PUBLICATIONS OF
THE UNIVERSITY OF EASTERN FINLAND

Dissertations in Health Sciences

HEIDI HAKKARAINEN

LONG-TERM HEALTH IN WOMEN WHO HAVE HAD GESTATIONAL DIABETES OR AN LGA NEWBORN

LONG-TERM HEALTH IN WOMEN WHO HAVE HAD GESTATIONAL DIABETES OR AN LGA NEWBORN

Heidi Hakkarainen

LONG-TERM HEALTH IN WOMEN WHO HAVE HAD GESTATIONAL DIABETES OR AN LGA NEWBORN

Publications of the University of Eastern Finland
Dissertations in Health Sciences
No 517

University of Eastern Finland
Kuopio
2019

Distributor:
University of Eastern Finland
Kuopio Campus Library
P.O.Box 1627
FI-70211 Kuopio, Finland
www.uef.fi/kirjasto

Grano
Jyväskylä, 2019

ISBN: 978-952-61-3133-7 (print)
ISBN: 978-952-61-3134-4 (PDF)
ISSNL: 1798-5706
ISSN: 1798-5706
ISSN: 1798-5714 (PDF)

Author's address: Department of Obstetrics and Gynecology
Kuopio University Hospital
University of Eastern Finland
KUOPIO
FINLAND

Doctoral programme: Doctoral Programme of Clinical Research

Supervisors: Professor Seppo Heinonen, M.D, Ph.D., MBA.
Department of Obstetrics and Gynecology
Helsinki University Central Hospital
University of Helsinki
HELSINKI
FINLAND

Docent Hanna Huopio, M.D., Ph.D.
Department of Pediatrics
Kuopio University Hospital
University of Eastern Finland
KUOPIO
FINLAND

Reviewers: Professor Risto Kaaja, M.D., Ph.D.
Department of Medicine
Turku University Hospital
University of Turku
TURKU
FINLAND

Professor Pertti Kirkinen, M.D., Ph.D.
Department of Obstetrics and Gynecology
University of Tampere
TAMPERE
FINLAND

Opponent: Docent Hanna Savolainen-Peltonen M.D., Ph.D.
Department of Obstetrics and Gynecology
Helsinki University Central Hospital
University of Helsinki
HELSINKI
FINLAND

Hakkarainen, Heidi
Long-term health in women who have had gestational diabetes or an LGA newborn
University of Eastern Finland, Faculty of Health Sciences
Kuopio: University of Eastern Finland
Dissertations in Health Sciences 517. 2019. 137 p.
ISBN: 978-952-61-3133-7 (print)
ISSNL: 1798-5706
ISSN: 1798-5706
ISBN: 978-952-61-3134-4 (PDF)
ISSN: 1798-5714 (PDF)

ABSTRACT

Gestational diabetes mellitus (GDM) adversely affects womens' long-term health. The incidences of type 2 diabetes (T2DM), metabolic syndrome (MetS) and later cardiovascular diseases (CVD) are increased in women with a history of GDM. Various factors during pregnancy contribute to the later risk of these metabolic disorders, including glucose tolerance. An oral glucose tolerance test (OGTT) can be used as a predictive factor of later maternal health. However, studies concerning the specific risks of T2DM and MetS associated with glycemia are sparse. The aim of this study was to evaluate the glycemic measures from an OGTT during pregnancy as predictors of incident T2DM and MetS. Furthermore, this study explored the ability of having a large-for-gestational-age (LGA) newborn to predict later risk of T2DM and MetS in women with and without GDM during their pregnancies.

The study population consisted of 876 women being followed for their pregnancies in Kuopio University Hospital in 1989-2009, of whom 489 had GDM and 385 were normoglycemic. These women were invited for a re-examination of glucose tolerance and other metabolic components after a mean follow-up of 7.3 (SD 5.1) years.

Women with two or more abnormal values in the OGTT during pregnancy had the greatest risk of later T2DM and MetS, with a T2DM incidence of 25% and MetS incidence of 62.5% after 10 years of follow-up, compared to 0.8% and 24.2% of normoglycemic women, respectively. The incidence of T2DM increased with time and the degree of glycemic abnormality, whereas the incidence of MetS remained nearly constant during follow-up. The women with milder dysglycemia had an incidence of 3.8% for T2DM and 46.2% for MetS after 10 -years of follow-up. The incidence of MetS was significantly higher (39.3%) in women with one abnormal value already within five years after pregnancy. The post-challenge glycemia in OGTT was the best predictor of incident T2DM, whereas the fasting glucose value in OGTT predicted later MetS best. An LGA delivery nearly doubled the risk of

later T2DM and tripled the risk of MetS in women with a history of GDM but did not increase these risks in women with a normoglycemic pregnancy.

In conclusion, an OGTT during pregnancy offers important information for more detailed prediction of womens' risk for later metabolic diseases. Women with several abnormal values in an OGTT and GDM women with an LGA delivery represented a high-risk target group for interventions to prevent future T2DM and MetS. However, the follow-up of women with milder GDM in also indicated. An LGA delivery without GDM did not reflect adverse long-term health outcomes in the mother.

National Library of Medicine Classification: WQ 248, WQ 211, WQ 500, WQ 105, WG 120, WK 810, WD 200

Medical Subject Headings: Pregnancy; Diabetes, Gestational; Glucose Tolerance Test; Fetal Macrosomia; Maternal Health; Follow-up Studies; Diabetes Mellitus, Type 2; Prediabetic State; Metabolic Syndrome; Cardiovascular Diseases; Primary Prevention

Hakkarainen, Heidi
Raskausdiabeteksen ja LGA-vastasyntyneen merkitys naisten pitkäaikaisterveyteen
Kuopio: Itä-Suomen yliopisto
Publications of the University of Eastern Finland
Dissertations in Health Sciences 517. 2019, 137 s.
ISBN: 978-952-61-3133-7 (nid.)
ISSNL: 1798-5706
ISSN: 1798-5706
ISBN: 978-952-61-3134-4 (PDF)
ISSN: 1798-5714 (PDF)

TIIVISTELMÄ

Raskausdiabetes (gestational diabetes mellitus; GDM) lisää naisen riskiä sairastua tyypin 2 diabetekseen (T2DM), metaboliseen oireyhtymään (MBO) ja sydän- ja verisuonisairauksiin raskauden jälkeen. Raskaudenaikaisia myöhempää sairastuvuusriskiä ennakoivia tekijöitä on tunnistettu monia. Myös raskaudenaikaisen sokerirasitustestin (oral glucose tolerance test, OGTT) tulosten perusteella voidaan tehdä päätelmiä myöhemmästä riskistä T2DM:een ja MBO:ään. Tutkimukset, jotka ennustavat T2DM:n ja MBO:n riskiä OGTT:n poikkeavuuksien lukumäärän perusteella, ovat harvassa. Tämän tutkimuksen tarkoituksena oli selvittää myöhempää sairastumisriskiä T2DM:een ja MBO:ään OGTT:n tulosten perusteella. Lisäksi tarkoituksena oli saada selville, lisääkö raskauden kestoon nähden ylipainoinen (large-for-gestational-age, LGA) vastasyntynyt äidin myöhempää sairastumisriskiä T2DM:een ja MBO:ään.

Tutkimukseen osallistui vuosina 1989–2009 Kuopion yliopistollisen sairaalan seurannassa olleet 876 naista, joilla 489:lla oli GDM ja 385:lla normaali verensokeri raskausaikana. Heidät kutsuttiin seurantakäynnille sokeritasapainon ja muiden metabolisten komponenttien tarkistamiseksi 7.3 (SD5.1) vuotta raskauden jälkeen.

Suurimmassa riskissä myöhempään T2DM:een ja MBO:ään olivat naiset, joilla oli raskaudenaikaisessa OGTT:ssä useampi poikkeavaa arvo. Näillä naisilla T2DM:n esiintyvyys oli 25% ja MBO:n 62.5% yli 10 vuoden seurannassa. Mikäli OGTT:ssä oli vain yksi poikkeava arvo, T2DM:n esiintyvyys oli 3.8% ja MBO:n 46.2%. Vastaavat luvut naisilla, joilla oli normaali sokeritasapaino raskausaikana, oli 0.8% ja 24.2%. T2DM:n esiintyvyys lisääntyi seuranta-ajan kasvaessa ja OGTT:n poikkeavien arvojen lukumäärän perusteella, kun taas MBO:n esiintyvyys pysyi tasaisena seuranta-aikana ja oli merkittävä jo alle viisi vuotta synnytyksestä, myös naisilla joilla oli vain yksi poikkeava sokeriarvo OGTT:ssä. Raskaudenaikaisen OGTT:n poikkeavat 1- ja 2-tunnin arvot ennustivat parhaiten myöhempää T2DM:sta, kun taas MBO:ää ennusti poikkeava paastosokeri. Mikäli GDM:ää

sairastanut nainen synnytti LGA-vauvan, T2DM:n riski lähes kaksinkertaistui ja MBO:n riski kolminkertaistui. LGA vastasyntynyt ei kuitenkaan lisännyt myöhempää T2DM- ja MBO-riskiä naisilla, joiden sokeritasapaino oli raskausaikana normaali.

Raskaudenaikaisen OGTT:n perusteella voidaan tehdä yksilöllistä riskinarviota myöhempää T2DM:sta ja MBO:ää koskien. Naiset, joilla on useampi poikkeava arvo OGTT:ssä tai GDM-raskaus ja LGA vastasyntynyt, tulisi ottaa tarkkaan seurantaan GDM-raskauden jälkeen T2DM:n ja MBO:n ja näistä johtuvien kansanterveydellisesti tärkeiden sydän- ja verisuonisairauksien ehkäisemiseksi. Naiset, jotka synnyttävät LGA-vauvan ilman GDM:ää, eivät ole suurentuneessa riskissä sairastua myöhempään T2DM:een tai MBO:ään.

Luokitus: WQ 248, WQ 211, WQ 500, WQ 105, WG 120, WK 810, WD 200
Yleinen suomalainen ontologia: raskaus; raskausdiabetes; glukoosi; rasituskokeet; sikiö; kasvu; äidit; terveys; seurantatutkimus; aikuistyypin diabetes; metabolinen oireyhtymä; sydän- ja verisuonitaudit; ennaltaehkäisy

To my precious ones, Beata and Amanda

ACKNOWLEDGEMENTS

This study was carried out at the Department of Obstetrics and Gynecology, Kuopio University Hospital. I express my considerable thanks to all women that participated to this study.

I own my deepest gratitude to my supervisor, Professor Seppo Heinonen, M.D., PhD., who proposed the current study to me and guided me through these years with great expertise and supporting attitude. You responded immediately to all questions whenever needed and that feature in you is awesome.

I am everlastingly thankful to my other supervisor, Docent Hanna Huopio, M.D., PhD for guidance, encouragement and advice during the current study. Especially your words "one task to one woman at a time" infused faith in my own abilities and confidence to finalize my thesis.

I am very grateful the other co-authors Professor Raimo Voutilainen, M.D., PhD., Docent Henna Cederberg, M.D., PhD. for your participation and expert knowledge in the original publications.

I want to thank Professor Leea Keski-Nisula, M.D., PhD. and Professor Maritta Hippeläinen, M.D., PhD. for your enthusiasm and genuine interest in my project. Professor Marjo Tuppurainen, thank you for your supportive attitude towards my research.

I express my gratitude to my official reviewers Professor Risto Kaaja, M.D., PhD. and Professor Pertti Kirkinen, M.D., PhD.

I want to express my warmest thanks to Olavi Kauhanen of helping me get started with data and Tuomas Selander for kind assistance with statistical questions.

I am grateful to Docent David Laaksonen, M.D., PhD. for his careful language revision of the previously unpublished part of this thesis.

I express my sincere thanks to all my psesent and former colleagues in the Department of Obstetrics and Gynecology in Kuopio University Hospital for working together and supporting me in my clinical and scientific work. Special thanks to Marja Komulainen, M.D., Ph.D. for allowing time away from clinical work to carry out research and for giving me an opportunity to work in this department. The obstetric team Maija-Riitta Orden, Heli Saarelainen, Maija Harju, Leena Alanne and Outi Kavasmaa, thank you for working together and teaching me. Thank you Paula Kuivasaari-Pirinen and Henna Kärkkäinen for the historic moments in "the top-floor unit". That time and peer support there really helped me to get started.

My special thanks go to my lovely friends Mira, Reeta, Suski, Minna, Jonna, all three Leenas and their husbands and children. Thank you for supporting me during this project and most importantly, thank you for full of life moments with

you outside working life. Reeta, I will never forget your help and support during these years. The life without friends would be nothing!

I am deeply thankful to my parents Irmeli and Reijo, who have always believed in me. You, and my step-father Arto and step-mother Helena, have always come to help when needed. Thank you to my sisters Miia and Mila for belonging in my life.

Lastly, I owe my loving thanks to my own family, Ari-Pekka and our two little sunshines Beata and Amanda. I am deeply grateful for your existence.

Kuopio, February 2019

Heidi Hakkarainen

This study has been financially supported by Kuopio University Hospital EVO- and VTR-grants, Kuopio University Hospital Research Foundation, Kuopio University Foundation, the Finnish Cultural Foundation of Northern Savo, the Finnish Medical Foundation, the Emil Aaltonen Foundation, the Maud Kuistila Memorial Foundation and Paavo Nurmi Foundation.

LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications:

I Hakkarainen H, Huopio H, Cederberg H, Pääkkönen M, Voutilainen R, Heinonen S. Post-challenge glycemia during pregnancy as a marker of future risk of type 2 diabetes: A prospective cohort study. *Gynecological Endocrinology Jul;31(7):573-7, 2015.*

II Hakkarainen H, Huopio H, Cederberg H, Pääkkönen M, Voutilainen R, Heinonen S. The risk of metabolic syndrome in women with previous GDM in a long-term follow-up. *Gynecological Endocrinology. Nov;32(11):920-925, 2016.*

III Hakkarainen H, Huopio H, Cederberg H, Voutilainen R, Heinonen S. Delivery of an LGA infant and the maternal risk of diabetes: a prospective cohort study. *Primary Care Diabetes. Aug;12(4):364-370, 2018.*

IV Hakkarainen H, Huopio H, Cederberg H, Voutilainen R, Heinonen S. Future risk of metabolic syndrome in women with a previous LGA delivery stratified by gestational glucose tolerance: a prospective cohort study. *BMC Pregnancy Childbirth. Aug 10;18(1):326, 2018.*

CONTENTS

ABSTRACT **7**

TIIVISTELMÄ **9**

ACKNOWLEDGEMENTS **13**

1 INTRODUCTION **23**

2 REVIEW OF THE LITERATURE **25**
2.1 Gestational diabetes mellitus (GDM) 25
2.1.1 Background 25
2.1.2 Pathophysiology 26
2.1.3 Risk factors 27
2.1.4 Screening and diagnosis 27
2.1.5 Treatment of GDM 31
2.1.6 Follow-up during pregnancy 35
2.2 Short- and long-term consequences of GDM and having an lga newborn 36
2.2.1 Factors affecting fetal growth and classification of birth weight 36
2.2.2 Influence of GDM for fetal development 39
2.2.3 Consequences of GDM for the offspring 41
2.2.4 Consequences of having an LGA newborn for maternal health 42
2.3 Maternal metabolic health after gdm pregnancy 43
2.3.1 Recurrence risk of GDM 43
2.3.2 Dysglycemia 43
2.3.3 Metabolic syndrome 48
2.3.4 Cardiovascular diseases 52
2.3.5 Follow-up and prevention of future morbidity 52

3 AIMS OF THE STUDY **55**

4 POST-CHALLENGE GLYCEMIA DURING PREGNANCY AS A MARKER OF FUTURE RISK OF TYPE 2 DIABETES: A PROSPECTIVE COHORT STUDY **57**
4.1 Abstract 57
4.2 Introduction 58
4.3 Methods 58
4.3.1 Desing, setting and population 58
4.3.2 Data collection during pregnancy 59
4.3.3 The follow-up study 59
4.3.4 Laboratory determinations 59
4.3.5 Statistical analyses 60
4.4 Results 61
4.5 Discussion 66
4.6 Conclusion 67

5 THE RISK OF METABOLIC SYNDROME IN WOMEN WITH PREVIOUS GDM IN A LONG-TERM FOLLOW-UP 69
5.1 Abstract 69
5.2 Introduction 70
5.3 Methods 70
5.3.1 Desing, setting and population 70
5.3.2 Data collection during pregnancy 71
5.3.3 The follow-up study 71
5.3.4 Laboratory determinations 72
5.3.5 Statistical analyses 73
5.3.6 Ethical approval 73
5.4 Results 73
5.5 Discussion 77
5.6 Conclusion 78

6 DELIVERY OF AN LGA INFANT AND THE MATERNAL RISK OF DIABETES: A PROSPECTIVE COHORT STUDY 79
6.1 Abstract 79
6.2 Introduction 80
6.3 Methods 80
6.3.1 Data collection during pregnancy 81
6.3.2 The follow-up study 81
6.3.3 Laboratory determinations 82
6.3.4 Statistical analyses 82
6.4 Results 82
6.5 Discussion 86
6.6 Conclusion 88

7 FUTURE RISK OF METABOLIC SYNDROME IN WOMEN WITH A PREVIOUS LGA DELIVERY STRATIFIED BY GESTATIONAL GLUCOSE TOLERANCE: A PROSPECTIVE COHORT STUDY 89
7.1 Abstract 89
7.2 Background 90
7.3 Methods 90
7.3.1 Data collection during pregnancy 91
7.3.2 The follow-up study 91
7.3.3 Laboratory determinations 92
7.3.4 Statistical analysis 92
7.4 Results 92
7.5 Discussion 95
7.6 Conclusion 98

8 GENERAL DISCUSSION 99
8.1 The main findings 99
8.2 Findings in relation to other studies 99
8.3 Validity and limitations of the study 102
8.4 Clinical significance and generalizability of the result 103

9 CONCLUSIONS 105

REFERENCES 106

ABBREVIATIONS

AACE	American Association of Clinical Endocrinologists
ACOG	American College of Obstetrics and Gynaecology
ADA	American Diabetes Association
AGA	appropriate for gestational age
A1GDM	gestational diabetes mellitus White class 1
A2GDM	gestational diabetes mellitus White class 2
BMI	body mass index
CVD	cardiovascular diseases
EGIR	European Group for Study of Insulin Resistance
FIGO	International Federation of Gynecology and Obstetrics
GAD	glutamic acid decarboxylase
GCT	glucose challenge test
GDM	gestational diabetes mellitus
HAPO	hyperglycemia and adverse pregnancy outcome study
HAPO FUS	HAPO Follow-up Study
HDL	high-density lipoprotein
hs-CRP	high-sensitive C-reactive protein
IADPS	international consensus group with representatives from multiple obstetrical and diabetes organizations
IDF	International Diabetes Federation
IFG	impaired fasting glucose
IGF-1	insulin-like growth factor 1
IGT	impaired glucose tolerance
IL-1	interleukin 1
IL-6	interleukin 6
IOM	the Institute of Medicine

LADA	latent autoimmune diabetes mellitus in the adult
LGA	large for gestational age
MetS	metabolic syndrome
MODY	maturity-onset of diabetes of the young
NCEP-ATPIII	National Cholesterol Education Program Adult Treatment Panel III
NDDG	National Diabetes Data Group
NICE	UK National Institute of Health and Care Excellence
NPH	Neutral Protamine Hagedorn
OGTT	oral glucose tolerance test
SGA	small for gestational age
SD	standard deviation
TNF-α	tumor necrosis factor α
T1DM	type 1 diabetes
T2DM	type 2 diabetes mellitus
PCOS	polycystic ovary syndrome
WHO	World Health Organization

1 INTRODUCTION

The pregnancy-related dysglycemic state that affects adversely fetal outcome and resolves after pregnancy was named gestational diabetes mellitus (GDM) in the 1950's (Carrington et al. 1957). Before that a decade earlier researchers recognized that women who develop type 2 diabetes (T2DM) many years postpartum had experienced high fetal and neonatal mortality (Miller 1946). In the 1960s, O'Sullivan and Mahan showed that the severity of gestational glucose intolerance influences the later risk of T2DM. They set the optimal thresholds for GDM diagnosis using oral glucose tolerance test (OGTT) with a lifetime risk of T2DM exceeding 70% (O'sullivan and Mahan 1964).

Subsequently, the criterions of GDM have been modified several times. Even today, different organizations use different cut offs. However, nowadays guidelines of GDM diagnosis are uniformly targeted to reduce adverse obstetrical outcomes and to improve the neonatal period and long-term health of the offspring and the mother. In addition to elevated risk for hypertensive disorders during pregnancy, women with GDM are at an increased risk of having a large-for-gestational-age (LGA) infant that predisposes the fetus and mother to adverse delivery outcomes.

With regards to the long-term health of the mother, GDM increases the future risks of T2DM and metabolic syndrome (MetS), and further, cardiovascular diseases (CVD). Due to this risk, women with previous GDM are advised to have follow-up with an OGTT after their pregnancy. In addition to OGTT, lipid status, weight and blood pressure should be followed. Several studies have demonstrated that the follow-up of women with previous GDM is far from optimal. Unfortunately, less than 50% of women attend to a post-partum oral glucose tolerance test (OGTT) (Eggleston et al. 2016, Tovar et al. 2011). This period of womens' lives is an important target for diabetes and MetS prevention programs.

In the present study, the aim was to assess the risk of T2DM and MetS in women with previous GDM from North Savo region in Finland. Another aim was to investigate the impact of a previous LGA delivery to the woman's later risk of T2DM and MetS.

2 REVIEW OF THE LITERATURE

2.1 GESTATIONAL DIABETES MELLITUS (GDM)

2.1.1 Background

Gestational diabetes is carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy (Alberti and Zimmet 1998, Metzger et al. 2007). This definition includes the possibility that unrecognized glucose intolerance may have antedated the present pregnancy. The prevalence of GDM has inceased worldwide throughout years due to the ongoing epidemic of obesity and sedentary lifestyles in women at childbearing age. In Finland, during the year 2017, the OGTT was pathological in 19.0% of the pregnant population and the proportion has increased by 9.3% since 2007 (Figure 1) (The national Institute for Health and Welfare, Finland. Finnish Medical Birth Register. 2016.). Similarly, the proportion of overweight (BMI ≥ 25 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) has continuously increased among pregnant women in Finland over a 10-year period (Figure 1). (The national Institute for Health and Welfare, Finland. Finnish Medical Birth Register. 2016).

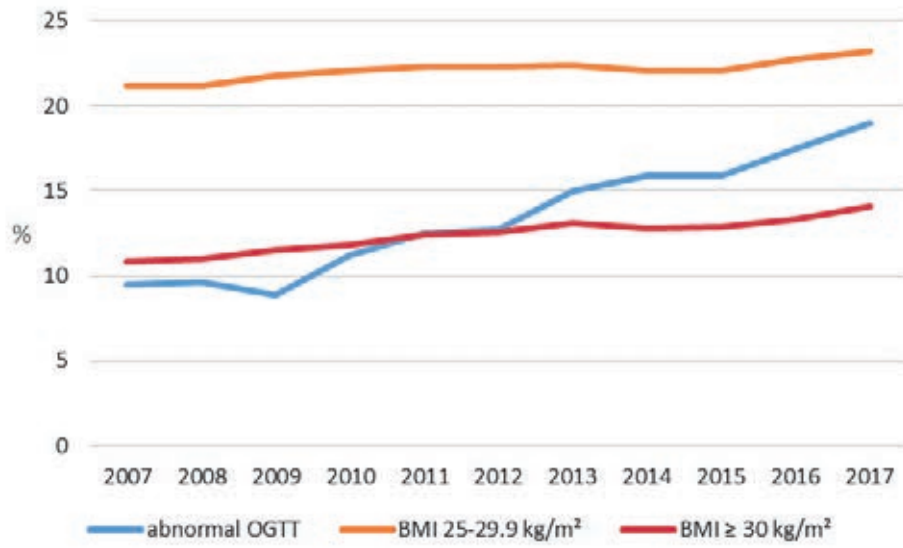


Figure 1. The incidence of GDM, overweigth and obesity in Finland.

2.1.2 Pathophysiology

Pregnancy induces progressive insulin resistance that begins in mid-pregnancy and approaches the level of insulin resistance seen in individuals with type 2 diabetes during the third trimester (Buchanan et al. 1990, Catalano et al. 1993). Insulin resistance is caused by insulin-desensitizing effects of hormonal products of the placenta (growth hormone, corticotrophin-releasing hormone, human placental lactogen and progesterone) combined with increased maternal adiposity. Human placental lactogen plays a major role in maternal insulin resistance and peaks at 30 weeks of pregnancy (Handwerger and Freemark 2000). In normal pregnancies, pancreatic β-cells increase their insulin secretion to compensate for pregnancy-induced insulin resistance (Butte 2000) and thus, the overall glucose concentration normally remains quite stable during pregnancy.

Previous studies have demonstrated that nonpregnant women with a history of GDM have higher insulin resistance before and after pregnancy (Catalano et al. 1993, Homko et al. 2001). In addition, obesity clearly worsen pre-pregnancy insulin resistance increasing the risk of GDM (Poston et al. 2016). According to Parker's hypothesis, metabolic dysfunction beyond the GDM pregnancy have been present long before pregnancy and started probably when the woman herself was developing *in utero* (Barker and Osmond 1986). Therefore, pregnancy-induced insulin resistance occurs on top of a background of chronic insulin resistance. Thus, pregnant women with GDM are initially more insulin resistant than normoglycemic pregnant women (Kautzky-Willer et al. 1997). Moreover, pancreatic β-cells are unable to meet the increased demand for insulin due the elevated insulin resistance in women with GDM (Homko et al. 2001, Huopio et al. 2014). This β-cell dysfunction has been observed already before pregnancy and continues years after pregnancy (Kramer et al. 2014, Xiang et al. 2013, Moleda et al. 2013). Pregnancy-induced insulin resistance resolves right after the delivery, and the woman returns her prepregnancy glycemic stage.

In addition to placental diabetogenic hormones and existing baseline insulin resistance, adipose tissue has a role to play as an endocrine organ. It synthetizes and secretes various bioactive molecules, called adipokines or adipocytokines. Furthermore, the placenta has a profile of cytokine gene expression and protein and secretion somewhat similar to white adipose tissue (Hauguel-de Mouzon and Guerre-Millo 2006, Radaelli et al. 2003). The contributions of these cytokines to conditions associated with insulin resistance, such as obesity and T2DM have been previously demonstrated (Fernandez-Real et al. 1998, Fruhbeck and Salvador 2000). Elevated levels of tumor necrosis factor and leptin have been found to be related to insulin resistance in the last trimester of pregnancy (Melczer et al. 2003). Resistin is another adipose tissue-related protein that is expressed and secreted by the placenta in human pregnancy, and it peaks at the third trimester (Yura et al. 2003). However, studies comparing resistin levels between GDM pregnancies and normoglycemic pregnancies have found inconsistent results (Kuzmicki et al. 2009, Lobo et al. 2013). Adiponectin is an adipose tissue-derived protein counteracting

insulin resistance and inflammation. Low adiponectin levels have been reported in women with gestational diabetes (Ranheim et al. 2004). Moreover, the increased macrophage population in the placenta and increased expression of pro-inflammatory cytokines such as IL-6, TNF-α and IL-1 are increased two- to three-fold in obese women compared to lean women (Challier et al. 2008). These inflammatory changes are associated with elevated plasma concentrations of C-reactive protein and IL-6 and may be one of the mechanisms behind the increased insulin resistance among obese women with gestational diabetes. The level of high-sensitive C-reactive protein (hs-CRP) has been found to be higher among pregnant women who develop GDM later in pregnancy, suggesting that hs-CRP is an early predictor of GDM (Maged et al. 2014).

