced risk of foetal overgrowth, shoulder dystocia, caesarean delivery and hypertensive disorders.

In another RCT from Crowther et al. with a group called ACHOIS (Australian Carbohydrate Intolerance Study in Pregnant Women), women with 'glucose intolerance of pregnancy' according to pre-1998 WHO criteria (fasting glucose < 7.8 mmol/l and a two-hour, 75-g OGTT between 7.8 mmol/l and 11.1 mmol/l) were randomised into treatment vs. no treatment groups (Crowther et al., 2005). The results showed that treating these women with GDM with dietary advice, glucose monitoring and insulin if necessary reduced serious perinatal morbidities, including neonatal death, shoulder dystocia, bone fracture and brachial nerve palsy.

In a study from a Canadian centre (Nguyen, Yang, Mahone, & Godbout, 2016), which is currently using even stricter GDM diagnostic criteria than stipulated by the IADPSG, it was found that milder forms of hyperglycaemia that would not be identified by IADPSG guidelines may benefit from treatment. Their findings also

suggest a continuous association between adverse outcomes and maternal hyperglycaemia.

2.6.2 Lifestyle treatment

Dietary treatment and exercise are the cornerstone of GDM treatment (Brown et al., 2017). Carbohydrates are the main source affecting glucose levels, and both the type and amount of carbohydrates are important. According to the Finland CCGs, equal distribution of carbohydrates throughout the day, and restriction to less than 40–50% of energy, are recommended (Kaaja, 2013). Fat consumption should account for 30–40% of energy intake, and polyunsaturated fatty acids should account for two-thirds of energy intake. Recommendations for gestational weight gain depend on the pre-pregnancy BMI. Physical exercise is generally recommended as part of the lifestyle advice. Low- to moderate-intensity training influences glucose levels and is safe for all pregnant women without complications of pregnancy – for example, pre-eclampsia or SGA. For patients who fail to achieve the target level of glycaemic control, pharmacologic therapy is considered (Langer, 2018).

2.6.3 Pharmacologic treatment

The standard pharmacotherapy for GDM, if adequate glucose target levels in self-monitoring are not achieved, is insulin (Balsells et al., 2015). The prevalence of insulin therapy among GDM mothers has varied globally from 10.8% to 35% (Fadl et al., 2015; Meshel et al., 2016). Insulin use is more common among pregnant women diagnosed with GDM early on in their pregnancy compared to women with late-onset GDM (Immanuel & Simmons, 2017). Also, prior GDM, the number of abnormal values in the OGTT, family history of diabetes, maternal age > 30 years and pre-pregnancy BMI > 30 kg/m^2 have been reported to be associated with the need for insulin treatment (Meshel et al., 2016; Sapienza, Francisco, Trindade, & Zugaib, 2010).

Unlike oral glucose agents, insulin does not cross the placenta at a measurable level (Dugan & Ma Crawford, 2019; Langer, 2018). Unlike insulin, the commonly used oral glucose agent metformin crosses the placenta and is present at clinically relevant concentrations in foetal and placental tissues (50–100% of maternal concentrations) (Tarry-Adkins, Aiken, & Ozanne, 2019). Traditionally, neutral protamine hagedorn (NPH) insulin has been used as a cornerstone of insulin

treatment in combination with short-acting insulin for meals. Insulin analogues lispro, aspart, detemir and glargine also appear to be effective and safe for the treatment of GDM (Lepercq et al., 2012; Mathiesen et al., 2012; Nørgaard, Sukumar, Rafnsson, & Saravanan, 2018).

Oral drugs for GDM treatment have been thought to be a better alternative to insulin due to their easier administration, lower cost and better acceptance. Glibenclamide was considered to be a promising drug around 10 years ago, especially in the US, where it replaced insulin as the more common pharmacotherapy for GDM (Camelo Castillo et al., 2014). Later, however, it was found to be worse for neonatal outcomes, leading to higher rates of respiratory distress syndrome, hypoglycaemia, macrosomia and birth injury with glibenclamide treatment compared to insulin (Camelo Castillo et al., 2015; L. Guo et al., 2019). According to these study results, glibenclamide should not be used for the treatment of women with GDM if metformin or insulin is available (Balsells et al., 2015).

In 2017, the ACOG recommended the continued use of insulin as a first-line therapy, and metformin as a reasonable second-line choice (ACOG, 2018). In a Finnish RCT of 100 women, metformin treatment was not associated with an increased risk of pregnancy or neonatal complications compared with insulin treatment (Ijäs et al., 2011). Also, network meta-analyses have suggested that metformin has the highest probability of being the most effective treatment to reduce the risk of the most adverse outcomes compared to insulin (Farrar, Simmonds, Bryant, Sheldon, et al., 2017). However, 32–46% of metformin-treated women have needed additional insulin treatment (Farrar, Simmonds, Bryant, Sheldon, et al., 2017; Ijäs et al., 2011; Rowan, Hague, Gao, Battin, & Moore, 2008). This need for additional insulin was associated with maternal obesity, an earlier need during pregnancy for pharmacotherapy and fasting hyperglycaemia in the 75-g OGTT (Ijäs et al., 2011). In addition, the side effects of treatment (mainly gastrointestinal) with metformin are more common than those of insulin, and consequently a higher rate of treatment failure can be attributed to metformin treatment (Balsells et al., 2015).

In the literature, it has been reported that thousands of women have been treated with oral glucose agents during pregnancy with no teratogenic effects on the foetus. Following intrauterine exposure to metformin for the treatment of maternal GDM, neonates are significantly smaller than neonates whose mothers were treated with insulin during pregnancy (Ijäs, Vääräsmäki, Saarela, Keravuo, & Raudaskoski, 2015; Tarry-Adkins et al., 2019). Despite lower average birth weight, metformin-

exposed children appear to be heavier until nine years of age compared to children whose mothers were treated with insulin (Ijäs et al., 2015; Tarry-Adkins et al., 2019). Low birth weight and postnatal catch-up growth have also been reported to be associated with adverse long-term cardio-metabolic outcomes (Tarry-Adkins et al., 2019).

2.7 Consequences of GDM

Maternal genetic predisposition coupled with environmental and fetoplacental factors initiates a chain of events affecting both mother and foetus. The increase in plasma glucose effects a significant risk of complications to the mother, the foetus and the newborn (Di Cianni et al., 2003). The gradient between maternal and foetal glucose levels affects the passive transportation of high maternal glucose to the foetus through the placenta (Desoye & van Poppel, 2015).

2.7.1 Mother

Short-term

GDM exposes mothers to several complications during pregnancy and labour. There is a clear association between GDM and pre-eclampsia (Ostlund, Haglund, & Hanson, 2004; Yogev, Xenakis, & Langer, 2004). Obesity is a major confounding factor but does not explain the total excess risk for pre-eclampsia among GDM women (Ostlund et al., 2004). Both GDM and obesity are independently associated with adverse pregnancy outcomes, but their combination has a greater impact than either condition alone (Ijäs et al., 2019). The pre-eclampsia risk is 2.3 times higher in GDM women (Yogev et al., 2004).

Many short-term consequences of GDM are associated with accelerated foetal growth and macrosomia, which is in turn associated with greater risk for delivery induction, preterm delivery and maternal birth canal trauma, such as vaginal instrumental deliveries, vaginal tears, external and internal sphincter ruptures, and increased rate of caesarean section (Catalano et al., 2012; Kong, Nilsson, Gissler, & Lavebratt, 2019; Landon et al., 2011). Risk ratios for these adverse pregnancy outcomes vary according to the diagnostic criteria used, i.e. WHO 1999 or IADPSG criteria, but there are no similar studies about the NICE (Table 5).

Table 5. Relative risks for pregnancy and perinatal outcomes in untreated women according to the different GDM screening and diagnostic criteria based on the 75-g OGTT as a diagnostic test.

Outcome	WHO 1999[1]	IADPSG[2]
LGA[3]	1.53 (1.39–1.69)	1.73 (1.28–2.35)
Pre-eclampsia	1.69 (1.31–2.18)	1.71 (1.38–2.13)
Caesarean section	1.37 (1.24–1.51)	1.23 (1.01–1.51)

[1] WHO 1999 diagnostic criteria for GDM: fasting ≥ 7.0 mmol/l, 2h ≥ 7.8 mmol/l, [2] IADPSG diagnostic criteria for GDM: fasting ≥ 5.1 mmol/l, 1h ≥ 10.0 mmol/l, 2h ≥ 8.5 mmol/l, [3] as defined by the authors (Wendland et al., 2012).

Long-term

GDM is frequently the first manifestation of increased risk of type II diabetes, as up to two-thirds of women with a history of GDM are estimated to develop subsequent type II diabetes in future years (T2DM) (Ferrara, 2007; Li et al., 2020; Vounzoulaki et al., 2020). In a recent follow-up study of HAPO mothers and their offspring, GDM with the IADPSG criteria was significantly associated with a higher maternal risk for a glucose metabolism disorder over 11.4 years (W. L. Lowe, Jr. et al., 2018). Among GDM mothers, 52.2% developed a glucose metabolism disorder vs. 20.1% of mothers without GDM, odds ratio (OR) 3.44 (95% CI 2.85 to 4.14). The severity of GDM is associated with future diabetes risk. The main factors related to diabetes risk are medically treated or early diagnosed GDM, higher concentrations in HbA1C during pregnancy, multiparity, hypertensive disorders during pregnancy, PCOS and preterm delivery (Hakkarainen et al., 2015; Rayanagoudar et al., 2016).

Women with a history of GDM also have an increased risk of metabolic syndromes and a two-fold higher risk of cardiovascular disease (Ijäs et al., 2013; Kramer et al., 2019; Pirkola, Pouta, Bloigu, Miettola, et al., 2010). The long-term risk for cardiovascular disease in the case of those diagnosed with GDM according to previous WHO criteria (two-hour plasma glucose ≥ 7.8 mmol/l) was higher compared to those diagnosed by the IADPSG criteria (fasting plasma glucose ≥ 5.1 mmol/l, one-hour ≥ 10.0 mmol/l, two-hour ≥ 8.5 mmol/l) (Lekva et al., 2015).

Due to the higher risk for type II diabetes, metabolic syndromes and cardiovascular diseases, many guidelines recommend an OGTT and a lipid profile check postpartum according to the individual risk estimate every 1–3 years (ADA,

2019; Kaaja, 2013). Breastfeeding and avoiding obesity are also recommended to avoid or delay the development of type II diabetes (Bajaj et al., 2017; Kaaja, 2013).

2.7.2 Offspring

Short-term

Exposure in utero to maternal diabetes can have several short-term consequences due mainly to maternal hyperglycaemia and consequent foetal hyperinsulinemia. Current evidence also supports the hypothesis that adult health and disease have developmental origins, and that disorders in early-life environments prompt metabolic imprinting that results in a greater risk of negative metabolic outcomes later in life. (Burlina, Dalfrà, & Lapolla, 2019) The most important short-term aim for GDM treatment is to avoid foetal macrosomia, which is associated with several foetal complications, such as birth traumas due to shoulder dystocia, respiratory distress syndrome and perinatal asphyxia (Billionnet et al., 2017). GDM is also associated with an increased risk for preterm birth, hypoglycaemia and hyperbilirubinemia (Farrar, Simmonds, Bryant, Sheldon, et al., 2017; Metzger et al., 2008; Voormolen et al., 2018).

Long-term

In addition to short-term consequences, children born from GDM pregnancies also have an increased risk for later type II diabetes, metabolic syndrome, cardiovascular disease and cognitive decline (Kaseva et al., 2018; Kaseva et al., 2019; Metzger et al., 2008; Pirkola, Pouta, Bloigu, Hartikainen, et al., 2010; Wan, Zhang, Li, Luan, & Liu, 2018). Across the maternal glucose spectrum, exposure to higher levels of glucose in utero is significantly associated with childhood glucose and insulin resistance independent of maternal and childhood BMI and family history of diabetes (Scholtens et al., 2019). The offspring of mothers with GDM have a four- to eight-fold increased risk of prediabetes and type II diabetes than non-GDM mothers' offspring, with a 20-year cumulative incidence rate of up to 20% (Clausen et al., 2008). GDM has also been associated with an increased risk of hypertension in offspring (Lu et al., 2019).

2.8 Prevention

2.8.1 Prevention of GDM

Numerous studies have evaluated intervention strategies for GDM prevention. In a review of GDM prevention studies from 2015, an effect of these intervention strategies on the incidence of GDM was not found (Bain et al., 2015). However, in 2017, an updated Cochrane review including 23 studies found a moderate effect of lifestyle interventions, such as health diet and physical activity, on reducing GDM, preterm birth and gestational weight gain (Shepherd et al., 2017). Another systematic review by Song and colleagues included 29 trials and found similar effects on reducing the incidence of GDM (Song, Li, Leng, Ma, & Yang, 2016).

Among individual studies, the Australian LIMIT study has been the largest, with 2 152 overweight or obese women (Dodd et al., 2014). The intervention did not influence maternal outcomes, but it did reduce the number of newborns weighing over 4 000 g in this study. In the European collaboration study DALI (Vitamin D and Lifestyle Intervention for GDM prevention), which also included obese women (n = 436) and compared the effect of diet, exercise or combined lifestyle intervention (Simmons et al., 2017), diet intervention improved healthy eating, exercise intervention resulted in increased physical activity, and combined intervention in addition to lifestyle improvement reduced gestational weight gain. In relation to GDM prevention, however, all interventions were ineffective.

Notwithstanding, some successful intervention studies on the prevention of GDM have been conducted. The randomised controlled study RADIEL from Finland showed a 36% decrease in GDM incidence (Koivusalo et al., 2016). This study recruited women with risk factors including obesity and a history of previous GDM. Women in the intervention group increased their physical activity during leisure time and also improved their dietary quality compared with women in the control group. The incidence of GDM was 13.9% in the intervention group and 21.6% in the control group (95% CI 0.40–0.98%)

2.8.2 Prevention of type II diabetes

As a risk factor for type II diabetes, GDM can also be seen as a window of opportunity. Although it is clear that women with GDM are at increased risk of type II diabetes, many studies have shown that by making lifestyle changes, these women can reduce their risk of diabetes or prevent or delay the progression to type

II diabetes (Aroda et al., 2015; Ferrara et al., 2011; J. Guo, Chen, Whittemore, & Whitaker, 2016). While the prevalence of type II diabetes is increasing rapidly, a diagnosis of GDM represents an opportunity for early intervention to reduce the burden of type II diabetes.

Pregnancy is often considered to be an optimal period for implementing lifestyle changes, such as weight control, due to greater motivation on the part of pregnant women. The Danish Lifestyle in Pregnancy study focused on obese women with the aim of promoting weight control during pregnancy to reduce gestational weight gain. And yet, no effect was found on postpartum weight retention six months after delivery (Vinter, Jensen, Ovesen, Beck-Nielsen, & Jørgensen, 2011). Similarly, the Norwegian Fit-for-Delivery study managed to decrease gestational weight gain, but again no effect on postpartum weight was found (Sagedal et al., 2017). The longest follow-up results came from the Finnish study, Nelli, on women at high risk of GDM (Luoto & Kinnunen, 2011). In this study, there were no effects on maternal metabolic outcomes seven years after delivery either. However, in other Finnish study, RADIEL, on the effects of a lifestyle intervention during pregnancy and first postpartum year, a lifestyle intervention successfully reduced the incidence of impaired glucose regulation postpartum (Huvinen et al., 2018).

3 Aims of the study

The overall aim of the thesis was to assess the effect of the change in the GDM screening policy on the prevalence and adverse pregnancy and perinatal outcomes between different screening strategies.

More specifically, the study objectives were:

I To evaluate the effect of the change in the gestational diabetes screening policy in Finland from risk factor-based to comprehensive screening on the prevalence and type of GDM and the characteristics of GDM pregnancies. (Study I).

II To evaluate the effect of the change in the national gestational diabetes screening policy on perinatal outcomes, and how this change of policy affected the need for care at a neonatal ward. (Study II).

III To evaluate the impact of two different international screening criteria for GDM, the IADPSG and the NICE, on the prevalence of GDM and perinatal outcomes in Finland. (Study III).

IV To assess the effect of the severity of glucose disturbance defined by the number of abnormal values in an OGTT for pregnancy and perinatal outcomes. (Study IV).

4 Study population and methods

4.1 Study data

The data from all studies included in this thesis were based on the Finnish Medical Birth Register (MBR). Studies I and II were based only on the MBR data, whereas Studies III and IV were in addition based on the register-based arm of the Finnish Gestational Diabetes study (FinnGeDi) from the MBR supplemented by numerical OGTT data. Detailed descriptions of the data used are presented below.

4.1.1 The Finnish Medical Birth Register (MBR)

The MBR includes data on the course and complications of pregnancy and delivery and on the perinatal health of newborns. All pregnancies resulting in a live-born infant or stillbirth at ≥ 22 gestational weeks (gw) or weighing ≥ 500 g are reported to the MBR. For each delivery in Finland, a structured form for the MBR is completed by the delivery hospital within seven days after delivery. Since 2004, the MBR has included information on whether an OGTT was performed, whether it was abnormal, and whether insulin treatment was initiated during pregnancy.

The data are checked at the MBR, and the hospitals are contacted to correct missing or potentially incorrect information. Data are completed by linkage to the Central Population Register on live births and to cause-of-death data compiled by Statistics Finland on stillbirths and early neonatal deaths. The coverage of the register is complete and, in general, the quality of the data is high (Gissler & Shelley, 2002; Gissler et al., 1995; Keikkala et al., 2020).

4.1.2 The Finnish Gestational Diabetes (FinnGeDi) study

The FinnGeDi study comprised population-based prospective cohorts (Keikkala et al., 2020). It was established after the national Finnish CCGs were introduced in 2008, when risk factor-based GDM screening was replaced by comprehensive screening (Current Care Guideline Gestational diabetes).

To approach the questions from different perspectives, two arms were included in the FinnGeDi: the case-control arm, including questionnaires, hospital and antenatal data, MBR data and a DNA sample from the pregnant woman, her child and the child's father; and the register-based arm, utilising the unique resource of

Finnish comprehensive national registers. The aims of the cohorts were to identify potential genetic and epigenetic biomarkers of GDM and to assess putative risk factors and clinical characteristics of GDM to enable the characterisation of clinically identifiable, mechanistically meaningful subgroups of the disorder. The short- and long-term health of the mother and child were followed to evaluate the consequences of GDM. Also, the cohorts were designed to assess the incidence, distribution and consequences of GDM in different socioeconomic and demographic groups and across generations.

In this study, the register-based arm was used. This arm includes all 59 057 singleton pregnancies of women who gave birth in Finland in 2009 and were identified through the MBR. Women were reported to have GDM if they, according to the MBR, had an abnormal OGTT result and/or insulin initiation during pregnancy and/or an ICD-10 code of GDM (ICD-10 codes O24.4 or O24.9) (Keikkala et al., 2020). A total of 6 583 (11.1%) women had GDM, while the remaining 52 004 (88.9%) women served as controls.

4.2 Study population

4.2.1 Changing from risk factor-based screening to comprehensive screening (Studies I–II)

A total of 59 051 women in 2006 and 61 371 women in 2010 and their offspring were identified using the MBR. After the exclusion of multiple births and mothers with pre-existing type I or type II diabetes, 5 185 (9.1%) women in 2006 and 6 683 (11.3%) in 2010 fulfilled the GDM criteria. All other women served as controls (51 759 in 2006 and 52 398 in 2010) (Figure 2). The number of women in these two studies differed slightly because of some missing data. Preterm infants with abnormally high birth weight for length of gestation (< 37 weeks and > 3 standard deviation (SD) according to Finnish standards) were excluded from birth weight analyses (n = 35) (Sankilampi, Hannila, Saari, Gissler, & Dunkel, 2013).

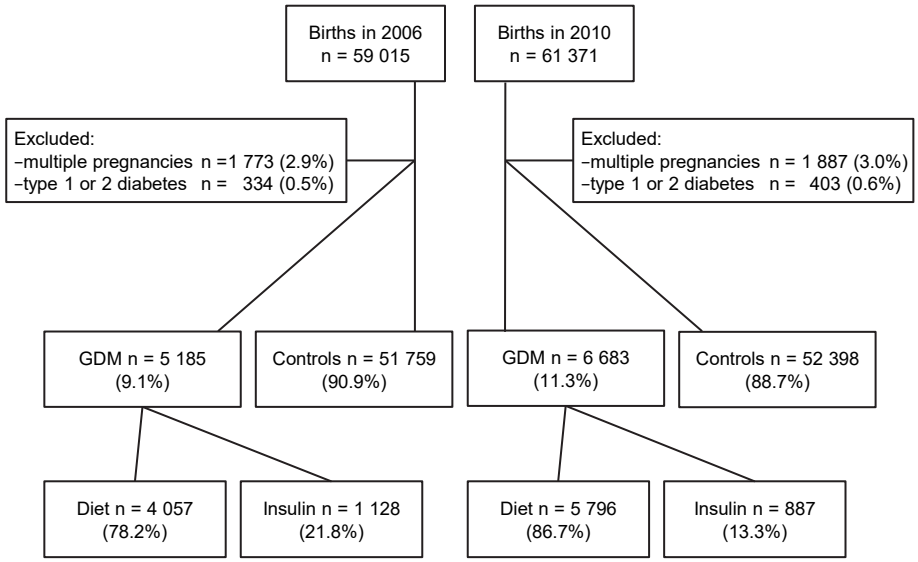

Fig. 2. Flow chart of Studies I–II. All births are divided by year, and further by GDM status and type of GDM (diet- or insulin-treated).

4.2.2 The comparison of the gestational diabetes screening policies of IADPSG and NICE (Study III) and the significance of the number of abnormal values in the OGTT (Study IV)

Studies III–IV were based on the register-based arm of the FinnGeDi study. The MBR register data include information on whether an OGTT was performed during pregnancy and whether the result was abnormal, but it does not include data on the actual glucose concentrations. Therefore, numerical OGTT data were collected from all women (n = 4 954) who delivered during 2009 in six delivery units/hospitals in Finland: two tertiary-level (Oulu and Tampere) and four secondary-level (Southern Karelia, Seinäjoki, Kainuu and Satakunta) hospitals. Each of these hospitals serves a specific geographical area, and together they handle around 15 000 births per year. Each hospital district is served by one laboratory. Numerical OGTT data were available from these hospitals through their laboratory data records. The linkage was performed by personnel uninvolved in this study using unique personal identification numbers.

In Study III, women with GDM diagnosis or insulin treatment during pregnancy according to the MBR but with normoglycemic OGTT results were

excluded from the study, as were women with an OGTT performed at only < 24 weeks (Figure 3). The population from Study IV was similar to that from Study III, except that in Study IV, women on whom an OGTT had been performed from the 12th gw to the 40th gw were included (Figure 4). Mothers with pre-existing type I or type II diabetes were excluded based on ICD-10 codes in the MBR. Only singleton pregnancies were included and, in the event a mother had two pregnancies during the same year, only the first one was included.

4.3 Study design

The study designs and a detailed description of the data sources are summarised in Table 6. All studies were register-based cohort studies.

4.3.1 Changing from risk factor-based screening to comprehensive screening (Studies I–II)

In Studies I and II, a woman was defined as having GDM if she, according to the MBR, had an abnormal OGTT result or insulin therapy was initiated during her pregnancy. GDM women were further divided into diet- or insulin-treated GDM women.

4.3.2 The comparison of the gestational diabetes screening policies of IADPSG and NICE (Study III) and the significance of the number of abnormal values in the OGTT (Study IV)

In Study III, women were divided into different GDM groups according to different GDM diagnosing policies. OGTT glucose concentrations were used to identify women who fulfilled IADPG and NICE criteria. The diagnostic cut-off values for plasma samples according to the IADPSG criteria are ≥ 5.1 mmol/l at baseline (fasting sample), ≥ 10.0 mmol/l at one hour and ≥ 8.5 mmol/l at two hours after a glucose load (Metzger et al., 2010). The NICE criteria for the diagnostic cut-off values were, for fasting, ≥ 5.6 mmol/l, and, for two-hour postprandial glucose, ≥ 7.8 mmol/l, while the one-hour concentration was not included at all (NICE, 2015). The diagnosis of GDM was based on one or more abnormal values in the OGTT.

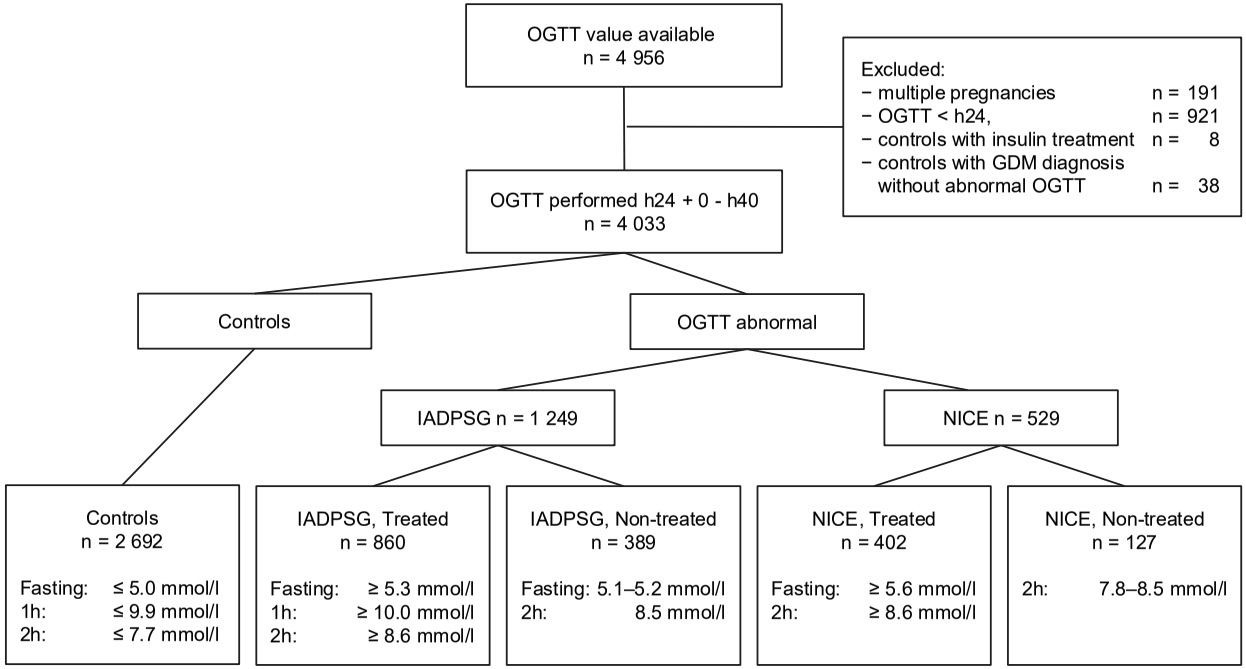

Fig. 3. Flow chart of Study III and diagnostic cut-off values for the diagnosis of GDM. IADPSG: International Association of the Diabetes and Pregnancy Study Group; NICE: The National Institute for Health and Care Excellence.

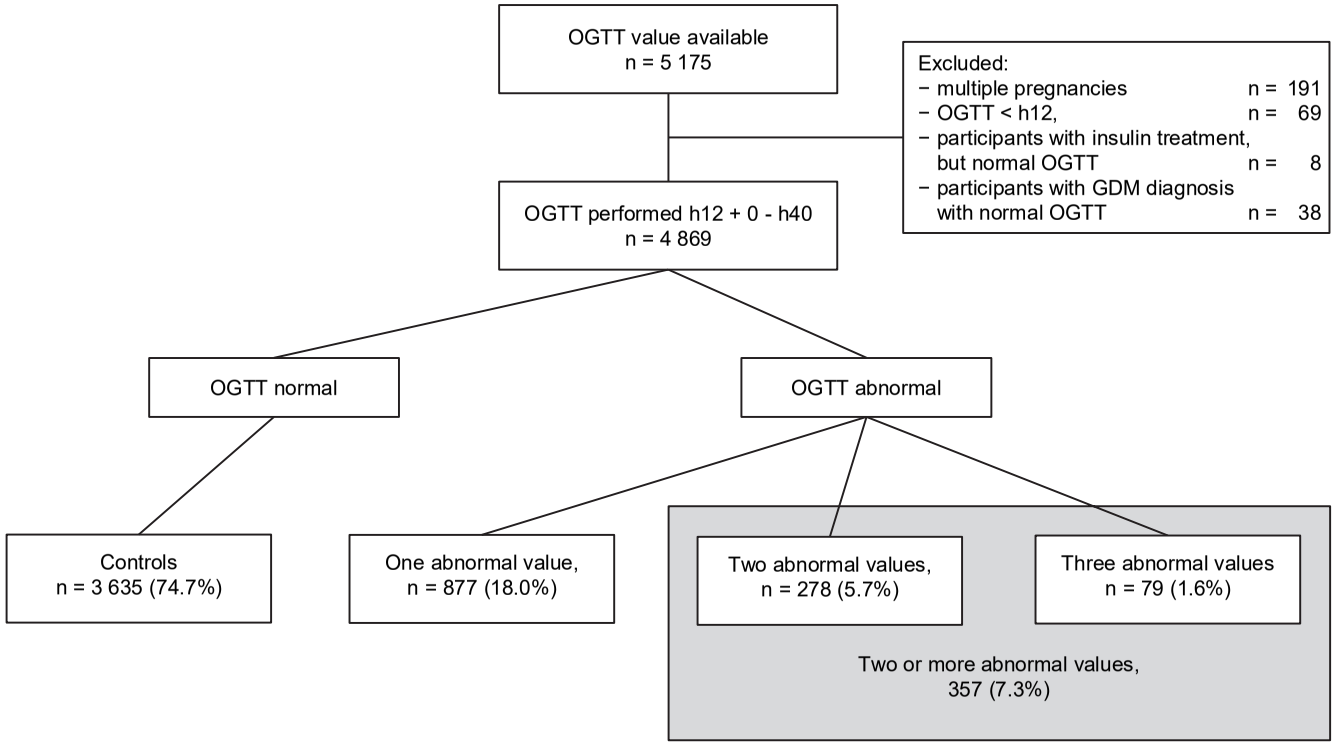

Fig. 4. Flow chart of Study IV.

Table 6. Study designs.

Study details	Study I	Study II	Study III	Study IV
Aim	The effect of the change in the GDM screening policy from risk factor-based to comprehensive screening on the prevalence and type of GDM and characteristics of GDM pregnancies.	To evaluate how this change of policy affected the perinatal outcome and the need for care at a neonatal ward.	To compare the impact of the IADPSG and NICE GDM screening criteria on the prevalence of GDM and pregnancy outcomes.	To assess the significance of one and several abnormal OGTT values on pregnancy and perinatal outcomes.
Study design	Register-based cohort	Register-based cohort	Register-based cohort	Register-based cohort
Data source	Medical Birth Register	Medical Birth Register	FinnGeDi register-based arm	FinnGeDi register-based arm
Study period	2006–2010	2006–2010	2009	2009
Number of subjects	Controls 2006 n = 51 759	Controls 2006 n = 51 746	Controls n = 2 692	Controls n = 3 635
	GDM 2006[1] n = 5 185	GDM 2006[1] n = 5 179	IADPSG[2] n = 1 249	1 abnormal OGTT value n = 877
	Controls 2006 n = 6 683	Controls 2006 n = 6 679	NICE[2] n = 529	≥ 2 abnormal OGTT values n = 357
	GDM 2010[1] n = 52 398	GDM 2010[1] n = 52 386		

[1] Also, subgroups of diet- and insulin-treated GDM women, [2] Also, subgroups of treated and non-treated GDM women according to the criteria used.

Because the diagnostic criteria for GDM according to current Finnish CCGs overlap with those of the IADPSG and NICE, a proportion of women diagnosed with mild GDM by the IADPSG or NICE criteria remained untreated for GDM during pregnancy. These groups were evaluated in sub-analyses as non-treated IADPSG or NICE GDM women.

In Study IV, the study population consisted of 4 869 women with OGTT test results (Figure 4). The women with GDM according to Finnish CCG criteria were categorised according to the number of abnormal glucose values: 877 (18.0%) had one, 278 (5.7%) had two and 79 (1.6%) had three abnormal OGTT values, while 3 635 (74.7%) women had normal values. Women with two or more abnormal OGTT values were analysed as one group (n = 357, 7.3%). The OGTT was performed after a 12-hour overnight fast in the laboratory nearest to the patient's residence. The samples were drawn from an antecubital vein into fluoride citrate tubes and were analysed within 24 hours in a local laboratory using commercial enzymatic assays, which varied between laboratories. GDM was diagnosed if the venous plasma glucose concentration was 5.3 mmol/l or more at baseline, 10.0 mmol/l or more at one hour, or 8.6 mmol/l or more at two hours after the glucose load.

4.4 Data collection

Table 7 summarises the collected variables and data used in different studies.

4.4.1 Changing from risk factor-based screening to comprehensive screening (Studies I–II)

The diagnoses of hypertensive pregnancy disorders were based on recorded ICD-10 codes: pre-existing essential hypertension (O10), superimposed pre-eclampsia (O11), chronic hypertension (O10), gestational proteinuria (O12), gestational hypertension (O13), pre-eclampsia (O14), eclampsia (O15) or maternal hypertension (O16) in Studies I–II. During these years, a systematic ultrasound examination to determine gestational age was offered to all pregnant women between 10+0 and 13+6 gw, and a detailed examination of foetal anatomy was offered between 19+0 and 22+0 gw. Preterm delivery was defined as a delivery prior to 37+0 gw. Antenatal visits included the number of all visits to maternal welfare clinics or the delivery hospital during pregnancy. Special care visits included only visits to the delivery hospital. Information about inducted delivery

was obtained from the MBR. Delivery mode was divided into vaginal, instrumental vaginal (vacuum extraction/assisted vaginal delivery), or caesarean section.