2.1.3 Risk factors

Development of gestational diabetes is dependent on several risk factors. The history of GDM in a previous pregnancy is well-known risk factor for the recurrence of GDM in a subsequent pregnancy (Getahun et al. 2010). A family history of diabetes, especially in first-degree relatives, increases the risk of GDM (Kim et al. 2009). Several gene variants increasing the risk of T2DM and hyperglycemia are also associated with GDM, indicating a common genetic background with both these conditions (Huopio et al. 2013). Women with non-white ethnicity such as Hispanic, African American, Native American, Asian, Pacific Islander women, have a high prevalence of GDM, whereas in Caucasian women the prevalence is lower (Caughey et al. 2010). Increased prepregnancy BMI, significant weight gain in early adulthood and between pregnancies, and excessive weight gain during pregnancy are all associated with an increased risk of GDM (Solomon et al. 1997, Hedderson et al. 2008). The risk of GDM is also increasing by maternal ageing, and therefore screening efforts have been focused on women older than 25 years (Solomon et al. 1997, Marquette et al. 1985). Medical conditions such as MetS, polycystic ovary syndrome (PCOS) (Boomsma et al. 2006) and some medications like corticosteroids (Yildirim et al. 2006) may also increase the risk of GDM. Moreover, a recent observational study demonstrated that increasing income and educational attainment level decrease the incidence of GDM in primiparous women (Rono et al. 2019).

2.1.4 Screening and diagnosis

All pregnant women should be assessed for clinical characteristics to determine the overall risk of GDM and undergo glucose testing, unless they have a low-risk clinical profile (Table 2). Universal screening for GDM is recommended by an international consensus group with representatives from several obstetrical and diabetes organizations (IADPS), the American Diabetes Association (ADA) and the World Health Organization (WHO) since risk factor-based screening does not identify GDM women adequately (Farrar et al. 2017). For example, nearly half of

women diagnosed with GDM were without any risk factors in a prospective Finnish study in 532 unselected women (Poyhonen-Alho et al. 2005). If a woman is at high risk for GDM (marked obesity, history of previous GDM or delivery of an LGA infant, strong family history of diabetes, polycystic ovary syndrome or glycosuria), an oral glucose tolerance test should be performed as early as pregnancy weeks 12-16. The diagnosis of GDM is based on an oral glucose tolerance test and this can be performed as a one-step 75-gram two-hour test or a two-step 100-gram three-hour test with a preceding abnormal 50-gram oral glucose challenge test (OGCT) that is mostly used in Northern America.

Criteria for diagnosing GDM have varied widely over the decades (Table 1). The first recommendation for diagnosis of GDM was launched in 1964 by O'Sullivan and Mahan, aiming to find women who would subsequently develop T2DM (O'sullivan and Mahan 1964). Subsequent information led to alterations in O'Sullivan's criteria and the most commonly used thresholds were presented by Carpenter and Coustan (Carpenter and Coustan 1982) and by the National Diabetes Data Group (NDDG) (Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. National Diabetes Data Group. 1979), both of which were actuall modifications of the criteria by O'Sullivan and Mahan. The American Diabetes Association (ADA) published guidelines in 2003 that recommended an evaluation for GDM in women with average or high-risk characteristics (American Diabetes Association 2003). Subsequently, the hyperglycemia and adverse pregnancy outcome (HAPO) study was designed to assess the relationship between the level of maternal hyperglycemia and adverse pregnancy outcomes. The HAPO study was published in 2008 (HAPO Study Cooperative Research Group, Metzger et al. 2008) and revealed strong continuous associations of maternal glucose levels below those diagnostic of diabetes with several perinatal outcomes.

After the HAPO Study, the IADPSG revised recommendations for diagnosing GDM in 2010 (International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger et al. 2010). The recommendations were endorsed by ADA in 2011 and have remained the same thereafter (American Diabetes Association 2018). Accoding to this recommendation, all women not known to have diabetes undergo a 75-g OGTT at 24-28 weeks of gestation. Diagnostic thresholds were calculated using the HAPO data for fasting, 1-h and 2-h plasma glucose measurements at which odds for birth weight > 90th percentile, cord C-peptide > 90th percentile, and percent body fat > 90th percentile reached 1.75 times the estimated odds of these outcomes at the mean glucose values (International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger et al. 2010) (Table 1). The World Health Organization (WHO) also published an updated recommendation for diagnosing GDM in 2014, in line with the IADPSG criteria, aiming for universal standard recommendation for the diagnosis of GDM (Diagnostic criteria and classification of hyperglycemia first detected in pregnancy: a World Health Organization Guideline. 2014). More recently the International

Federation of Gynecology and Obstetrics (FIGO) endorsed these updated criteria (Hod et al. 2015). Whether there is a benefit of treating GDM women diagnosed by more stringent IADPSG criteria is not known, and randomized controlled trials are still lacking. Therefore, recommendations still have differences between national and international organizations (Feldman et al. 2016). For instance, the UK National Institute of Health and Care Excellence (NICE) (National Collaborating Centre for Women's and Children's Health (UK) 2015) and American College of Obstetrics and Gynaecology (ACOG) (Diagnostic criteria and classification of hyperglycemia first detected in pregnancy: a World Health Organization Guideline. 2014, Committee on Practice Bulletins-Obstetrics 2018) have their own guidelines (Table 1).

The debate concerning optimal thresholds continues. A recently published systematic review and meta-analysis with 25 reports and up to 207 172 women observed a positive linear association between fasting and post-load glucose concentrations and caesarean section, induction of labor, large for gestational age, macrosomia, and shoulder dystocia (Farrar et al. 2016). The association between fasting glucose level and these outcomes were more robust than those of post-challenge levels. This review, like precursors, was unable to provide clear thresholds for diagnosing GDM above which adverse outcomes risks increase. Additionally, the authors of this review criticized thresholds proposed by the IADPSG for considering only three outcomes and criticized the odds ratio of at least 1.75 as arbitrary.

Table 1. The dianostic criteria of GDM over decades.

Guideline	Year published	OGTT Approach	Abnormal values required for diagnosis	Fasting (mmol/l)	One-hour post-load (mmol/l)	Two-hour post-load (mmol/l)	Three-hour post-load (mmol/l)
O'Sullivan	1964	100g	2	≥5.0	≥9.2	≥8.1	≥6.9
NDDG	1979	100g	2	≥5.8	≥10.6	≥9.2	≥8.0
C & C	1982	100g	2	≥5.3	≥10.0	≥8.6	≥7.8
WHO	1999	75g	1	≥6.1		≥7.8	
	2014	75g	1	≥5.1	≥10.0	≥8.5	
ADA	2003	75/100g	1	≥5.3	≥10.0	≥8.6	
	2018	75/100g	1	≥5.1	≥10.0	≥8.5	
IADPSG	2010	75g	1	≥5.1	≥10.0	≥8.5	
NICE	2015	75g	1	≥5.6		≥7.8	
ACOG	2013	100g	1	≥5.3	≥10.0	≥8.6	≥7.8
	2018*	100g	2	≥5.3/5.8	≥10.0/10.6	≥8.6/9.2	≥7.8/8.0

NDDG= The National Diabetes Data Group; C&C= Carpenter and Coustan; WHO= The World Health Organization; ADA= The American Diabetes Association; IADPSG= An international consensus group with representatives from multiple obstetrical and diabetes organisations; NICE= UK National Institute of Health and Care Excellence; ACOG= American College of Obstetrics and Gynaecology; OGTT= oral glucose tolerance test. *Selection of a single set of either C&C or NDDG criterion

In Finland, the screening of GDM was risk-based before 2008 (Table 2). Women targeted for screening were older, overweight, had glycosuria, or had a previous macrosomic infant or GDM in a previous pregnancy. In the area of Kuopio University Hospital, the threshold of fasting glucose was as low as 4.8 mmol/l based on local research at the maternity clinics of Helsinki and Kuopio (Hyvönen 1991). This fasting level, endorsed and recommended by the Finnish Diabetes Association, represented the 97.5 percentile value in the Finnish pregnant population. According to the Birth Register of Kuopio University hospital, risk-based screening of GDM was performed on every third women (before the year 2008) (Viljanen 2013). The latest criteria of The Finnish Current Care Guidelines were issued in year 2008 and thereafter the screening and diagnostic criteria of GDM became uniform nationally (Table 2). In Finland, the screening recommendation for GDM is uniform, except for very low risk women (Table 2). The proportion of screened women increased to every other women after the newest criteria in the area of Kuopio University Hospital. On the other hand, the change in fasting glucose threshold to a less stringent concentration in 2008 led to a declining prevalence of GDM in the North-Savo region, from 17.7% to 13.7%, respectively (Viljanen 2013).

Table 2. The screening and diagnostic criteria of GDM in Finland.

Screening of GDM for all pregnant women, with exception of:

Nullipara with age < 25 years, BMI < 25 kg/m^2 and no family history of T2DM.
Multipara with age < 40 years, BMI < 25 kg/m^2 and no history of previous GDM or newborn macrosomia.

Guideline	Year published	Approach	Fasting (mmol/l)	One-hour post-load (mmol/l)	Two-hour post-load (mmol/l)
The Finnish Diabetes Association	1993	75g OGTT			
		capillary whole blood glucose	≥ 4.8	≥ 10.0	≥ 8.7
		capillary plasma glucose	≥ 4.8	≥ 11.2	≥ 9.9
		venous plasma glucose	≥ 4.8	≥ 10.0	≥ 8.7
The Current Care Guideline	2008 updated 2013	75g OGTT venous plasma glucose	≥ 5.3	≥ 10.0	≥ 8.6

OGTT= oral glucose tolerance test; BMI= Body mass index; T2DM= type 2 diabetes

2.1.5 Treatment of GDM

The treatment of GDM aims to minimize maternal and neonatal complications (Crowther, Hiller et al. 2005). Adequate management of GDM reduces adverse obstetrical and neonatal outcomes (Crowther et al. 2005, Hartling et al. 2013, Landon et al. 2009). The main influence of treatment was particularly a decrease in neonatal fat mass, in the numbers of LGA infants, shoulder dystocia and preeclampsia. A trial (Landon et al. 2009) also showed a reduction in cesarean delivery rates. Although the number of prenatal visits usually increases in women with GDM, close obstetrical follow-up is necessary to ensure both maternal and fetal well-being, including normal fetal growth. The cornerstones in the treatment of GDM are self-glucose monitoring, physical activity and nutritional therapy, and administration of insulin when required.

2.1.5.1 Conservative treatment

Self-monitoring of glucose

After the diagnosis of GDM, women are requested to measure their blood glucose levels, and the results should be recorded. Self-monitoring of glucose concentrations has been shown to be the most effective way to improve glucose control (Crowther et al. 2005) and reduce the requirement of anti-hyperglycemic agents. In GDM treated successfully with diet the frequency of testing can be reduced, whereas in the case of poor glycemic control daily measurements are required (Committee on Practice Bulletins-Obstetrics 2018). The Finnish Current Care Guidelines recommend 5-7 measurements per day including fasting glucose before breakfast and one-hour postprandial value after each meal (Gestational Diabetes: Current Care Guidelines, 2013) and the frequency of measurement days are planned individually based on the glycemic balance.

The targets of the treatment are the fasting glucose concentration < 5.5 mmol/l and the one-hour postprandial blood glucose concentration < 7.8 mmol/l. These thresholds recommended by the fifth international workshop-conference on gestational diabetes, are initially generalized from the recommendations intended for women with pre-existing diabetes (American Diabetes Association 2018, Metzger et al. 2007).

Dietary therapy

Dietary therapy is the most important treatment for GDM. Most women with GDM remain euglycemic with nutritional management alone, and their condition is classified as diet-treated GDM or class A1GDM according to the White classification (White 1949). The goals of diet treatment are to provide sufficient energy and nutrients for fetal growth and to provide adequate weight gain while achieving normoglycemia in the absence of ketosis (Dornhorst and Frost 2002). Overall, the dietary guidance for GDM should emphasize healthy food, portion

controls, and cooking practices that can be continued postpartum to prevent later diabetes and the metabolic syndrome (Metzger et al. 2007).

Dietary guidelines for GDM are based on the recommendations for the management of diabetes in pregnancy. Daily caloric uptake and pregnancy weight gain is stratified by pre-pregnancy BMI (American Diabetes Association 2018). Recommendations for the daily uptake of energy is 1600-1800 kcal for women with overweight or obesity and 1800-2000 kcal for women with normal weight (Gestational Diabetes: Current Care Guidelines, 2013).

There is scarce evidence for the efficacy of different types of dietary interventions on maternal and neonatal outcomes. The latest (2017) Cochrane Database review, including 19 randomised controlled trials and 1398 women with GDM, reported no clear differences between different type of dietary advice for high blood pressure, LGA babies, perinatal deaths or type 2 diabetes development for the mother (Han et al. 2017). The trials included for this review suffered from smallness, unclear or moderate risk of bias resulting from methodological limitations and low quality of the evidence supporting further large, well-designed trials. However, a systematic review and meta-analysis from 2014 revealed that a low glycemic index (GI) diet was associated with diminished administration of insulin and lower birth weight than other diets, suggesting that it could be the most suitable dietary intervention (Viana et al. 2014).

The institute of Medicine (IOM) published revised pregnancy weight gain guidelines in 2009 (Figure 2.) (Institute of Medicine (US) and National Research Council (US) Committee to Reexamine IOM Pregnancy Weight Guidelines 2009) and these are the generally accepted guidelines in Finland as well. However, the appropriate weight gain in pregnancy in women with GDM is unknown and the Finnish Current Care Guidelines recommend that the weight of obese women should not increase at all after the diagnosis of GDM (Gestational Diabetes: Current Care Guidelines, 2013). Excessive weight gain is associated with an increased risk of having a large for gestational age infant, preterm birth, and cesarean delivery, and conversely weight gain below guidelines increases the risk of SGA neonates and the likelihood of avoiding medical therapy (Cheng et al. 2008).

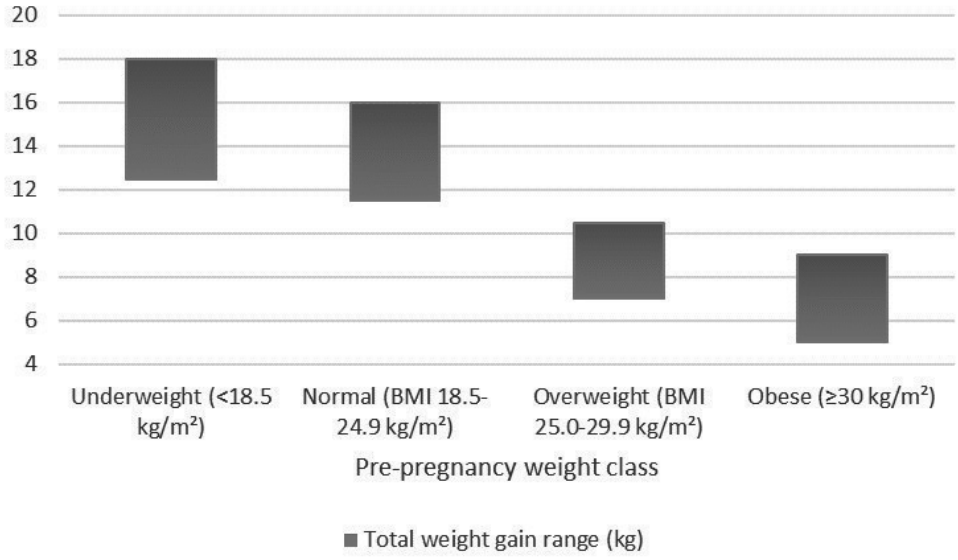


Figure 2. The 2009 IOM guidelines for weight gain and rate of weight gain during pregnancy for women with singleton fetuses.

Exercise

The other important lifestyle treatment for GDM is exercise. In general, regular exercise appears to lower fasting and postprandial glucose concentrations by increasing tissue sensitivity to insulin and glucose uptake in skeletal muscle (Asano et al. 2014). Physical activity during pregnancy maintains physical and mental health, helps maintaining adequate weight gain, can prevent the development of GDM and reduces the risk of fetal overgrowth (Koivusalo et al. 2016, Tobias et al. 2011, Wiebe et al. 2015). Neither the risk for intrauterine growth restriction or preterm birth has been shown to be increased (Wiebe et al. 2015). Exercise during pregnancy has also improved the chance for normal delivery among healthy pregnant women (Poyatos-Leon et al. 2015).

The recommendations for exercise during uncomplicated pregnancy are equivalent to recommendations in the background population, including moderate-intensity aerobic or strength-conditioning exercise for at least 20-30 minutes daily (ACOG Committee Opinion No. 650: Physical Activity and Exercise During Pregnancy and the Postpartum Period. 2015). The newest Cochrane Database review demonstrated that all lifestyle interventions, such as education, diet, exercise and self-monitoring of blood glucose are the primary therapeutic strategy for women with GDM to decrease the risk of neonatal macrosomy and adiposity, and further, to achieve postpartum weight goals (Brown et al. 2017). However, this review could not demonstrate which specific intervention is the most useful, and further research to address this issue is needed. Nevertheless, based on the general knowledge of the favorable effects of exercise, the ADA recommends exercise as a part of the treatment plan for women with GDM (Colberg et al. 2010).

2.1.5.2 Medical treatment

Women with GDM who are unable to maintain glucose levels in the targeted level with lifestyle interventions should receive medical treatment to reduce perinatal complications (Crowther et al. 2005). These women are termed as class A2GDM (White 1949). The most common and traditional treatment is insulin therapy. If the fasting glucose values are elevated repeatedly the intermediate-acting Neutral Protamine Hagedorn (NPH) insulin is administered before bedtime and dosing can be enhanced every third day (Gestational Diabetes: Current Care Guidelines, 2013) based on self-monitoring glucose levels. The long-acting insulin analogs (detemir or glargine) have not been studied extensively but based on the existing data, both seem to be safe for use in pregnancy (Callesen et al. 2013). NPH-insulin is more widely used than long-acting insulin analogs for the treatment of GDM in Finland (Gestational Diabetes: Current Care Guidelines, 2013). If recurrent excursions in postprandial glucose above the threshold are observed, the rapid-acting insulin analog (lispro or aspart) is added before meals (Gestational Diabetes: Current Care Guidelines, 2013). The rapid-acting insulins have a better influence on postprandial hyperglycemia than human insulin (Pettitt et al. 2003). The rapid-acting insulin analogs show low antigenicity, good clinical effectiveness and no evidence of teratogenesis when used by pregnant women (Metzger et al. 2007, Mathiesen et al. 2007). Diet treatment should continue along with medical treatment.

The other medical treatment for GDM is the oral anti-hyperglycemic agent metformin, which can be considered for women who fail diet therapy or refuse or are unable to use insulin therapy. Metformin treatment is suitable for mild gestational diabetes and appears to be safe, but approximately 30% of women using metformin require supplemental insulin (Balsells et al. 2015). Hence, the use of metformin as the primary medication for GDM is not recommended. Metformin is widely used for type 2 diabetes and polycystic ovary syndrome. Its main influence is to decrease liver glucose production (Kirpichnikov et al. 2002). Metformin also has an impact on insulin sensitization by increasing peripheral glucose uptake (Kirpichnikov et al. 2002).

Metformin crosses the placenta, and its concentration in umbilical artery is comparable with the maternal venous concentration (Tertti et al. 2014). However, Metformin in Gestational diabetes (MiG) trial reported no difference in neurodevelopmental outcomes at 2 years of age between the offspring of metformin- and insulin-treated GDM mothers (Wouldes et al. 2016). Studies concerning fetal exposure in metformin and offspring long-term safety are still missing. A meta-analysis of randomized trials with 2509 GDM subjects demonstrated that metformin can reduce weight gain during pregnancy and lower the mean birth weight and the rate of neonatal hypoglycemia (Balsells et al. 2015). On the other hand, this review revealed a slightly increased risk of preterm delivery.

2.1.6 Follow-up during pregnancy

Women with GDM regularly visit parental clinics where the self-monitoring of glucose is reviewed. Attention is paid to hypertensive disorders in every visit, as the incidence of pre-eclampsia is elevated in women with GDM (Billionnet et al. 2017). If glucose control is unsatisfactory, the woman is sent to a prenatal outpatient clinic for fetal surveillance and assessement of possible medication treatment of GDM. Women with medication-requiring GDM are recommended to have antenatal fetal follow-up regularly at the prenatal outpatient clinic until delivery (Gestational Diabetes: Current Care Guidelines, 2013, Committee on Practice Bulletins-Obstetrics 2018). However, women with diet-treated GDM and good glycemic control require secondary level clinic follow-up only when antenatal fetal ultrasound in third trimester is carried out to estimate fetal size and well-being. Among women with medical treatment for GDM, the induction of labor is usually preferred on expected date of the delivery at the latest due to the overall increased risk of asphyxia (Philips et al. 1982, Committee on Practice Bulletins-Obstetrics 2018). In case of macrosomia, the induction of labor is advisable before term to enable normal birth. If estimated fetal weight is over 4.5 kg, a cesarean section is preferred (Committee on Practice Bulletins-Obstetrics 2018). For GDM women on diet and with no other complications, expectant management after the expected date of the delivery is an acceptable option (Committee on Practice Bulletins-Obstetrics 2018).

2.2 SHORT- AND LONG-TERM CONSEQUENCES OF GDM AND HAVING AN LGA NEWBORN

2.2.1 Factors affecting fetal growth and classification of birth weight

Fetal growth reflects in-utero well-being, and it is affected by various growth stimulating or decelerating factors, many of which act simultaneously. The main regulatory factors of fetal growth are presented in Figure 3.

Genetic factors influence up to 50% of the birth size according to the population-spaced and twin studies (Magnus 1984, Lunde et al. 2007, Clausson et al. 2000). Maternal genes have greater influence on birthweight and than paternal genes. For example, mothers who were LGA themselves deliver more likely LGA infants. In addition, race, ethnicity and gender have an influence on infants' birthweight. Fetal genetic and chromosomal abnormalities and confined placental mosaicism (Wolstenholme et al. 1994) affect both growth retardation (Eydoux et al. 1989) and overgrowth (Vora and Bianchi 2009). Furthermore, many structural malformations without chromosomal and genetic abnormalities can also affect fetal growth (Khoury et al. 1988).

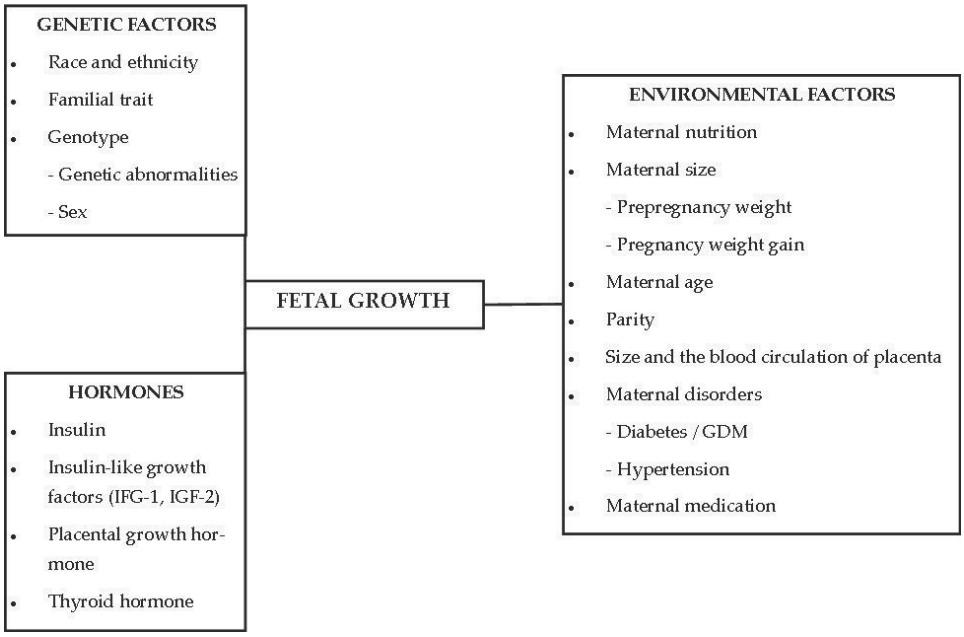


Figure 3. Different factors influencing fetal growth.

Part of intrauterine growth is influenced by certain hormones that are essential for the normal growth and development of the fetus. The fetus responds to the glucose of maternal origin by secreting insulin. Insulin has a key role in fetal growth as it increases the fetal body weigth and growth of insulin sensitive tissues (Hill and Milner 1985). Insulin-like growth factor I (IGF-I), secreted by fetal tissues after 12 weeks of gestation, correlates positively with fetal growth contributing cell growth and division (Chellakooty et al. 2004, Luo et al. 2012). In contrast, a reduction in IGF levels is associated with fetal growth restriction. The level of IGF-I has shown to be significantly higher in women with GDM (Luo et al. 2012). Studies made with transgenic mice have observed that mutation of the gene encoding either IGF-I or IGF-II leads to a weight reduction of the offspring of up to 40% (Efstratiadis 1998). Human placental growth hormone, expressed in syncytiotrophoblast cells and extravillous cytotrophoblast cells, regulates fetal growth by increasing nutritient availability via regulation of maternal IFG-I levels (Chellakooty et al. 2004, Caufriez et al. 1993). Placental growth hormone levels have been shown to be lower in pregnancies with intra-uterine growth restriction (IUGR) fetus (Chellakooty et al. 2004, Caufriez et al. 1993). In contrast, the influence of fetal pituitary growth hormone to fetal growth appears to be minimal (Hill 1992). The thyroid hormones, thyroxine (T4) and triiodothyronine (T3) are important to normal development and growth of the fetus (Forhead and Fowden 2014). Before the fetal thyroid gland is functional in mid pregnancy, the maternal thyroid hormones are essential in fetal development (Morreale de Escobar et al. 2004). Umbilical T4 concentration correlates positively with fetal body weigth and length (Shields et al. 2011). In contrast, low consentrations of the thyroid hormones have been detected in pregnancies with growth restricted fetuses (Thorpe-Beeston et al. 1991).

Environmental factors, in addition to genetic ground and fetal hormonal regulation, influence fetal growth considerably. Maternal nutrition and pre-pregnancy body mass index associate with fetal growth, with both accelerating and decelerating effects. Maternal tall stature, high BMI and pregnancy weight gain increase the incidence of delivering an LGA infant, whereas smaller materal size and deficient weigth gain increase the probability of having an SGA infant (Smith 1947, Yu et al. 2013, Kim et al. 2014, Voigt et al. 2010). Another environmental factor for a larger birth weight is multiparity, with more permissive uterine capacity (Seidman et al. 1988). In contrast, in pregnancies with multiple gestation, growth restriction is more prevalent due to the limited intrauterine environment (Blickstein 2004).