Table 7. Data collection of the studies.

Characteristic	Study I	Study II	Study III	Study IV
Background				
Maternal age	x	x	x	x
Prepregnancy BMI	x	x	x	x
Parity	x	x	x	x
Socioeconomic status	x		x	x
Smoking	x		x	x
Pregnancy				
Numerical OGTT results			x	x
Insulin treatment	x	x	x	x
Gestational hypertension or pre-eclampsia[1]	x		x	x
Antenatal and special health care visits	x			x
Delivery				
Preterm delivery (prior to 37 gw)	x	x	x	x
Induction of labour	x		x	x
Gestational age	x	x	x	x
Type of delivery	x		x	x
Hospital stay of mother	x		x	x
Offspring				
Birth weight	x	x	x	x
Birth weight SD score	x	x	x	x
SGA		x	x	x
LGA		x	x	x
Ponderal index		x		
NICU treatment		x		
5-min Apgar score		x		
Cord arterial pH < 7.15		x		
Neonatal diagnoses		x		
Perinatal mortality		x		
Hospital stay of offspring		x	x	x
Location at 7 days of age		x		

1 See the differences in ICD 10 codes in the text below.

Neonatal outcomes

The MBR data include the newborns' weight in grams and length in full centimetres. The ponderal index, representing the newborns' body constitution, was calculated using weight/length (kg/m^3). Macrosomia was defined as being large for gestational age (LGA), as indicated by a birth weight +2 SD from a reference value, and small for gestational age (SGA) as indicated by a birth weight -2 SD from a reference value. The birth weight SD score is a sex-specific parameter estimating birth weight and length in singletons born at 23–43 gw to primiparous or multiparous mothers according to Finnish standards (Pihkala et al., 1989; Sankilampi et al., 2013).

Data of umbilical cord artery pH, Apgar score, and the need and indication for treatment at a neonatal ward were obtained from the MBR. The six most frequent neonatal diagnoses, according to the ICD-10 set by a paediatrician, were used to evaluate neonatal morbidity. These diagnoses were hypoglycaemia (P70.0–70.9), hyperbilirubinemia (P59.0–59.9), neonatal respiratory distress syndrome (P22.0), transient tachypnea of the newborn (P22.1), fracture of the clavicle (P13.4), and Erb's and Klumpke's palsy (P14.0; P14.1).

Perinatal mortality included the combined rate of stillbirths and early neonatal mortality within the first seven days of life. The time for hospital treatment in days and the location of the newborn at the seventh day after birth (at home, in a neonatal ward, in a maternal ward with the mother, or in another hospital) were recorded.

4.4.2 The comparison of the gestational diabetes screening policies of the IADPSG and NICE (Study III) and the significance of the number of abnormal values in the OGTT (Study IV)

Data collection for Studies III–IV was similar to that for Studies I–II, excluding the following issues. In Studies III and IV, the term 'gestational hypertension (GHT) or pre-eclampsia' (ICD-10 codes O13 and O14) was used. Gestational age was based on the best estimate of the duration of pregnancy at delivery. In addition to previous macrosomia outcomes, in Studies III–IV, we also reported our results with LGA defined as a birth weight SD score over the 90th percentile.

4.5 Statistics

All statistical analyses were carried out using the SPSS 21 statistical package. Categorical variables were reported as frequencies (%), while continuous variables

were reported using the mean (standard deviation) or median (range). Pearson's χ^2 test was used to compare the difference in proportions, while the independent samples t-test was used to compare the difference in the means. A two-sided p-value of < 0.05 was considered statistically significant. Logistic regression was used to calculate ORs and 95% CIs for the risk of development of outcomes associated with GDM in different study periods. Mean differences with 95% CIs were calculated using linear regression. All logistic regression results were adjusted for maternal age, parity and pre-pregnancy BMI.

4.5.1 Covariates

The outcome measures for all studies were obtained from the MBR. Maternal age was defined as the mother's age at the time of delivery. BMI was calculated as the mother's pre-pregnancy weight divided by the square of her height.

Socioeconomic status was defined using the occupation reported to the MBR. Coding was based on national standards published by Statistics Finland. The socioeconomic groups were divided into four different categories, as follows: (1) upper-level employees with administrative, managerial, professional and related occupations, (2) lower-level employees with administrative and clerical occupations, (3) manual workers and (4) others, including stay-at-home mothers, students, pensioners and self-employed persons. In terms of smoking, women were categorised as non-smokers, those who stopped smoking in the first trimester, smokers after the first trimester, and no information. Of Finnish women aged 15 to 49 years, 94.7% were of Finnish ancestry.

4.6 Ethics

According to Finnish legislation, the study participants did not need to provide an information consent form when only anonymous register data were used. The Finnish Institute for Health and Welfare gave their permission for the use of MBR data. Hospital administration gave permission to use and combine OGTT laboratory test results with the register data. The FinnGeDi study was approved by the regional ethics committee in Northern Ostrobothnia Hospital District (Number: 2008/43, date of approval: 2008-6-19).

5 Results

5.1 Changing from risk factor-based screening to comprehensive screening (Studies I–II)

The total number of all deliveries in 2006 and 2010 were 59 051 and 61 371, respectively (Figure 2, flow chart of Studies I–II). Of these, 56 944 and 59 081, respectively, were singleton pregnancies of mothers without pre-pregnancy type I or type II diabetes and were therefore included in Study I.

The proportion of mothers undergoing an OGTT increased from 27.5% under the risk factor-based screening method to 51.4% under the comprehensive screening (Table 8). Together with this increase, the prevalence of GDM rose from 9.1% to 11.3%. Of all screened mothers, the number needed to screen for one GDM diagnosis was 3.13 during risk factor-based screening and 4.71 during comprehensive screening. Positive predictive values were 27.3% for risk factor-based screening and 20.8% for comprehensive screening.

5.1.1 Characteristics of study participants

The mean ages of all women giving birth in 2006 and 2010 were 29.5 and 29.6 years, respectively. Over 40% of the women were primiparous in both years (Table 9). The pre-pregnancy BMI in the whole study population was 24.1 kg/m^2 (SD 4.6) in 2006 and 24.3 kg/m^2 (SD 4.8) in 2010.

The baseline characteristics of the study population during different study periods are presented in Table 9. During comprehensive screening in 2010, GDM women were more often primiparous (39.4% vs. 34.5%) and had a lower pre-pregnancy BMI (28.2 vs. 28.6 kg/m^2) than during risk factor-based screening. The mean age and socioeconomic status were similar in the GDM groups in both study years.

Table 8. Comparison of risk factor-based and comprehensive screening of GDM.

Screening method/ Indication for screening	OGTT[1] performed, n (%)	GDM[2] diagnosed, n (%)	NNS[3]
Risk factor-based screening (2006)	15 688 (27.5%)	5 185 (9.1%)	3.13
Prior gestational diabetes			
Overweight (BMI[4] > 25 kg/m^2)			
Glucosuria			
Age > 40 years			
Previous macrosomic offspring (weight 4 500 g or more)			
Suspected macrosomia in the current pregnancy			
Comprehensive screening (2010)	30 372 (51.4%)	6 683 (11.3%)	4.71
All women except those with very low GDM risk:			
Primiparous: age < 25 years, BMI < 25 kg/m^2, no family history of diabetes			
Multiparous: age < 40 years, BMI < 25 kg/m^2, no previous macrosomic offspring			

[1] oral glucose tolerance test, [2] gestational diabetes, [3] number needed to screen, [4] body mass index

Table 9. Characteristics of the mothers with and without gestational diabetes during risk factor-based (2006) and comprehensive (2010) screening.

Characteristics	GDM 2006	GDM 2010	p-value	Control 2006	Control 2010	p-value	p-value / year[1]
n	5 185 (9.1%)	6 683 (11.3%)		51 759 (90.9%)	52 398 (88.7%)		
Maternal age (years)	31.1 (5.7)	31.0 (5.5)	0.526	29.3 (5.4)	29.4 (5.3)	0.007	0.140
Pre-pregnancy BMI (kg/m^2)	28.6 (5.8)	28.2 (6.1)	< 0.001	23.7 (4.3)	23.8 (4.4)	< 0.001	< 0.001
Primiparous	1 788 (34.5%)	2 635 (39.4%)	< 0.001	22 229 (43.1%)	22 293 (42.5%)	0.085	< 0.001
Non-smoking	4 237 (81.7%)	5 385 (80.6%)	0.116	42 732 (82.6%)	43 458 (82.9%)	0.100	0.043
Insulin treatment	1 128 (21.8%)	887 (13.3%)	< 0.001				
Hypertensive pregnancy disorders1	422 (8.1%)	608 (9.1%)	0.066	2 144 (4.1%)	2 282 (4.4%)	0.089	0.341
Induction of delivery	1 334 (25.7%)	1 893 (28.3%)	0.002	7 712 (14.9%)	8 875 (16.9%)	< 0.001	0.647
Gestational age (weeks)	39.6 (1.6)	39.6 (1.6)	0.328	39.8 (1.8)	39.9 (1.8)	< 0.001	0.036
Birth weight (grams)	3 695 (434)	3 635 (434)	< 0.001	3 516 (434)	3 497 (434)	< 0.001	< 0.001
Type of delivery							
Vaginal delivery	3 702 (71.4%)	4 610 (69.3%)	0.005	39 386 (76.1%)	39 754 (75.9%)	0.619	0.013
Vaginal, instrumental delivery	386 (7.4%)	573 (8.6%)	0.011	4 267 (8.2%)	4 584 (8.7%)	0.005	0.223
Caesarean section	1 076 (20.8%)	1 469 (22.1%)	0.045	7 811 (15.1%)	7 696 (14.7%)	0.169	0.031

The numbers are n (%) or mean (SD). [1] ICD-10 codes from O10 to O16.

5.1.2 Perinatal outcome

The proportion of induced deliveries increased from 2006 to 2010 in both GDM (25.7% to 28.3%) and non-GDM (14.9% to 16.9%; Table 9) women, and the increase was similar for both groups (p-value for interaction GDM*year of birth: unadjusted p-value 0.6, p-value adjusted for maternal age, parity and pre-pregnancy BMI 0.7; Table 10). The caesarean section rate increased in the GDM group from 20.8% to 22.1%, but decreased in the non-GDM mothers (15.1% to 14.7%, respectively; Table 9). The total caesarean section rate remained similar (17.1% and 17.1%, respectively). The adjusted ORs for caesarean section for GDM as compared with controls were 1.10 during risk factor-based screening and 1.22 during comprehensive screening. P-values for the interaction between the effects of screening method and GDM on caesarean section were 0.052 (unadjusted) and 0.018 (adjusted) (Table 10).

5.1.3 Neonatal outcome

Both the mean birth weight and the rate of LGA decreased among newborns of GDM mothers after the implementation of comprehensive screening (65 g from 3 660 [SD 542] to 3 595 g [SD 561], and from 5.6% to 4.1% [adjusted ORs 1.81 and 1.46, respectively]; Table 11). In the GDM group, the ponderal index decreased between the study years. After adjustment for maternal age, parity and pre-pregnancy BMI, the mean difference of the birth weight SD score decreased between the study periods from 0.20 to 0.11 SD. This decrease corresponds to 50 g birth weight at term (Table 10).

Newborns of GDM mothers were 1.7-fold more likely to require care in a neonatal ward than controls during both study years (Table 11). The need for care at a neonatal ward decreased similarly between the study years in both the GDM and control groups. Although the proportion of GDM group newborns treated at a neonatal ward decreased, their absolute number did not change substantially.

The incidence of neonatal hypoglycaemia clearly increased in the GDM group (18.0% vs. 22.1%) after the new screening policy was introduced. It was the most common indication for care at a neonatal ward during both study years, but it was less often treated at a neonatal ward during comprehensive (12.9%) as opposed to risk factor-based screening (16.1%).

Table 10. Multivariate logistic (odds ratios) and linear regression (mean differences) of peri- and neonatal outcomes in patients with GDM during risk factor-based (2006) and comprehensive (2010) screening adjusted for maternal age parity and pre-pregnancy BMI.

Outcome	Risk-factor based screening (2006)				Comprehensive screening (2010)				p-value for interaction[4] unadjusted/ adjusted
	Unadjusted		Adjusted		Unadjusted		Adjusted		
	OR[1]	95% CI[2]	OR	95% CI	OR	95% CI	OR	95% CI	
Induction of delivery	1.98	1.85–2.12	1.50	1.40–1.62	1.94	1.83–2.05	1.53	1.44–1.63	0.647 / 0.703
Caesarean section	1.47	1.36–1.58	1.10	1.02–1.19	1.65	1.55–1.75	1.22	1.14–1.31	0.018 / 0.052
Neonatal hypoglycaemia	8.06	7.38–8.81	6.20	5.61–6.86	10.3	9.52–11.14	8.40	7.71–9.15	< 0.001 / < 0.001
Birth weight SD score[3]	0.37	0.34–0.40	0.20	0.17–0.23	0.26	0.23–0.28	0.11	0.08–0.13	< 0.001 / < 0.001

[1] odds ratio, [2] confidence interval, [3] mean difference, 95% confidence interval, [4] p-values for interaction indicate whether the association of GDM with the outcome is different during comprehensive as compared to risk factor-based screening.

Table 11. Clinical characteristics and outcome in GDM and control mothers and their offspring during risk factor-based (2006) and comprehensive screening (2010).

Characteristic	GDM 2006	GDM 2010	p-value	Control 2006	Control 2010	p-value
Neonatal characteristics						
Ponderal index, kg/m^3	28.3 (2.7)	28.1 (3.2)	< 0.001	27.9 (3.4)	27.8 (4.0)	0.015
LGA[1]	289 (5.6)	276 (4.1)	< 0.001	1 011 (2.0)	966 (1.8)	0.153
Neonatal outcome						
5-min Apgar score < 7	109 (2.1)	136 (2.0)	0.795	974 (1.9)	1 049 (2.0)	0.160
Cord arterial pH < 7.15	333 (6.4)	505 (7.6)	0.017	3 305 (6.4)	3 755 (7.2)	< 0.001
Asphyxia	206 (4.0)	371 (5.6)	< 0.001	2 167 (4.2)	2 712 (5.2)	< 0.001
Care at neonatal ward	834 (16.1)	861 (12.9)	< 0.001	5 075 (9.8)	4 119 (7.9)	< 0.001
Neonatal diagnoses						
Hypoglycemia	932 (18.0)	1 478 (22.1)	< 0.001	1 371 (2.6)	1 407 (2.7)	0.716
Hyperbilirubinemia	303 (5.9)	324 (4.9)	0.016	2 160 (4.2)	1 776 (3.4)	< 0.001
Respiratory distress syndrome	18 (0.3)	15 (0.2)	0.207	202 (0.4)	139 (0.3)	< 0.001
Fracture of the clavicle	87 (1.7)	53 (0.8)	< 0.001	533 (1.0)	378 (0.7)	< 0.001
Erb's or Klumke's palsy	26 (0.5)	22 (0.3)	0.142	120 (0.2)	72 (0.1)	< 0.001

The numbers are n (%) or mean (SD). [1] large for gestational age, > +2SD

5.1.4 Comparison of diet- or insulin-treated GDM pregnancies

Between 2006 and 2010, both the proportion and absolute number of insulin-treated GDM women were reduced significantly, from 1 128 to 887 (21.8% to 13.3% of all GDM mothers) (Table 12). Regardless of the screening policy, insulin-treated GDM mothers were older, had a higher pre-pregnancy BMI, and were more often parous than those with diet treatment. During comprehensive screening, insulin-treated mothers had a significantly higher pre-pregnancy BMI than during the previous study period (30.2 vs. 28.8, respectively).

Induced deliveries and caesarean sections were more frequent among insulin- than diet-treated mothers, with the proportions being higher during comprehensive screening. Although the ponderal index and LGA rate of offspring of diet-treated mothers decreased significantly from the risk factor-based to the comprehensive screening period, a similar change was not seen among offspring of insulin-treated mothers – the ponderal index of their offspring was higher during comprehensive screening (Table 13). Offspring of insulin-treated mothers were also more likely to be admitted to a neonatal ward. The most common indication for care at a neonatal ward with both diet- and insulin-treated mothers was neonatal hypoglycaemia.

5.2 The comparison of the gestational diabetes screening policies of the IADPSG and NICE (Study III)

5.2.1 Characteristics of study population

Study III included 4 033 women who delivered in the six delivery hospitals in Finland in 2009 and on whom an OGTT was performed between 24+0 and 40+0 gw (mean 27.5, SD 2.5). Of them, 860 (21.3%) had GDM according to the prevailing Finnish criteria and were counselled and insulin-treated when needed. Of women with an OGTT, 1 249 (31.0%) and 529 (13.1%) had GDM according to the IADPSG and NICE criteria, respectively (Table 14). The control group consisted of 2 692 (66.7%) women who were normoglycemic according to all criteria.

Table 12. Characteristics and outcome of offspring of GDM mothers divided according to diet and insulin treatment during risk factor-based (2006) and comprehensive screening (2010).

Characteristic	Diet 2006	Diet 2010	p-value	Insulin 2006	Insulin 2010	p-value	p-value[1]
n	4 053 (78.3%)	5 795 (86.8%)	< 0.001	1 126 (21.7%)	884 (13.2%)	< 0.001	
Maternal age, years	30.9 (5.7)	30.9 (5.4)	0.504	31.6 (5.6)	32.1 (5.4)	0.064	< 0.001
Pre-pregnancy BMI	28.6 (5.7)	27.9 (5.9)	< 0.001	28.8 (6.3)	30.2 (6.9)	< 0.001	< 0.001
Primiparous	1 404 (34.6)	2 325 (40.1)	< 0.001	384 (34.0)	310 (34.9)	0.671	0.004
Non-smoking	3 330 (82.1)	4 685 (80.8)	0.117	907 (80.4)	700 (78.9)	0.409	0.096
Hypertensive pregnancy disorders[2]	343 (8.5)	503 (8.7)	0.696	79 (7.0)	105 (11.8)	< 0.001	0.428
Induction of delivery	961 (23.7)	1 495 (25.8)	0.017	373 (33.1)	398 (44.9)	< 0.001	< 0.001
Gestational age, weeks	39.8 (1.6)	39.7 (1.7)	0.006	39.2 (1.7)	39.3 (1.4)	0.606	< 0.001
Birth weight, grams	3 651 (472)	3 580 (472)	< 0.001	3 685 (473)	3 712 (472)	0.200	0.679
Type of delivery							
Vaginal delivery	2 888 (71.5)	4 041 (70.0)	0.117	814 (72.4)	569 (64.6)	< 0.001	0.141
Instrumental	305 (7.5)	506 (8.8)	0.031	81 (7.2)	67 (7.6)	0.735	0.186
Caesarean section	847 (21.0)	1 224 (21.2)	0.771	229 (20.4)	245 (27.8)	< 0.001	0.012

[1] p-value for diet vs. insulin treatment, [2] ICD-10 codes from O10 to O16.

Table 13. Characteristics and outcome of offspring of GDM mothers divided according to diet and insulin treatment during risk factor-based (2006) and comprehensive screening (2010).

Characteristic	Diet 2006	Diet 2010	p-value	Insulin 2006	Insulin 2010	p-value
n	4 053 (78.3%)	5 795 (86.8%)	< 0.001	1 126 (21.7%)	884 (13.2%)	< 0.001
Birth weight, grams	3 651 (472)	3 580 (472)	< 0.001	3 685 (473)	3 712 (472)	0.200
Ponderal index, kg/m^3	28.4 (2.7)	28.0 (3.2)	< 0.001	28.1 (2.8)	28.7 (3.3)	< 0.001
LGA[1]	216 (5.3)	213 (3.7)	< 0.001	73 (6.5)	63 (7.1)	0.564
Neonatal outcome						
5-min Apgar score < 7	80 (2.8)	118 (2.0)	0.824	31 (2.7)	19 (2.1)	0.385
Cord arterial pH < 7.15	253 (6.2)	448 (7.7)	0.005	80 (7.1)	57 (6.4)	0.562
Asphyxia	161 (4.0)	321 (5.5)	< 0.001	45 (4.0)	50 (5.7)	0.082
Admitted to neonatal ward	531 (13.1)	710 (12.3)	0.211	303 (26.9)	151 (17.1)	< 0.001
Neonatal diagnoses						
Hypoglycaemia	619 (15.3)	1 184 (20.4)	< 0.001	313 (27.8)	294 (33.3)	0.008
Respiratory distress syndrome	10 (0.2)	12 (0.2)	0.682	8 (0.7)	3 (0.3)	0.268
Hyperbilirubinemia	199 (4.9)	256 (4.4)	0.252	104 (9.2)	68 (7.7)	0.219
Fracture of the clavicle	74 (1.8)	51 (0.9)	< 0.001	14 (1.2)	3 (0.3)	0.028
Erb's or Klumpke's palsy	16 (0.4)	19 (0.3)	0.653	10 (0.9)	3 (0.3)	0.127

[1] large for gestational age.

As compared with the controls, women who had GDM according to both the IADPSG and NICE criteria were older and had a higher pre-pregnancy BMI. In the NICE and IADPSG groups, 7.2% and 4.6% of women, respectively, received insulin treatment (Table 14).

Of those who had GDM by Finnish criteria, 57 (6.6%) needed insulin treatment. When the pregnancy outcomes of the GDM groups were compared with controls, the rates of labour induction and caesarean sections were higher in both the IADPSG and NICE GDM groups, and the gestational age at delivery was lower. In the NICE group, the proportion of pre-term deliveries was higher than that in the IADPSG group and in the controls (Table 14). The LGA rate in the two GDM groups did not differ from that in the controls.

The cut-off values for plasma glucose levels in the different screening guidelines partly overlapped with those used in Finland. In the IADPSG and NICE groups, 68.9% and 76.0% of women, respectively, received counselling and treatment according to the Finnish guidelines. Hence, 31,1% and 24.0% of women, respectively, did not receive treatment for GDM. The delivery induction and caesarean section rates in both treated GDM groups were higher than those in the normoglycemic controls. The caesarean section rates, in addition to birth weight (SD score and SD score > 90%), were higher in the non-treated IADPSG group as compared with those in all other GDM groups (treated or non-treated) (Table 15) and in the controls.

After adjustment for maternal age, parity and pre-pregnancy BMI in a multivariate logistic regression analysis, the OR of induction of labour increased in both treated GDM groups (Table 16). The caesarean section rate increased in both the treated and untreated IADPSG groups. It also increased in the treated NICE group but not in the untreated group.

Table 14. Characteristics and outcome of pregnancies with GDM classified according to the different criteria based on the OGTT at 24 to 40 gestational weeks.

Characteristics	Normoglycemic according to all criteria	CCG		IADPSG		NICE	
		n (%/SD)	p-value	n (%/SD)	p-value	n (%/SD)	p-value
n	2 692 (66.7)	860 (21.3)		1 249 (31.0)		529 (13.1)	
Maternal age, years	29.4 (5.3)	30.2 (5.6)	< 0.001	30.2 (5.6)	< 0.001	30.3 (5.8)	< 0.001
Pre-pregnancy BMI, kg/m^2	25.5 (4.3)	27.4 (5.2)	< 0.001	27.3 (5.1)	< 0.001	27.0 (5.1)	< 0.001
Primiparity	1 333 (49.5)	378 (44.0)	< 0.001	560 (44.8)	0.006	259 (49.0)	0.815
Gestational age, weeks	39.9 (1.6)	39.5 (1.9)	< 0.001	39.6 (1.8)	< 0.001	39.4 (2.0)	< 0.001
Birth weight, grams	3 571 (524)	3 530 (558)	0.061	3 558 (558)	0.442	3 490 (620)	0.002
Birth weight, SD score	-0.05 (1.0)	0.02 (1.0)	0.120	0.04 (1.0)	0.012	0.01 (1.1)	0.293
Birth weight > 90%	250 (9.3)	88 (10.2)	0.411	141 (11.3)	0.050	65 (12.3)	0.034
Insulin treatment	0	57 (6.6)	< 0.001	57 (4.6)	< 0.001	38 (7.2)	< 0.001
Induced delivery	414 (15.4)	191 (22.4)	< 0.001	259 (20.7)	< 0.001	121 (22.9)	< 0.001
Preterm birth	22 (0.8)	54 (6.3)	0.002	18 (1.4)	0.069	11 (2.1)	0.008
GHT or pre-eclampsia[1]	165 (6.1)	75 (8.7)	0.008	100 (8.0)	0.029	48 (9.1)	0.013
Type of delivery							
Vaginal	2 048 (76.1)	611 (71.6)	0.010	894 (71.6)	0.003	372 (70.3)	0.005
Instrumental	242 (9.0)	65 (7.6)	0.229	95 (7.6)	0.148	40 (7.6)	0.288
Caesarean section	402 (14.9)	177 (20.8)	< 0.001	260 (20.8)	< 0.001	117 (22.1)	< 0.001

[1] International classification of diseases ICD-10: O13, O14.

Table 15. Characteristics and outcome of pregnancies with GDM classified according to the IADPSG and the NICE GDM screening criteria, with or without treatment.

Characteristics	Control group	IADPSG				p-value[1]	NICE				p-value[1]
		Treated		Non-treated			Treated		Non-treated		
	n (%/SD)	n (%/SD)	p-value	n (%/SD)	p-value		n (%/SD)	p-value	n (%/SD)	p-value	
n	2 692 (66.7)	860 (21.3)		389 (9.6)			402 (10.0)		127 (3.1)		
Maternal age, years	29.4 (5.3)	30.2 (5.6)	< 0.001	30.0 (5.7)	0.033	0.462	30.4 (5.9)	0.001	30.3 (5.5)	0.223	0.498
Pre-pregnancy BMI, kg/m^2	25.5 (4.3)	27.4 (5.2)	< 0.001	26.9 (4.7)	< 0.001	0.150	27.4 (5.1)	< 0.001	25.4 (4.6)	0.799	< 0.001
Primiparity	1 333 (49.5)	378 (44.0)	0.004	182 (46.8)	0.314	0.351	193 (48.0)	0.573	66 (52.0)	0.589	0.437
Gestational age, weeks	39.9 (1.6)	39.5 (1.9)	< 0.001	39.9 (1.6)	0.377	0.001	39.3 (2.0)	< 0.001	39.5 (2.0)	0.002	0.339
Birth weight, grams	3 571 (524)	3 530 (558)	0.061	3 620 (552)	0.095	0.008	3 499 (624)	0.013	3 463 (610)	0.025	0.565
Birth weight > 90%	250 (9.3)	88 (10.2)	0.411	53 (13.6)	0.007	0.079	49 (12.2)	0.066	16 (12.6)	0.212	0.903
Insulin treatment	0	57 (6.6)	< 0.001	0		< 0.001	38 (9.5)	< 0.001	0		< 0.001
Induced delivery	414 (15.4)	192 (22.3)	< 0.001	67 (17.2)	0.349	0.039	94 (23.4)	< 0.001	27 (21.3)	0.075	0.619
Preterm birth	22 (0.8)	13 (1.5)	0.073	5 (1.3)	0.354	0.756	7 (1.7)	< 0.073	4 (3.1)	0.007	0.332
GHT or pre-eclampsia1	165 (6.1)	75 (8.7)	0.008	25 (6.4)	0.820	0.167	38 (9.5)	0.012	10 (7.9)	0.426	0.589
Type of delivery											
Vaginal	2 048 (76.1)	616 (71.6)	0.009	278 (71.5)	0.048	0.953	278 (69.2)	0.003	94 (74.0)	0.595	0.296
Instrumental	242 (9.0)	65 (7.6)	0.193	30 (7.7)	0.406	0.924	32 (8.0)	0.498	8 (6.3)	0.297	0.537
Caesarean section	402 (14.9)	179 (20.8)	< 0.001	81 (20.8)	0.003	0.997	92 (22.9)	< 0.001	25 (19.7)	0.144	0.447

[1] p-value between treated and non-treated.

Table 16. Multivariate logistic and linear regression analysis of peri- and neonatal outcomes in patients according to the application of the different GDM screening methods compared to normoglycemic controls adjusted for maternal age, pre-pregnancy BMI and parity.

Outcome	Non-treated IADPSG				Treated IADPSG				Non-treated NICE				Treated NICE			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
	OR	CI	OR	CI	OR	CI	OR	CI	OR	CI	OR	CI	OR	CI	OR	CI
Induced delivery	1.15	0.86-1.52	1.10	0.83-1.47	1.58	1.31-1.92	1.46	1.20-1.78	1.49	0.96-2.30	1.48	0.95-2.30	1.68	1.30-2.16	1.68	1.30-1.99
Caesarean section	1.50	1.15-1.96	1.42	1.08-1.87	1.50	1.23-1.82	1.37	1.12-1.68	1.40	0.89-2.19	1.34	0.84-2.13	1.69	1.31-2.18	1.47	1.13-1.92
Birth weight SD score > 90%	1.54	1.12-2.12	1.51	1.09-2.08	1.11	0.86-1.44	1.07	0.82-1.39	1.41	0.82-2.42	1.43	0.83-2.46	1.36	0.98-1.88	1.29	0.93-1.81

5.3 The significance of the number of abnormal values in the OGTT (Study IV)

5.3.1 Baseline characteristics of the study groups

OGTTs were performed between 12 and 40 gw (mean 26 gw, SD 4.4) for 4 869 women who delivered in six delivery hospitals during 2009. The OGTT was abnormal according to the Finnish CCG criteria in 1 234 (25.3%) women, and the control group consisted of 3 635 (74.7%) women with normal OGTT results (Table 17). Of the women with GDM, 877 (18.0%) had one, 278 (5.7%) had two and 79 (1.6%) had three abnormal OGTT values. Women with two or more abnormal OGTT values were analysed as one group (n = 357, 7.3%). When the baseline characteristics were considered, the only difference between women with one and ≥ two abnormal OGTT values was pre-pregnancy BMI (mean 27.9 kg/m^2 vs. 29.7 kg/m^2, p-value < 0.001).

5.3.2 Pregnancy and delivery

Perinatal characteristics according to the number of abnormal OGTT values are presented in Table 17. Gestational age was higher among women with one abnormal value than ≥ two abnormal values in the OGTT (mean 39.6 gw vs. 39.1 gw, p-value < 0.001). Of the women with one abnormal OGTT value, 7.2% needed insulin treatment, while the proportion was 17.3% in women with ≥ two abnormal values (p-value between these groups < 0.001).

Women with one abnormal OGTT value had similar proportions of preterm deliveries, gestational hypertension (GHT) and pre-eclampsia, macrosomia and mother and offspring hospital stay periods as normoglycemic controls. Regardless of the number of abnormal OGTT values, GDM women had induced deliveries more often than the normoglycemic controls.

When women with ≥ two abnormal OGTT values were compared to those with one abnormal value, the risk of delivery induction (29.5% vs. 22.7%, p = 0.010), caesarean section (25.9% vs. 19.1%, p = 0.005) and macrosomia (14.5% vs. 10.0%, p = 0.020) increased. After adjustments with maternal age, pre-pregnancy BMI and parity, the risk of delivery induction was higher despite the number of abnormal values in the OGTT when compared to normoglycemic controls (Table 18). The

rate of caesarean section, macrosomia and preterm delivery risk increased only in women with two or more abnormal values. The risk of GHT or pre-eclampsia did not differ from the controls in either of the study groups.

Table 17. Characteristics of pregnancies with different numbers of abnormal and normal glucose values based on a two-hour, 75-g oral glucose tolerance test (OGTT).

Characteristics	Normoglycemic women	One abnormal OGTT value	p-value normoglycemic vs. one abnormal OGTT value	Two or more abnormal OGTT values	p-value normoglycemic vs. two or more abnormal OGTT values	p-value one vs. two or more abnormal OGTT values
N (%)	3 635 (74.7)	877 (18.0)		357 (7.3)		
Maternal age, years	29.5 (5.3)	30.4 (5.5)	< 0.001	30.7 (5.7)	< 0.001	0.266
Pre-pregnancy BMI, kg/m^2	25.8 (4.6)	27.9 (5.7)	< 0.001	29.7 (6.3)	< 0.001	< 0.001
Primiparity	1 720 (47.3)	228 (38.5)	< 0.001	137 (37.0)	< 0.001	0.867
Gestational age at delivery, wk	39.9 (1.6)	39.6 (1.7)	< 0.001	39.1 (2.1)	< 0.001	< 0.001
Delivery induction	594 (16.3)	197 (22.5)	< 0.001	109 (29.5)	< 0.001	0.010
Insulin treatment	— (0.0)	63 (7.2)	< 0.001	64 (17.3)	< 0.001	< 0.001
Gestational hypertension and pre-eclampsia[1]	234 (6.4)	69 (7.9)	0.129	36 (9.7)	0.015	0.206
Preterm delivery	144 (4.0)	45 (5.1)	0.121	31 (8.4)	< 0.001	0.025
Birth weight, g (SD)	3 578 (532)	3 567 (527)	0.571	3 547 (642)	0.363	0.589
Birth weight, SD score	−0.02 (1.0)	0.03 (1.0)	0.110	0.16	0.001	0.079
LGA > 90%[2]	343 (9.4)	88 (10.0)	0.589	54 (14.6)	0.002	0.020
Type of delivery						
Vaginal non-instrumental	2 767 (76.1)	646 (73.7)	0.128	247 (66.8)	< 0.001	0.009
Instrumental	303 (83)	63 (7.2)	0.262	27 (7.3)	0.489	0.876
Caesarean section	565 (15.5)	168 (19.2)	0.009	96 (25.9)	< 0.001	0.005
Hospital stay of mother in days	3.1 (1.4)	3.2 (1.4)	0.170	3.4 (1.5)	< 0.001	0.022
Hospital stay of offspring in days	3.1 (2.4)	3.3 (2.1)	0.086	3.5 (2.0)	0.008	0.106

[1] International classification of diseases ICD-10: O13 and O14 included, O10 and O11 excluded, [2] large for gestational age, 90%.