Moreover, fetal growth is regulated by placental factors. Increased size of the placenta in early pregnancy has been shown to be associated with delivering an LGA infant (Schwartz et al. 2014). Inadequate uterine-placental perfusion, and thus fetal malnutrition, is a common reason for fetal growth restriction (Dashe et al. 2000, Battaglia and Lubchenco 1967, Salafia et al. 1995, Parra-Saavedra et al. 2013). Certain placental disorders such as numerous infarctions, placenta circumvallate,

hemangioma and chorioangioma can contribute to fetal decelerated growth (Laurini et al. 1994, Shanklin 1970). Velamentous insertion of the umbilical cord and the presence of a single umbilical artery without chromosomal abnormalities have been associated with the fetal growth restriction (Battarbee et al. 2015).

Finally, several maternal medical conditions may affect fetal growth. In general, chronic disorders associated with vascular disease such as pregnancy-related hypertensive diseases often cause restriction of fetal growth (Ounsted et al. 1985). These conditions are usually a consequence of inadequate placentation in which trophoblast invasion of the myometrial portion of the spiral arteries does not occur appropriately, and this in turn leads to reduced uteroplacental perfusion. Abuse of tobacco, alcohol and other drugs decelerates fetal growth (Shu et al. 1995, Ounsted et al. 1985, Fulroth et al. 1989, Gunn et al. 2016). Certain medications, such as anti-seizure medications, warfarin-type anticoagulants (Hall et al. 1980) and antineoplastic agents (Brewer et al. 2011) are possible etiological factors of IUGR. Maternal infections passing into the intrauterine space may also be the underlying primary etiology of SGA fetus (Neerhof 1995).

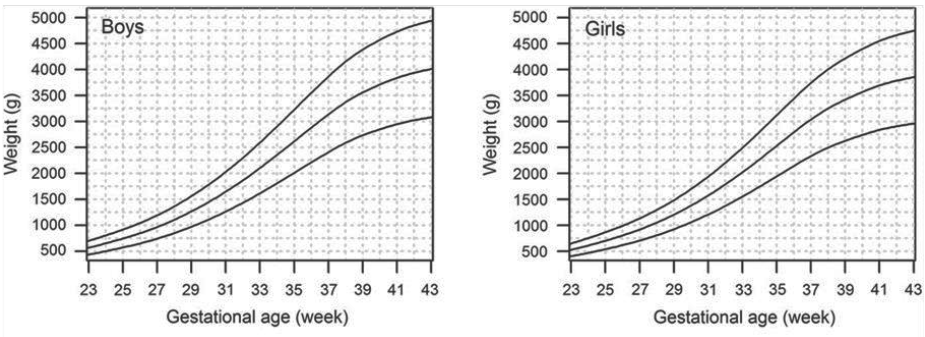


Figure 4. The birth weight reference curves for singleton boys and girls born between 1996–2008. (Data and figure adapted from ref. Sankilampi et al. 2013)

In United States and many European countries, an infant with birthweight between of 10th and 90th percentile is classified as AGA and birthweight over 90th percentile (+ 1.28 SD) for gestational age is broadly referred to as an LGA newborn (Battaglia and Lubchenco 1967). In Finland, the latest population-based references for optimal birth weight were published in 2013 (Sankilampi et al. 2013) (Figure 4.), replacing the references from 1979-1983 (Pihkala et al. 1989). These were required since the average adult height in women increased by 1.9 cm over these years (Saari et al. 2011). In this study, the mean birth weight for gestational age ±2 SD was categorized as appropriate for gestational age (AGA), whereas small for gestational age (SGA) was defined as birth weight 2 SD below and large for gestational age (LGA) 2 SD above the sex- and the gestational age- specific mean. In other words, +2 SD corresponds to 97.7 percentiles. These cut-offs have been shown to

differentiate the infants with the greatest risk for perinatal morbidity and mortality (Xu et al. 2010). According to the Finnish national birth register, 2.4% of neonates were born macrosomic (birth weight > 4500g) in 2016 (The national Institute for Health and Welfare, Finland. Finnish Medical Birth Register. 2016)

2.2.2 Influence of GDM for fetal development

Infants of women with glucose impairment during pregnancy have an increased risk for various conditions that should be recognized prenatally. As presented in the previous section, fetal overgrowth is affected by several genetic, hormonal and environmental factors. However, the most well-known causal factor for fetal overgrowth is maternal hyperglycemia which leads to fetal hyperglycemia, and further to hyperinsulinemia. According to Pedersen's hypothesis (Pedersen 1952), this leads to fetus overgrowth of insulin-sensitive tissues such as liver, muscle, cardiac muscle and subcutaneous fat, especially in the abdominal and interscapulum areas (Crowther et al. 2005, Kwik et al. 2007, Billionnet et al. 2017, Pedersen 1952) Generally, the growth of the fetus is disproportionate: the ponderal index is increased, with a higher chest-to-head and shoulder-to-head ratio, higher body fat and thicker upper extremity skinfolds than LGA newborns in nondiabetic mothers (Persson et al. 2013). The HAPO study showed that the risk of birth weight above the 90th percentile increases continuously when maternal plasma glucose levels increase, even before it fulfils the criteria of overt diabetes (HAPO Study Cooperative Research Group, Metzger et al. 2008).

Already a few decades ago, the Pedersen's hypothesis from 1954 was extended to the Pedersen-Freinkel hypothesis (Freinkel 1980) (Figure 5.). This hypothesis proposes, that fetal overgrowth is also affected by other maternal nutritients, such as lipids and amino acids. Previous studies have repeatedly demonstrated that besides of GDM, excessive maternal weight gain and obesity significantly increase the risk of having an LGA infant (Black et al. 2013, Berntorp et al. 2015, Henriksen 2008, Cosson et al. 2016). In one large population-based study, the prevalence of LGA was 12.2%, 13.5% and 17.3% among women with BMIs of 25 or higher, with excess gestational weight gain, and with GDM, respectively (Kim et al. 2014). According to the HAPO study, in the group of women with GDM obesity nearly doubled the risk of macrosomia (Catalano et al. 2012). Thus, obese women with GDM have a higher risk of developing an LGA fetus than nonobese women with GDM.

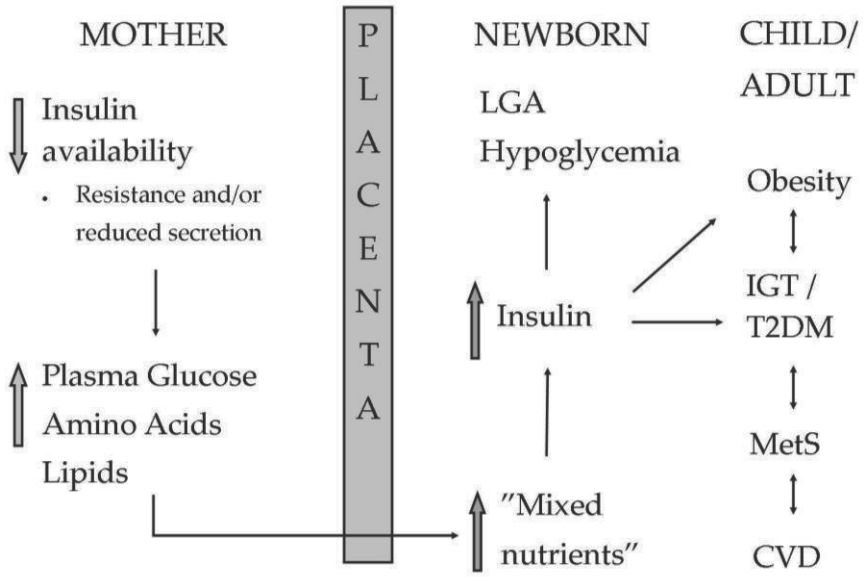


Figure 5. The classic hyperglycemia-hyperinsulinemia hypothesis of Pedersen-Freinkel. (Figure modified from ref. Freinkel 1980)
LGA= a large-for-gestational-age; IGT= impaired glucose tolerance; T2DM= type 2 diabetes; MetS= metabolic syndrome; CVD= cardiovascular diseases

Hyperinsulinemia due to maternal dysglycemia alters fetal cardiac remodeling; the amounts of fat and glycogen are increased, leading to hypertrophic cardiomyopathy, especially thickening of the interventricular septum (Lehtoranta et al. 2013, Hornberger 2006). Moreover, the gene expression in the heart is altered (Lehtoranta et al. 2013). Fetal hyperinsulinemia caused by maternal hyperglycemia leads to elevated metabolic rates and oxygen consumption, and consequently fetal hypoxemia (Philips et al. 1982). Prolonged hypoxemic state can lead to metabolic acidosis, modifications in fetal iron distribution and erythropoiesis leading to polycythemia (Widness et al. 1990). As a consequence of this, redistribution of iron results in iron deficiency in developing organs (Petry et al. 1992). This also can contribute to changes in fetal neurodevelopment (Lozoff et al. 2000).

Because of the fetal hyperinsulinemic state and hypoxemia, the risk of stillbirth is increased in pregnancies with poor glycemic control and is highest in women with pregestational diabetes. However, the difference was not observed when GDM women with good glycemic control were compared to the general obstetrical population (Ovesen et al. 2015). GDM exposes a woman to hypertensive disorders such as pre-eclampsia (Casey et al. 1997, Yogev et al. 2004, HAPO Study

Cooperative Research Group, Metzger et al. 2008, Billionnet et al. 2017). These disorders and increased prevalence of LGA fetuses lead more often to labor induction, which in turn elevates the risk of prematurity and caesarean section among women with GDM (Casey et al. 1997, Cordero et al. 1998).

2.2.3 Consequences of GDM for the offspring

At birth, LGA infants of diabetic pregnancies are at a risk for shoulder dystocia due to increased shoulder and abdominal girth (Bjorstad et al. 2010). This may lead to brachial plexus injury, clavicular fracture and asphyxia (Billionnet et al. 2017). After delivery, LGA infants of diabetic mothers are susceptible to hypoglycemia due to persistent hyperinsulinemia (Flores-le Roux et al. 2012). Moreover, fetal hyperinsulinemia inhibits pulmonary surfactant synthesis (Miakotina et al. 1998), leading to delayed lung maturation and increased risk for respiratory distress syndrome after the birth (Robert et al. 1976). This risk is especially increased in pregnancies in women with early diagnosed or insulin-treated GDM. Erythropoiesis-derived polycythemia in utero can lead to neonatal symptomatic blood hyperviscosity and is one cause of neonatal jaundice. These together predispose the newborn to admission to a neonatal intensive care unit (Boulet et al. 2003).

Several studies concerning the influence of maternal hyperglycemia and offspring risk for diabetes and obesity have been published. Children of women with GDM have an eight-fold increased risk for prediabetes or diabetes, four-fold increased risk for MetS and two-fold greater risk for being overweight (Clausen et al. 2008, Clausen et al. 2009). A study of 970 women who had participated in the HAPO study showed that maternal hyperglycemia is associated with the offsprings' risk for abnormal glucose tolerance, obesity and higher blood pressure at 7 years of age (Tam et al. 2017). This association was independent of prepregnancy BMI and being born LGA. The association of GDM with offspring's hypertension was confirmed by the recent study as well (Lu et al. 2019). Furthermore, an elevated level of hs-CRP, a marker of low-grade inflammation, has been detected in prepubertal children exposed to maternal GDM (Antikainen et al. 2018).

There are conflicting findings concerning adiposity and obesity in GDM offspring, because some studies have demonstrated that the strong association of GDM with childhood obesity deteorites after adjustment for maternal obesity (Pirkola et al. 2010, Boerschmann et al. 2010). However, the HAPO Follow-up Study (HAPO FUS) showed that GDM based on IADPSG criteria was associated with an increased risk for obesity and other measures of adiposity such as sum of skinsfolds, per cent body fat and waist circumference > 85th percentile in children aged 10-14 years. (Lowe et al. 2018). Furthermore, the recent study conducted with HAPO FUS participants demonstrated a positive continuous association between maternal glucose levels during pregnancy and childhood adiposity outcomes independent of maternal BMI, even at glucose levels below of the diagnostic

thresholds for IADPSG-defined GDM (Lowe et al. 2019). Similarly, LGA infants without exposure to maternal diabetes have greater childhood adiposity (Hammami et al. 2001, de Zegher et al. 2014). The long-term risks of the offspring being born LGA are likely due to increased in utero nutrition directly or via epigenetic mechanisms (Ma et al. 2015). However, nutritional excess in utero leads to accelerated fetal growth and fat accretion. Thus, the hypothesis of Pedersen-Freinkel of accelerated fetal growth leading to long-term morbidity of the offspring is still relevant (Pedersen 1952, Freinkel 1980) (Figure 3.) Whatever the reason for higher birthweight (< 4000g) is, the offspring's long-term risk for overweight and overweight-related diseases is increased (Schellong et al. 2012).

2.2.4 Consequences of having an LGA newborn for maternal health

Due to fetal overgrowth, the labor can be prolonged or arrested and therefore end with operative vaginal or cesarean delivery (Bjorstad et al. 2010). Vaginal delivery of an atypically large baby increases the risk of vaginal lacerations and perineal tears, and the risk of uterine atony is elevated (Bjorstad et al. 2010).

In women with normal glucose tolerance during pregnancy, an LGA delivery does not increase the risk of future T2DM according to several studies (Spjuth et al. 1993, Tehrani et al. 2012, Moses et al. 1997, Kew et al. 2011). Only two studies have reported an increased incidence of T2DM after an LGA delivery in women who were normoglycemic during the pregnancy (James-Todd et al. 2013, Larsson et al. 1986). In these studies, however, GDM was not exluded appropriately among study participants, which may explain the conflicting results. In addition, normoglycemic women with an LGA delivery showed no differences in the waist circumference, blood pressure, insulin sensitivity and β-cell function three months after delivery (Kew et al. 2011). Moreover, studies adjusting for GDM have found no increased risks for later cardiovascular disease, in women giving birth to an LGA infant (Fraser et al. 2012, Bonamy et al. 2011).

Studies focusing on the risk of T2DM, MetS and CVD in women with a history of GDM and delivery of an LGA infant are sparse. Several studies have explored the risk of future T2DM or CVD risk after an LGA delivery by excluding the women with dysglycemia during pregnancy. In a study of 12 153 women, women with a history of delivering an LGA infant demonstrated a 1.44-fold higher risk of developing diabetes in results adjusted only by family history of diabetes. However, the gestational glucose status was not identified among study participants. Thus, the individual risk of T2DM in GDM women with LGA infants is not clear (Kabeya et al. 2013). A recent meta-analysis with nearly 100 000 women reported that having macrosomic infant was not associated with maternal risk of later developing T2DM independently of GDM and other risk factors (Rayanagoudar et al. 2016).

2.3 MATERNAL METABOLIC HEALTH AFTER GDM PREGNANCY

After delivery, the majority of the women with GDM achieve normoglycemic status shortly after delivery when effects of placental hormones evaporate. However, based on chronic insulin resistance and usually obesity, they are at risk for recurrence of GDM, prediabetic stages, T2DM, MetS, and cardiovascular diseases. Therefore, a postpartum intervention for these women is needed to prevent or early diagnose these conditions.

2.3.1 Recurrence risk of GDM

Women with prior GDM have the recurrence risk for GDM in subsequent pregnancies. In a study including over 65,000 pregnancies, the risks of GDM in the second pregnancy among women with and without previous GDM were 41.3% and 4.2%, respectively (Getahun et al. 2010). A recent meta-analysis revealed, that the risk of recurrence is multifactorial, but the strongest association with recurrence was related to insulin use, BMI, multiparity, macrosomia, and weight gain between pregnancies (Schwartz et al. 2016).

2.3.2 Dysglycemia

Prediabetes is a hyperglycemic stage where blood glucose is abnormally high but does not fulfil the criteria overt diabetes. It can manifest by impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). The diagnostic criteria are shown in Table 3. Prediabetes (IFG, IGT or both) is present in up to 30% of women with a history of GDM in two to three months postpartum (Retnakaran et al. 2008, Katon et al. 2012), as well as many years postpartum (Lauenborg et al. 2004). Prediabetes can be stable or progress to diabetes. This progression is influenced by the stage of chronic insulin resistance and decreasing β-cell function. Prediabetes has shown to be associated with an increased risk of cardiovascular disease events in women (Levitzky et al. 2008). With appropriate lifestyle interventions, this progression could be prevented.

Table 3. The diagnostic criteria of prediabetes and diabetes

	Fasting glucose (mmol/l)	2-hour postprandial glucose (mmol/l)
Normal	≤ 6.0 (WHO), ≤ 5.5 (ADA)	< 7.8
IFG	6.1-6.9 (WHO), 5.6-6.9 (ADA)	-
IGT	-	7.8-11.0
Diabetes	> 7.0	> 11.0

IFG=impaired fasting glucose; IGT=impaired glucose tolerance; WHO= World Health Organization; ADA=American Diabetes Association

T2DM is a metabolic disorder characterized by hyperglycemia, insulin resistance and a relative defect in insulin secretion. Generally, the onset of T2DM is preceded by a long-term prediabetic stage with nearly compensated hyperglycemia and accelerated insulin secretion towards to insulin resistance. WHO and ADA have defined diabetic thresholds (Table 4.) and required a single raised glucose value with symptoms, or raised values on two occasions to fulfil the criteria (American Diabetes Association 2011).

The prevalence of T2DM is increasing worldwide. Over the past three decades the prevalence of T2DM has quadrupled, reaching 422 million people with T2DM in 2014 globally (World Health Organization 2017). The highest prevalence of T2DM is found among populations of Pacific Islanders, Asian Indians and Native Americans (Unnikrishnan et al. 2017). It has been estimated, that 450,000 people suffer from T2DM in Finland, and this number is predicted to increase in the future (Diabeteksen ehkäisyn ja hoidon kehittämisohjelma, DEHKO 2000–2010. Tampere: Suomen Diabetesliitto 2000.)

Several studies have investigated the risk of T2DM after GDM pregnancy. According to the systematic reviews, women with previous GDM have a seven-fold increased risk for later development of T2DM (Bellamy et al. 2009), and this risk is related to lower degrees of glucose intolerance during pregnancy as well (Carr et al. 2008, Retnakaran and Shah 2009a). The cumulative incidence of T2DM varies from 2.6% to 70%, depending on the length of follow-up, populations and diagnostic criteria of GDM (Kim et al. 2002). The incidence is markedly increased during the first five years postpartum, reaching a plateau after 10 years according to a systematic review based on 28 studies. After adjustment of confounders, progression rates to T2DM after GDM diagnosis were similar among the reviewed studies. Moreover, the recent the HAPO-FUS study revealed a five-fold and three-fold increased risk for later development of T2DM and prediabetes, respectively, among 4697 women with and without GDM diagnosed with IADPSG criteria after a median follow-up of 11.4 years (Lowe et al. 2018). This study and studies included to both systematic rewiews published by Bellamy and Kim consisted populations with highly variable ethnicity. Therefore, studies in Caucasian populations published since 2000 are summarized in Table 4.

The predictive risk factors for later T2DM after GDM pregnancy are obesity and weight gain after pregnancy (Pirkola et al. 2010, Lauenborg et al. 2004, Rayanagoudar et al. 2016), family history of diabetes (InterAct Consortium, Scott et al. 2013, Rayanagoudar et al. 2016), non-Caucasian ethnicity and advanced maternal age (Rayanagoudar et al. 2016). A prospective follow-up study of 1695 women revealed that women with BMI > 30.0 kg/m^2 at the time of GDM diagnosis and weight gain > 5kg after pregnancy were at 43-fold increased risk for later T2DM compared to woman with BMI < 25.9 kg/m^2 and weight gain < 5 kg (Bao et al. 2015). The severity of glucose intolerance during pregnancy has an influence on the T2DM risk, appearing as early diagnosis of GDM (Baptiste-Roberts et al. 2009), elevated fasting glucose (Rayanagoudar et al. 2016), increased HbA1c (Katon et al. 2012,

Rayanagoudar et al. 2016, Claesson et al. 2017) and need for insulin during GDM pregnancy (Rayanagoudar et al. 2016, Baptiste-Roberts et al. 2009, Lobner et al. 2006). The fasting glucose level on OGTT during pregnancy has been revealed to be predictive for later T2DM in most studies (Damm et al. 1992, Rayanagoudar et al. 2016), although less often studied post-prandial glucose levels associates with this risk as well (Rayanagoudar et al. 2016, Akinci et al. 2011). T2DM risk is increased also in women with hypertensive disorders in pregnancy and GDM pregnancy ending to preterm delivery (Rayanagoudar et al. 2016). The association with milder forms of elevated blood pressure during late pregnancy has also been demonstrated (Saramies et al. 2006). Furthermore, a second pregnancy in women with previous GDM is associated with a three-fold increase in the risk of developing T2DM reflecting that recurrent insulin resistant episodes can accelerate the deteriorating of β-cells (Peters et al. 1996).

The development of T2DM is characterized by a combination of several genetic and lifestyle factors, and thus, the pathophysiology and phenotype of T2DM is very heterogenous (Tuomi et al. 2014). Traditionally, the other forms of diabetes such as LADA (Latent Autoimmune Diabetes in Adults) and MODY (Maturity-Onset Diabetes of the Young) must be considered when the diagnosis of T2DM is made. LADA is a common form of diabetes in which glutamic acid decarboxylase (GAD) antibodies are detected, but progression to insulin dependency diabetes is slower than classical type 1 diabetes (T1DM) (Carlsson 2019). MODY is a monogenic disorder that results in a familial, young-onset non-insulin dependent form of diabetes, typically presenting in lean young adults or adolescence and is frequently misdiagnosed as T1DM or T2DM (Kim 2015). Mody represent only a small fraction of the all diabetes.

Because ethnicity affects the risk of GDM, it similarly reflects the prevalence of T2DM in certain population. The association between common type 2 diabetes risk gene variants and GDM has been discovered (Huopio et al. 2013, Lauenborg et al. 2009), and at least 36 diabetes-associated genes have been identified previously (Herder and Roden 2011). The heritability of T2DM is well established. Individuals with a family history of T2DM in any first-degree relative have a two to three-fold increased risk of developing diabetes, and this risk increases significantly with a biparental history of T2DM (InterAct Consortium, Scott et al. 2013, Meigs et al. 2000). However, the previously discovered 36 genes explain only about 10% of the heritability, and additional studies are required concerning of hidden heritability (Stancakova and Laakso 2016, Herder and Roden 2011).

In addition to genetic burden for insulin resistance and impaired insulin secretion associated with T2DM, several lifestyle factors contribute to T2DM. The prevalence of obesity is increasing worldwide. According to the WHO report from the year 2014, worldwide obesity has more than doubled between 1980 and 2014 (World Health Organization 2016). Overall in 2014, about 15% of the world's women were obese (BMI ≥30 kg/m^2) and 40% of women were overweight (≥25 kg/m^2). The corresponding prevalence figures in Finland were 20% and 46%,

respectively, based on the FINRISK -health study in 2012 (Männistö et al. 2015). Obesity causes peripheral resistance to insulin-mediated glucose uptake (Bonadonna et al. 1990, Kolterman et al. 1980), and adipose tissue releases various adipocytokines influencing insulin resistance (Jung and Choi 2014). The risk of T2DM is increased with increasing body weight and insulin resistance (Mokdad et al. 2003, Nguyen et al. 2011). Therefore, insulin resistance has been regarded as the best predictor of T2DM (Lillioja et al. 1993). In addition to obesity, low physical activity, western diet, smoking, excessive alcohol consumption and short sleep duration increase the risk of T2DM (Reis et al. 2011).

Table 4. Some studies concerning the incidence of type 2 diabetes after GDM pregnancy in Caucasian women.

Study	Study type, country	GDM criteria[a]	Total number of women studied GDM / controls	Mean maternal age (years; SD or 95% CI) GDM / controls	Mean follow-up (SD or 95% CI) GDM / controls (years)	Definition of T2DM	Proportion of women with T2DM at follow-up	
							GDM (%)	Controls (%)
Linne et al. 2002	Retrospective cohort, Sweden	Local	28 / 52	47.6 (4.2) / 45.6 (4.7)	15	Local	21	0
Aberg et al. 2002	Retrospective cohort, Sweden	European Association for Study of Diabetes	226 / 60	Matched range 20-45	1	WHO, 1985	9.2	0
Albareda et al. 2003	Retrospective cohort, Spain	Second and third GDM workshop conference	696 / 70	30.7 / 30.4	6.16 (0.05-13.73)	WHO, 1998	5.6	0
Jarvela et al. 2006	Retrospective cohort, Finland	Finnish Diabetes Association	435 / 435	31.6 (17.7-46.5) / 31.3 (18.8-46.0)	5.7 (1-11.6) / 6.1 (1.5-13.1)	Questionnaire	5.3	0
Corrado et al. 2007	Prospective cohort, Italy	Carpenter and Coustan	56 / 56	34.6 (3.8)	34.6 (3.8) / 32.7 (5.2)	ADA, 1997	10.7	1.8
Huopio et al. 2014	Prospective cohort, Finland	Finnish Diabetes Association	489 / 385	37.8 (7.2) / 38.4 (6.3)	6.0 (4.4) / 9.0 (5.5)	ADA	5.7	0.3
Noctor et al. 2016	Prospective cohort, Ireland	IADPSG	270 / 288	36.6 (5.0) / 37.6 (5.1)	2.6 (1.0) / 3.3 (0.7)	ADA	2.2	0

[a]please see Table 1 for definitions. WHO = The World Health Organization; ADA = American Diabetes Association

2.3.3 Metabolic syndrome

The metabolic syndrome is a cluster of risk factors predisposing to T2DM and CVD (Alberti et al. 2009, Isomaa et al. 2001). These risk factors include insulin resistance, hyperglycemia, dyslipidemia (raised triglycerides and lowered high-density lipoproteins (HDL)), hypertension and central obesity. The condition predisposes to endothelial dysfunction, proinflammation and prothrombotic state. All of these risk factors contribute to the development of atherosclerosis and cardiovascular diseases (Ridker et al. 2000).

The criteria for MetS have changed over time. The concept of the MetS was described in the 1920s (Kylin 1923). After several modifications (Vague 1947, Reaven 1988, Alberti and Zimmet 1998), currently there are five different criteria of the MetS (Table 5). The most often used definition was proposed by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) (Alberti et al. 2009), in which the MetS was defined as having at least three of five cardiometabolic traits. The other widely used definition was released by the International Diabetes Federation (IDF) in 2005 (Alberti et al. 2005) targeting to identify people who are at risk for both CVD and T2DM and to endeavor to create a definition to allow comparability of subsequent long-term studies. According to the IDF, central obesity, specified by different cut-off points depending on ethnicity and sex, is an obligatory trait with any of two other traits. In European women, the risk of CVD has been shown to increase after exceeding the cut-off value for waist circumference of 80cm used in the IDF definition (Lean et al. 1998).