Table 18. Multivariate logistic regression analysis of perinatal and neonatal outcomes in patients according to the number of pathological abnormal values in a two-hour, 75-g oral glucose tolerance test (OGTT) compared to normoglycemic controls.

Characteristics	One abnormal value				Two or more abnormal values			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Outcome								
Gestational hypertension and pre-eclampsia[1]	1.24	0.94–1.64	1.16	0.87–1.54	1.53	1.05–2.23	1.31	0.88–1.96
Induced delivery	1.48	1.24–1.78	1.33	1.11–1.61	2.10	1.65–2.69	1.74	1.35–2.25
Preterm delivery	1.31	0.93–1.84	1.32	0.93–1.88	2.22	1.48–3.35	2.20	1.41–3.44
Caesarean section	1.29	1.06–1.56	1.17	0.96–1.43	1.94	1.51–2.50	1.64	1.25–2.15
Macrosomia[2]	1.07	0.84–1.36	0.96	0.75–1.23	1.64	1.20–2.23	1.41	1.01–1.95

Adjusted for maternal age, parity and pre-pregnancy body mass index. [1] International classification of diseases ICD-10: O13 and O14 included, O10 and O11 excluded, [2] Birth weight, large for gestational age > 90%.

6 Discussion

6.1 Interpretation of results

6.1.1 Main findings

The change from risk factor-based to comprehensive GDM screening offered an excellent opportunity to study the effect of different screening strategies. Comprehensive GDM screening seems to identify more primiparous and normal weight women with GDM but fewer women who need insulin treatment than in risk factor-based screening. The proportion of macrosomic newborns was lower after comprehensive GDM screening, but there was an increased incidence of neonatal hypoglycaemia. However, the 24% increased prevalence of GDM places substantial demands on the health care system.

The definitive answer to the question of which screening and diagnostic method of GDM is most effective remains unclear. The NICE screening policy might identify smaller numbers of GDM women, thus excluding a substantial number of women at risk for adverse pregnancy outcomes. A large-scale screening of GDM with IADPSG criteria might be reasonable, while the treatment of even mild hyperglycaemia has been demonstrated to be associated with improved perinatal outcomes. Based on previous research, it is important to find mothers with even mild GDM in order to identify efficient interventions to avoid later diabetes (W. L. Lowe et al., 2018).

When evaluating the significance of the number of abnormal values in the OGTT, the proportion of delivery inductions was already higher after one abnormal value when compared with those which had two or three abnormal values. By contrast, in women with two or three abnormal values, there was increased risk of insulin treatment, preterm deliveries, caesarean section and macrosomia. Hence, after counselling and blood glucose self-monitoring, the pregnancy and perinatal risks in women with one abnormal glucose value seem to be similar to those in the controls.

6.1.2 Changing from the risk factor-based screening to the comprehensive screening of GDM

In Finland, GDM screening was limited to women with risk factors until 2008, when CCGs to screen and diagnose GDM were introduced; these CCGs were subsequently updated in 2013. Unlike previous policy, the new guidelines recommend that all women except those with very low GDM risk should be tested via a 75-g OGTT. Before CCGs made uniform national guidelines possible, many hospital districts in Finland had their own modified instructions for GDM screening and diagnosis. The change from risk factor-based to comprehensive screening led to a 24% increase in the prevalence of GDM. The number of women who need to be screened to find one woman with GDM was higher during comprehensive than risk factor-based screening.

While in the present study, 27.5% of pregnant women underwent risk factor-based screening, two years after launching the new national guidelines, the screening rate was 51%. The CCG working group estimated that the number of mothers who were supposed to undergo comprehensive screening would be around 80%. However, it takes time to reach full implementation. In 2018, the GDM screening frequency was 66.0% and the prevalence of GDM was 21.3% in Finland (Statistics Finland). We believe that the target will be reached in future years.

Effect for mothers

Risk factor-based screening has been described as controversial, inadequate and inconsistent (Avalos, Owens, & Dunne, 2013; Dahanayaka et al., 2012; Murphy et al., 2016; Reece, Leguizamón, & Wiznitzer, 2009). In previous studies, 20% to 50% of women with GDM had no risk factors for this condition (Avalos et al., 2013; Pöyhönen-Alho et al., 2005). One reason for the lack of risk factors in GDM women might be the nature of these factors: Many of them are based on previous pregnancy history, including prior GDM or previous macrosomic newborns, which are not informative in primiparous women or which cannot be used until after the first pregnancy. The increased proportion of primiparous women diagnosed by comprehensive screening may reflect this. Another reason may be the classification of family history of diabetes as a GDM risk factor and/or the new definition of risk factors: During comprehensive screening, an OGTT was recommended if there was a family history of diabetes, even in women who would otherwise have been exempted from the test because of a very low risk of GDM. Therefore, these

findings support comprehensive screening as the first-line policy to identify women with abnormal glucose metabolism. Unfortunately, we did not have specific information about GDM risk factors.

As opposed to risk factor-based screening, comprehensive screening seems to identify more primiparous and normal weight women but not more GDM women who need insulin. The latter group (i.e. insulin, or medical, treated GDM women) represents an essential risk group for maternal and perinatal complications. In the present study, only short-term outcomes were considered, but according to CGGs and IADPSG criteria, which have lower diagnostic glucose thresholds than those used in Finland, the long-term risks for type II diabetes and cardiovascular diseases after GDM have been shown to increase (Hakkarainen et al., 2016; W. L. Lowe et al., 2018).

Although the total number of GDM mothers increased between the study periods, the proportion and absolute number of women treated with insulin decreased significantly. Uniform guidelines, together with revised uniform cut-off levels for pharmacologic treatment, may be important reasons for this change: Target levels in self-monitoring for fasting glucose concentration rose from 5.3 mmol/l to 5.5 mmol/l, while target levels in self-monitoring for postprandial glucose rose from 6.7 mmol/l one hour after a meal to 7.8 mmol/l 1.5 hours after a meal (Kaaja, 2013; Teramo, 2006). Women with insulin treatment belong to a group requiring special attention during the antenatal period as well as care during delivery. However, the MBR did not have information about the use of oral glucose agents, like metformin, even though insulin has been replaced by metformin in certain cases which may be seen as a decreased use of insulin. In addition, the decrease may also reflect successful diet and physical activity counselling to some extent.

In our study, the overall caesarean section rate among all women remained similar between the study periods – however, the caesarean section rate increased in GDM women after the change from risk factor-based to comprehensive screening, but decreased in the control group. It has been suggested previously that GDM diagnosis as such would predispose women to delivery induction, instrumental delivery and caesarean section with relative medical indication (Liao et al., 2014; Moss, Crowther, Hiller, Willson, & Robinson, 2007). In our study, the delivery induction rate increased from 2006 to 2010, but this increase was also seen in women without GDM. In addition, it has been debated whether a diagnosis of GDM may ‘medicalise’ a pregnancy, leading to questionable operations and related actions, higher resource usage and associated costs (Long & Cundy, 2013).

Effect for offspring

During comprehensive screening, infants born to GDM mothers were less often macrosomic and had less clavicle fractures compared to risk factor-based screening. There are some possible explanations for this decrease. First, comprehensive screening seems to identify milder cases than in risk factor-based screening, and therefore macrosomia is less probable (Crowther et al., 2005; Landon et al., 2009). Another explanation for this decrease might be uniform, successful counselling and follow up based on the new CCGs.

In offspring, the change of the screening policy led to an increased prevalence of neonatal hypoglycaemia in both diet- and insulin-treated groups. However, this was not accompanied by an increase in care at a neonatal ward. This may be due to the increased proportion of mainly diet-treated GDM leading to less severe hypoglycaemia, which was mainly treated at a maternity ward with intensified oral feedings. The administration of intravenous glucose generally requires treatment at a neonatal ward. Detailed CCGs may also have encouraged a more intensive neonatal hypoglycaemia screening policy in which all newborns of GDM mothers were monitored regardless of their symptoms, leading to increased rates of mainly mild hypoglycaemia rates which previously would have been undiagnosed.

6.1.3 Different screening guidelines and diagnostic cut-off values

The prevalence of GDM varies widely depending on the diagnostic criteria used. In Study III, the proportion of GDM was 2.4-fold higher when diagnosed by the IADPSG (31.0%) criteria as compared to diagnosis by the NICE criteria (13.1%). In the earlier studies, the prevalence of GDM according to universal IADPSG criteria varied from 10.3% to 35.5% and, according to risk factor-based NICE criteria, from 12.8% to 17.8% (Djelmis et al., 2016; Duran et al., 2014; Mayo, Melamed, Vandenberghe, & Berger, 2015; Wong, Lin, & Russell, 2017). According to the prevailing Finnish criteria, 21.3% of the study population had GDM. However, the study population did not cover all pregnant women, just those selected to have an OGTT. Hence, women with a very low risk for GDM were not included.

Mild, untreated hyperglycaemia is associated with an increased caesarean section rate and higher birth weight, as found in the HAPO study and in some other recent studies (Black et al., 2010; Disse, Graeppi-Dulac, Joncour-Mills, Dupuis, & Thivolet, 2013; Djelmis et al., 2016; Meek et al., 2015; Metzger et al., 2008). I n

our study, the proportion of LGA infants was similar in both GDM groups and controls. While the diagnostic cut-offs partly overlapped, we also had the possibility of evaluating a subgroup without treatment. The IADPSG criteria use lower fasting plasma glucose cut-off values (5.1 mmol/l) than the NICE criteria (5.5 mmol/l) or the CCGs (5.3 mmol/l). In Study III, those women with fasting plasma concentrations of 5.1 mmol/l–5.2 mmol/l (below CCG) or 5.1–5.5 mmol/l (below NICE) were also at increased risk of adverse pregnancy outcomes, such as increased birth weight and caesarean sections, a phenomenon that has also been shown to be significant in other studies (Black et al., 2010; Djelmis et al., 2016; Meek et al., 2015). However, it seems that CCGs found GDM cases with the most adverse pregnancy outcomes. Lower diagnostic cut-off values than in CCGs might still have a positive influence on mothers and newborns, especially in the long term, by finding those who are at risk for later diabetes (W. L. Lowe et al., 2018).

NICE criteria emphasise postload glucose values, with a two-hour glucose limit of 7.8 mmol/l compared to 8.5 mmol/l for the IADPSG or 8.6 mmol/l for the CCGs (Kaaja, 2013; Metzger et al., 2010; NICE, 2015). In a previous study of women diagnosed via the IADPSG criteria, normal fasting and elevated postload values indicated higher risk for preterm delivery, gestational hypertension and neonatal hyperbilirubinemia (Black et al., 2010). In our study, preterm deliveries were more common in the NICE group than in the IADPSG group or in the controls without a clear explanation for this phenomenon.

While the NICE screening policy might lead to short-term savings in terms of a smaller number of GDM women, it may also lead to a substantial number of women with adverse outcomes, such as macrosomia and caesarean section, remaining unidentified according to other widely used guidelines. Due to this risk, large-scale screening of GDM, perhaps with IADPSG criteria, is reasonable, while the treatment of even mild hyperglycaemia has been demonstrated to be associated with improved perinatal outcomes. In addition, previous GDM with glucose thresholds in the OGTT according to IADPSG criteria also found women who were at long-term risk of a glucose metabolism disorder with a mean follow-up time of 11.4 years (W. L. Lowe, Jr. et al., 2018). In that study, 52.2% of women with previous GDM developed a glucose metabolism disorder (OR 3.44, 95% CI, 2.85 to 4.14). Hence, it is important to prevent or postpone disease in this high-risk group with counselling and regular follow up.

6.1.4 The significance of the number of abnormal values in the OGTT

The significance of one abnormal OGTT value has been debated. In Study IV, the pregnancy outcome of women whose GDM diagnosis was based on only one abnormal OGTT value did not differ much from normoglycemic controls; only the proportion of delivery inductions was higher in this group. Although we did not have detailed data about how counselling was nationally put into practice, we did have access to information about how health care workers were educated after the release of the uniform guidelines.

In women with two or three abnormal values, there was increased risk of insulin treatment, caesarean section and macrosomia, as well as an increased rate of preterm deliveries. Hence, after counselling and blood glucose self-monitoring, the pregnancy and perinatal risks in women with one abnormal glucose value seem to be similar to those in the controls.

Some criteria – for example, Carpenter-Coustan and National Diabetes Data Group criteria – recommend diagnosing GDM after only two or more abnormal values. According to recommendations by the IADPSG, the WHO and the FIGO, GDM is diagnosed after detecting only one abnormal OGTT value (Hod et al., 2015; WHO, 2014). In a systematic review and meta-analysis a three-hour 100-g OGTT was done after an abnormal one-hour 50-g GCT to diagnose GDM and women with only one abnormal OGTT value remained untreated. The researchers also found that a single abnormal value, hence untreated and not defined as GDM, was associated with adverse maternal and neonatal outcomes (Roeckner et al., 2016). According to our study, counselling and treatment were found to be beneficial in women with only one abnormal OGTT value. Women with two or three abnormal OGTT values were at increased risk of adverse pregnancy outcomes and also required more health care resources: the total number of all antenatal and special health care visits was higher, and their hospital stay period after delivery was longer, compared to women with only one abnormal value.

Any degree of abnormal glucose metabolism in pregnancy has been shown to independently predict an increased risk of glucose intolerance after delivery (Corrado, D'Anna, Laganà, & Di Benedetto, 2014; Retnakaran et al., 2008). In a study of Sicilian women with a single abnormal value in the OGTT during pregnancy, they had an increased risk of developing abnormal glucose tolerance in later life; and among these women, overweightness was the most predictive factor for later diabetes. In recent Finnish studies, it has been shown that the incidence of subsequent type II diabetes mellitus and metabolic syndrome increases in women

after one abnormal OGTT value during pregnancy (Hakkarainen et al., 2015, 2016). The probability of these disturbances was reported to increase together with the number of abnormal OGTT values obtained during follow up after 10 years.

6.1.5 Burden to health care system

Current concerns about high health care costs have increased because of the increasing prevalence of GDM and the already resource-constrained health care system. In the Atlantic Diabetes in Pregnancy study from Ireland, the costs of GDM care during pregnancy were 34% greater than in pregnancies without GDM – the mean cost for maternity care for GDM women was 6 092 € (SD 4 422 €); in non-GDM women, the cost of maternity care was 4 028 € (SD 2 938 €) (Gillespie, Cullinan, O'Neill, Dunne, & Collaborators, 2013). When evaluating the total costs of health care and GDM screening in our study with regard to the change from risk factor-based to comprehensive screening, the total cost of treating one GDM mother was 12.8% less expensive during comprehensive screening than during risk factor-based screening. This evaluation included OGTTs, primary and special health care visits, and hospital stays of mothers and offspring, including delivery. We calculated the unit and total costs of care of GDM and control women during both time periods. In all groups, the highest single cost was the hospital stay of the newborn. By implementing a uniform national policy to screen and treat GDM, the costs per single pregnancy can be reduced.

After 2008, for the first time, uniform national guidelines were introduced, and cooperation between primary and special health care services was also encouraged. Although the number of antenatal visits per woman decreased at both the primary and secondary levels during comprehensive screening, the significant increase in the number of GDM women poses a burden on the health care system. However, via the national follow-up and treatment guidelines, more visits can be accommodated in primary care. In another Finnish study, costs were 25.1% higher among women diagnosed with GDM than among women without GDM (6 432 € vs. 5 143 €, $p < 0.001$). In this study, the costs of inpatient visits and neonatal intensive care unit use were 44% and 49% higher, respectively, in the GDM group than in the non-GDM group.

Treating even mild GDM has been found to be cost-effective in terms of improving maternal and neonatal outcomes, including decreased rates of pre-eclampsia, caesarean sections, macrosomia, shoulder dystocia, permanent and transient brachial plexus injury, neonatal hypoglycaemia, neonatal

hyperbilirubinemia, and neonatal intensive care unit admissions (Ohno, Sparks, Cheng, & Caughey, 2011). According to Ohno and colleagues, lowering the thresholds for diagnosing GDM might be cost-effective. However, the benefits of diagnosing and providing treatment for GDM must be weighed against the increased costs and use of health care resources, especially in women with mild GDM. It is conceivable that the mildest form of GDM could be followed-up in primary care with comprehensive guidelines.

GDM increases the short-term morbidity of the mother and offspring, but it also serves as an indicator of increased risk for subsequent type II diabetes and other metabolic disturbances (Freire et al., 2012; Ijäs et al., 2013; Pirkola, Pouta, Bloigu, Hartikainen, et al., 2010; Pirkola, Pouta, Bloigu, Miettola, et al., 2010). Thus, the cost-effectiveness of GDM screening is reported to be mainly based on identifying these risk groups and on the possibility of preventing or delaying the onset of type II diabetes (Werner et al., 2012). Therefore, it is probable that the costs of effective screening will be compensated in the future.