The prevalence of MetS has varied in previous studies a result of different definitions and different populations. The FINRISK survey carried out in the spring 1992 as part of the FINMONICA cardiovascular risk factor survey found that MetS was present in 22.2% of middle-aged women according to the WHO criteria (Ilanne-Parikka et al. 2004). The Cardiovascular Risk in Young Finns study in 2007 observed a 15.9% prevalence of MetS in women 30-39 years of age according to the IDF definition, and the prevalence increased during a six-year follow up as a result increasing of waist circumference, glucose levels and blood pressure (Raiko et al. 2010). Obesity is a major metabolic trait of MetS, and the prevalence of MetS increased to 64.8% of obese women in Finnish Health 2000- cohort according to NCEP criteria (van Vliet-Ostaptchouk et al. 2014). A recent meta-analysis with 34 635 participants of both sexes in 21 studies observed a prevalence of MetS of 22.9% (Cuspidi et al. 2017). MetS was defined mostly by the NCEP, IDF and WHO criteria. The studies included were distributed in three different geographical areas: 33.1% in Asia, 21.1% in Europe and 46.9% in America. Overall, 51.9% of all participants were women, in whom the prevalence of MetS between studies varied from 6 to 49%. As a consequence of the obesity epidemic, the prevalence of MetS is increasing worldwide (Hu et al. 2008, World Health Organization 2016).

Table 5. The currently used criteria of the metabolic syndrome.

	Criterion	Abdominal obesity	Blood Pressure (mmHg)	Dyslipidemia (mmol/l)	Fasting plasma glucose (mmol/l)	Other
WHO 1998	Dysglycemia + ≥ 2 other components	BMI > 30 kg/m^2 or waist-to-hip ratio > 0.85	≥ 140/90	TG ≥ 1.7 or HDL < 1.0	T2DM or IFG or IGT	Microalbuminuria: albumin excretion ≥20 µg/min
EGIR 1999	Insulin resistance defined as the top 25% of the fasting insulin values among nondiabetic individuals + ≥ 2 other components	Waist ≥ 80 cm	≥ 140/90 or medication	TG > 1.7 or HDL < 1.0	≥ 6.1	
NCEP-ATP III 2001	≥ 3 components	Waist > 88 cm	≥ 135/85 or medication	TG ≥ 1.7 or HDL < 1.3	≥ 6.1	
AACE	Impaired glucose tolerance + ≥ 2 other components	BMI > 25 kg/m^2	≥ 130/85	TG ≥ 1.7 or HDL < 1.3	6.1–7.0	
IDF 2006	Waist + ≥ 2 other components	Waist > 80 cm	≥ 130/85	TG ≥ 1.7 or HDL < 1.3	≥ 5.6 or T2DM	

WHO= The World Health Organization; EGIR= The European Group for Study of Insulin Resistance; NCEP-ATP III= The National Cholesterol Education Program Adult Treatment Panel III; AACE= The American Association of Clinical Endocrinologists; IDF= The International Diabetes Federation; BMI= body mass index; TG= triglycerides; HDL= high-density lipoprotein; T2DM= type 2 diabetes; IFG= impaired fasting glucose; IGT= impaired glucose tolerance.

Insulin resistance is a widely accepted central mechanism in the pathophysiology of MetS, and most of the syndrome traits are linked to insulin resistance. When insulin resistance occurs, glucose uptake is impaired in insulin-sensitive tissues, such as skeletal muscle, adipose tissue and liver, leading to hyperglycemia and hyperinsulinemia. Central obesity is associated with increased size of adipocytes and number of macrophages, which releases inflammatory cytokines and adipokines, leading to low-grade inflammation and systemic insulin resistance (Van de Voorde et al. 2013). Furthermore, the insulin sensitivity of large adipocytes diminishes, leading to an influx of free fatty acids to the liver and overproduction of VLDL and thus, dyslipidemia (Gastaldelli et al. 2010). The excess of free fatty acids contributes to insulin resistance in muscle, liver and other tissues (DeFronzo 2010). Insulin resistance alters vascular endothelial function, leading to impaired vasodilatation and release of markers of endothelial damage (Manrique et al. 2014). In persons with obesity or hypertension, activation of the renin-

angiotensin-aldosterone system is present with systemic and vascular insulin resistance (Manrique et al. 2014).

The pathophysiology of MetS and GDM share common factors: insulin resistance, endothelial dysfunction and chronic inflammation (Di Cianni et al. 2007). Therefore, women with previous GDM are at increased risk for development of MetS. The latest systematic review detected a four-fold increased risk for MetS in women with previous GDM compared to women with a normal pregnancy, and the risk of MetS was increased over five-fold if the women had higher BMI (Xu et al. 2014). Several studies in Caucasian women have observed an association between previous GDM and MetS (Table 6). In continuum, elevated levels of CRP have been associated with T2DM, myocardial inflammation, stroke and peripheral vascular disease (Ridker 2003) and make CRP a notable predictive marker of cardiovascular diseases. Collectively, women with MetS are at increased risk for cardiovascular diseases and mortality (Isomaa et al. 2001), suggesting that screening may be worthwhile. Whatever the definition of MetS that is used, all women share elevated risks for future ischemic stroke and coronary heart disease according to six Finnish and Swedish studies, suggesting the need for preventive measures for all MetS women (Qiao et al. 2009).

Table 6. The incidence of metabolic syndrome after GDM pregnancy in Caucasian women

Study, year	Study type, country	GDM criteria[a]	Total number of women studied GDM / controls	Mean maternal age (years; SD or 95% CI) GDM / controls	Mean follow-up (years; SD or 95%CI) GDM / controls	Definition of metabolic syndrome[b]	Proportion of women with MetS at follow-up	
							GDM (%)	Controls (%)
Albareda et al. 2005	Prospective cohort, Spain	NDDG	262 / 66	39.1 (5.5) / 40.6 (4.8)	5	NCEP-ATP III	11.1	6.1
Lauenborg et al. 2005	Prospective cohort, Denmark	Danish	457 / 987	42.9 (37.7–47-8) / 45.0 (39.9–50.2)	9.8 (6.4–17.2)	NCEP-ATP III	43.5	14.8
Bo et al. 2006	Retrospective cohort, Italy	Carpenter and Coustan	182 / 161	40.6 (4.6) / 41.4 (4.6)	6.5	NCEP-ATP III	18.7	2.5
Di Cianni et al. 2007	Prospective cohort, Italy	Carpenter and Coustan	166 / 98	34.7 (4.2) / 33.9 (3.9)	1.4	IDF	14.5	2
Wender-Ozegowska et al. 2007	Prospective cohort, Poland	WHO	153 / 155	28.3 (6.0) / 26.5 (3.7)	6.0 (2.7) / 5.1 (2.7)	NCEP-ATP III	30.7	5.2
Akinci et al. 2010	Prospective cohort, Turkey	Carpenter and Coustan	164 / 65	33.7 (5.9) / 33.5 (4.5)	3.4 (1.9) / 3.6 (1.8)	IDF	26.2	4.6
Ijas et al. 2013	Prospective cohort, Finland	Finnish Diabetes Association	61 / 55	52.8 (7.5) / 51.7 (6.4)	18.6 (1.7) / 19.0 (1.7)	NCEP-ATP III	62.3	30.9
Noctor et al. 2015	Prospective cohort, Ireland	IAPDSG	265 / 378	36.7 (5.0) / 37.6 (5.1)	2.6 (1.0) / 3.3 (0.7)	NCEP-ATP III	25.3	6.6
Vilmi-Kerala et al. 2015	Prospective cohort, Finland	Current Care Guidelines	120 / 120	35.8 (4.4) / 35.9 (4.6)	3.7	NCEP-ATP III	15.8	6.7
Puhkala et al. 2017	Prospective cohort, Finland	ADA	40 / 44	38.6 (4.3) / 37.0 (5.2)	7	IDF	50	7

[a] please see Table 1 for definitions.
[b] please see Table 5 for definitions.

2.3.4 Cardiovascular diseases

Cardiovascular diseases (CVD), such as heart disease, strokes and arteriosclerosis obliterans, are remarkable causes of morbidity and mortality of the women worldwide causing enormous health and economic burdens (Writing Group Members, Mozaffarian et al. 2016). The increased risk for CVD associated with T2DM and MetS, is well documented (Isomaa et al. 2001). Thus, women with previous GDM with an increased risk for later T2DM and MetS also represent a risk group for CVD. The pathogenic features related to these conditions, such as insulin resistance and chronic inflammation, contribute to the development of atherosclerosis over decades, leading later to CVD (Esser et al. 2015, Gast et al. 2012). Several studies concerning vascular health of women with prior GDM have demonstrated increased vascular dysfunction (Bo et al. 2007), such as impaired vasodilatation (Anastasiou et al. 1998) and greater vessel stiffness (Lekva et al. 2015) as a part of the background pathophysiology of CVD.

Based on literature, CVD events occur at relatively young women who have had GDM during pregnancy. Shah and colleagues compared over 8000 women with GDM to over 80 000 women without GDM and showed a nearly doubled risk for CVD in women with a mean age of 31 years and previous GDM and median follow-up of 11 years (Shah et al. 2008). They concluded that CVD risk was mostly explained by a higher incidence of T2DM in women with prior GDM. However, Retnakaran and Shah compared nearly 57 000 of women with previous GDM with or without subsequent T2DM and median age of 32. They found a hazard ratio 2.82 and 1.3 for CVD, respectively, when compared to women without GDM (Retnakaran and Shah 2017). A recent systematic review and meta-analysis including over 5 million women demonstrated that GDM is associated with a twofold increased risk for cardiovascular events relatively young women and incident T2DM did not affect this risk (Kramer et al. 2019). Moreover, the risk of having cardiovascular event was 2.3-fold in the first decade after pregnancy. A similarly increased risk for early CVD events within 7 years postpartum has been documented in a nationwide study including nearly 63 000 women with previous GDM (Goueslard et al. 2016). It has been also demonstrated that even mild glucose intolerance below the diagnostic criteria of GDM during pregnancy increases the risk of cardiovascular events in relatively young women in a study performed 12 years postpartum (Retnakaran and Shah 2009).

2.3.5 Follow-up and prevention of future morbidity

Although women usually return to normoglycemia after a GDM pregnancy, all organizations worldwide recommend long-term follow-up after a GDM pregnancy due to the increased long-term morbidity associated with this condition (American Diabetes Association 2018, Metzger et al. 2007, Committee on Practice Bulletins-Obstetrics 2018). Based on the Finnish Current Care Guidelines, all women with insulin-treated GDM are advised to have OGTT 6-12 weeks after delivery, and

women treated with diet therapy should have an OGTT one year postpartum. Thereafter, all women with previous GDM should have a long-term follow-up at the health center at intervals of one to three years (American Diabetes Association 2018, Committee on Practice Bulletins-Obstetrics 2018). These visits should include an OGTT, blood lipid profile, measurements of blood pressure, BMI and waist circumference as well as guidance on preventive lifestyle habits (Gestational Diabetes: Current Care Guidelines, 2013). For reclassification of glucose status, an OGTT is the most recommended test since its sensitivity is superior to a single fasting glucose measurement (Ferrara et al. 2009) or HbA1c (Picon et al. 2012). In a previous study, a fasting plasma glucose level alone detected only 15.8% of women with abnormal glucose status postpartum (Reinblatt et al. 2006).

The risk of later T2DM, and evidently MetS and CVD, can be reduced in a high-risk population with healthy diet, regular exercise and weight loss (Tuomilehto et al. 2001). The Diabetes Prevention Program (DPP) demonstrated that the risk of later T2DM was halved in the intensive lifestyle therapy group compared to placebo group three years after randomization in women with impaired glucose tolerance after GDM pregnancy (Ratner et al. 2008). Recently, the subsequent results from DPP were published (Aroda et al. 2015). Ten years after lifestyle intervention, the progression of T2DM was still reduced by 35% in women with previous GDM compared to placebo group. Overall, women with prior GDM and no intervention had a 48% higher risk of developing T2DM. Similarly, in recent review of intervention studies, the pooled estimate of absolute risk reduction of T2DM was significant with any lifestyle intervention starting up till one year postpartum compared with no intervention (Pedersen et al. 2017). Breastfeeding is beneficial among women with a history of GDM, because studies have reported a lower incidence of T2DM (Stuebe et al. 2005, Tanase-Nakao et al. 2017) and MetS (Gunderson et al. 2010) with longer and exclusive lactation. Breastfeeding also helps women to achieve prepregnancy weight (Dewey et al. 1993).

There is some evidence that pharmacotherapy could diminish the progression rate to T2DM especially in women with previous GDM. According to the DPP - study, metformin treatment halved the risk of later T2DM compared to women without GDM history after three years of randomization. In a subgroup of women without GDM, metformin treatment reduced T2DM risk only by 14% compared to placebo group (Ratner et al. 2008). This study concluded that metformin may be more effective in glucose intolerant women with previous GDM than in those without. Similarly, the post-hoc analysis of the DPP demonstrated that metformin treatment significantly reduced the risk of T2DM only in those subjects with the highest risk for diabetes, whereas lifestyle interventions were consistent across the T2DM risk levels (Sussman et al. 2015). According to the American Diabetes Association guidelines, metformin is a choice of treatment in women with previous GDM, in addition to a healthy lifestyle (American Diabetes Association 2017).

The intensity of intervention can be personalized according to the individual's risk profile for T2DM. A recent study of nearly 96 000 women with prior GDM

demonstrated that the factors associated with increased risk for T2DM include BMI, family history of diabetes, non-white ethnicity, advanced maternal age, multiparity, hypertensive disorders during pregnancy and preterm delivery (Rayanagoudar et al. 2016). However, the strongest predictive factors were early diagnosis of GDM, elevated fasting glucose, increased HbA1c and use of insulin. The authors concluded that postnatal counseling should be personalized according to the risk of later T2DM.

The preventive measures should be offered shortly after GDM pregnancy, because the incidence of T2DM tends to increase during the first five years postpartum and then after 10 years appears to plateau (Kim et al. 2002). Moreover, the risk for cardiovascular events is 2.3-fold higher in GDM women in the first decade after delivery, suggesting a unique opportunity for primary prevention of CVD in young women (Kramer et al. 2019). A review concerning barriers of healthy lifestyle after GDM pregnancy illustrated a poorer impact of intervention trials that were started during pregnancy or early postpartum (Nielsen et al. 2014). Furthermore, an important barrier in postpartum could be the role of being a new mother; the lack of time, feeling overwhelmed and possible emotional distress in postpartum. Another plausible reason is that this relatively young group of women underestimates their risk for T2DM since they feel healthy. Therefore, it could be preferable to carry out interventions after the first postpartum months.

In practice, compliance with follow-up visits after GDM pregnancies is far from optimal. Several studies throughout the world have shown that only part of these women have undergo an OGTT after a GDM pregnancy. This inadequate compliance with follow-up is a significant global problem (Ferrara et al. 2009, Chamberlain et al. 2015, Shah et al. 2011, Benhalima et al. 2016). Bernstein and colleagues found a remarkable failure in postpartum follow-up, where among nearly 13 000 women, only 21.8% underwent at least one glucose test by the end of the first year and 51% by the third year after delivery (Bernstein et al. 2017). Of those women, 48% had an OGTT and only 24% had optimal care, i.e. a primary care visit in addition to glucose testing. They concluded that a linkage between maternity clinics and primary care should be strengthened to avoid missed prevention opportunities. Another recently published study demonstrated that 75% of over 32 000 women with previous GDM were not tested for diabetes within one year after the index pregnancy (Eggleston et al. 2016). Fortunately, the latest studies report a slow increase in screening rates after GDM pregnancy over the past decades (Eggleston et al. 2016, Ferrara et al. 2009, Shah et al. 2011).

3 AIMS OF THE STUDY

The overall aim of this study was to investigate the long-term morbidity of women with previous GDM in the North Savo region and acquire information for counseling these women after pregnancy.

The specific aims of this study were:

1. To define the incidence of T2DM among women with previous GDM after a long-term follow-up and determine the optimal thresholds of an OGTT performed during the pregnancy to predict later T2DM. (Publication I)

2. To investigate the incidence of MetS and its components in women with a history of GDM. (Publication II)

3. To explore the effect of delivery of an LGA infant on the maternal risk for later development of T2DM. (Publication III)

4. To determine the association between delivery of an LGA infant and the later risk of maternal MetS. (Publication IV)

4 POST-CHALLENGE GLYCEMIA DURING PREGNANCY AS A MARKER OF FUTURE RISK OF TYPE 2 DIABETES: A PROSPECTIVE COHORT STUDY[1]

4.1 ABSTRACT

The aim of this study was to evaluate the glycemic measures from an oral glucose tolerance test (OGTT) during pregnancy as predictors of incident type 2 diabetes mellitus (T2DM). Patients diagnosed with gestational diabetes mellitus (GDM) were divided into two groups according to the results of OGTT: one abnormal value = GDM1 (n=338) and two abnormal values = GDM2 (n=151), while women with normal glucose tolerance served as controls (n=385). Glucose tolerance was re-evaluated with an OGTT in a follow-up study (average follow-up time 7.3 ± 5.1 years). The incidence of T2DM after ten years follow-up increased progressively by the degree of the glycemic abnormality during pregnancy: 0.8 % in controls, 3.8 % in GDM1 (adjusted HR 17.6, 95% CI 1.9-162.5) and 25.0 % in GDM2 (adjusted HR 72.9, 95% CI 9.6-553.7), respectively (p= < 0.0001). The risk of T2DM is significantly increased in women with two or more abnormal values in OGTT during pregnancy. Post-challenge glucose levels in OGTT were the best predictors the incident T2DM in ROC analysis and they therefore identify the greatest risk group for targeted prevention of T2DM after GDM.

[1] Adapted with permission of Taylor & Francis from: Hakkarainen H, Huopio H, Cederberg H, Pääkkönen M, Voutilainen R, Heinonen S. Post-challenge glycemia during pregnancy as a marker of future risk of type 2 diabetes: a prospective cohort study. Gynecol Endocrinol. Jul;31(7):573-7, 2015.
The table and figure numbers are modified from original publication to correspond sequential numbers of this thesis.

4.2 INTRODUCTION

Gestational diabetes mellitus (GDM), defined as abnormal glucose tolerance detected for the first time in pregnancy (American Diabetes Association 2011), is a well-known risk factor for impaired fasting glucose (IFG) and type 2 diabetes mellitus (T2DM). GDM and T2DM share several of the same risk factors including age, body mass index (BMI), family history of diabetes and genetic factors (Kim et al. 2002, Huopio et al. 2013). The incidence of GDM has varied between different studies reflecting the different diagnostic criteria, populations and ethnic groups, but is estimated to affect approximately 7% of all pregnancies (ranging from 1 to 14%) (American Diabetes Association 2011). In Finland, the prevalence of GDM was 12.7% in 2012 (The national Institute for Health and Welfare, Finland. Finnish Medical Birth Register 2012). Both the incidence of GDM and T2DM are on the increase globally, with a significant impact on health care and economic costs (Hunt and Schuller 2007).

In a recent review (Bellamy et al. 2009), GDM was associated with a seven-fold increased risk of developing T2DM after the pregnancy, as compared to normoglycemic pregnancy. The range of the cumulative incidence of T2DM has varied as much as from 2.6% up to 70% (Kim et al. 2002), largely explained by different follow-up times and ethnic groups evaluated in the studies.

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study has shown that the risk of perinatal disorders increases continuously when maternal plasma glucose levels increase even before it fulfills the criteria of overt GDM (HAPO Study Cooperative Research Group, Metzger et al. 2008). However, whether fasting, 1-h and 2-h post-challenge glycemia in an oral glucose tolerance test (OGTT) during pregnancy differ in the associated risk of future T2DM is not well known. To this aim, we evaluated fasting and post-challenge glycemia during OGTT in pregnancy as predictors of incident maternal T2DM later in life in a prospective follow-up setting of 874 women, and furthermore determined the optimal cutoff points for the three different glucose levels of OGTT in predicting future T2DM.

4.3 METHODS

4.3.1 Desing, setting and population

The hospital register-based cohort study included patients whose pregnancies were treated in Kuopio University Hospital, Finland, between 1989 and 2009. All patients who had OGTT during pregnancy within the time period were contacted by a letter and invited for the study. A total of 489 patients with GDM and 385 controls with normal OGTT during pregnancy attended the follow-up study. All participants gave written informed consent. Patients were classified based on the OGTT during pregnancy as normoglycemic controls, GDM with one abnormal value in OGTT (GDM1) (n = 338) and GDM with two or more abnormal values in OGTT (GDM2)

(n = 151). Patients with overt T2DM at the time of pregnancy, type 1 diabetes diagnosed after index pregnancy and multiple pregnancies were excluded to eliminate confounding factors.

4.3.2 Data collection during pregnancy

Patients were considered to be at risk of GDM and underwent a 2-h OGTT (75 g glucose dose after overnight fasting) if one or more following factors were present: age over 40 years, BMI ≥25 kg/m^2, prior GDM, previous delivery of a macrosomic infant, glucosuria, and suspected fetal macrosomia in the current pregnancy. The diagnostic criteria of GDM were as follows: until September 2001 lower limits of abnormal fasting, 1-h and 2-h capillary whole-blood glucose were 4.8, 10.0 and 8.7 mmol/l and since September 2001 lower limits of fasting, 1-h and 2-h capillary plasma glucose were 4.8, 11.2 and 9.9 mmol/l. For patients with more than one delivery during the study period, the first pregnancy with abnormal OGTT was selected as the index pregnancy. The information on the large for gestational age (+2 SD) was based on the register-based Finnish data (Sankilampi et al. 2013).

4.3.3 The follow-up study

Participants were recruited into the follow-up study between 2006 and 2009 (Figure 6). To study the glucose tolerance after the pregnancy, the participants underwent a 2-h OGTT (75 g of glucose). T2DM was defined according to American Diabetes Association (ADA) recommendations: fasting plasma glucose ≥7 mmol/l or 2-h plasma glucose ≥11.1 mmol/l. Fasting plasma glucose between 5.6 and 6.9 mmol/l was defined as impaired fasting plasma glucose (IFG) (American Diabetes Association 2011). Women who had been diagnosed with T2DM during the follow-up time (N=15) did not undergo an OGTT.

Height was measured in meters and weight in kilograms to one decimal place. Body mass index (BMI) was calculated as weight (kg) divided by the height (m) squared.

The study population was divided to three groups by the length of the follow-up time (the time between the abnormal result in OGTT during the index pregnancy and the follow-up study visit): less than 5 years, 5–10 years and after 10 years.

4.3.4 Laboratory determinations

Plasma glucose was measured by enzymatic hexokinase photometric assay (Konelab Systems reagents; Thermo Fischer Scientific, Vantaa, Finland). Insulin was determined by immunoassay (ADVIA Centaur Insulin IRI no. 02230141; Siemens Medical Solutions Diagnostics, Tarrytown, NY). HbA1c was measured using the high-performance liquid chromatography assay (TOSOH G7 glycohemoglobin

analyzer, Tosoh Bioscience, Inc., San Francisco, CA), calibrated to calibrated to direct-current current transformers (DCCT) standard.

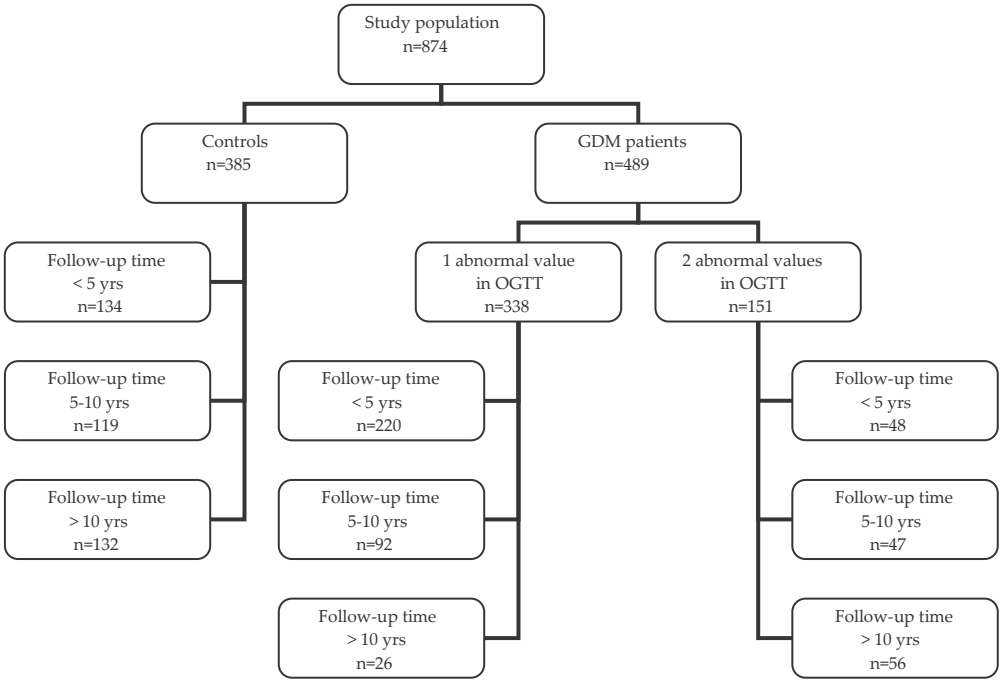


Figure 6. Flowchart of the study population.

4.3.5 Statistical analyses

The statistical analyses were conducted using SPSS version 19 (SPSS Inc., Chicago, IL). The value of $p < 0.05$ was considered statistically significant. Results were given as the mean ± SD or number of cases and percentages. Statistical differences in categorical variables between the patients with GDM and controls were evaluated using $\chi 2$ test. Anthropometric and biochemical continuous variables were analyzed using Student's t-test, and log-transformed variables were used to correct for their skewed distribution when appropriate. Cox regression analysis was used to assess the effect of various factors on the risk for later development of T2DM and hazard ratios (HR) with 95% confidence intervals (CIs) were calculated. Receiver operating characteristic (ROC) curve was generated to determine predictability of fasting, 1-h and 2-h plasma glucose in the OGTT of the index pregnancy for the subsequent development of T2DM. Furthermore, the most adequate glycemic cutoff levels with maximum sensitivity and specificity were determined with ROC curve for the incident T2DM. Since the diagnosis of GDM was made based on different criteria depending on the origin of the blood during the data collection, a correlation

coefficient was used to convert all values to plasma venous values. The correlation coefficient was based on the information from the department of clinical chemistry at Kuopio University Hospital. This study was approved by the local Ethics Committee of the Kuopio University Hospital in accordance with the Helsinki Declaration.

4.4 RESULTS

Clinical characteristics of the patients with GDM (N=489) and the controls (N=385) at prepregnancy and in index pregnancy are shown in Table 7. The patients with GDM were older, more overweight and parous than the controls. However, patients with GDM gained less weight during pregnancy than the controls and there were no statistically significant differences in the mean birth weight of the newborn child between the groups.

Age, BMI and the results of OGTT stratified by GDM status at the index pregnancy (controls, GDM1, GDM2) and by the duration of follow-up time are shown in Table 8. Minimum follow-up time was 0.5 years and maximum 19.3 years. Overall, the glucose and insulin levels were higher in the patients with a history of GDM as compared to the controls, and glucose abnormalities were more severe in the GDM2 patients than the GDM1 patients.