GDM is also associated with increased costs postpartum. In an Irish study, an additional 680 € in annual health care costs accrued among GDM mothers from two to five years after pregnancy compared to a normal glucose tolerance group (Danyliv et al., 2015). The postponing and prevention of type II diabetes demands effective postpartum follow-up programmes with a high attendance rate (Korpi-Hyövälti, Laaksonen, Schwab, Heinonen, & Niskanen, 2012; Lauenborg et al., 2004). However, the incorporation of long-term benefits of GDM screening and treatment has an enormous impact on cost-effectiveness. Most studies focused on the costs of screening itself leave eventual long-term cost savings unidentified, which might unfavourably bias the cost-effectiveness estimates (Weile et al., 2015). Estimating the cost-effectiveness of type II diabetes prevention after GDM is more difficult to study. For this purpose, different decision analysis models have been developed (Werner et al., 2012).

6.2 Strengths of the study

The strengths of the present study include the use of a large national cohort with high data validity (Gissler & Shelley, 2002; Gissler, Teperi, Hemminki, & Meriläinen, 1995; Keikkala et al., 2020). The population in Finland is also very homogenous – during the study period, 94.7% of women aged 15–49 years were of Finnish ancestry and can therefore be generalised for the Caucasian population.

In Finland, antenatal care is free of charge and is practically universally used. It is obligatory for the delivery hospital to report every birth to the MBR. Therefore, the study population was unselected and virtually complete (Gissler & Shelley, 2002; Gissler et al., 1995; Keikkala et al., 2020).

The diagnosis of GDM was established according to recorded abnormal OGTT results or initiated insulin treatment, which can be considered reliable and comparable during the two study years. In addition, in Studies III and IV, we also had numerical OGTT results, so the diagnosis of GDM was complete. The number of OGTT results was considerable, and the number of different subgroups was also sufficient.

6.3 Limitations of the study

There were also some limitations in this study. The use of comprehensive screening has resulted in an increase in the prevalence of GDM during recent years. The screening frequency has increased from 51.4% in 2009–2012 to 66.0% in 2018, and the prevalence of GDM has increased from 11.3% to 21.3%. Thus, the implementation of new national screening guidelines was not fully comprehensive during the study period.

Moreover, in the observational studies, Studies I and II, it was difficult to distinguish between changes resulting from the new screening policy and those occurring due to time trends, i.e. changes that would have occurred anyway. However, the strongly statistically significant interactions between GDM and study year show that changes in characteristics such as maternal pre-pregnancy BMI and parity between the two study years were different in mothers with and without GDM, thereby supporting the effect of a policy change.

The change in the screening protocol led to a substantial increase in the number of OGTTs performed, and consequently an increase in GDM diagnoses and the need for counselling and follow up. However, we did not have an information about how the counselling guidelines were fulfilled in primary care. We also only had data for insulin treatment, not for the use of oral glucose agents, such as metformin. Because Finland has low perinatal mortality and advanced perinatal care, the effect of intensive screening on short-term perinatal outcomes may be difficult to detect. In addition, despite the large amount of data, the power to estimate rare severe outcomes (such as shoulder dystocia or perinatal death) was insufficient. Women at very low risk of GDM were not included in this study because, according to the national guidelines, they were not tested during pregnancy.

6.4 Future research

The significance of abnormal fasting and postprandial values of the OGTT needs more research. Additionally, the timing and repeatability of the OGTT would be interesting avenues for future research. In addition, in Nordic countries, the seasonality of the OGTT and the prevalence of GDM may represent an additional factor in interpreting OGTT results because, in Scandinavia, there are wide fluctuations in ambient temperatures, and this phenomenon could serve as an interesting basis for future studies.

Whether GDM screening and management by different screening criteria are cost-effective has been the subject of an ongoing debate for more than a decade, and the suggestion of new, even tighter criteria by the IADPSG has only added to the discussion. Although the association between GDM and the long-term health of mothers and their offspring has been demonstrated, we are only beginning to understand which interventions might be effective at reducing the health care burden, and at what cost. Further, the cost-effectiveness of large-scale screening, and the implementation and effect of counselling and treatment, should be further evaluated, with the increased pressures on maternal care balanced against the possible improvements in perinatal outcomes. Then, interventions at the national and global levels should be implemented.

Future research should address the potential of GDM screening to prevent the effects of type II diabetes in later maternity and in the lives of offspring. The long-term consequences of different screening methods require further study. Different diagnostic criteria have yielded conflicting results, although the Finnish system appears to be quite effective. The FinnGeDi register study is planned to continue for decades, thereby permitting the long-term follow up of mothers and their offspring.

7 Conclusions

Based on the results of the present study, the following conclusions can be made:

I The change from risk factor-based to comprehensive GDM screening led to a significant increase in GDM prevalence, mainly with mild, diet-treated disease. Women with GDM were more often primiparous and had a lower BMI. The increase in the caesarean section rate was more concentrated in GDM mothers, while the overall caesarean section rate remained unchanged.

II During comprehensive screening, infants of GDM mothers had a lower birth weight, were less often macrosomic, and were more often hypoglycaemic. However, hypoglycaemia cases were treated in a neonatal ward less often.

III The GDM prevalence was 2.4-fold higher when the IADPSG diagnostic criteria for GDM were compared to the NICE criteria. Finnish guidelines seem to identify GDM cases with the most adverse pregnancy outcomes, but birth weight and the caesarean section rate began to increase slightly under nationally used cut-offs in the mild, untreated hyperglycaemia group.

IV All women with abnormal OGTT results are at increased risk of induced labour, but risks of macrosomia or caesarean section are increased only when there are two or three abnormal OGTT values. Lifestyle counselling of all GDM women regardless of the number of abnormal values in the OGTT is important to improve the pregnancy outcome, but also because of the risk of subsequent diabetes reported in previous studies.

References

ACOG. (2018). ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. *Obstet Gynecol, 131*(2), e49–e64. https://doi.org/10.1097/aog.0000000000002501

ADA. (1980). American Diabetes Association Workshop-Conference on gestational diabetes: summary and recommendations. *Diabetes Care, 3*(3), 499–501.

ADA. (2019). 2. Classification and Diagnosis of Diabetes: *Diabetes Care, 42*(Suppl 1), S13–S28. https://doi.org/10.2337/dc19-S002

Aroda, V. R., Christophi, C. A., Edelstein, S. L., Zhang, P., Herman, W. H., Barrett-Connor, E., … Ratner, R. E. (2015). The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes: the Diabetes Prevention Program outcomes study 10-year follow-up. *J Clin Endocrinol Metab, 100*(4), 1646–1653. https://doi.org/10.1210/jc.2014-3761

Avalos, G. E., Owens, L. A., & Dunne, F. (2013). Applying current screening tools for gestational diabetes mellitus to a European population: is it time for change? *Diabetes Care, 36*(10), 3040–3044. https://doi.org/10.2337/dc12-2669

Bain, E., Crane, M., Tieu, J., Han, S., Crowther, C. A., & Middleton, P. (2015). Diet and exercise interventions for preventing gestational diabetes mellitus. *Cochrane Database Syst Rev*(4), Cd010443. https://doi.org/10.1002/14651858.CD010443.pub2

Bajaj, H., Ye, C., Hanley, A. J., Connelly, P. W., Sermer, M., Zinman, B., & Retnakaran, R. (2017). Prior lactation reduces future diabetic risk through sustained postweaning effects on insulin sensitivity. *Am J Physiol Endocrinol Metab, 312*(3), E215–e223. https://doi.org/10.1152/ajpendo.00403.2016

Balsells, M., García-Patterson, A., Solà, I., Roqué, M., Gich, I., & Corcoy, R. (2015). Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis. *BMJ, 350*, h102. https://doi.org/10.1136/bmj.h102

Behboudi-Gandevani, S., Amiri, M., Bidhendi Yarandi, R., & Ramezani Tehrani, F. (2019). The impact of diagnostic criteria for gestational diabetes on its prevalence: a systematic review and meta-analysis. *Diabetol Metab Syndr, 11*, 11. https://doi.org/10.1186/s13098-019-0406-1

Billionnet, C., Mitanchez, D., Weill, A., Nizard, J., Alla, F., Hartemann, A., & Jacqueminet, S. (2017). Gestational diabetes and adverse perinatal outcomes from 716,152 births in France in 2012. *Diabetologia, 60*(4), 636–644. https://doi.org/10.1007/s00125-017-4206-6

Black, M. H., Sacks, D. A., Xiang, A. H., & Lawrence, J. M. (2010). Clinical outcomes of pregnancies complicated by mild gestational diabetes mellitus differ by combinations of abnormal oral glucose tolerance test values. *Diabetes Care, 33*(12), 2524–2530. https://doi.org/10.2337/dc10-1445

Blumer, I., Hadar, E., Hadden, D. R., Jovanovič, L., Mestman, J. H., Murad, M. H., & Yogev, Y. (2013). Diabetes and pregnancy: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab, 98*(11), 4227–4249. https://doi.org/10.1210/jc.2013-2465

Brown, J., Alwan, N. A., West, J., Brown, S., McKinlay, C. J., Farrar, D., & Crowther, C. A. (2017). Lifestyle interventions for the treatment of women with gestational diabetes. *Cochrane Database Syst Rev, 5*(5), Cd011970. https://doi.org/10.1002/14651858.CD011970.pub2

Buchanan, T. A., Xiang, A., Kjos, S. L., & Watanabe, R. (2007). What is gestational diabetes? *Diabetes Care, 30 Suppl 2*, S105–111. https://doi.org/10.2337/dc07-s201

Burlina, S., Dalfrà, M. G., & Lapolla, A. (2019). Short- and long-term consequences for offspring exposed to maternal diabetes: a review. *J Matern Fetal Neonatal Med, 32*(4), 687–694. https://doi.org/10.1080/14767058.2017.1387893

Camelo Castillo, W., Boggess, K., Stürmer, T., Brookhart, M. A., Benjamin, D. K., Jr., & Jonsson Funk, M. (2014). Trends in glyburide compared with insulin use for gestational diabetes treatment in the United States, 2000–2011. *Obstet Gynecol, 123*(6), 1177–1184. https://doi.org/10.1097/aog.0000000000000285

Camelo Castillo, W., Boggess, K., Stürmer, T., Brookhart, M. A., Benjamin, D. K., Jr., & Jonsson Funk, M. (2015). Association of Adverse Pregnancy Outcomes With Glyburide vs Insulin in Women With Gestational Diabetes. *JAMA Pediatr, 169*(5), 452–458. https://doi.org/10.1001/jamapediatrics.2015.74

Carpenter, M. W., & Coustan, D. R. (1982). Criteria for screening tests for gestational diabetes. *Am J Obstet Gynecol, 144*(7), 768–773. https://doi.org/10.1016/0002-9378(82)90349-0

Carrington, E. R., Shuman, C. R., & Reardon, H. S. (1957). Evaluation of the prediabetic state during pregnancy. *Obstet Gynecol, 9*(6), 664–669. https://doi.org/10.1097/00006250-195706000-00008

Catalano, P. M., Avallone, D. A., Drago, N. M., & Amini, S. B. (1993). Reproducibility of the oral glucose tolerance test in pregnant women. *Am J Obstet Gynecol, 169*(4), 874–881. https://doi.org/10.1016/0002-9378(93)90019-f

Catalano, P. M., Huston, L., Amini, S. B., & Kalhan, S. C. (1999). Longitudinal changes in glucose metabolism during pregnancy in obese women with normal glucose tolerance and gestational diabetes mellitus. *Am J Obstet Gynecol, 180*(4), 903–916. https://doi.org/10.1016/s0002-9378(99)70662-9

Catalano, P. M., McIntyre, H. D., Cruickshank, J. K., McCance, D. R., Dyer, A. R., Metzger, B. E., … Oats, J. J. (2012). The hyperglycemia and adverse pregnancy outcome study: associations of GDM and obesity with pregnancy outcomes. *Diabetes Care, 35*(4), 780–786. https://doi.org/10.2337/dc11-1790

Chen, P., Wang, S., Ji, J., Ge, A., Chen, C., Zhu, Y., … Wang, Y. (2015). Risk factors and management of gestational diabetes. *Cell Biochem Biophys, 71*(2), 689–694. https://doi.org/10.1007/s12013-014-0248-2

Clausen, T. D., Mathiesen, E. R., Hansen, T., Pedersen, O., Jensen, D. M., Lauenborg, J., & Damm, P. (2008). High prevalence of type 2 diabetes and pre-diabetes in adult offspring of women with gestational diabetes mellitus or type 1 diabetes: the role of intrauterine hyperglycemia. *Diabetes Care, 31*(2), 340–346. https://doi.org/10.2337/dc07-1596

Colagiuri, S., Falavigna, M., Agarwal, M. M., Boulvain, M., Coetzee, E., Hod, M., … Yang, H. X. (2014). Strategies for implementing the WHO diagnostic criteria and classification of hyperglycaemia first detected in pregnancy. *Diabetes Res Clin Pract, 103*(3), 364–372. https://doi.org/10.1016/j.diabres.2014.02.012

Corrado, F., D'Anna, R., Laganà, A. S., & Di Benedetto, A. (2014). Abnormal glucose tolerance later in life in women affected by glucose intolerance during pregnancy. *J Obstet Gynaecol, 34*(2), 123–126. https://doi.org/10.3109/01443615.2013.841658

Crowther, C. A., Hiller, J. E., Moss, J. R., McPhee, A. J., Jeffries, W. S., & Robinson, J. S. (2005). Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med, 352*(24), 2477–2486. https://doi.org/10.1056/NEJMoa042973

Dahanayaka, N. J., Agampodi, S. B., Ranasinghe, O. R., Jayaweera, P. M., Wickramasinghe, W. A., Adhikari, A. N., … Dissanayaka, U. T. (2012). Inadequacy of the risk factor based approach to detect gestational diabetes mellitus. *Ceylon Med J, 57*(1), 5–9. https://doi.org/10.4038/cmj.v57i1.4193

Desoye, G., & van Poppel, M. (2015). The feto-placental dialogue and diabesity. *Best Pract Res Clin Obstet Gynaecol, 29*(1), 15–23. https://doi.org/10.1016/j.bpobgyn.2014.05.012

Di Cianni, G., Lacaria, E., Lencioni, C., & Resi, V. (2018). Preventing type 2 diabetes and cardiovascular disease in women with gestational diabetes - The evidence and potential strategies. *Diabetes Res Clin Pract, 145*, 184–192. https://doi.org/10.1016/j.diabres.2018.04.021

Di Cianni, G., Miccoli, R., Volpe, L., Lencioni, C., & Del Prato, S. (2003). Intermediate metabolism in normal pregnancy and in gestational diabetes. *Diabetes Metab Res Rev, 19*(4), 259–270. https://doi.org/10.1002/dmrr.390

Disse, E., Graeppi-Dulac, J., Joncour-Mills, G., Dupuis, O., & Thivolet, C. (2013). Heterogeneity of pregnancy outcomes and risk of LGA neonates in Caucasian females according to IADPSG criteria for gestational diabetes mellitus. *Diabetes Metab, 39*(2), 132–138. https://doi.org/10.1016/j.diabet.2012.09.006

Djelmis, J., Pavić, M., Mulliqi Kotori, V., Pavlić Renar, I., Ivanisevic, M., & Oreskovic, S. (2016). Prevalence of gestational diabetes mellitus according to IADPSG and NICE criteria. *Int J Gynaecol Obstet, 135*(3), 250–254. https://doi.org/10.1016/j.ijgo.2016.07.005

Dodd, J. M., Turnbull, D., McPhee, A. J., Deussen, A. R., Grivell, R. M., Yelland, L. N., … Robinson, J. S. (2014). Antenatal lifestyle advice for women who are overweight or obese: LIMIT randomised trial. *BMJ, 348*, g1285. https://doi.org/10.1136/bmj.g1285

Dugan, J. A., & Ma Crawford, J. (2019). Managing gestational diabetes. *Jaapa, 32*(9), 21–25. https://doi.org/10.1097/01.JAA.0000578760.60265.e0

Duncan, J. (1882). On puerperal diabetes. . *Trans Obstet Soc London., 24(256)*.