Table 7. Clinical characteristics of controls and GDM patients at prepregnancy and in index pregnancy

	Controls	GDM 1 patients	GDM 2 patients	*p*	*p**
	%	%	%		
Number of patients	385	338	151		
Prepregnancy risk factors					
Age < 18 yrs	0.3	0	0	1.000	1.000
Age > 35 yrs	14.2	28.8	34.0	**<0.0001**	**<0.0001**
Nulliparity	54.7	35.9	37.9	**<0.0001**	**<0.0001**
Spontaneous abortion	16.1	22.3	23.5	**0.037**	**0.043**
Prior cesarean section	7.0	6.5	15.0	0.803	**0.004**
Time since previous delivery ≥ 6 yrs	25.5	23.6	31.7	0.655	0.240
Pregravid BMI > 25 kg/m²	32.2	47.7	57.8	**<0.0001**	**<0.0001**
Not married	33.4	40.9	34.0	**0.036**	0.900
Self-reported infertility	6.2	8.9	11.1	0.171	0.053
Smoking (>5 cigarettes/d)	15.0	20.2	21.7	0.067	0.060
Alcohol consumption	48.9	42.5	39.9	0.084	0.057
Peripartum characteristics of the patients and newborns	Mean ± SD	Mean ± SD	Mean ± SD	*p*	*p**
Maternal age (yrs)	29.5 ± 5.3	31.7 ± 5.9	32.7 ± 5.7	**<0.0001**	**<0.0001**
Maternal BMI (kg/m²)	29.3 ± 4.0	31.0 ± 4.7	30.7 ± 4.5	**<0.0001**	**<0.0001**
Maternal weight gain (kg)	13.7 ± 4.9	12.8 ± 6.0	10.8 ± 6.0	0.065	**<0.0001**
Preeclampsia (%)	2.3	6.2	4.6	**0.009**	0.169
Female fetus (%)	49.0	44.8	49.0	0.264	0.991
Gestational age (d)	279 ± 11	278 ± 10	278 ± 10	0.232	0.141
Birth weight (g)	3581 ± 571	3637 ± 571	3671 ± 531	0.190	0.089
Large for gestational age (+2SD) (%)	4.4	5.9	5.9	0.351	0.470
Placental/fetal weight ratio (%)	17.8 ± 6.6	17.3 ± 2.8	17.8 ± 3.4	0.379	0.569
Low Apgar score 5 min < 7 (%)	0	1.8	2.0	**0.010**	**0.023**

GDM1 = patients with one abnormal value in OGTT during pregnancy; GDM2 = patients with two or more abnormal values in OGTT during pregnancy; BMI = body mass index
p, compared controls to GDM patients with one abnormal value in OGTT (GDM 1)
*p**, compared controls to GDM patients with two or more abnormal values in OGTT (GDM 2)

Table 8. Glucose tolerance and insulin levels in OGTT at the follow-up.

	Follow-up time (years)	Controls Mean ± SD	GDM 1 Mean ± SD	GDM 2 Mean ± SD	*p*	*p**
Number of patients†		385	338	153		
Age at follow-up	<5	34.9 ± 5.9	34.8 ± 6.1	34.9 ± 6.2	0.772	0.968
	5-10	36.9 ± 5.4	38.2 ± 5.8	41.2 ± 5.6	0.090	**<.0001**
	>10	43.2 ± 4.3	43.5 ± 7.1	45.9 ± 5.6	0.981	**0.002**
BMI (kg/m^2)	<5	27.2 ± 4.7	28.1 ± 5.4	29.9 ± 5.6	0.142	**0.002**
	5-10	26.5 ± 4.9	27.3 ± 5.1	29.6 ± 5.1	0.212	**<.0001**
	>10	26.9 ± 5.0	28.6 ± 5.7	28.8 ± 6.0	0.133	**0.031**
Fasting plasma	<5	5.4 ± 0.4	5.5 ± 0.5	5.6 ± 0.4	**0.039**	**0.001**
	5-10	5.3 ± 0.4	5.5 ± 0.4	5.8 ± 0.6	**<.0001**	**<.0001**
	>10	5.3 ± 0.4	5.6 ± 0.5	5.9 ± 0.7	**<.0001**	**<.0001**
30-min plasma	<5	7.2 ± 1.5	7.6 ± 1.6	8.8 ± 1.6	**0.020**	**<.0001**
	5-10	6.9 ± 1.4	7.7 ± 1.5	9.0 ± 2.0	**0.001**	**<.0001**
	>10	7.1 ± 1.7	8.0 ± 1.8	9.2 ± 1.9	**0.030**	**<.0001**
2-h plasma glucose	<5	5.5 ± 1.1	5.7 ± 1.3	6.7 ± 1.8	0.066	**<.0001**
	5-10	5.4 ± 1.0	5.8 ± 1.3	6.2 ± 1.9	**0.020**	**0.049**
	>10	5.6 ± 1.4	6.0 ± 1.4	7.2 ± 3.0	0.205	**<.0001**
Fasting plasma	<5	9.3 ± 4.6	11.7 ± 9.4	12.2 ± 7.4	**0.009**	**0.017**
	5-10	9.4 ± 8.1	10.1 ± 5.9	12.9 ± 5.8	0.155	**0.001**
	>10	8.6 ± 5.3	9.8 ± 5.6	11.4 ± 6.3	0.243	**0.007**
30-min plasma	<5	63.9 ± 34.2	80.3 ±	71.5 ±	**0.026**	0.235
	5-10	63.7 ± 42.9	66.8 ±	70.2 ±	0.792	0.291
	>10	61.9 ± 37.9	55.0 ±	62.7 ±	0.579	0.919
2-h plasma insulin	<5	38.6 ± 25.4	49.6 ±	61.9 ±	**0.025**	**<.0001**
	5-10	40.2 ± 40.7	41.2 ±	62.7 ±	0.455	0.063
	>10	41.5 ± 37.1	49.1 ±	52.0 ±	0.381	0.130

GDM1 = patients with one abnormal value in OGTT during pregnancy; GDM2 = patients with two abnormal values in OGTT during pregnancy; BMI = body mass index.
The bolded values are considered statistically significant.
p, compared controls to GDM patients with one abnormal value in OGTT (GDM 1).
*p**, compared controls to GDM patients with two or more abnormal value in OGTT (GDM 2).
†Patients diagnosed with type 2 diabetes during the follow up time (n=15) were not included in OGTT.

The incidence of IFG and T2DM after the index pregnancy is shown in Figure 7. Subsequent to 10 years' follow-up, the incidence of IFG appeared to increase in the GDM1 and GDM2 groups, whereas the incidence decreased in the control group. The incidence of T2DM increased with time: from 0.5% and 8.3% < 5 years after index pregnancy to 2.2% and 12.8% at 5–10 years, and up to 3.8% and 25.0% > 10 years of follow-up in GDM1 and GDM2 groups, respectively. The incidence of T2DM was significantly greater in GDM2 versus controls ($p < 0.0001$) but not in GDM1 versus controls. The HR for incident T2DM in GDM1 patients compared to the controls was 17.6 (95% CI 1.9–162.3) after adjustment for BMI, age and follow-up time. The corresponding risk of the GDM2 group was 72.9 (CI 9.6–553.7). When BMI was considered as a continuous variable, the probability of future T2DM rose by 14.6% along with the increase of every BMI unit in the patients with abnormal OGTT during pregnancy, but not in the controls.

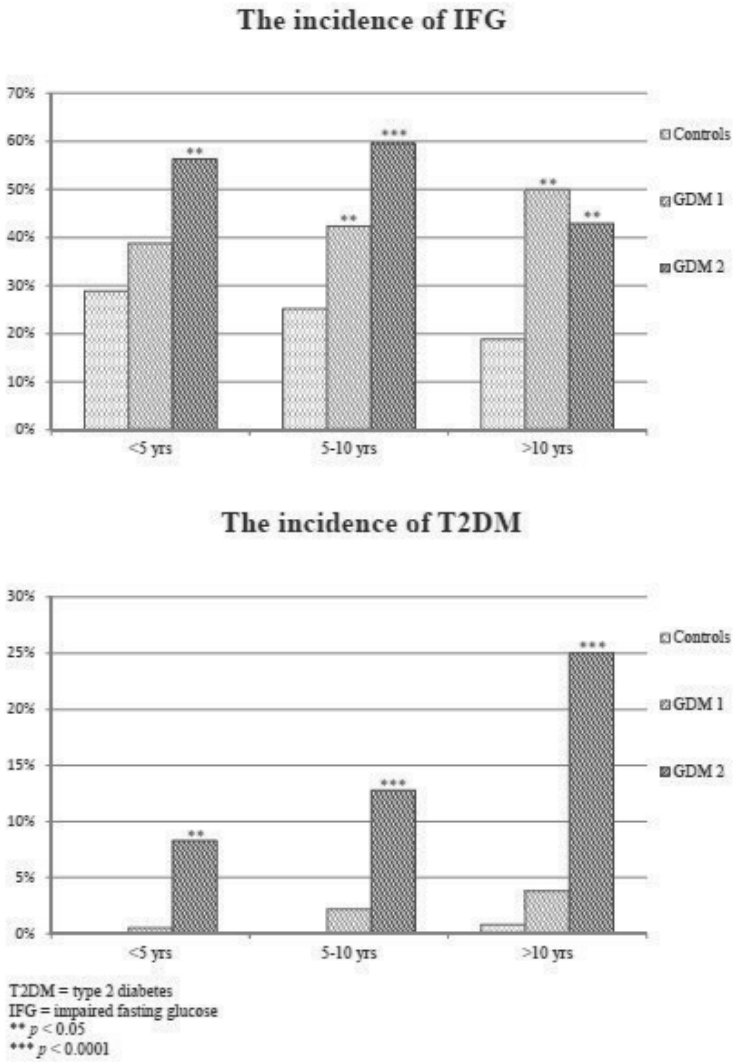


Figure 7. The incidence of T2DM and IFG among the study groups at the follow-up study in categories of follow-up time.

Figure 8 shows the ROC curves for fasting, 1-h and 2-h plasma glucose during pregnancy in predicting T2DM. Post-challenge glucose levels had the highest area under the ROC curve (1-h plasma glucose 0.893 and 2-h plasma glucose 0.889) and fasting plasma glucose the smallest area (0.783). Optimal cutoff points for glycemia during pregnancy with maximum sensitivity and specificity for predicting incident T2DM at the follow-up are shown in Table 9.

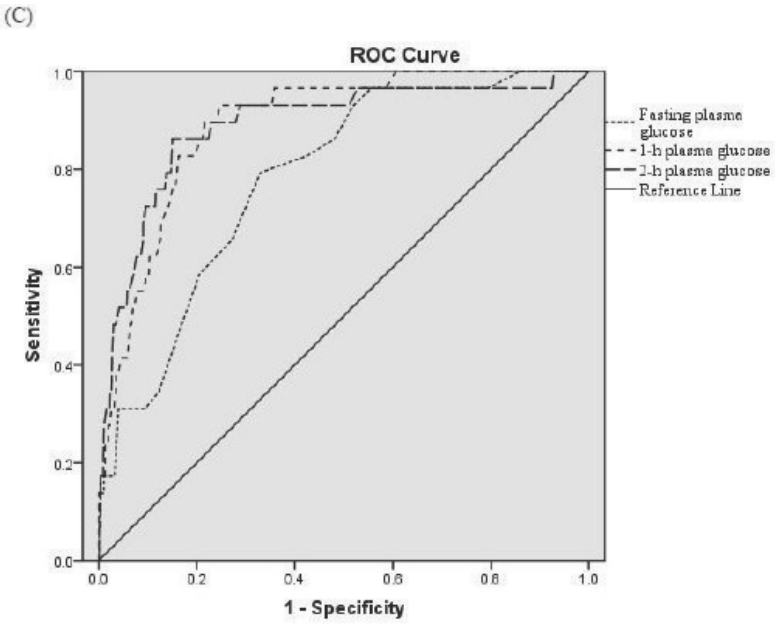


Figure 8. Receiver operating characteristics (ROC) curves for fasting plasma glucose, 1-h plasma glucose and 2-h plasma glucose measures for predicting future T2DM.

Table 9. Performance of maximum sensitivity and specificity cutoff points for fasting plasma glucose (FPG), 1-h plasma glucose (1-h PG) and 2-h plasma glucose (2-h PG) in predicting future T2DM compared to the diagnostic criteria of the Finnish Current Care and criteria of the International Association of the Diabetic Pregnancy Study Groups (IADPSG).

	FPG (mmol/l)	1-h PG (mmol/l)	2-h PG (mmol/l)	Any above the limit
The cutoff points of maximum sensitivity and specificity				
Cutoff point	4,55	9,55	7,92	560
Sensitivity	0,966	0,931	0,862	0,966
Spesificity	0,443	0,753	0,850	0,370
The Finnish Current Care criterion				
Cutoff point	5,3	10,0	8,6	307
Sensitivity	0,448	0,828	0,724	0,966
Spesificity	0,844	0,804	0,904	0,670
The IADPSG criterion				
Cutoff point	5,1	10,0	8,5	386
Sensitivity	0,655	0,828	0,724	0,966
Spesificity	0,729	0,804	0,898	0,576

FPG, fasting plasma glucose; 1-h PG, 1-h plasma glucose in oral glucose tolerance test; 2-h PG, 2-h plasma glucose in oral glucose tolerance test; IADPSG, The International Association of the Diabetic Pregnancy Study Groups.

4.5 DISCUSSION

In our prospective long-term study of women with and without GDM, elevated post-challenge glucose levels during pregnancy were the strongest predictors of incident T2DM. A total of 25% of the GDM2 patients developed incident T2DM after 10 years follow-up. The difference between the GDM2 and GDM1 patients was remarkable, with two or more abnormal values in OGTT during pregnancy being associated with a 72.9-fold increased risk of T2DM, even after the adjustment with BMI, age and follow-up time. The patients with normal OGTT during pregnancy had a 0.8% risk of incident T2DM only, after the 10-year period; even though the risk based GDM screening placed them in the high risk group during pregnancy. However, one in five of the controls had IFG after the 10-year follow-up period. Finally, we found that the currently used plasma glucose cutoffs (fasting 5.3, 1-h 10.0 and 2-h 8.6 mmol/l) for the diagnosis of GDM appear to be highly sensitive in predicting the risk of overt disease after a 10-year period, since only 0.8% of the T2DM cases occurred among controls. Collectively, OGTT during pregnancy appeared to be a good marker of future T2DM risk despite of other risks.

GDM is an important risk factor for abnormal glucose tolerance after pregnancy, and this group is easy to recognize by screening during pregnancy. Thus, development of abnormal glucose tolerance later in life can largely be prevented by means of targeted intervention to this patient group after GDM pregnancy. T2DM and GDM share several common risk factors: obesity, history of abnormal glucose tolerance, diabetes in a first-degree relative, and membership in an ethnic group with a high risk of T2DM (Kim et al. 2002). There are also studies concerning the genetics of GDM and its association with T2DM (Huopio et al. 2013, Lauenborg et al. 2009, Robitaille and Grant 2008). The prevalence of GDM in a population is reflective of the prevalence of T2DM in that population. The patients who have obesity, early diagnosis of GDM before 24 weeks of gestation, high pregnancy OGTT blood glucose or insulin-therapy during pregnancy are at the greatest risk for having T2DM after GDM. A recent study also found that higher HbA1c at GDM diagnosis is associated with increased risk of abnormal postpartum glucose tolerance (Katon et al. 2012).

Our findings largely agree with previously published studies of GDM and risk of T2DM later in life. Previous studies have reported the risk of incident T2DM after a GDM pregnancy to range from 3.6 to 38.38 in Caucasian women (Albareda et al. 2003, Jarvela et al. 2006, Linne et al. 2002, Madarasz et al. 2008, Aberg et al. 2002). A recent systematic review and meta-analysis reported a seven-fold higher risk for diabetes manifestation in participants with a GDM history (Bellamy et al. 2009).

Other studies have shown that prepregnancy overweight is associated with increased risk for diabetes (Rosenberg et al. 2003, Pirkola et al. 2010). Especially prepregnancy overweight (BMI > 25 kg/m2) and IFG postpartum were identified as independent predictors of future diabetes (Lauenborg et al. 2004). Such independent risk of overweight was not seen clearly in our study where the

probability of future T2DM rose by 14.6% along with the increase of every BMI unit in the patients with abnormal OGTT during pregnancy, but not in the controls. In other words, the role of maternal overweight for the development of T2DM was not independent of abnormal OGTT during pregnancy in the present study. The overweight prevalence in this study was similar to that reported in Finland among pregnant patients according to the Finnish Medical Birth Register (The national Institute for Health and Welfare, Finland. Finnish Medical Birth Register 2012).

The strengths of the study include the long-term follow-up of well-characterized cohort of women and the similar treatment received by all participants with GDM during pregnancy. To our knowledge, this is the first study to evaluate a cohort of women with GDM in the more detailed subgroups of glycemia during pregnancy. The range of follow-up times was rather large, and address to this the analyses were done in subgroups according to different follow-up times.

4.6 CONCLUSION

Taken together, our study shows that elevated post-challenge glucose levels in OGTT during pregnancy are the best predictors of the future T2DM. Moreover, the patients with two or more abnormal values in OGTT are at significantly increased risk for the development of T2DM as compared to those with only one abnormal value in OGTT. Therefore, the importance of OGTT during pregnancy to screen GDM cannot be overemphasized. Overall, patients with previous GDM represent a potential target group for intervention to delay or prevent the development of overt diabetes.

5 THE RISK OF METABOLIC SYNDROME IN WOMEN WITH PREVIOUS GDM IN A LONG-TERM FOLLOW-UP[2]

5.1 ABSTRACT

The aim of this study was to evaluate the incidence of the metabolic syndrome (MetS) during long-term follow-up of women with gestational diabetes (GDM). Furthermore, we evaluated the glycemic measures from an oral glucose tolerance test (OGTT) during pregnancy as predictors of incident MetS. Women diagnosed with GDM were divided into two groups according to the results of OGTT: one abnormal value = GDM1 (n=338) and two abnormal values = GDM2 (n=151), while women with normal glucose tolerance (n=385) served as controls. MetS and its components were evaluated in a follow-up study (mean follow-up time 7.3 ± 5.1 years) according to the International Diabetes Federation (IDF) criteria. Fasting plasma glucose in OGTT was the best predictor of incident MetS in ROC (area under the curve) analysis. The incidence of MetS during a < 5-year follow-up was 22.2% in controls, 39.3 % in GDM1 and 60.4 % in GDM2; and > 10-year follow-up 24.2%, 46.2 % and 62.5 %, respectively. In controls and GDM2, the incidence of MetS remained nearly constant during the follow-up, whereas in GDM1 it increased. In conclusion, already mild gestational glucose intolerance may progress to MetS and therefore merits intervention measures to prevent future cardiovascular disease.

[2] Adapted with permission of Taylor & Francis from: Hakkarainen H, Huopio H, Cederberg H, Pääkkönen M, Voutilainen R, Heinonen S. The risk of metabolic syndrome in women with previous GDM in a long-term follow-up. Gynecol Endocrinol. Nov;32(11):920-925, 2016.
The table and figure numbers are modified from original publication to correspond sequential numbers of this thesis.

5.2 INTRODUCTION

Gestational diabetes mellitus (GDM), a common and increasing medical complication, is defined as ''any degree of glucose intolerance with onset or first recognition during pregnancy'' (Metzger et al. 2007). The incidence of GDM varies among studies due to different diagnostic criteria, populations and ethnic groups, but it is estimated to be approximately 7% in all pregnancies (ranging from 1% to 14%) (American Diabetes Association 2011). In Finland, the prevalence of GDM in 2012 was 12.7% based on the National Medical Birth Register (The national Institute for Health and Welfare, Finland. Finnish Medical Birth Register 2012). GDM has been linked to subsequent high risk of type 2 diabetes mellitus (T2DM), metabolic syndrome (MetS) and cardiovascular diseases (CVD) (Lauenborg et al. 2005, Kim et al. 2002, Bellamy et al. 2009, Ijas et al. 2013, Fraser et al. 2012), altogether posing a heavier burden to society. Therefore, pregnancy offers an opportunity to identify women at risk for these conditions.

The MetS represents a cluster of risk factors predisposing to leading CVD and T2DM (Alberti et al. 2009). Central factors in the pathogenesis of MetS are insulin resistance, hyperglycemia, visceral obesity, hypertension and dyslipidemia. Various diagnostic criteria for MetS have been proposed by different organizations over the past decade; the main difference arising from the measure of central obesity. The recent ''harmonized'' version suggests that national or regional cut points for waist circumference can be used (Alberti et al. 2009).

With GDM have at least a seven-fold increased risk of developing type 2 diabetes compared with those who have had normal glycemic control (Bellamy et al. 2009). Pre-diabetic stages after a GDM pregnancy are also frequent (Huopio et al. 2014). We recently showed that elevated post-challenge glucose levels in an oral glucose tolerance test (OGTT) during pregnancy were the best predictors of incident T2DM, and two abnormal values in OGTT were at significantly increased risk for developing T2DM compared to those with only one abnormal value in OGTT (Hakkarainen et al. 2015). However, whether the OGTT reflects a similar gradual increase in future risks of MetS and thus CVD, is not known.

To this aim, we evaluated the incidence of MetS and its components in women with previous GDM using the International Diabetes Federation (IDF) 2005 criteria (Alberti et al. 2005). Moreover, we compared plasma glucose levels during different time points of OGTT during pregnancy as predictors subsequent MetS.

5.3 METHODS

5.3.1 Desing, setting and population

This hospital register-based cohort study included patients whose pregnancies were treated in Kuopio University Hospital, Finland, during 1989–2009. The study protocol has been described in detail previously (Hakkarainen et al. 2015). All women who had OGTT during pregnancy were contacted by a letter and invited

for the study. A total of 874 women responded. The subjects were categorized based on the OGTT results during pregnancy as normoglycemic controls (n = 385), women with one abnormal value in OGTT (GDM1) (n = 338) and those with two or more abnormal values in OGTT (GDM2) (n = 151). The hospital register included data on maternal characteristics and pregnancy risk factors, complications, pregnancy outcome and the neonatal period of the offspring. The women with overt T2DM at the time of pregnancy or T1DM diagnosed after the index pregnancy, and those with multiple pregnancy were excluded to eliminate confounding factors.

5.3.2 Data collection during pregnancy

In Finland, cost-free maternity care is offered to all pregnant. The women considered to be at risk of GDM underwent a 2-h OGTT (75 g glucose after overnight fasting) between the 24th and 28th weeks of gestation if one or more following factors were present: age over 40 years, BMI ≥ 25 kg/m2, prior GDM, previous delivery of a macrosomic infant (birth weight > 4500 g), glucosuria, suspected fetal macrosomia in the current pregnancy. The diagnostic criteria of GDM were as follows: until September 2001 the lower limits of abnormal fasting, 1-h and 2-h capillary whole-blood glucose 4.8, 10.0 and 8.7 mmol/l and since September 2001 the lower limits of fasting, 1-h and 2-h capillary plasma glucose 4.8, 11.2 and 9.9 mmol/l as per contemporary guidelines. For women with more than one delivery during the study period, the first pregnancy with abnormal OGTT was selected as the index pregnancy. The patients with GDM were seen regularly in Kuopio University Hospital Maternity Clinic and they received dietary advice, regular blood glucose monitoring and insulin treatment when necessary.

5.3.3 The follow-up study

The participants were recruited to the follow-up study between 2006 and 2009, as shown in the flow chart (Figure 9). The participants underwent a 2 h OGTT (75 g of glucose) and routine laboratory test, body composition and blood pressure measurements, and answered to a questionnaire concerning their family history and health behavior (Hakkarainen et al. 2015). MetS was diagnosed by waist circumference ≥80 cm, and at least two of the following four criteria met according to the IDF 2005 criteria (Alberti et al. 2005): blood pressure ≥130/85 mmHg, fasting plasma glucose ≥5.6 mmol/l, serum triglycerides ≥1.7 mmol/l and HDL cholesterol ≥1.29 mmol/l. These criteria were selected since they are similar to the current care guidelines of MetS in Finland. The women using medication for hyperglycemia, hypertension or dyslipidemia were included in the analysis for the components of MetS.

Height was measured to the nearest 0.5 cm and weight to the nearest 0.1 kg. Body mass index (BMI) was calculated as weight (kg) divided by the height (m) squared. Waist circumference (at the midpoint between the lateral iliac crest and

the lowest rib) was measured to the nearest 0.5 cm. The study population was divided into three groups by the length of follow-up time (the time between OGTT during the index pregnancy and the follow-up study visit): < 5 years, 5–10 years and > 10 years.

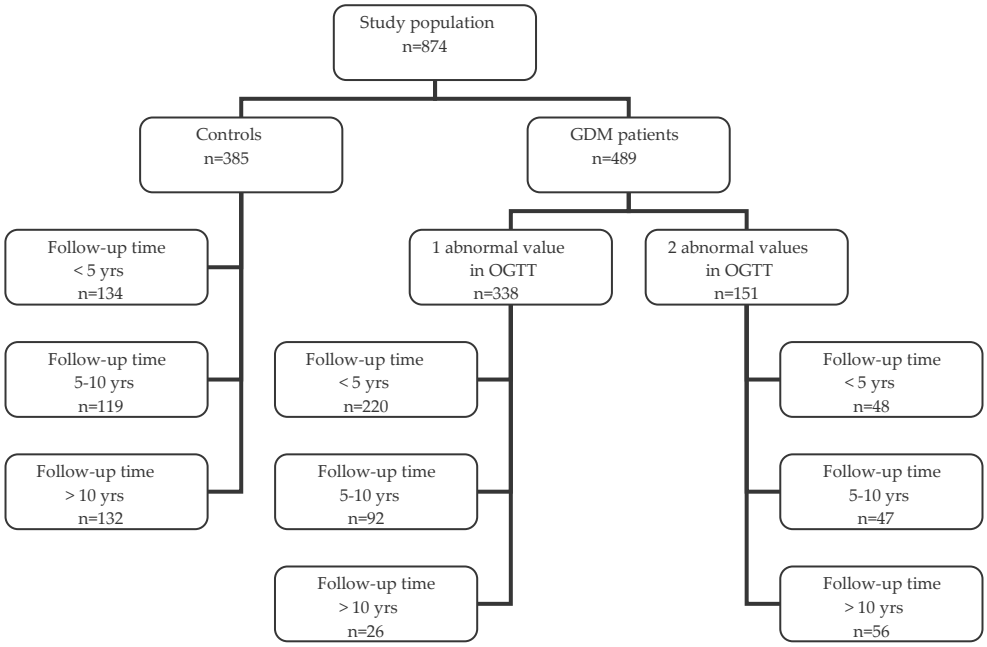


Figure 9. Flowchart of the study population.

5.3.4 Laboratory determinations

Plasma glucose was measured by an enzymatic hexokinase photometric assay (Konelab Systems reagents; Thermo Fischer Scientific, Vantaa, Finland), insulin by an immunoassay (ADVIA Centaur Insulin IRI no. 02230141; Siemens Medical Solutions Diagnostics, Tarrytown, NY), and HbA1c by high-performance liquid chromatography (TOSOH G7 glycohemoglobin analyzer, Tosoh Bioscience, Inc. San Francisco, CA), calibrated to DCCT standard. LDL-cholesterol, HDL-cholesterol and total triglycerides were measured by enzymatic colorimetric tests (Konelab Systems reagents). Homeostasis model assessment for insulin resistance (HOMA-IR) and Matsuda-ISI were calculated to assess insulin resistance and sensitivity, respectively. Disposition index (DI30) was used as a measure of the b-cell response to insulin sensitivity. Calculation of insulin sensitivity (Matsuda ISI), insulin secretion (InsAUC0–30/GluAUC0–30) and disposition indices (DI30) have been previously described (Stancakova et al. 2009).