Duran, A., Sáenz, S., Torrejón, M. J., Bordiú, E., Del Valle, L., Galindo, M., … Calle-Pascual, A. L. (2014). Introduction of IADPSG criteria for the screening and diagnosis of gestational diabetes mellitus results in improved pregnancy outcomes at a lower cost in a large cohort of pregnant women: the St. Carlos Gestational Diabetes Study. *Diabetes Care, 37*(9), 2442–2450. https://doi.org/10.2337/dc14-0179

Eades, C. E., Cameron, D. M., & Evans, J. M. M. (2017). Prevalence of gestational diabetes mellitus in Europe: A meta-analysis. *Diabetes Res Clin Pract, 129*, 173–181. https://doi.org/10.1016/j.diabres.2017.03.030

Fadl, H. E., Gärdefors, S., Hjertberg, R., Nord, E., Persson, B., Schwarcz, E., … Hanson, U. S. (2015). Randomized controlled study in pregnancy on treatment of marked hyperglycemia that is short of overt diabetes. *Acta Obstet Gynecol Scand, 94*(11), 1181–1187. https://doi.org/10.1111/aogs.12717

Fadl, H. E., Ostlund, I. K., Magnuson, A. F., & Hanson, U. S. (2010). Maternal and neonatal outcomes and time trends of gestational diabetes mellitus in Sweden from 1991 to 2003. *Diabet Med, 27*(4), 436–441. https://doi.org/10.1111/j.1464-5491.2010.02978.x

Farrar, D., Simmonds, M., Bryant, M., Lawlor, D. A., Dunne, F., Tuffnell, D., & Sheldon, T. A. (2017). Risk factor screening to identify women requiring oral glucose tolerance testing to diagnose gestational diabetes: A systematic review and meta-analysis and analysis of two pregnancy cohorts. *PLoS One, 12*(4), e0175288. https://doi.org/10.1371/journal.pone.0175288

Farrar, D., Simmonds, M., Bryant, M., Sheldon, T. A., Tuffnell, D., Golder, S., & Lawlor, D. A. (2017). Treatments for gestational diabetes: a systematic review and meta-analysis. *BMJ Open, 7*(6), e015557. https://doi.org/10.1136/bmjopen-2016-015557

Ferrara, A. (2007). Increasing prevalence of gestational diabetes mellitus: a public health perspective. *Diabetes Care, 30 Suppl 2*, S141–146. https://doi.org/10.2337/dc07-s206

Ferrara, A., Hedderson, M. M., Albright, C. L., Ehrlich, S. F., Quesenberry, C. P., Jr., Peng, T., … Crites, Y. (2011). A pregnancy and postpartum lifestyle intervention in women with gestational diabetes mellitus reduces diabetes risk factors: a feasibility randomized control trial. *Diabetes Care, 34*(7), 1519–1525. https://doi.org/10.2337/dc10-2221

Gissler, M., & Shelley, J. (2002). Quality of data on subsequent events in a routine Medical Birth Register. *Med Inform Internet Med, 27*(1), 33–38. https://doi.org/10.1080/14639230110119234

Gissler, M., Teperi, J., Hemminki, E., & Meriläinen, J. (1995). Data quality after restructuring a national medical registry. *Scand J Soc Med, 23*(1), 75–80. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/7784857

Goldstein, R. F., Abell, S. K., Ranasinha, S., Misso, M., Boyle, J. A., Black, M. H., … Teede, H. J. (2017). Association of Gestational Weight Gain With Maternal and Infant Outcomes: A Systematic Review and Meta-analysis. *JAMA, 317*(21), 2207–2225. https://doi.org/10.1001/jama.2017.3635

Guo, J., Chen, J. L., Whittemore, R., & Whitaker, E. (2016). Postpartum Lifestyle Interventions to Prevent Type 2 Diabetes Among Women with History of Gestational Diabetes: A Systematic Review of Randomized Clinical Trials. *J Womens Health (Larchmt), 25*(1), 38–49. https://doi.org/10.1089/jwh.2015.5262

Guo, L., Ma, J., Tang, J., Hu, D., Zhang, W., & Zhao, X. (2019). Comparative Efficacy and Safety of Metformin, Glyburide, and Insulin in Treating Gestational Diabetes Mellitus: A Meta-Analysis. *J Diabetes Res, 2019*, 9804708. https://doi.org/10.1155/2019/9804708

Hadden, D. R. (1998). A historical perspective on gestational diabetes. *Diabetes Care, 21 Suppl 2*, B3–4.

Hakkarainen, H., Huopio, H., Cederberg, H., Pääkkönen, M., Voutilainen, R., & Heinonen, S. (2015). Post-challenge glycemia during pregnancy as a marker of future risk of type 2 diabetes: a prospective cohort study. *Gynecol Endocrinol, 31*(7), 573–577. https://doi.org/10.3109/09513590.2015.1032926

Hakkarainen, H., Huopio, H., Cederberg, H., Pääkkönen, M., Voutilainen, R., & Heinonen, S. (2016). The risk of metabolic syndrome in women with previous GDM in a long-term follow-up. *Gynecol Endocrinol, 32*(11), 920–925. https://doi.org/10.1080/09513590.2016.1198764

Hildén, K., Magnuson, A., Hanson, U., Simmons, D., & Fadl, H. (2020). Trends in pregnancy outcomes for women with gestational diabetes mellitus in Sweden 1998–2012: a nationwide cohort study. *Diabet Med*. https://doi.org/10.1111/dme.14266

Huvinen, E., Koivusalo, S. B., Meinilä, J., Valkama, A., Tiitinen, A., Rönö, K., … Eriksson, J. G. (2018). Effects of a Lifestyle Intervention During Pregnancy and First Postpartum Year: Findings From the RADIEL Study. *J Clin Endocrinol Metab, 103*(4), 1669–1677. https://doi.org/10.1210/jc.2017-02477

Ijäs, H., Koivunen, S., Raudaskoski, T., Kajantie, E., Gissler, M., & Vääräsmäki, M. (2019). Independent and concomitant associations of gestational diabetes and maternal obesity to perinatal outcome: A register-based study. *PLoS One, 14*(8), e0221549. https://doi.org/10.1371/journal.pone.0221549

Ijäs, H., Morin-Papunen, L., Keränen, A. K., Bloigu, R., Ruokonen, A., Puukka, K., … Vääräsmäki, M. (2013). Pre-pregnancy overweight overtakes gestational diabetes as a risk factor for subsequent metabolic syndrome. *Eur J Endocrinol, 169*(5), 605–611. https://doi.org/10.1530/eje-13-0412

Ijäs, H., Vääräsmäki, M., Morin-Papunen, L., Keravuo, R., Ebeling, T., Saarela, T., & Raudaskoski, T. (2011). Metformin should be considered in the treatment of gestational diabetes: a prospective randomised study. *BJOG, 118*(7), 880–885. https://doi.org/10.1111/j.1471-0528.2010.02763.x

Ijäs, H., Vääräsmäki, M., Saarela, T., Keravuo, R., & Raudaskoski, T. (2015). A follow-up of a randomised study of metformin and insulin in gestational diabetes mellitus: growth and development of the children at the age of 18 months. *BJOG, 122*(7), 994–1000. https://doi.org/10.1111/1471-0528.12964

Immanuel, J., & Simmons, D. (2017). Screening and Treatment for Early-Onset Gestational Diabetes Mellitus: a Systematic Review and Meta-analysis. *Curr Diab Rep, 17*(11), 115. https://doi.org/10.1007/s11892-017-0943-7

Jørgensen, J. M., Hedley, P. L., Gjerris, M., & Christiansen, M. (2014). Ethical issues related to screening for preeclampsia. *Bioethics, 28*(7), 360–367. https://doi.org/10.1111/j.1467-8519.2012.02005.x

Kaaja, R. (2013). [Update on current care guideline: gestational diabetes]. *Duodecim, 129*(17), 1798–1799.

Kaseva, N., Vääräsmäki, M., Matinolli, H. M., Sipola-Leppänen, M., Tikanmäki, M., Heinonen, K., … Kajantie, E. (2018). Pre-pregnancy overweight or obesity and gestational diabetes as predictors of body composition in offspring twenty years later: evidence from two birth cohort studies. *Int J Obes (Lond), 42*(4), 872–879. https://doi.org/10.1038/ijo.2017.277

Kaseva, N., Vääräsmäki, M., Sundvall, J., Matinolli, H. M., Sipola, M., Tikanmäki, M., … Kajantie, E. (2019). Gestational Diabetes But Not Prepregnancy Overweight Predicts for Cardiometabolic Markers in Offspring Twenty Years Later. *J Clin Endocrinol Metab, 104*(7), 2785–2795. https://doi.org/10.1210/jc.2018-02743

Kawasaki, M., Arata, N., Miyazaki, C., Mori, R., Kikuchi, T., Ogawa, Y., & Ota, E. (2018). Obesity and abnormal glucose tolerance in offspring of diabetic mothers: A systematic review and meta-analysis. *PLoS One, 13*(1), e0190676. https://doi.org/10.1371/journal.pone. 0190676

Keikkala, E., Mustaniemi, S., Koivunen, S., Kinnunen, J., Viljakainen, M., Männisto, T., … Vääräsmäki, M. (2020). Cohort Profile: The Finnish Gestational Diabetes (FinnGeDi) Study. *Int J Epidemiol*. https://doi.org/10.1093/ije/dyaa039

Koivusalo, S. B., Rönö, K., Klemetti, M. M., Roine, R. P., Lindström, J., Erkkola, M., … Stach-Lempinen, B. (2016). Gestational Diabetes Mellitus Can Be Prevented by Lifestyle Intervention: The Finnish Gestational Diabetes Prevention Study (RADIEL): A Randomized Controlled Trial. *Diabetes Care, 39*(1), 24–30. https://doi.org/10.2337/dc15-0511

Kong, L., Nilsson, I. A. K., Gissler, M., & Lavebratt, C. (2019). Associations of Maternal Diabetes and Body Mass Index With Offspring Birth Weight and Prematurity. *JAMA Pediatr, 173*(4), 371-378. https://doi.org/10.1001/jamapediatrics.2018.5541

Kramer, C. K., Campbell, S., & Retnakaran, R. (2019). Gestational diabetes and the risk of cardiovascular disease in women: a systematic review and meta-analysis. *Diabetologia, 62*(6), 905–914. https://doi.org/10.1007/s00125-019-4840-2

Lain, K. Y., & Catalano, P. M. (2007). Metabolic changes in pregnancy. *Clin Obstet Gynecol, 50*(4), 938–948. https://doi.org/10.1097/GRF.0b013e31815a5494

Landon, M. B., Mele, L., Spong, C. Y., Carpenter, M. W., Ramin, S. M., Casey, B., … Anderson, G. D. (2011). The relationship between maternal glycemia and perinatal outcome. *Obstet Gynecol, 117*(2 Pt 1), 218–224. https://doi.org/10.1097/aog.0b013e318203ebe0

Landon, M. B., Spong, C. Y., Thom, E., Carpenter, M. W., Ramin, S. M., Casey, B., … Anderson, G. B. (2009). A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med, 361*(14), 1339–1348. https://doi.org/10.1056/NEJMoa0902430

Langer, O. (2018). Pharmacological treatment of gestational diabetes mellitus: point/counterpoint. *Am J Obstet Gynecol, 218*(5), 490–499. https://doi.org/10.1016/j.ajog. 2018.01.024

Lapolla, A., & Metzger, B. E. (2018). The post-HAPO situation with gestational diabetes: the bright and dark sides. *Acta Diabetol, 55*(9), 885–892. https://doi.org/10.1007/s00592-018-1146-7

Lekva, T., Bollerslev, J., Norwitz, E. R., Aukrust, P., Henriksen, T., & Ueland, T. (2015). Aortic Stiffness and Cardiovascular Risk in Women with Previous Gestational Diabetes Mellitus. *PLoS One, 10*(8), e0136892. https://doi.org/10.1371/journal.pone.0136892

Lepercq, J., Lin, J., Hall, G. C., Wang, E., Dain, M. P., Riddle, M. C., & Home, P. D. (2012). Meta-Analysis of Maternal and Neonatal Outcomes Associated with the Use of Insulin Glargine versus NPH Insulin during Pregnancy. *Obstet Gynecol Int, 2012*, 649070. https://doi.org/10.1155/2012/649070

Li, Z., Cheng, Y., Wang, D., Chen, H., Chen, H., Ming, W. K., & Wang, Z. (2020). Incidence Rate of Type 2 Diabetes Mellitus after Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis of 170,139 Women. *J Diabetes Res, 2020*, 3076463. https://doi.org/10.1155/2020/3076463

Lowe, W. L., Jr., Scholtens, D. M., Lowe, L. P., Kuang, A., Nodzenski, M., Talbot, O., … Metzger, B. E. (2018). Association of Gestational Diabetes With Maternal Disorders of Glucose Metabolism and Childhood Adiposity. *JAMA, 320*(10), 1005–1016. https://doi.org/10.1001/jama.2018.11628

Lowe, W. L., Scholtens, D. M., Lowe, L. P., Kuang, A., Nodzenski, M., Talbot, O., … Group, H. F.-u. S. C. R. (2018). Association of Gestational Diabetes With Maternal Disorders of Glucose Metabolism and Childhood Adiposity. *JAMA, 320*(10), 1005–1016. https://doi.org/10.1001/jama.2018.11628

Lu, J., Zhang, S., Li, W., Leng, J., Wang, L., Liu, H., … Hu, G. (2019). Maternal Gestational Diabetes Is Associated With Offspring's Hypertension. *Am J Hypertens, 32*(4), 335–342. https://doi.org/10.1093/ajh/hpz005

Mathiesen, E. R., Hod, M., Ivanisevic, M., Duran Garcia, S., Brøndsted, L., Jovanovic, L., … McCance, D. R. (2012). Maternal efficacy and safety outcomes in a randomized, controlled trial comparing insulin detemir with NPH insulin in 310 pregnant women with type 1 diabetes. *Diabetes Care, 35*(10), 2012–2017. https://doi.org/ 10.2337/dc11-2264

McIntyre, H. D., Catalano, P., Zhang, C., Desoye, G., Mathiesen, E. R., & Damm, P. (2019). Gestational diabetes mellitus. *Nat Rev Dis Primers, 5*(1), 47. https://doi.org/10.1038/s41572-019-0098-8

McIntyre, H. D., Jensen, D. M., Jensen, R. C., Kyhl, H. B., Jensen, T. K., Glintborg, D., & Andersen, M. (2018). Gestational Diabetes Mellitus: Does One Size Fit All? A Challenge to Uniform Worldwide Diagnostic Thresholds. *Diabetes Care, 41*(7), 1339–1342. https://doi.org/10.2337/dc17-2393

Meek, C. L. (2017). Natural selection? The evolution of diagnostic criteria for gestational diabetes. *Ann Clin Biochem, 54*(1), 33–42. https://doi.org/10.1177/0004563216674743

Meek, C. L., Lewis, H. B., Patient, C., Murphy, H. R., & Simmons, D. (2015). Diagnosis of gestational diabetes mellitus: falling through the net. *Diabetologia, 58*(9), 2003–2012. https://doi.org/10.1007/s00125-015-3647-z

Meltzer, S. J., Snyder, J., Penrod, J. R., Nudi, M., & Morin, L. (2010). Gestational diabetes mellitus screening and diagnosis: a prospective randomised controlled trial comparing costs of one-step and two-step methods. *BJOG, 117*(4), 407–415. https://doi.org/ 10.1111/j.1471-0528.2009.02475.x

Meshel, S., Schejter, E., Harel, T., Maslovitz, S., Germez, N., Elimelech, B., … Azuri, J. (2016). Can we predict the need for pharmacological treatment according to demographic and clinical characteristics in gestational diabetes? *J Matern Fetal Neonatal Med, 29*(13), 2062–2066. https://doi.org/10.3109/14767058.2015.1077225

Metzger, B. E., & Coustan, D. R. (1998). Summary and recommendations of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus. The Organizing Committee. *Diabetes Care, 21 Suppl 2*, B161–167. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9704245

Metzger, B. E., Gabbe, S. G., Persson, B., Buchanan, T. A., Catalano, P. A., Damm, P., … Panel, I. A. o. D. a. P. S. G. C. (2010). International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care, 33*(3), 676–682. https://doi.org/10.2337/dc09-1848

Metzger, B. E., Lowe, L. P., Dyer, A. R., Trimble, E. R., Chaovarindr, U., Coustan, D. R., … Group, H. S. C. R. (2008). Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med, 358*(19), 1991–2002. https://doi.org/10.1056/NEJMoa0707943

Mijatovic-Vukas, J., Capling, L., Cheng, S., Stamatakis, E., Louie, J., Cheung, N. W., … Flood, V. M. (2018). Associations of Diet and Physical Activity with Risk for Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis. *Nutrients, 10*(6). https://doi.org/10.3390/nu10060698

Murphy, N. M., McCarthy, F. P., Khashan, A. S., Myers, J. E., Simpson, N. A., Kearney, P. M., … Kenny, L. C. (2016). Compliance with National Institute of Health and Care Excellence risk-based screening for Gestational Diabetes Mellitus in nulliparous women. *Eur J Obstet Gynecol Reprod Biol, 199*, 60–65. https://doi.org/10.1016/j.ejogrb.2016.01.044

Mustaniemi, S., Vääräsmäki, M., Eriksson, J. G., Gissler, M., Laivuori, H., Ijäs, H., … Morin-Papunen, L. (2018). Polycystic ovary syndrome and risk factors for gestational diabetes. *Endocr Connect, 7*(7), 859–869. https://doi.org/10.1530/EC-18-0076

Najafi, F., Hasani, J., Izadi, N., Hashemi-Nazari, S. S., Namvar, Z., Mohammadi, S., & Sadeghi, M. (2019). The effect of prepregnancy body mass index on the risk of gestational diabetes mellitus: A systematic review and dose-response meta-analysis. *Obes Rev, 20*(3), 472–486. https://doi.org/10.1111/obr.12803

Nguyen, T. H., Yang, J. W., Mahone, M., & Godbout, A. (2016). Are There Benefits for Gestational Diabetes Mellitus in Treating Lower Levels of Hyperglycemia Than Standard Recommendations? *Can J Diabetes, 40*(6), 548–554. https://doi.org/10.1016/j.jcjd.2016.05.009

NICE. (2015). Diabetes in pregnancy: management from preconception to the postnatal period. In.