5.3.5 Statistical analyses

The statistical analyses were conducted using SPSS version 19 (SPSS Inc., Chicago, IL). $p < 0.05$ was considered statistically significant. The results were given as the mean ± SD or number of cases and percentages. Statistical differences in categorical variables between the subjects with GDM and controls were evaluated using χ^2 test. Anthropometric and biochemical continuous variables were analyzed using Student's t-test, and log-transformed variables were used to correct for their skewed distribution when appropriate. Variable distributions were assessed by the Kolmogorov–Smirnov normality test. Cox regression analysis was used to assess the effect of age and BMI on the risk for subsequent development of MetS during the follow-up. Receiver operating characteristic (ROC) curve was generated to determine fasting (FPG), 1-h and 2-h plasma glucose in OGTT as predictors of subsequent MetS. The patients started on medication for hyperglycemia between index pregnancy and follow-up were excluded from the analysis of HOMA-IR, Matsuda-ISI and DI30.

5.3.6 Ethical approval

This study was approved by the local Ethics Committee of the Kuopio University Hospital in accordance with the Helsinki Declaration. All participants gave written informed consent.

5.4 RESULTS

The clinical characteristics of the study groups [controls (n = 385), GDM1 (n = 338), GDM2 (n = 151)] are shown in Table 10. The women with GDM were older, obese and have higher parity than the controls at the index pregnancy. There were no statistically significant differences in the duration of pregnancy or in the mean birth weight of the newborns between the groups. At the follow-up, women with GDM2 were obese and older than the controls. Moreover, women with GDM2 were more insulin resistant according to HOMA-IR and Matsuda-ISI. Insulin sensitivity-corrected insulin secretion (DI30) was significantly decreased in women with GDM as compared to the controls. Mean follow-up time was 7.3 ± SD 5.1 years.

Table 10. Clinical characteristics of controls and GDM patients in index pregnancy and at the follow-up study.

		Controls Mean ± SD	GDM 1 patients Mean ± SD	GDM 2 patients Mean ± SD	*p*	*p**
Number of patients		358	338	151		
At the index pregnancy						
Primiparity (%)		54.7	35.9	37.9	<0.0001	<0.0001
Age at delivery		29.5 ± 5.3	31.7 ± 5.9	32.7 ± 5.7	<0.0001	<0.0001
Age > 35 yrs (%)		14.2	28.8	34.0	<0.0001	<0.0001
Pregestational BMI (kg/m²)		67.1	72.6	75.0	<0.0001	<0.0001
Pregestational BMI > 25 kg/m² (%)		32.2	47.7	57.8	<0.0001	<0.0001
Pre-eclampsia (%)		2.3	6.2	4.6	0.009	0.169
Gestational age at delivery (d)		279 ± 11	278 ± 10	278 ± 10	0.232	0.141
Mean birth weight (g)		3581 ± 571	3637 ± 571	3671 ± 531	0.190	0.089
At the follow-up study	Follow-up time (years)					
Age at follow-up	<5	34.9 ± 5.9	34.8 ± 6.1	34.9 ± 6.2	0.772	0.968
	5-10	36.9 ± 5.4	38.2 ± 5.8	41.2 ± 5.6	0.090	<0.0001
	>10	43.2 ± 4.3	43.5 ± 7.1	45.9 ± 5.6	0.981	0.003
BMI (kg/m²)	<5	27.2 ± 4.7	28.1 ± 5.4	29.9 ± 5.6	0.142	0.002
	5-10	26.5 ± 4.9	27.3 ± 5.1	29.7 ± 5.1	0.212	<0.0001
	>10	26.9 ± 5.0	28.6 ± 5.7	28.9 ± 6.0	0.133	0.023
Family history of diabetes (%)	<5	73.9	80.1	83.3	0.177	0.186
	5-10	71.2	78.0	83.0	0.263	0.117
	>10	69.7	80.8	85.5	0.343	0.025
Smoker (%)	<5	12.7	17.4	25.0	0.241	0.045
	5-10	14.4	22.2	17.0	0.144	0.672
	>10	14.5	3.8	20.0	0.201	0.352
HOMA-IR	<5	2.2 ± 1.2	2.9 ± 2.4	3.1 ± 1.9	0.008	0.008
	5-10	2.2 ± 2.0	2.5 ± 1.6	3.4 ± 1.6	0.066	<0.0001
	>10	2.0 ± 1.4	2.5 ± 1.6	2.9 ± 1.7	0.108	0.001
Matsuda-ISI	<5	6.8 ± 3.8	5.7 ± 3.0	5.0 ± 3.1	0.003	<0.0001
	5-10	7.1 ± 3.1	6.2 ± 3.2	5.1 ± 4.3	0.072	<0.0001
	>10	7.6 ± 4.0	6.4 ± 3.6	5.5 ± 3.5	0.193	0.003
DI30	<5	199.1 ± 72.6	184.7 ± 66.0	139.6 ± 54.7	0.057	<0.0001
	5-10	207.7 ± 72.0	169.3 ± 49.7	132.6 ± 58.0	<0.0001	<0.0001
	>10	212.0 ± 87.5	160.7 ± 90.8	129.0 ± 53.8	0.001	<0.0001

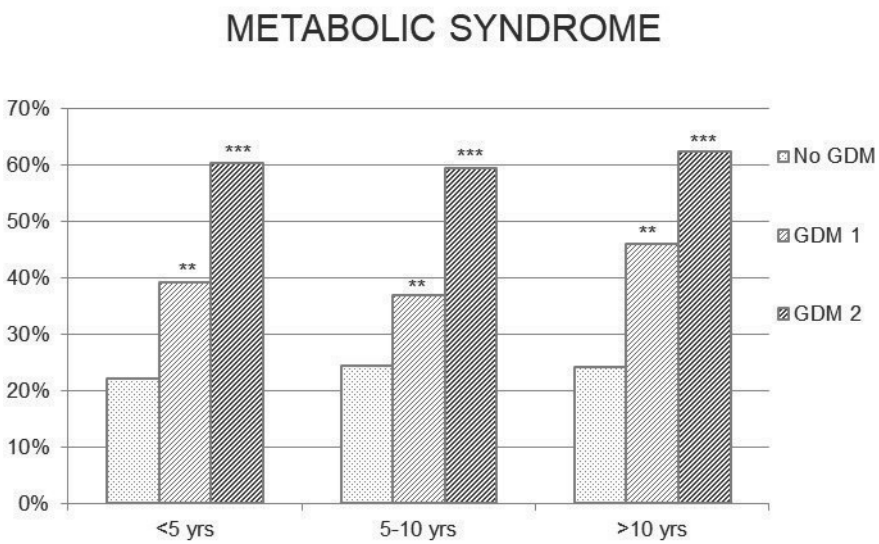
GDM1: patients with one abnormal value in OGTT during pregnancy; GDM2: patients with two abnormal values in OGTT during pregnancy; BMI: body mass index; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; Matsuda-ISI: Matsuda insulin sensitivity index (ISI); DI30: Disposition index.
p, compared controls to GDM patients with 1 abnormal value in OGTT (GDM 1).
*p**, compared controls to GDM patients with 2 abnormal values in OGTT (GDM 2).

Regarding the components of MetS, women with GDM2 had significantly higher waist circumference, > 80% of them reaching the limit 80 cm (Table 11). Both GDM groups had significantly higher FPG levels than the controls, and 64.3% of those with GDM2 had FPG > 5.6 mmol/l after ten years follow-up. Those with GDM2 had significantly higher levels of triglycerides and lower HDL cholesterol in all follow-up groups. No difference in elevated blood pressure was observed between the GDM groups and controls (Table 11).

The overall incidence of MetS in the control, GDM1 and GDM2 groups < 5 years after the index pregnancy was 22%, 39% and 60%, respectively, and > 10 years follow-up 24%, 46% and 63%, respectively (Figure 10). The difference was significant in both GDM groups compared to the controls. However, in the course of the follow-up, the incidence of MetS remained about the same in the control and GDM2 groups, whereas it appeared to increase in the GDM1 group.

After adjustment for BMI and age at the follow-up visit, and the follow-up time as a continuous variable, the hazard ratio (HR) of subsequent MetS was 2.3 (95%CI 1.7–3.0) in the GDM1 and 2.2 (95%CI 1.6–2.9) in the GDM2 group compared with the controls. The risk of subsequent MetS increased by 9.0% per one BMI unit increase.

Regarding the ROC-curves, FPG was the best predictor of MetS, with the area under the curve (AUC) of 0.656 (p= < 0.0001) and 2-h plasma glucose the poorest (AUC 0.595) (data not shown).



GDM= gestational diabetes mellitus
GDM1= GDM women with one abnormal value in OGTT during pregnancy
GDM2= GDM women with two abnormal values in OGTT during pregnancy
**p<0.05, ***p<0.0001 compared with the controls

Figure 10. The indicence of MetS among the study groups at the follow-up study according to the follow-up tme.

Table 11. Components and incidence of metabolic syndrome (MetS).

	Follow-up time (years)	Controls Mean ± SD or %	GDM1 patients Mean ± SD or %	GDM2 patients Mean ± SD or %	*p*	*p**
Number of patients		385	338	151		
Waist circumference (cm)	<5	87.1 ± 11.2	90.3 ± 12.8	94.5 ± 12.7	0.018	0.001
	5-10	85.5 ± 12.2	88.5 ± 12.8	94.1 ± 12.3	0.075	<0.0001
	>10	86.3 ± 11.7	92.1 ± 16.4	93.8 ± 15.7	0.055	0.001
Waist ≥ 80 cm	<5	74.1	78.9	83.3	0.301	0.194
	5-10	62.2	76.1	87.2	0.031	0.002
	>10	67.4	73.1	85.7	0.571	0.010
Fasting plasma glucose (mmol/l)	<5	5.4 ± 0.4	5.5 ± 0.5	5.8 ± 1.4	0.039	<0.0001
	5-10	5.3 ± 0.4	5.6 ± 0.7	6.1 ± 1.1	<0.0001	<0.0001
	>10	5.3 ± 0.4	5.6 ± 0.5	6.1 ± 1.0	<0.0001	<0.0001
Fasting plasma glucose ≥ 5.6 mmol/l	<5	28.9	39.3	62.5	0.052	<0.0001
	5-10	25.2	44.6	72.3	0.003	<0.0001
	>10	19.7	53.8	64.3	<0.0001	<0.0001
Triglycerides (mmol/l)	<5	1.0 ± 0.6	1.1 ± 0.5	1.2 ± 0.6	0.364	0.029
	5-10	0.9 ± 0.5	1.0 ± 0.5	1.2 ± 0.7	0.051	0.001
	>10	1.0 ± 0.5	1.1 ± 0.5	1.4 ± 0.6	0.447	<0.0001
Triglycerides ≥ 1.70 mmol/l	<5	9.0	11.0	20.8	0.537	0.030
	5-10	7.6	10.9	19.1	0.405	0.031
	>10	13.0	15.4	25.0	0.754	0.043
HDL cholesterol (mmol/l)	<5	1.5 ± 0.3	1.4 ± 0.4	1.3 ± 0.3	0.028	0.003
	5-10	1.5 ± 0.4	1.4 ± 0.4	1.3 ± 0.4	0.007	<0.0001
	>10	1.6 ± 0.4	1.5 ± 0.3	1.4 ± 0.4	0.190	0.001
HDL cholesterol < 1.29 mmol/l	<5	28.1	43.4	58.3	0.004	<0.0001
	5-10	26.9	39.1	53.2	0.059	0.001
	>10	26.5	42.3	50.0	0.105	0.002
Systolic pressure (mmHg)	<5	121 ± 14	124 ± 12	125 ± 12	0.067	0.082
	5-10	123 ± 15	129 ± 14	128 ± 14	0.001	0.032
	>10	126 ± 13	132 ± 20	132 ± 17	0.052	0.005
Diastolic pressure (mmHg)	<5	78 ± 10	78 ± 9	80 ± 9	0.829	0.317
	5-10	78 ± 11	82 ± 10	80 ± 8	0.007	0.056
	>10	80 ± 8	80 ± 9	83 ± 11	0.971	0.113
Blood pressure ≥ 130/85 mmHg	<5	31.1	34.2	39.6	0.542	0.285
	5-10	34.5	46.7	42.6	0.071	0.329
	>10	44.7	53.8	57.1	0.392	0.118
Metabolic syndrome	<5	22.2	39.3	60.4	0.001	<0.0001
	5-10	24.4	37.0	59.6	0.048	<0.0001
	>10	24.2	46.2	62.5	0.023	<0.0001

GDM1: patients with one abnormal value in OGTT during pregnancy; GDM2: patients with two abnormal values in OGTT during pregnancy.
p, compared controls to GDM patients with 1 abnormal value in OGTT (GDM 1).
*p**, compared controls to GDM patients with 2 or more abnormal values in OGTT (GDM 2).

5.5 DISCUSSION

This long-term prospective follow-up study demonstrated that already mildly impaired glucose tolerance during pregnancy, measured by one abnormal value in OGTT during pregnancy, increases the risk of incident MetS after pregnancy. To our knowledge, this is the first study to evaluate the prevalence of MetS among women with GDM in the more detailed subgroups of glycemia during pregnancy. The incidence of MetS was about 60% in women with previous GDM with two or more abnormal values in OGTT already after < 5 years follow-up showing that the lifestyle intervention was delayed or missing. During further follow-up, the incidence of MetS remained constant in the control and GDM2 groups, whereas it appeared to increase in the GDM1 group. Our data confirmed the previously reported finding (Akinci et al. 2010, Bo et al. 2006, Tam et al. 2013) that fasting plasma glucose is the best predictor of subsequent development of MetS. Thus, the women with one abnormal value in OGTT during pregnancy represent a significant target group for targeted lifestyle intervention to prevent incident MetS and later cardiovascular disease after pregnancy and should be followed up carefully after pregnancy.

Our results are in agreement with previous studies having shown that women with a history of GDM are at increased risk for developing MetS (Lauenborg et al. 2005, Akinci et al. 2010, Bo et al. 2006, Puhkala et al. 2013, Retnakaran et al. 2010). This risk varied between 16 and 43.5% in these studies according to the IDF criteria. Our data showed that after 10 years follow-up about 46% of the GDM1 and 63% of GDM2 women met MetS definition. In accordance with other studies (Lauenborg et al. 2005, Bo et al. 2006, Retnakaran et al. 2010, Cameron et al. 2008), our data showed that the women with previous GDM exhibited more dysglycemia, were more insulin resistant, had lower insulin secretion and more atherogenic lipid profiles than the controls. The incidence of hypertension in women with a history of GDM has varied in previous studies (Lauenborg et al. 2005, Akinci et al. 2010, Bo et al. 2006, Retnakaran et al. 2010, Albareda et al. 2005). Hypertension was the only component of MetS the incidence of which did not differ significantly between our study groups.

Insulin resistance is a major pathophysiological mechanism in MetS and GDM and it is closely related to central adiposity (Cameron et al. 2008, Albareda et al. 2005). Thus, both prepregnancy overweight and current overweight are strongly associated with the subsequent development of MetS (Ijas et al. 2013, Akinci et al. 2010, Puhkala et al. 2013, Albareda et al. 2005, Verma et al. 2002). Because of the risk-based screening of GDM used in our study, 32% of the controls and half of the women with GDM were overweight (BMI > 25 kg/m2). Consequently, the diagnosis of MetS after 10 years follow-up time was present in about 24% of the control subjects. In the Finnish background population, the prevalence of MetS has been 7–14% according to the IDF criteria (Raiko et al. 2010).

We have recently shown that abnormal post-challenge glucose levels in OGTT during pregnancy were the best predictors of incident T2DM (Hakkarainen et al. 2015). Concerning the predictability of different glucose levels during OGTT for incident MetS, we detected that the fasting glucose was the best predictor for developing MetS in women with previous GDM. Fasting glucose levels reflect particularly hepatic insulin resistance closely linked to visceral adiposity, and our finding agrees with previous studies that have demonstrated the significance of the fasting glucose level as a predictor of MetS (Akinci et al. 2010, Bo et al. 2006, Tam et al. 2013). Interestingly, the GDM1 group had low risk for MetS shortly after pregnancy, a markedly higher risk during longer follow-up. Women with GDM1 had nearly comparable risk of MetS compared to GDM2 after 10 years. Thus, women with GDM1 may benefit the most from timely interventions and preventive measures. To date, in current practice this group has often been considered low-risk and been easily left out from the follow-up programs. The strengths of our study include the long-term follow-up of a well-characterized cohort of subjects and the similar treatment received by all participants with GDM during pregnancy. The study does, however, have some limitations. The practice to perform risk-based screening to pregnant women is causing selection bias in this study. In addition, the study setting was cross-sectional at the time of follow-up OGTT, not longitudinal which would have been optimal to standardize the protocol.

5.6 CONCLUSION

In conclusion, women with two abnormal glucose values in OGTT during pregnancy are at highest risk for incident MetS after the pregnancy as compared to those with one abnormal value or controls with GDM risk factors. Interestingly, the incidence of MetS appears to remain stable in the controls and women with GDM2, whereas it seems to increase in those with GDM1 during follow-up. Therefore, women with even a minor abnormality in OGTT during pregnancy represent an important group for targeted lifestyle intervention to prevent the development of overt MetS and subsequent cardiovascular disease.

6 DELIVERY OF AN LGA INFANT AND THE MATERNAL RISK OF DIABETES: A PROSPECTIVE COHORT STUDY[3]

6.1 ABSTRACT

Aims: Was to determine whether the birth weight of the infant predicts prediabetes (impaired fasting glucose, impaired glucose tolerance, or both) and type 2 diabetes (T2DM) during long-term follow-up of women with or without gestational diabetes mellitus (GDM).

Methods: The women with or without GDM during their pregnancies in Kuopio University Hospital in 1989-2009 (n=874) were contacted and invited for an evaluation. They were stratified into two groups according to the newborn's birth weight: 10-90th percentile (appropriate-for-gestational-age; AGA) (n=662) and > 90th percentile (large-for-gestational-age; LGA) (n=116). Glucose tolerance was investigated with an oral glucose tolerance test after a mean follow-up time of 7.3 (SD 5.1) years.

Results: The incidence of T2DM was 11.8% and 0% in the women with and without GDM, respectively, after an LGA delivery. The incidence of prediabetes increased with offspring birth weight categories in the women with and without GDM: from 46.3% and 26.2% (AGA) to 52.9% and 29.2% (LGA), respectively.

Conclusions: GDM women with LGA infants are at an increased risk for subsequent development of T2DM and therefore represent a target group for intervention to delay or prevent T2DM development. In contrast, an LGA delivery without GDM does not increase T2DM risk.

[3] Adapted with permission of Elsevier from: Hakkarainen H, Huopio H, Cederberg H, Voutilainen R, Heinonen S. Delivery ofan LGA infant and the maternal risk of diabetes: A prospective cohort study. Prim Care Diabetes. Aug;12(4):364-370, 2018.
The table and figure numbers are modified from original publication to correspond sequential numbers of this thesis.

6.2 INTRODUCTION

Women with gestational diabetes mellitus (GDM) have an increased risk of both adverse obstetrical outcomes, mainly related to a large birth size of the newborn and subsequent development of type 2 diabetes (T2DM) (Bellamy et al. 2009, Kim et al. 2002, HAPO Study Cooperative Research Group, Metzger et al. 2008, Hakkarainen et al. 2015). GDM pathophysiology consists of insulin resistance accompanied by impaired β-cell function leading to maternal hyperglycemia (Catalano 2014). Consequently, increased placental glucosetransfer to the fetus causes fetal hyperinsulinemia and further macrosomia (Pedersen 1952). The underlying and worsening β-cell dysfunction coupled with a background of chronic insulin resistance usually due to overweight or obesity exposes a woman to an increased risk of developing diabetes. In clinical practice, a woman who delivers a large-for-gestational-age (LGA, birth weight above the 90th percentile for gestational age) infant is more likely to have GDM and this combination is considered a risk factor for GDM in a subsequent pregnancy. However, studies focusing on T2DM risk in women with a history of LGA birth (but without GDM) have given conflicting results, probably due to the variation of the follow-up time, ascertainment of the cases and controls and women's overall T2DM risk profile (Larsson et al. 1986, Tehrani et al. 2012, Moses et al. 1997, Kew et al. 2011).

In other words, based on the pathophysiology of prenatal growth of LGA newborns, women with a history of an LGA infant delivery could be at an increased risk of subsequent development of diabetes. To test this hypothesis, our objective was to compare the incidence of subsequent prediabetes and T2DM in women with GDM to women without GDM in different birth size groups.

6.3 METHODS

This hospital register-based cohort study included women whose pregnancies were treated in Kuopio University Hospital, Finland, in 1989–2009. Women who had the diagnosis of GDM and a random sample of normoglycemic control women, both groups with completed oral glucose tolerance test (OGTT) during pregnancy, were contacted by a letter and invited for the study. A total of 489 women with GDM and 385 controls with a normal OGTT result during pregnancy attended the follow-up study. 1234 women did not reply or refused to participate in the study. All participants gave a written informed consent.

The women with and without GDM were classified based on the birth weight of the newborn: between 10–90th percentile (appropriate-for-gestational-age; AGA) (n = 662) and over 90th percentile (LGA) (n = 116). The women without GDM and delivering a child with birth weight between 10-90th percentile served as a control group. In this study, LGA was defined as sex-specific birth weight for gestational age above the 90th percentile of the current Finnish newborn growth charts (Sankilampi et al. 2013).

6.3.1 Data collection during pregnancy

In Finland, cost-free maternity care is offered to all pregnant women. The women considered to be at risk of GDM underwent 2-h OGTT (75 g glucose after overnight fasting) between the 24th and 28th weeks of gestation if one or more following factors were present: age over 40 years, BMI = 25 kg/m^2, prior GDM or a delivery of a macrosomic infant, glucosuria, suspected fetal macrosomia in the current pregnancy. The diagnostic criteria of GDM were as follows: until September 2001 the lower limits of abnormal fasting, 1-h and 2h capillary whole-blood glucose 4.8, 10.0 and 8.7 mmol/l and since September 2001 the lower limits of fasting, 1-h and 2-h capillary plasma glucose 4.8, 11.2 and 9.9 mmol/l as per contemporary guidelines. For the women with more than one delivery during the study period, the first pregnancy with an abnormal OGTT result was selected as the index pregnancy. The women with GDM were seen regularly in the Prenatal Outpatient Clinic in Kuopio University Hospital and they received dietary advice, regular blood glucose monitoring and insulin treatment when necessary. The hospital register included data on maternal characteristics and pregnancy risk factors, complications, pregnancy outcome, and on the neonatal period of the offspring. The women with overt T2DM at the time of pregnancy or T1DM diagnosed after the index pregnancy, and those with a multiple pregnancy were excluded to eliminate confounding factors.

6.3.2 The follow-up study

The participants were recruited to the follow-up study between 2006 and 2009. The women underwent laboratory tests, body composition and blood pressure measurements, and answered to a questionnaire concerning their family history and health behavior. To study glucose tolerance, the participants underwent 2-h OGTT (75 g of glucose). T2DM was defined according to the American Diabetes Association (ADA) recommendations: fasting plasma glucose =7 mmol/l or 2-h plasma glucose =11.1 mmol/l. Fasting plasma glucose between 5.6 and 6.9 mmol/l was defined as impaired fasting plasma glucose (IFG) and 2-h plasma glucose between 7.8–11.0 as impaired glucose tolerance (IGT) (American Diabetes Association 2011). Women who had been diagnosed with T2DM during the follow-up time (N = 15) did not undergo OGTT.

Height was measured to the nearest 0.5 cm and weight to the nearest 0.1 kg. Body mass index (BMI) was calculated as weight (kg) divided by the height (m) squared. Waist circumference (at the midpoint between the lateral iliac crest and the lowest rib) was measured to the nearest 0.5 cm.

6.3.3 Laboratory determinations

Plasma glucose was measured by an enzymatic hexokinase photometric assay (Konelab Systems reagents; Thermo Fischer Scientific, Vantaa, Finland), insulin by an immunoassay (ADVIA Centaur Insulin IRI no. 02230141; Siemens Medical Solutions Diagnostics, Tarrytown, NY), and HbA1c by a high-performance liquid chromatography assay (TOSOH G7 glycohemoglobinanalyzer, Tosoh Bioscience, Inc., San Francisco, CA), calibrated to direct-current current transformers (DCCT) standard.

6.3.4 Statistical analyses

The statistical analyses were conducted using SPSS version 19 (SPSS Inc., Chicago, IL). The results were given as the mean ± SD or number of cases and percentages. Statistical differences in categorical variables between the study groups and controls were evaluated using the $\chi 2$ test. Anthropometric and biochemical continuous variables were analyzed using Student's t-test, and log-transformed variables were used to correct for their skewed distribution when appropriate. $p < 0.05$ was considered statistically significant. Since the diagnosis of GDM was based on slightly different criteria depending on the origin of the blood during the data collection, a correlation coefficient was used to convert all values to correspond venous plasma levels. The correlation coefficient was based on the information from the Department of Clinical Chemistry at Kuopio University Hospital.

This study was approved by the local Ethics Committee of the Kuopio University Hospital in accordance with the Helsinki Declaration.

6.4 RESULTS

The prepregnancy and peripartum characteristics of the women with and without GDM stratified according to the birth weight of the offspring are shown in Table 12. The women with previous GDM were older and heavier in both birth weight categories than those without GDM. Parity was higher in the women with GDM and in those with an LGA delivery without GDM. The women with GDM in the AGA group had more diabetes in family history and smoked more often. Otherwise, the study groups had comparable family history of diabetes, marital, smoking and alcohol consumption status. Prior spontaneous abortion rate was higher in the women with GDM in the LGA group. The women with LGA infants had more frequently a history of a macrosomic offspring than those in the normal birth weight groups. However, prior cesarean section was more common in the women with LGA infants and absence of GDM. The women with GDM in the AGA group gained less weight during pregnancy, had shorter gestational age and lower Apgar score at delivery than the controls. The incidence of pre-eclampsia was higher in both GDM groups compared to controls. No significant difference was observed in the gender of the offspring between the subgroups.

Table 12. Prepregnancy and peripartum characteristics of the study subjects stratified according to the birth weight of the offspring.