Nørgaard, K., Sukumar, N., Rafnsson, S. B., & Saravanan, P. (2018). Efficacy and Safety of Rapid-Acting Insulin Analogs in Special Populations with Type 1 Diabetes or Gestational Diabetes: Systematic Review and Meta-Analysis. *Diabetes Ther, 9*(3), 891–917. https://doi.org/10.1007/s13300-018-0411-7

O'Sullivan, J. B., Charles, D., Mahan, C. M., & Dandrow, R. V. (1973). Gestational diabetes and perinatal mortality rate. *Am J Obstet Gynecol, 116*(7), 901–904. https://doi.org/10.1016/s0002-9378(16)33834-0

O'Sullivan, J. B., Gellis, S. S., Dandrow, R. V., & Tenney, B. O. (1966). The potential diabetic and her treatment in pregnancy. *Obstet Gynecol, 27*(5), 683–689. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/5936737

O'Sullivan, J. B., & Mahan, C. M. (1964). CRITERIA FOR THE ORAL GLUCOSE TOLERANCE TEST IN PREGNANCY. *Diabetes, 13*, 278–285. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/14166677

Ojo, O., Weldon, S. M., Thompson, T., & Vargo, E. J. (2019). The Effect of Vitamin D Supplementation on Glycaemic Control in Women with Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. *Int J Environ Res Public Health, 16*(10). https://doi.org/10.3390/ijerph16101716

Ostlund, I., Haglund, B., & Hanson, U. (2004). Gestational diabetes and preeclampsia. *Eur J Obstet Gynecol Reprod Biol, 113*(1), 12–16. https://doi.org/10.1016/j.ejogrb.2003.07.001

Ostlund, I., Hanson, U., Björklund, A., Hjertberg, R., Eva, N., Nordlander, E., … Wager, J. (2003). Maternal and fetal outcomes if gestational impaired glucose tolerance is not treated. *Diabetes Care, 26*(7), 2107–2111. https://doi.org/10.2337/diacare.26.7.2107

Palm, C. V. B., Glintborg, D., Kyhl, H. B., McIntyre, H. D., Jensen, R. C., Jensen, T. K., … Andersen, M. (2018). Polycystic ovary syndrome and hyperglycaemia in pregnancy. A narrative review and results from a prospective Danish cohort study. *Diabetes Res Clin Pract, 145*, 167–177. https://doi.org/10.1016/j.diabres.2018.04.030

Pirkola, J., Pouta, A., Bloigu, A., Hartikainen, A. L., Laitinen, J., Järvelin, M. R., & Vääräsmäki, M. (2010). Risks of overweight and abdominal obesity at age 16 years associated with prenatal exposures to maternal prepregnancy overweight and gestational diabetes mellitus. *Diabetes Care, 33*(5), 1115–1121. https://doi.org/10.2337/dc09-1871

Pirkola, J., Pouta, A., Bloigu, A., Miettola, S., Hartikainen, A. L., Järvelin, M. R., & Vääräsmäki, M. (2010). Prepregnancy overweight and gestational diabetes as determinants of subsequent diabetes and hypertension after 20-year follow-up. *J Clin Endocrinol Metab, 95*(2), 772–778. https://doi.org/10.1210/jc.2009-1075

Powe, C. E., Allard, C., Battista, M. C., Doyon, M., Bouchard, L., Ecker, J. L., … Hivert, M. F. (2016). Heterogeneous Contribution of Insulin Sensitivity and Secretion Defects to Gestational Diabetes Mellitus. *Diabetes Care, 39*(6), 1052–1055. https://doi.org/10.2337/dc15-2672

Pöyhönen-Alho, M. K., Teramo, K. A., Kaaja, R. J., & Hiilesmaa, V. K. (2005). 50gram oral glucose challenge test combined with risk factor-based screening for gestational diabetes. *Eur J Obstet Gynecol Reprod Biol, 121*(1), 34–37. https://doi.org/10.1016/j.ejogrb.2004.10.008

Rayanagoudar, G., Hashi, A. A., Zamora, J., Khan, K. S., Hitman, G. A., & Thangaratinam, S. (2016). Quantification of the type 2 diabetes risk in women with gestational diabetes: a systematic review and meta-analysis of 95,750 women. *Diabetologia, 59*(7), 1403–1411. https://doi.org/10.1007/s00125-016-3927-2

Reece, E. A., Leguizamón, G., & Wiznitzer, A. (2009). Gestational diabetes: the need for a common ground. *Lancet, 373*(9677), 1789–1797. https://doi.org/10.1016/s0140-6736(09)60515-8

Retnakaran, R., Qi, Y., Sermer, M., Connelly, P. W., Hanley, A. J., & Zinman, B. (2008). Glucose intolerance in pregnancy and future risk of pre-diabetes or diabetes. *Diabetes Care, 31*(10), 2026–2031. https://doi.org/10.2337/dc08-0972

Roeckner, J. T., Sanchez-Ramos, L., Jijon-Knupp, R., & Kaunitz, A. M. (2016). Single abnormal value on 3-hour oral glucose tolerance test during pregnancy is associated with adverse maternal and neonatal outcomes: a systematic review and metaanalysis. *Am J Obstet Gynecol, 215*(3), 287–297. https://doi.org/10.1016/j.ajog.2016.04.040

Rowan, J. A., Hague, W. M., Gao, W., Battin, M. R., & Moore, M. P. (2008). Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med, 358*(19), 2003–2015. https://doi.org/10.1056/NEJMoa0707193

Sacks, D. A., Hadden, D. R., Maresh, M., Deerochanawong, C., Dyer, A. R., Metzger, B. E., … Trimble, E. R. (2012). Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG consensus panel-recommended criteria: the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. *Diabetes Care, 35*(3), 526–528. https://doi.org/10.2337/dc11-1641

Sagedal, L. R., Sanda, B., Øverby, N. C., Bere, E., Torstveit, M. K., Lohne-Seiler, H., … Vistad, I. (2017). The effect of prenatal lifestyle intervention on weight retention 12 months postpartum: results of the Norwegian Fit for Delivery randomised controlled trial. *BJOG, 124*(1), 111–121. https://doi.org/10.1111/1471-0528.13863

Sapienza, A. D., Francisco, R. P., Trindade, T. C., & Zugaib, M. (2010). Factors predicting the need for insulin therapy in patients with gestational diabetes mellitus. *Diabetes Res Clin Pract, 88*(1), 81–86. https://doi.org/10.1016/j.diabres.2009.12.023

Sauni, R. (2014). Seulonnat Suomessa. Screenings in Finland. Sosiaali- ja terveysministeriö. Retrieved from http://julkaisut.valtioneuvosto.fi/bitstream/handle/ 10024/70316/ URN_ISBN_978-952-00-3534-1.pdf

Scholtens, D. M., Kuang, A., Lowe, L. P., Hamilton, J., Lawrence, J. M., Lebenthal, Y., … Metzger, B. E. (2019). Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study (HAPO FUS): Maternal Glycemia and Childhood Glucose Metabolism. *Diabetes Care, 42*(3), 381–392. https://doi.org/10.2337/dc18–2021

Shepherd, E., Gomersall, J. C., Tieu, J., Han, S., Crowther, C. A., & Middleton, P. (2017). Combined diet and exercise interventions for preventing gestational diabetes mellitus. *Cochrane Database Syst Rev, 11*(11), Cd010443. https://doi.org/10.1002/ 14651858.CD010443. pub3

Simmons, D., Devlieger, R., van Assche, A., Jans, G., Galjaard, S., Corcoy, R., … van Poppel, M. N. (2017). Effect of Physical Activity and/or Healthy Eating on GDM Risk: The DALI Lifestyle Study. *J Clin Endocrinol Metab, 102*(3), 903–913. https://doi.org/10.1210/jc.2016-3455

Song, C., Li, J., Leng, J., Ma, R. C., & Yang, X. (2016). Lifestyle intervention can reduce the risk of gestational diabetes: a meta-analysis of randomized controlled trials. *Obes Rev, 17*(10), 960–969. https://doi.org/10.1111/obr.12442

Tarry-Adkins, J. L., Aiken, C. E., & Ozanne, S. E. (2019). Neonatal, infant, and childhood growth following metformin versus insulin treatment for gestational diabetes: A systematic review and meta-analysis. *PLoS Med, 16*(8), e1002848. https://doi.org/10.1371/journal.pmed.1002848

Teramo, K. A. (2006). Raskausdiabetes. In: Ilanne-Parikka P, Kangas T, Kaprio, EA, Rönnemaa T (eds). *Diabetes*, 383–385.

Turunen, S., Vääräsmäki, M., Männistö, T., Hartikainen, A. L., Lahesmaa-Korpinen, A. M., Gissler, M., & Suvanto, E. (2019). Pregnancy and Perinatal Outcome Among Hypothyroid Mothers: A Population-Based Cohort Study. *Thyroid, 29*(1), 135–141. https://doi.org/10.1089/thy.2018.0311

Wan, H., Zhang, C., Li, H., Luan, S., & Liu, C. (2018). Association of maternal diabetes with autism spectrum disorders in offspring: A systemic review and meta-analysis. *Medicine (Baltimore), 97*(2), e9438. https://doi.org/10.1097/md.0000000000009438

Vandorsten, J. P., Dodson, W. C., Espeland, M. A., Grobman, W. A., Guise, J. M., Mercer, B. M., … Tita, A. T. (2013). NIH consensus development conference: diagnosing gestational diabetes mellitus. *NIH Consens State Sci Statements, 29*(1), 1–31. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23748438

Wendland, E. M., Torloni, M. R., Falavigna, M., Trujillo, J., Dode, M. A., Campos, M. A., … Schmidt, M. I. (2012). Gestational diabetes and pregnancy outcomes--a systematic review of the World Health Organization (WHO) and the International Association of Diabetes in Pregnancy Study Groups (IADPSG) diagnostic criteria. *BMC Pregnancy Childbirth, 12*, 23. https://doi.org/10.1186/1471-2393-12-23

WHO. (2014). Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy: a World Health Organization Guideline. *Diabetes Res Clin Pract, 103*(3), 341–363. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24847517

Wilson, J., & Jungner, G. (1968). Principles and practice of screening for disease. . *Geneva: WHO.* Retrieved from https://apps.who.int/iris/bitstream/handle/10665/37650/WHO_PHP_34.pdf

Vinter, C. A., Jensen, D. M., Ovesen, P., Beck-Nielsen, H., & Jørgensen, J. S. (2011). The LiP (Lifestyle in Pregnancy) study: a randomized controlled trial of lifestyle intervention in 360 obese pregnant women. *Diabetes Care, 34*(12), 2502–2507. https://doi.org/10.2337/dc11-1150

Voormolen, D. N., de Wit, L., van Rijn, B. B., DeVries, J. H., Heringa, M. P., Franx, A., … Lamain-de Ruiter, M. (2018). Neonatal Hypoglycemia Following Diet-Controlled and Insulin-Treated Gestational Diabetes Mellitus. *Diabetes Care, 41*(7), 1385–1390. https://doi.org/10.2337/dc18-0048

Vounzoulaki, E., Khunti, K., Abner, S. C., Tan, B. K., Davies, M. J., & Gillies, C. L. (2020). Progression to type 2 diabetes in women with a known history of gestational diabetes: systematic review and meta-analysis. *BMJ, 369*, m1361. https://doi.org/10.1136/bmj.m1361

Wu, L., Cui, L., Tam, W. H., Ma, R. C., & Wang, C. C. (2016). Genetic variants associated with gestational diabetes mellitus: a meta-analysis and subgroup analysis. *Sci Rep, 6*, 30539. https://doi.org/10.1038/srep30539

Yogev, Y., Xenakis, E. M., & Langer, O. (2004). The association between preeclampsia and the severity of gestational diabetes: the impact of glycemic control. *Am J Obstet Gynecol, 191*(5), 1655–1660. https://doi.org/10.1016/j.ajog.2004.03.074

Yuen, L., Wong, V. W., & Simmons, D. (2018). Ethnic Disparities in Gestational Diabetes. *Curr Diab Rep, 18*(9), 68. https://doi.org/10.1007/s11892-018-1040-2

Zhang, C., Rawal, S., & Chong, Y. S. (2016). Risk factors for gestational diabetes: is prevention possible? *Diabetologia, 59*(7), 1385–1390. https://doi.org/10.1007/s00125-016-3979-3

Zhang, Y., Gong, Y., Xue, H., Xiong, J., & Cheng, G. (2018). Vitamin D and gestational diabetes mellitus: a systematic review based on data free of Hawthorne effect. *BJOG, 125*(7), 784–793. https://doi.org/10.1111/1471-0528.15060

Zhu, Y., & Zhang, C. (2016). Prevalence of Gestational Diabetes and Risk of Progression to Type 2 Diabetes: a Global Perspective. *Curr Diab Rep, 16*(1), 7. https://doi.org/10.1007/s11892-015-0699-x

Original publications

I Koivunen, S., Kajantie, E., Torkki, A., Bloigu, A., Gissler, M., Pouta, A., & Vaarasmaki, M. (2015). The changing face of gestational diabetes: the effect of the shift from risk factor-based to comprehensive screening. *European Journal of Endocrinology / European Federation of Endocrine Societies, 173*(5), 623–632. https://doi.org/10.1530/EJE-15-0294

II Koivunen, S., Torkki, A., Bloigu, A., Gissler, M., Pouta, A., Kajantie, E., & Vääräsmäki, M. (2017). Towards national comprehensive gestational diabetes screening -consequences for neonatal outcome and care. *Acta Obstet Gynecol Scand., 96*(1), 106–113. https://doi.org/10.1111/aogs.13030

III Koivunen, S., Viljakainen, M., Männistö, T., Gissler, M., Pouta, A., Kaaja, R., Eriksson, J., Laivuori, H., Kajantie, E., & Vääräsmäki, M. (2020). Pregnancy outcomes according to the definition of gestational diabetes. *PLoS One, 15*(3), e0229496. https://doi.org/10.1371/journal.pone.0229496

IV Eteläinen, S., Viljakainen, M., Männistö, T., Gissler, M., Pouta, A., Kaaja, R., Eriksson, J., Laivuori, H., Kajantie, E., & Vääräsmäki, M. The number of abnormal values in oral glucose tolerance test: the significance to pregnancy and perinatal outcomes. Submitted.

Original publications are not included in the electronic version of the dissertation.

1583. Pohjola, Mari (2020) Thromboelastography for coagulation monitoring in obesity and cytoreductive surgery

1584. Järvinen, Jyri (2020) Lumbar degenerative Modic changes : association between bone turnover and low back symptoms, and the effect of a zoledronic acid treatment intervention

1585. Siddika, Nazeeba (2020) Prenatal exposure to ambient air pollution and the risk of preterm birth and stillbirth : synergy among air pollutants in causing preterm birth

1586. Karkkola, Sini (2020) Management of ankle fractures : long-term results and intramedullary nailing of high risk patients

1587. Kemi, Niko (2020) Novel histological prognostic factors in gastric cancer

1588. Länkimäki, Sami (2020) Prehospital airway management in Finnish emergency medical service by non-physicians

1589. Santala, Simi (2020) Prognostic role of cyclins A, B, and E and p27 in endometrial endometrioid adenocarcinoma

1590. Konttila, Jenni (2020) Hypoteettinen malli työssä kohdatun väkivallan ja työhyvinvoinnin välisestä yhteydestä aikuispsykiatrisessa avohoidossa

1591. Parviainen, Roope (2020) The intrauterine and genetic factors associated with the childhood fracture risk

1592. Juntunen, Mikael (2020) Technical and algorithmic approaches for medical photon counting computed tomography in the example of coronary artery calcium quantification

1593. Ilo, Arjaleena (2020) Infrared thermography in vascular disorders : screening and follow-up

1594. Daddali, Ravindra (2020) Molecular mechanisms regulating the onset of labor : comparative proteomics and miRNAomics of human spontaneous and elective labors

1595. Niemi-Nikkola, Ville (2021) Spinal fractures and spinal cord injuries : incidence, epidemiological characteristics and survival

1596. Nurkkala, Marjukka (2021) Häiriintynyt syömiskäyttäytyminen, paino ja fyysinen aktiivisuus : Nuoret miehet ja ylipainoiset työikäiset

Book orders:
Virtual book store
http://verkkokauppa.juvenesprint.fi

UNIVERSITY OF OULU P.O. Box 8000 FI-90014 UNIVERSITY OF OULU FINLAND

ACTA UNIVERSITATIS OULUENSIS

ISBN 978-952-62-2816-7 (Paperback)
ISBN 978-952-62-2817-4 (PDF)
ISSN 0355-3221 (Print)
ISSN 1796-2234 (Online)

UNIVERSITY OF OULU