Offspring's birth weight	AGA (10-90 percentile)		LGA (> 90 percentile)	
	Mean ± SD or %		Mean ± SD or %	
	No GDM	GDM	No GDM	GDM
	(Controls)	(Group 1)	(Group 2)	(Group 3)
Number of subjects	286	376	48	68
Prepregnancy characteristics				
Age (years)	29.5 ± 5.4	31.8 ± 6.0**	30.6 ± 5.0	32.6 ± 6.3**
Prepregnancy BMI (kg/m²)	23.8 ± 3.8	26.4 ± 5.0**	25.7 ± 3.5*	26.7 ± 4.1**
Primiparity (%)	54.4	37.8**	33.3*	22.1**
Family history of diabetes (%)	69.4	81.4**	75.0	80.6
Not married (%)	34.3	40.4	29.2	29.4
Smoking (>5 cigarettes/d) (%)	15.2	21.5*	12.8	18.5
Alcohol consumption (%)	47.2	40.2	34.0	52.3
Prior child's birth weight > 4000g (%)	25.4	25.6	43.8*	60.4**
Prior spontaneous abortion (%)	16.8	19.9	18.8	35.3*
Prior cesarean section (%)	5.9	9.6	16.7*	7.4
Peripartum characteristics of the subjects and newborns				
Weight gain in pregnancy (kg)	13.7 ± 4.8	11.8 ± 5.9**	14.7 ± 4.7	14.9 ± 6.1
Gestational age (d)	280 ± 11	278 ± 11*	279 ± 11	279 ± 8
Pre-eclampsia (%)	1.4	5.3*	2.1	5.9*
Female offspring (%)	47.2	43.6	47.9	55.9
Birth weight (g)	3595 ± 385	3596 ± 406	4365 ± 424**	4421 ± 370**
Placental-fetal mass ratio (%)	17.1 ± 3.0	17.5 ± 3.0	20.6 ± 15.8**	17.9 ± 2.5*
Apgar score < 7 at 1 min (%)	1.7	5.9*	6.3	4.4

GDM = gestational diabetes mellitus, BMI=body mass index, AGA=appropriate for gestational age; LGA=large for gestational age. All groups compared to controls separately.
* $p<0.05$
** $p<0.0001$

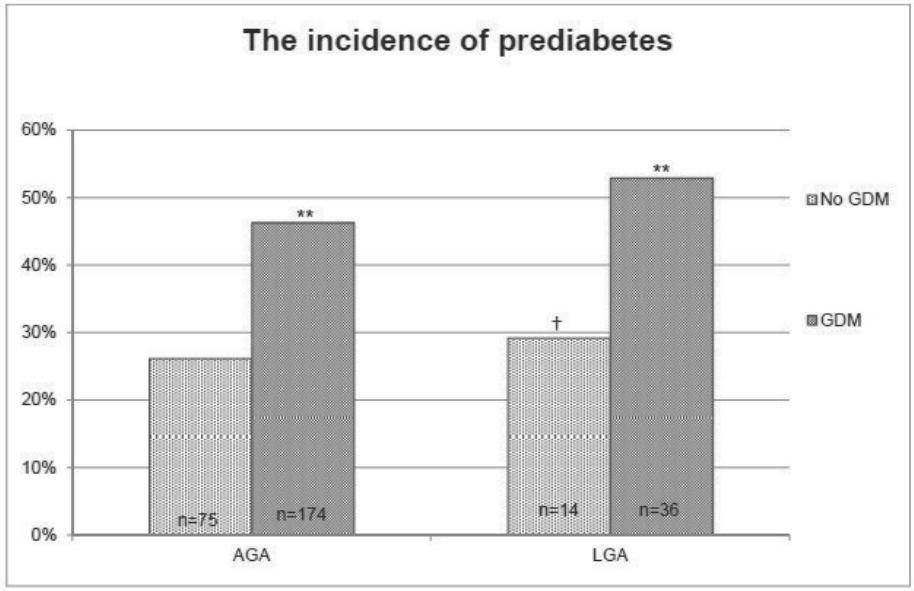
The clinical characteristics of the study groups at the follow-up study are shown in Table 13. The women with GDM had shorter follow-up time in both birth weight categories. As during the index pregnancy, the women with GDM were significantly heavier in both birth weight categories. However, the groups did not differ in weight gain during the follow-up time. The GDM women had higher basal glucose and insulin levels in both birth weight groups.

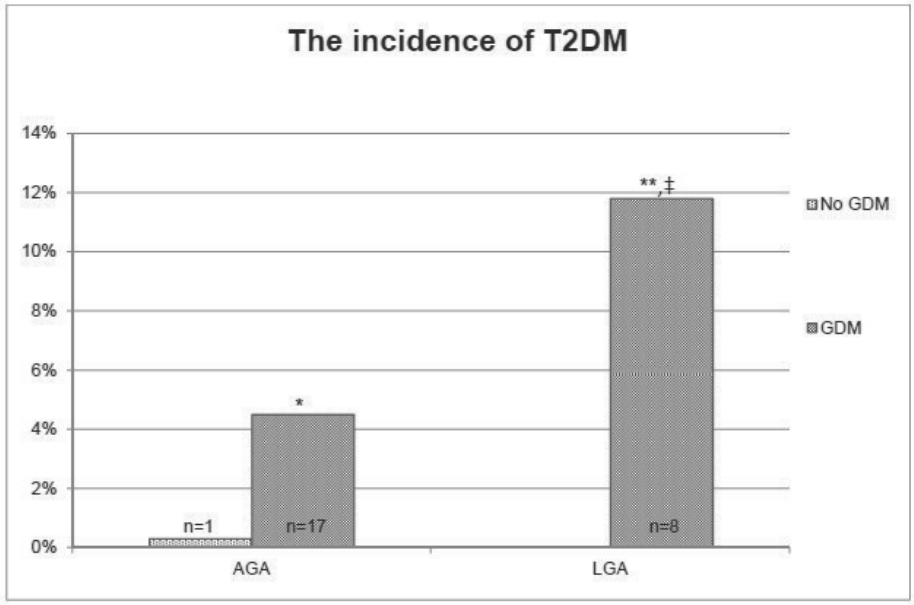
Table 13. Clinical characteristics and glucose tolerance data of the study subjects at the follow-up study.

Offspring's birth weight	AGA (10-90 percentile)		LGA (> 90 percentile)	
	Mean ± SD or *n* (%)		Mean ± SD or *n* (%)	
	No GDM	GDM	No GDM	GDM
	(Controls)	(Group 1)	(Group 2)	(Group 3)
Number of subjects	286	376	48	68
Follow-up time (yrs)	8.5 ± 5.5	5.3 ± 4.3**	7.4 ± 5.4	6.2 ± 4.9*
Age at follow-up (yrs)	38.4 ± 6.4	37.4 ± 7.2	38.3 ± 5.8	39.1 ± 7.5
BMI (kg/m²)	26.5 ± 4.9	28.3 ± 5.7**	27.9 ± 4.8*	29.2 ± 4.9**
Weight gain during follow-up time (kg)	5.7 ± 7.6	3.6 ± 7.9	4.3 ± 7.6	5.6 ± 9.3
HbA1c (mmol/mol)	35.0 ± 3.2	35.9 ± 4.8*	34.8 ± 3.5	38.4 ± 6.6**
Fasting plasma glucose (mmol/l)	5.3 ± 0.4	5.6 ± 0.8**	5.4 ± 0.4	5.8 ± 0.8**
30-min plasma glucose (mmol/l)	7.0 ± 1.5	7.9 ± 1.7**	7.1 ± 1.3	8.1 ± 1.7**
2-h plasma glucose (mmol/l)	5.5 ± 1.2	5.9 ± 1.6**	5.5 ± 1.0	6.6 ± 2.4**
Fasting plasma insulin (mU/l)	9.0 ± 6.6	11.7 ± 9.0**	8.0 ± 4.6	12.4 ± 7.3**
30-min plasma insulin (mU/l)	62.6 ± 38.9	72.5 ± 49.8*	57.6 ± 29.2	78.2 ± 59.8
2-h plasma insulin (mU/l)	39.1 ± 35.6	50.4 ± 48.6**	35.3 ± 26.0	49.1 ± 33.6*
Prediabetes	75 (26.2)	174 (46.3)**	14 (29.2)[a]	36 (52.9)**
T2DM	1 (0.3)	17 (4.5)*	0 (0)	8 (11.8)**,[b]

GDM=gestational diabetes mellitus, BMI=body mass index, AGA=appropriate for gestational age, LGA=large for gestational age. All groups compared to controls separately.
* p<0.05.
** p<0.0001.
[a] Significantly (p<0.05) different when comparing groups 1 and 2.
[b] Significantly (p<0.05) different when comparing groups 1 and 3.

The incidence of prediabetes (IFG and/or IGT) and T2DM at the follow-up study according to the birth weight of the offspring is shown in Figure 11. During the follow-up time after the index pregnancy, the incidence of prediabetes increased in the women with and without GDM from 46.3% and 26.2% (AGA) to 52.9% and 29.2% (LGA). The incidence of T2DM was 11.8% in the GDM women and 0% in the women without GDM who had given birth to LGA infants. The incidence of T2DM in the GDM women with previous LGA delivery was significantly higher compared to the GDM women with AGA delivery as well.





GDM=gestational diabetes mellitus, T2DM=type 2 diabetes mellitus, AGA=appropriate for gestational age, LGA=large for gestational age.
*p<0.05, **p<.0001 when comparing all groups separately to women without GDM in AGA group.
† Significantly (p<0.05) different when comparing women without GDM in LGA group to women with GDM in AGA group.
‡ Significantly (p<0.05) different when comparing women with GDM in LGA group to women with GDM in AGA group.

Figure 11. The incidence of glucose intolerance among the study groups at the follow-up according to the birth weight of the newborn.

6.5 DISCUSSION

This prospective long-term study of the women with and without GDM demonstrated that a history of an LGA infant in the absence of GDM did not predict T2DM. In contrast, 11.8% of the women with GDM and LGA infants developed T2DM during a ten-year follow-up. Moreover, the incidence of prediabetes was significantly greater in the GDM women in both birth weight categories; every other woman had prediabetes in the follow-up. Only one of four women without GDM had prediabetes when the infant's birth weight was between 10–90th percentile. Overall, the delivery of an LGA infant is predictive of maternal long-term outcomes in women with GDM but not in women with normal glucose tolerance during pregnancy.

The well-known Pedersen hypothesis (1952) states that maternal hyperglycemia causes macrosomia through fetal hyperglycemia and hyperinsulinemia (Pedersen 1952). To date, however, it is known that a variety of factors affects infant's birth weight, such as high parity and prepregnancy overweight (Henriksen 2008). Especially maternal BMI has much higher impact on the prediction of an LGA delivery than the 2-h glucose level in OGTT during pregnancy (Berntorp et al. 2015). This opens up a wider viewpoint reflecting the reasons behind an LGA delivery and, thus, for the consequences of an LGA delivery to the women's long-term health.

Infrequent studies exist on the association between an LGA delivery and subsequent maternal T2DM. In these studies, settings, follow-up times, ascertainment of cases and controls and LGA definitions vary substantially. To elucidate this complex ground, we performed a literature search and collected the appropriate data to Table 14. Contrary to our study, the review suggests that the risk of T2DM after an LGA delivery is somewhat increased: pooled OR 1.26 (95% CI 0.97–1.63). Taking into account available adjusted ORs, the risk became significant: pooled OR 1.37 (95% CI 1.14–1.65) (Table 14). There appeared to be a few factors affecting the results. Up to 27 years postpartum, Larsson et al. demonstrated that the incidence of T2DM had risen but this was explained by obesity and high parity (Larsson et al. 1986). Tehrani et al. included also stillbirths in the LGA study group which could have affected the results (Tehrani et al. 2012). Moreover, two studies included GDM women in the study groups (Kabeya et al. 2013, James-Todd et al. 2013), biasing the results, whereas GDM status was carefully defined and checked in the present study. In fact, these two studies (Kabeya et al. 2013, James-Todd et al. 2013) along with the Larsson et al.'s study (Larsson et al. 1986) were the only studies suggesting significantly increased T2DM risk after an LGA delivery. The remaining previous studies (Tehrani et al. 2012, Kew et al. 2011), and our findings did not demonstrate significantly increased risk of later T2DM. In addition, a study of 18 women with LGA compared to 18 women with appropriate-for-gestational-age (AGA) infants did not find significant differences in glucose, insulin or HbA1c levels between the groups two years after pregnancy (Moses et al. 1997). Taking

together, the predictability of later T2DM after an LGA delivery depended on various factors in study settings.

Table 14. Summary of studies on the association between a delivery of an LGA infant and the risk of incident T2DM.

Studies by follow up time	Follow-up time	LGA definition	Number of cases/ controls	BMI (kg/m²) cases/ controls mean(SD)	Outcome	Outcome incidence in cases/ controls	adjusted OR (95% CI)	unadjusted OR (95% CI)	p	Pooled OR adjusted + unadjusted (95% CI)	Pooled OR unadjusted (95% CI)
Kew et al. 2011, Canada	3 months	>90th percentile	62 / 364	24.7 /25.4	Prediabetes or T2DM	15.2 / 9.1%	1.7* (0.70-4.10)	1.79 (0.82-3.91)	-		
Moses et al. 1997, Australia	2 years	> 90th percentile	18 / 18	25.0 (4.0) / 24.6 (3.1)	fasting glucose (mmol/l)	4.5 (0.4) / 4.6 (0.5)	-	-	NS		
					HbA1c (%)	5.0 (0.4) / 5.2 (0.4)			NS		
Kabeya et al. 2013, Japan*	5 years	> 4kg	405 / 8408	24.3 (3.1) / 23.7 (3.1)	T2DM	6.8 / 4.6%	1.24* (0.80-1.94)	1.51 (1.01-2.27)	-	1.37 (1.14-1.65) $p<0.001$	1.26 (0.97-1.63) $p=0.085$
Tehrani et al. 2012, Iran**	9 years	> 4kg	570 / 570	30.5 (4.8) / 30.7 (5.1)	T2DM	9.5 / 11.1%	-	0.84 (0.57-1.23)	NS		
James-Todd et al. 2013, UK*	22 years	> 4.5kg	854 / 41 292	23.8 (4.4) / -	T2DM	-	aHR 1.61* (1.24-2.08)	-	-		
Larsson et al. 1998, Sweden	20-27 years	> 4.5kg	236 / 382	BMI ≥ 27 48.7 / 20.2%	T2DM	4.7 / 0.8%	-	6.12 (1.71-21.93)	0.002		

*The studies include GDM patients, **The LGA study group includes stillbirths, T2DM= type 2 diabetes mellitus, BMI=body mass index, OR=odds ratio, HR=hazard ratio
*Adjusted for age, months' postpartum, ethnicity, family history of diabetes, breastfeeding, and waist circumference.
*Adjusted for age, BMI, systolic BP, family history of diabetes and daily walking time.
*Adjusted for maternal age at first birth, age in 1998, race/ethnicity, pre-pregnancy BMI, family history of diabetes, menstrual irregularity, smoking during pregnancy, history of gestational diabetes mellitus, history of hypertensive disorders of pregnancy.

The present study demonstrated that GDM women with a previous LGA delivery have a considerable risk for incident T2DM. We identified a few factors associating with an LGA delivery in the GDM women; they were older and heavier in prepregnancy, had higher parity and probably severer dysglycemia during pregnancy than the GDM women without an LGA delivery. In a previous study, we have demonstrated that women with two or more abnormal values in OGTT during pregnancy are at an increased risk for the development of T2DM (Hakkarainen et al. 2015). Despite the fact that all the women in this study had one or more risk factors for GDM, an LGA delivery in women without GDM did not predict later T2DM. This was an interesting finding since despite clinical risks brought about by an LGA delivery and being overweight, these women clearly had some potential protective factors against T2DM.

The strengths of the current study included the long-term follow-up of a well-characterized cohort of women, and the similar treatment received by all participants with GDM during pregnancy. It should be noted that in the present study, the GDM criteria in years 1989–2008 were tight especially regarding the fasting glucose value in OGTT. Consequently, our results indicated that the absence of T2DM in women with an LGA delivery but without GDM was genuine. The limitations of this study involved the inclusion of subjects based on a risk-based screening, which may have caused some selection bias. In addition, the study setting was cross-sectional at the time of follow-up OGTT, not longitudinal that would have been optimal to standardize the protocol.

6.6 CONCLUSION

We conclude that GDM women with LGA infants are at increased risk for the subsequent development of T2DM and therefore represent a target group for intervention to delay or prevent development of T2DM. However, the findings also implied that an LGA delivery in the absence of GDM does not predict T2DM in the mean follow up time of 7.3 years. Thus, an LGA delivery in non-GDM women is likely to be related to other factors than maternal dysglycemia.

7 FUTURE RISK OF METABOLIC SYNDROME IN WOMEN WITH A PREVIOUS LGA DELIVERY STRATIFIED BY GESTATIONAL GLUCOSE TOLERANCE: A PROSPECTIVE COHORT STUDY[4]

7.1 ABSTRACT

Background: Whether the delivery of a large-for-gestational-age (LGA) infant predicts future maternal metabolic syndrome (MetS) is not known. To this aim, we investigated the incidence of MetS and its components in women with or without a history of gestational diabetes mellitus (GDM) with a view to the birth weight of the offspring.

Methods: 874 women treated for their pregnancies in Kuopio University Hospital in 1989-2009 underwent a follow-up study (mean follow-up time 7.3 (SD 5.1) years), of whom 489 women with GDM and 385 normoglycemic controls. The women were stratified into two groups according to the newborn's birth weight: 10-90th percentile (appropriate-for-gestational-age; AGA) (n=662) and > 90th percentile (LGA) (n=116). MetS and its components were evaluated in the follow-up study according to the International Diabetes Federation criteria.

Results: LGA vs. AGA delivery was associated with a higher incidence of MetS at follow-up in women with a background of GDM (54.4% vs. 43.6%), but not in women without GDM.

Conclusion: An LGA delivery in women with GDM is associated with a higher risk of future MetS and this group is optimal to study preventive measures for MetS. In contrast, an LGA delivery after a normoglycemic pregnancy was not associated with an increased future maternal MetS risk.

[4] Adapted with permission of Springer Nature from: Hakkarainen H, Huopio H, Cederberg H, Voutilainen R, Heinonen S. Future risk of metabolic syndrome in women with a previous LGA delivery stratified by gestational glucose tolerance: a prospective cohort study. BMC Pregnancy Childbirth. Aug 10;18(1):326, 2018.
The table and figure numbers are modified from original publication to correspond sequential numbers of this thesis.

7.2 BACKGROUND

Gestational diabetes mellitus (GDM) increases the risk of obstetric complications, largely due to fetal overgrowth. In addition, GDM is associated with an increased risk of developing type 2 diabetes (T2DM) (Bellamy et al. 2009, Kim et al. 2002, Hakkarainen et al. 2015), metabolic syndrome (MetS) and cardiovascular diseases (CVD) (Xu et al. 2014, Hakkarainen et al. 2016, Shah et al. 2008, Retnakaran and Shah 2009, Fraser et al. 2012) after the pregnancy. The key pathophysiological defects underlying the increased cardiometabolic morbidity after GDM pregnancy include chronic insulin resistance and impaired insulin secretion, together with visceral obesity, hypertension and dyslipidemia (Alberti et al. 2009). Disturbance in glucose metabolism is considered to be a major cause for a large-for-gestational-age (LGA) delivery (Pedersen 1952), albeit many environmental and genetic factors are also likely to play a role. In particular, maternal pre-pregnancy body mass index (BMI) and gestational weight gain have been shown to be independent determinants of the infant birth weight (Berntorp et al. 2015, Yu et al. 2013, Ludwig and Currie 2010). Women with pre-pregnancy overweight and obesity were at 1.5-fold and 2-fold increased risk of delivery of an LGA infant, respectively (Yu et al. 2013). Furthermore, maternal metabolic factors including decreased high-density lipoprotein (HDL) cholesterol, increased triglycerides (Kitajima et al. 2001) and insulin have previously been shown to be independent determinants of fetal macrosomia (Clausen et al. 2005). In continuum, infant born LGA and exposed to an intrauterine environment of diabetes or maternal obesity have also been shown to be at an increased risk of developing MetS later in their lives (Boney et al. 2005).

We therefore hypothesized that a previous LGA delivery would be associated with an increased risk of incident MetS in the mother after the pregnancy. To this aim, we investigated the incidence of MetS and its components in women with and without GDM by groups of different birth size.

7.3 METHODS

This hospital register-based cohort study included women whose pregnancies were treated in Kuopio University Hospital, Finland, in 1989–2009. Women who had the diagnosis of GDM and a random sample of normoglycemic women, both groups withc ompleted oral glucose tolerance test (OGTT) during pregnancy, were contacted by a letter and invited for the study. A total of 489 women with GDM and 385 women with normal OGTT result during pregnancy attended the follow-up study. 1234 women did not reply or declined to participate in the study.

The women with and without GDM were classified based on the birth weight of the newborn: between 10-90th percentile (appropriate-for-gestational-age; AGA) (n= 662) and over 90th percentile (LGA) (n= 116). The women without GDM and delivery of an AGA infant served as a control group. In this study, LGA was

defined as sex-specific birth weight for gestational age above the 90th percentile on the current Finnish newborn growth charts (Sankilampi et al. 2013).

7.3.1 Data collection during pregnancy

In Finland, cost-free maternity care is offered to all pregnant women. The women considered to be at risk of GDM underwent 2-h OGTT (75g glucose after overnight fasting) between the 24th and 28th weeks of gestation if one or more following factors were present: age over 40 years, BMI ≥ 25 kg/m2, prior GDM or a history of a macrosomic delivery, glucosuria, suspected fetal macrosomia in the current pregnancy. The diagnostic criteria of GDM were as follows: until September 2001 the lower limits of abnormal fasting, 1-h and 2-h capillary whole-blood glucose 4.8, 10.0 and 8.7 mmol/l and since September 2001 the lower limits of fasting, 1-h and 2-h capillary plasma glucose 4.8, 11.2 and 9.9 mmol/l as per contemporary guidelines. For the women with more than one delivery during the study period, the first pregnancy with an abnormal OGTT result was selected as the index pregnancy. The women with GDM were seen regularlyin the Prenatal Outpatient Clinic in Kuopio University Hospital and they received dietary advice, regular blood glucose monitoring and insulin treatment when necessary. The hospital register included data on maternal characteristics and pregnancy risk factors, complications, pregnancy outcome, and on the neonatal period of the offspring. The women with overt T2DM at the time of pregnancy or type 1 diabetes mellitus (T1DM) diagnosed after the index pregnancy, and those with a multiple pregnancy were excluded to eliminate confounding factors.

7.3.2 The follow-up study

The participants were recruited to the follow-up study between 2006 and 2009. The women underwent laboratory tests, body composition and blood pressure measurements, and answered questionnaires concerning their family history andhealth behavior. All participants underwent a 2-h OGTT (75g of glucose). MetS was diagnosed by waist circumference ≥ 80 cm, and at least two of the following four criteria in accordance with the International Diabetes Federation (IDF) 2005 criteria (Alberti et al. 2005): blood pressure ≥ 130/85 mmHg, fasting plasma glucose ≥ 5.6 mmol/l, serum triglycerides ≥ 1.7 mmol/l, and HDL cholesterol ≤ 1.29 mmol/l. These criteria were selected since they are similar to the current care guidelines of MetS in Finland. The women using medication for hyperglycemia, hypertension or dyslipidemia were included in the analysis for the components of MetS.

Height was measured to the nearest 0.5 cm and weight to the nearest 0.1kg. Body mass index (BMI) was calculated as weight (kg) divided by the height (m) squared. Waist circumference (at the midpoint between the lateral iliac crest and the lowest rib) was measured to the nearest 0.5 cm.

7.3.3 Laboratory determinations

Plasma glucose was measured by an enzymatic hexokinase photometric assay (Konelab Systems reagents; Thermo FischerScientific, Vantaa, Finland). LDL-cholesterol, HDL-cholesterol and total triglycerides were measured by enzymatic colorimetric tests (Konelab Systems reagents).

7.3.4 Statistical analysis

The statistical analyses were conducted using SPSS version 23 (SPSS Inc., Chicago, IL). $P < 0.05$ was considered statistically significant. The results were given as the mean ± SD or number of cases and percentages. Statistical differences in categorical variables between the study and comparison groups were evaluated using the $\chi 2$ test. Anthropometric and biochemical continuous variables were analyzed using Student's t-test, and log-transformed variables were used to correct for their skewed distribution when appropriate. Since the diagnosis of GDM was based on slightly different criteria depending on the origin of the blood during the data collection, a correlation coefficient was used to convert all values to correspond venous plasma levels. The correlation coefficient was based on the information from the Department of Clinical Chemistry at Kuopio University Hospital.

This study was approved by the local Ethics Committee of the Kuopio University Hospital in accordance with the Helsinki Declaration.

7.4 RESULTS

The clinical characteristics of the study groups stratified according to the birth weight of the offspring in index pregnancy and at the follow-up are shown in Table 15. Women with GDM were older in both birth weight categories as compared to controls during the index pregnancy. Women in both GDM groups and the women without GDM but with an LGA delivery were of higher weight and more frequently multiparous than the controls. Women with LGA infants had more frequently a history of prior child's birth weight over 4000 g as compared to than those with AGA offspring. Furthermore, women with GDM and an LGA delivery had more often a prior spontaneous abortion. The study groups did not differ in the rate of prior cesarean section. The incidence of pre-eclampsia was higher in women with GDM. No significant differences were observed in gestational age at birth between the study groups.

At the time of the follow-up study, the women with GDM in both birth weight categories had shorter follow-up time. However, no difference in the mean age of the women was observed between the study groups. The women with GDM and the ones without GDM but with an LGA delivery were of higher weight than the controls, although the study groups did not differ in weight gain during the follow-up time (Table 15).

Table 15. Clinical characteristics of the controls and GDM subjects in index pregnancy and at the follow-up study stratified according to the offspring's birth weight.

Offspring's birth weight	AGA (10-90th percentile) Mean ± SD or %		LGA (>90th percentile) Mean ± SD or %	
	No GDM (Controls)	GDM (Group 1)	No GDM (Group 2)	GDM (Group 3)
Number of subjects	286	376	48	68
At the index pregnancy				
Age (yrs)	29.5 ± 5.4	31.8 ± 6.0**	30.6 ± 5.0	32.6 ± 6.3**
Primiparity (%)	53.0	35.0**	34.1*	22.2**
Pre-pregnancy BMI (kg/m²)	23.8 ± 3.8	26.4 ± 5.0**	25.7 ± 3.5*	26.7 ± 4.1**
Family history of diabetes (%)	69.4	81.4**	75.0	80.9
Prior child's birth weight > 4000g (%)	25.4	25.6	43.8*	60.4**
Prior spontaneous abortion (%)	16.8	19.9	18.8	35.3*
Prior cesarean section (%)	5.9	9.6	16.7	7.4
Gestational age (d)	280 ± 11	279 ± 9	279 ± 11	278 ± 8
Pre-eclampsia (%)	1.4	5.3*	2.1	5.9*
Birth weight (g)	3595 ± 385	3596 ± 406	4365 ± 424**	4421 ± 370**
Placental-fetal mass ratio (%)	17.1 ± 3.0	17.5 ± 3.0	20.6 ± 15.8**	17.9 ± 2.5*
Low Apgar score 1 min < 7 (%)	1.7	5.9*	6.3	4.4
At the follow-up study				
Follow-up time (yrs)	8.5 ± 5.5	5.3 ± 4.3**	7.4 ± 5.4	6.2 ± 4.9*
Age at follow-up (yrs)	38.4 ± 6.4	37.4 ± 7.2	38.3 ± 5.8	39.1 ± 7.5
BMI (kg/m²)	26.5 ± 4.9	28.3 ± 5.7**	27.9 ± 4.8*	29.2 ± 4.9**
Weight gain during the follow-up time (kg)	5.7 ± 7.6	3.6 ± 7.9	4.3 ± 7.6	5.6 ± 9.3

GDM=gestational diabetes mellitus, BMI=body mass index, AGA=appropriate for gestational age, LGA=large for gestational age. All groups compared to controls separately.
*p<0.05
**p<.0001

The comparison of cardiovascular and metabolic parameters of the study groups at follow-up is shown in Table 16. The women with GDM in both birth weight groups and the women without GDM with an LGA delivery had significantly higher waist circumference than the control group; approximately 80% of the women in those three groups reached the 80 cm waist circumference limit. Both GDM groups had significantly lower HDL levels and higher fasting plasma glucose than the control group, with approximately 50% of the women with GDM exceeding the limit 5.6 mmol/l at the follow-up visit. The mean triglyceride levels were higher in women with GDM in both birth weight categories. However, the study groups did not differ significantly concerning the triglyceride level over 1.7 mmol/l required for MetS criterion. No significant differences were observed in total blood pressure between the study groups, even though the mean systolic blood pressure in both

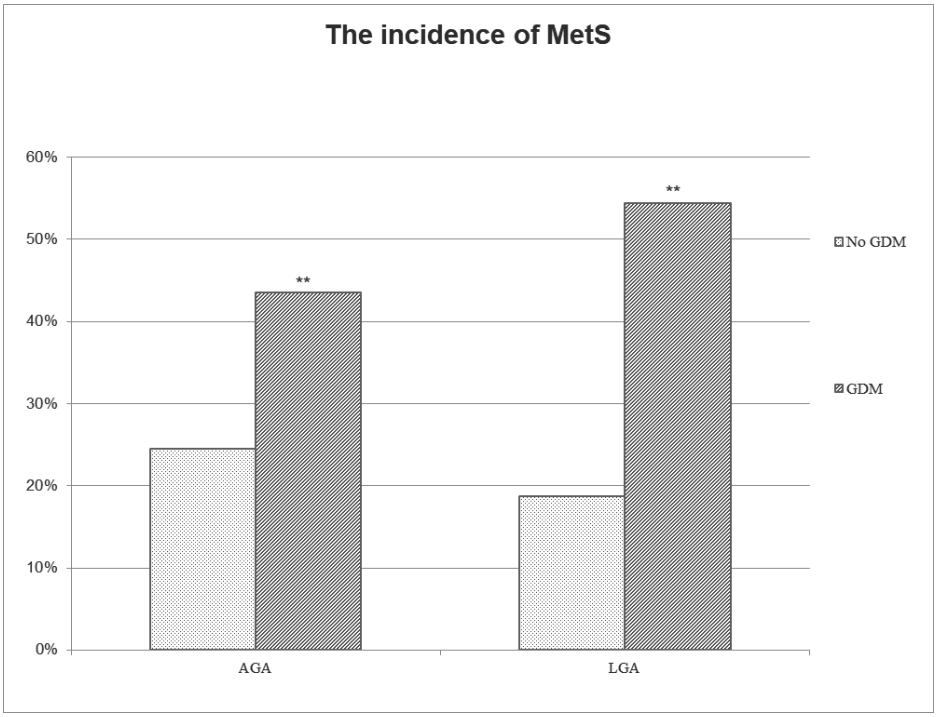
GDM groups and diastolic pressure in the women with GDM and LGA infants was significantly higher as compared to controls (Table 16).

Table 16. The components of the metabolic syndrome (MetS) in the study subjects at the follow-up study stratified according to the offspring's birth weight.

Offspring's birth weight	**AGA (10-90th percentile) Mean ± SD or %**		**LGA (>90th percentile) Mean ± SD or %**	
	No GDM (Controls)	**GDM (Group 1)**	**No GDM (Group 2)**	**GDM (Group 3)**
Number of subjects	286	376	48	68
Waist circumference (cm)	85.3 ± 11.6	91.0 ± 13.8**	88.8 ± 10.8*	94.2 ± 12.9**
Waist circumference ≥ 80 cm (%)	64.0	77.6**	81.3*	89.7**
Fasting glucose (mmol/l)	5.3 ± 0.4	5.6 ± 0.8**	5.4 ± 0.4	5.8 ± 0.8**
Fasting glucose ≥ 5.6 mmol/l (%)	25.2	46.8**	29.2	58.8**
Triglycerides (mmol/l)	1.0 ± 0.6	1.1 ± 0.6*	0.9 ± 0.4	1.2 ± 0.5*
Triglycerides ≥ 1,70 mmol/l (%)	10.6	15.2	4.2	16.2
HDL cholestrol (mmol/l)	1.5 ± 0.4	1.4 ± 0.4**	1.6 ± 0.3	1.3 ± 0.3**
HDL cholestrol < 1.29 mmol/l (%)	28.3	44.1**	20.8	57.4**
Systolic pressure (mmHg)	122.5 ± 14.3	125.8 ± 14.1*	121.4 ± 10.1	128.4 ± 14.2*
Diastolic pressure (mmHg)	78.3 ± 9.6	79.3 ± 9.2	77.5 ± 7.5	81.3 ± 10.0*
Blood pressure ≥ 130/≥85 mmHg (%)	34.3	38.8	27.1	45.6
Metabolic syndrome (IDF) (%)	24.5	43.6**	18.8	54.4**

GDM gestational diabetes mellitus, BMI body mass index, AGA appropriate for gestational age, LGA large for gestational age. All groups compared to controls separately
*p<0.05
**p<.0001

The incidence of MetS at the follow-up study stratified with the birth weight of the offspring is illustrated in Figure 12. The incidence of MetS was higher in women with GDM and an LGA (54.4%) than an AGA delivery (43.6%). Furthermore, the incidence of MetS in LGA study groups was three times higher in women with GDM as compared to the normoglycemic women. However, the incidence of MetS did not differ significantly in the non-GDM group between the AGA (24.5%) and LGA (18.8%) groups.



MetS=metabolic syndrome, GDM=gestational diabetes mellitus, AGA=appropriate for gestational age (offspring birth weight 10-90th percentile), LGA=large for gestational age (offspring birth weight >90th percentile). All groups compared to controls (subjects without GDM in the AGA group) separately.
* $p<0.05$
** $p<.0001$

Figure 12. The incidence of the metabolic syndrome among the study groups at the follow-up visit according to the birth weight of the newborn.

7.5 DISCUSSION

Our long-term study indicated that after an LGA delivery, the incidence of MetS is three times higher in women with GDM compared to those without GDM. Increased waist circumference was the only component of MetS in the non-GDM LGA group that was more prevalent than in the control group. Among the women with GDM, the limits of MetS in fasting glucose and HDL cholesterol were broken more often than in the control group. Overall, LGA delivery alone did not predict future MetS in women with normal glucose tolerance during pregnancy. In contrast, delivery of an LGA infant in women with GDM predicts future risk of MetS and thus risk for future cardiovascular disease.

Previously, only few studies have focused on the components of MetS separately after an LGA delivery without GDM. In our study, the mean waist circumference was significantly greater in women with GDM at follow-up in both birth weight categories. In addition, 81.3% of the women with a prior LGA delivery without GDM exceeded 80 cm waist circumference limit fulfilling the compulsory

criterion of MetS. An explanation for this could be high pre-pregnancy BMI in this study group and genetic susceptibility to such body composition. These results are in agreement with a previous 18-years follow-up study showing that waist circumference and fasting glucose were the only significant components of MetS in mothers with LGA infants with or without GDM during their pregnancies (Fraser et al. 2012). In agreement with our results, no difference was observed in waist circumference in women with macrosomic (> 4 kg) or stillborn newborns as compared to age-and BMI-matched women without macrosomic deliveries in a 9-year follow-up study in women without previous GDM (Tehrani et al. 2012).

The development of dysglycemia and type 2 diabetes in women with a background of GDM supported by a large body of evidence (Bellamy et al. 2009, Kim et al. 2002). In accordance, a higher percentage of fasting glucose > 5.6 mmol/l was detected at follow-up in both GDM groups as compared to controls regardless of the birth weight category. However, no significant difference in fasting glucose was observed in women with a previous LGA delivery without GDM comparedto controls. This is in agreement with a previous 2-year follow-up study, where fasting glucose levels did not differ between the non-GDM women with previous LGA and AGA deliveries (Moses et al. 1997). Moreover, a 9-year follow-up study did not find any differences in fasting glucose concentrations in women with and without previous macrosomic newborns with absence of GDM during pregnancy (Tehrani et al. 2012).

In our study, LGA delivery without previous GDM did not predict later dyslipidemia as compared to the controls. Mean HDL cholesterol levels were lower and triglycerides slightly higher in women with GDM in both birth weight categories. However, concerning the lipid components of MetS, only low HDL cholesterol was more prevalent in the GDM groups than in controls. In agreement with our findings, a study performed 2 years after pregnancy revealed that no significant differences were observed between 18 women with LGA infants and 18 women with AGA infants with respect to lipids (Moses et al. 1997). Correspondingly, a 9-year follow-up study demonstrated no differences in the incidence of dyslipidemia between 570 women with a history of macrosomia or stillbirth without GDM compared to age-and BMI-matched controls (Tehrani et al. 2012). In contrast to these reports, a study of 48 women with previous birth of large infants and without glucosuria during pregnancy demonstrated that after 20–27 years postpartum these women had significantly lower concentration of HDL-cholesterol compared to age-, parity-and BMI-matched controls with birth weight < 4500g (Spjuth et al. 1993). Further, a study of 332 women with a prior LGA delivery reported lower HDL-cholesterol levels than in 2630 women with an appropriate-for-gestational-age (AGA) newborns in an age-adjusted model 18 years after pregnancy (Fraser et al. 2012). However, when adjusted for confounders the statistical significance was lost.

No studies have reported on the prevalence of the MetS high blood pressure criterion (≥130/≥85 mmHg) after an LGA delivery. We found no differences in this

prevalence between the study groups. In agreement with our results, a prior macrosomic or LGA delivery in women without GDM did not predict later increased systolic or diastolic blood pressure in two-previous follow-up studies (Tehrani et al. 2012, Spjuth et al. 1993).

Although some previous research has been carried out on components of MetS after an LGA delivery, the overall incidence of MetS has not been known. Our results show that 54.4% of women with GDM and an LGA delivery developed incident MetS during the follow-up, as compared to 43.6% in the AGA group. Interestingly, in women without GDM, the incidence of MetS was not higher with a previous LGA delivery as compared to the group with AGA delivery even though maternal BMI was higher in the LGA group. In this study, a considerable part of the women without GDM were overweight (BMI = 25 kg/m2) in pre-pregnancy: 28.7% in the AGA and 51.1% in the LGA group (data not shown) as a result of risk-based screening for GDM. Therefore, it could be assumed that an LGA delivery in women without GDM is not predictive for later metabolic risk factors and MetS. Similarly, no association between an LGA delivery with the calculated 10-year CVD risk after adjustment for confounders was found in another study (Fraser et al. 2012).

The strengths of the current study included the long-term follow-up of a well-characterized cohort of women, and the similar treatment received by all participants with GDM during pregnancy. It should be noted that in the present study, the GDM criteria in years 1989– 2008 were tight especially regarding the fasting glucose value in OGTT. Thus, some women with GDM who would not be diagnosed with GDM using the current criteria

were included as GDM women. This analysis has concentrated on women who were chosen from an obstetric population with risk factors for GDM potentially causing some selection bias. In addition, the study setting was cross-sectional at the time of follow-up OGTT, not longitudinal which would have been optimal to standardize the protocol. Notwithstanding its limitations, this study does suggest that even though all subjects have GDM risk factors, an LGA delivery does not predict later MetS in women without GDM.

In conclusion, the women without GDM were at a lower risk than those with GDM for MetS even with an LGA delivery. This probably reflects good maternal vascular health and its effects on birth weight. In contrast, women with GDM and a previous LGA delivery should be considered as a high-risk target group for prevention of future MetS and CVD.

7.6 CONCLUSION

In summary, an LGA delivery without GDM was not significantly associated with future maternal MetS risk in the mean follow-up time of 7.3 years. High offspring birth weight in this group is likely to be related to maternal vascular health and genetic factors. In contrast, women with GDM who have had an LGA delivery should have a stringent follow-up after pregnancy to reduce the risk of future MetS and enhance women's cardiovascular health.

8 GENERAL DISCUSSION

8.1 THE MAIN FINDINGS

Women with previous GDM are at increased risk for later T2DM and MetS (Studies I and II). This risk increases substantially by the degree of glycemic abnormality during a pregnancy. After a 10-year follow-up, the risk of later T2DM in GDM women with ≥ 2 abnormal values in OGTT was 25% compared to 3.8% in women with one abnormal value. The corresponding risks for later MetS were 46.2% and 62.5%, respectively. The burden of T2DM in women with GDM continuously increased during the 10-year follow-up, whereas the incidence of MetS remained nearly constant. Abnormal post-challenge glucose levels were the best predictors of later T2DM, whereas abnormal fasting plasma glucose was the best marker to predict later MetS. Therefore, OGTT results in women with GDM provide an opportunity to identify a group at markedly high risk for later morbidity.

Fetal macrosomy associated with maternal GDM increases the maternal risk of later prediabetes, T2DM and MetS (Studies III and IV). The incidence of prediabetes, T2DM and MetS after a delivery of an LGA infant were 52.9%, 11.8% and 54.4% in GDM women. A delivery of an LGA infant without maternal dysglycemia was not associated with maternal adverse metabolic outcomes in the mean follow-up time of 7.3 years. These results demonstrate that women with previous GDM combined with an LGA newborn should be the target of more stringent follow-up and preventive measures after pregnancy to diminish morbidity and the risk of future cardiovascular diseases.

8.2 FINDINGS IN RELATION TO OTHER STUDIES

There is compelling evidence that GDM in pregnancy identifies women at risk for future T2DM (Bellamy et al. 2009), MetS (Xu et al. 2014) and also cardiovascular disease (Shah et al. 2008, Kramer et al. 2019). The incidences of T2DM, Mets and CVD vary depending on the GDM criterion, the population studied and the length of follow-up. This study performed on the Northern Savo population is in line with previous studies and demonstrates an incidence of up to 25% of later T2DM and up to 63% of later Mets after 10-year follow-up in women with a history of GDM. Specifically, these findings emphasize the elevated risk in women with two or more abnormal values in OGTT during pregnancy and therefore these women should be followed intensively after the pregnancy. In practice, women with several abnormal values in OGTT represent a more difficult form of GDM and more often require tight diet or insulin treatment. There are no previous studies that separate hyperglycemia into more detailed groups based on the number of abnormal values in OGTT, even though studies carried out in GDM women requiring insulin have been published.

However, women with one abnormal value in OGTT also require follow-up after delivery. According to the present study, after 10 years of follow-up 3.8% and 46.2% of these women developed T2DM and MetS, respectively. These findings are in parallel with previous studies concerning the risk of mild gestational hyperglycemia and the later development of T2DM and MetS. A recent study from United States found that MetS was present in 32.9% of women with a previous diagnosis of mild GDM 5-10 years after pregnancy (Varner et al. 2017). Mild GDM was defined as two or more abnormal glucose values in 3-hour OGTT with fasting value below 4.7 mmol/l. They also found that the incidence of later T2DM increased from 5.2% to 10.5% if women had subsequent pregnancies. Two other studies in women who screened positive in a GCT but had a normal OGTT demonstrated a two-fold higher risk for future MetS (Bo et al. 2006) and 20% higher risk for CVD (Retnakaran and Shah 2009) after pregnancy. The HAPO Study revealed a continuous association between increasing glucose levels and birthweight above 90th percentile and cord -blood serum C-peptide levels, showing that even mild hyperglycemia during pregnancy should be treated (HAPO Study Cooperative Research Group, Metzger et al. 2008). Based on the findings from the HAPO -data and the present study, it is obvious that the risks of future T2DM and MetS are a continuum, increasing linearly with the deteoriation of maternal glucose tolerance during pregnancy.

The present study demonstrated that post-challenge glucose levels in OGTT during pregnancy were the strongest predictors of incident T2DM, whereas the fasting glucose level was prognostic of future MetS. GDM associates with both insulin resistance and impaired β-cell function. Fasting glucose levels particularly reflect hepatic insulin resistance, which is closely linked to visceral adiposity. Therefore, fasting glucose better reflects the risk of later MetS. Abnormal post-challenge glucose level usually is derived from the defect in β-cell function in the presence of insulin resistance (Moleda et al. 2013). The findings of the present study are in line with previous studies that have demonstrated the significance of the fasting glucose value as a predictor of MetS (Akinci et al. 2010, Tam et al. 2013) and emphasize the fact that women with only an abnormal fasting value in the OGTT are an important group to target strategies to prevent the MetS. Furthermore, the present results are in line with the previous findings that postprandial glucose levels are the best predictors of T2DM (Akinci et al. 2011, Rayanagoudar et al. 2016), althougt there is also strong evidence that the fasting value is more predictive (Noctor et al. 2016, Akinci et al. 2011, Rayanagoudar et al. 2016). The present study was unable to demonstrate this. Overall, our findings emphasize that it is important to consider the prognostic value of the OGTT during pregnancy in a comprehensive way.

A previous systematic review consisting of 28 studies showed that the incidence of T2DM increased markedly in the first 5 years after delivery and appeared to plateau after 10 years follow-up (Kim et al. 2002). In the present study, the incidence of T2DM increased with time throughout the 10-years follow-up without

any detectable signs of a plateau. The incidence of MetS after GDM pregnancy remained constant during follow-up, affecting about 60% of women in the high-risk group already five years after pregnancy. This illustrates the fact that protective interventions after pregnancy were not very successful. In contrast, the incidence of MetS in women with a milder form of GDM increased continuously during the follow-up time after pregnancy. This strengthens the findings of previous studies that even mild gestational hyperglycemia is an important risk factor for adverse maternal long-term health (Varner et al. 2017) and needs to be targeted shortly after pregnancy.

The historical Pedersen theory proposed that all women delivering LGA infants would be at risk for later development of T2DM due to maternal hyperglycemia-derived fetal hyperinsulemia and thus, fetal overgrowth. However, the results of the present study demonstrated, that women who had normal glucose tolerance during the pregnancy and who gave birth to LGA infants were not at increased risk for later development of T2DM, which is in agreement with previous studies (Moses et al. 1997, Kew et al. 2011, Tehrani et al. 2012).

Our present study demonstrated that a delivery of an LGA infant after a GDM pregnancy increases the risk of later development of T2DM and thus shows a specific target group for interventions after the pregnancy. This result is in contrast with a recent meta-analysis of nearly 1021 women which reported, that having a macrosomic infant was not associated with the risk of future T2DM that appears to be mostly influenced by gestational glucose tolerance (Rayanagoudar et al. 2016).

The overall incidence of MetS has not been studied after a delivery of LGA infant. The present results demonstrated that after the delivery of a macrosomic infant, the incidence of MetS was three times higher in women with GDM than in those without GDM. Fasting glucose and HDL cholesterol were the most remarkable traits of MetS in these women. Previous studies concerning maternal long-term health after having an LGA newborn have concentrated separately on metabolic traits of MetS mainly in women without GDM. These studies have found no differences in waist circumference, fasting glucose, lipids or blood pressure between non-GDM women with a prior LGA or AGA deliveries (Tehrani et al. 2012, Moses et al. 1997, Spjuth et al. 1993). In the present study, 80% of women with a previous LGA delivery without GDM fulfilled the main criterion of waist circumference probably mirroring higher pre-pregancy BMI and the more stringent waist circumference criterion of the IDF. Therefore, the incidence of MetS was present already in 20% of these women. In summary, GDM women with an LGA delivery represent an especially high-risk group for later T2DM and MetS, and therefore, preventive practices should be targeted to them.

8.3 VALIDITY AND LIMITATIONS OF THE STUDY

This hospital register-based cohort study included women whose pregnancies were treated in Kuopio University Hospital, Finland, in 1989–2009. Women who had the diagnosis of GDM and a random sample of normoglycemic women who had also undergone an OGTT during pregnancy, were contacted by a letter and invited for the study. A total of 489 women with GDM and a random sample of 385 women with normal OGTT result during pregnancy attended the follow-up study. 1234 women did not reply or declined to participate in the study. This cohort study included women whose GDM diagnosis was retrospectively collected from the Hospital Register. The diagnosis of GDM was verified with the OGTT results of the Hospital Birth Register and by a questionnaire during follow-up visits. Women were classified as GDM if they had any GDM pregnancy during the data collection. To eliminate confounding factors, women with overt T2DM at the time of pregnancy or type 1 diabetes mellitus diagnosed after the index pregnancy and those with a multiple pregnancy were excluded.

The accumulated data of participants were affected by a selection bias caused by eligible women who did not reply to the invitation letter and who declined to participate in the study. Features among nonattenders and their risk for T2DM are unknown. Therefore, the results of this study are valid only in women who aim to attend the follow-up examination after pregnancy, not all women with a previous GDM pregnancy. Since screening of GDM was risk factor -based during the data collection time, all women included in this study belonged to the risk group for GDM. Therefore, they do not represent the whole population of pregnant women, limiting the generalization of the results. However, during the data collection, the GDM criteria in years 1989-2008 were more stringent with regard to the fasting value cut off. This emphasizes the fact, that the control women were certainly normoglycemic regarding of fasting glucose level (although they were at risk for GDM). This validated the comparison of GDM women to controls and made the results of the present study more reliable. This is a notable strength of the study, since the adverse outcomes of pregancy have been demonstrated to increase linearly with glucose thresholds already below those of GDM.

The incidence of T2DM is estimated to be 3.1% in women aged 30-49 years according to the FINNRISK- study in 2017 (Koponen et al. 2019). In this study, the incidence of later T2DM in GDM women with ≥ 2 abnormal values in OGTT was 15.9%. Therefore, the OR for later development of T2DM in GDM2 patients compared to the background population of women is 5.8 (95% CI 3.7 – 9.0), highlighting the role of OGTT during pregnancy in prediction of later T2DM. In contrast, there was only one case (0.3%) of T2DM among control women, indicating that the risk of T2DM is lower in control women than in women of same age in the background population (OR 0.08 (95% CI 0.01 – 0.57)). This emphasizes the finding that normal glucose tolerance during pregnancy protects against incident T2DM despite having risk factors for GDM.

The comparability of the present study findings with other studies is challenging because the diagnostic criteria of GDM vary worldwide, and there are wide variations in study settings, follow-up times and ascertainment of cases and controls. Other confounders such as lifestyle factors were not assessed in this study. Moreover, the present study was performed in Caucasian women and cannot be generalized to other ethnic groups.

8.4 CLINICAL SIGNIFICANCE AND GENERALIZABILITY OF THE RESULTS

There is compelling evidence of an increased risk for metabolic disturbances like T2DM and MetS in women with a history of GDM. The current study confirms the previous findings and provides data to implement follow-up services for these women after delivery to delay or prevent these metabolic disturbances. Based on the study results (I-IV), the individualized risk of later T2DM and MetS can be established with the information of the OGTT results during pregnancy and the knowledge of the newborn weight.

Study I and II show that women with two or more abnormal values were at greatest risk for incident T2DM and MetS. Women with one abnormal value in the OGTT also belong to a moderate -risk group. Moreover, this study demonstrated that the risk for future T2DM and MetS was increased at even milder fasting glucose levels in the OGTT during pregnancy than those presented in the recent Current Care Guidelines in Finland and in different guidelines used in other countries. This highlights the fact that the results of the OGTT during pregnancy should not be interpreted only with certain thresholds. The results should rather be considered more as a continuum of risk for later development of metabolic and cardiovascular diseases.

Fetal macrosomy without maternal dysglycemia during pregnancy did not place these women at risk for later T2DM and MetS (study III and IV). Therefore, an LGA newborn in such cases is presumably a consequence of factors other than maternal hyperglycemia during pregnancy. When an LGA delivery is accompanied by abnormal glucose tolerance during pregnancy, the risk for future T2DM and MetS appeared to be high.

Women with GDM are at increased risk for both T2DM and MetS. In practice, the risk of T2DM after GDM pregnancy has been the main theme of prevention in parental clinics. The results of this study add to this that also the incidence of MetS is very frequent among women with previous GDM. Thus, the metabolic traits of MetS need to be assessed appropriately to prevent later cardiovascular diseases.

Pregnancy is an important phase in a woman´s life since during that time she is in regular contact with the health care system. Therefore, it offers an exceptional opportunity to influence a woman´s future health. Moreover, the incident T2DM and CVD appears to manifest as early as the first decade after GDM pregnancy (Kim at al. 2002, Kramer et al. 2019). The economic costs of these diseases are

enormous. It has been estimated that outlays for diabetes was 3 384 million euros in Finland year 2011 (Koski et al. 2018). Therefore, efforts to prevent morbidity of these young women after a GDM pregnancy are extremely important and cost-efficient.

How to improve the follow-up of women with previous GDM after pregnancy is, however, challenging. Previous studies have shown that the follow-up of women with a history of GDM is inadequate, and a significant opportunity for interventional measures has been missed. A recent study mapped different postpartum reminding systems six month postpartum and found that the most preferred ones were electronic reminders like SMS (Van Ryswyk et al. 2016). Several women also desired a shorter and more convenient test for detecting T2DM. Another study has demonstrated that participation in any glucose test postpartum was higher in women who were reminded (Clark et al. 2009). Barriers to participate to postpartum tests are commonly lack of time, problems with childcare and generally feeling healthy. Thus, education during and after pregnancy should not be underestimated, and barriers between pregnancy-focused care and primary care must be diminished. In this regard, the role of the parental and child health clinic is highly important to intervene and prevent long-term morbidity in mothers. Further knowledge is needed on how to best utilize the information provided by the history of GDM in pregnancy to improve women's long-term health.

9 CONCLUSIONS

I. Women with two or more abnormal values in the OGTT during pregancy are at the greatest risk for later T2DM when compared to those with one abnormal value or women with a normal OGTT. Post-challenge glucose levels in the OGTT are the most predictive of incident T2DM. These findings emphasize the predictive value of an OGTT performed during pregnancy in the evaluation of the individualized risk for future dysglycemia in women with previous GDM.

II. The incidence of MetS is highest in women with two or more abnormal values in the OGTT during pregnancy as compared to those with one abnormal value or normoglycemic controls. The incidence of MetS is increased up to 60% five years postpartum and remains stable during a ten-year follow-up in women with several abnormal values in the OGTT, whereas the incidence of MetS seems to increase continuously in women with one abnormal value in the OGTT. This indicates that women with a milder dysglycemia during prenangy also represent an important group for lifestyle intervention.

III. Women diagnosed with GDM and who gave birth to a macrosomic newborn are at an increased risk for future T2DM, whereas normoglycemic women during pregnancy with an LGA newborn are not at risk for later T2DM. This result reveals an important target group for preventive measures and follow-up after the pregnancy.

IV. A delivery of macrosomic infant without GDM is not associated with future risk of maternal MetS. However, over 50% of woman with previous GDM and an LGA infant delivery developed MetS during the mean follow-up of 7.3 years. Thus, this risk group should be stringently followed up after delivery to enhance later cardiovascular health.

REFERENCES

ABERG, A.E., JONSSON, E.K., ESKILSSON, I., LANDIN-OLSSON, M. and FRID, A.H., 2002. Predictive factors of developing diabetes mellitus in women with gestational diabetes. *Acta Obstetricia et Gynecologica Scandinavica,* **81**(1), pp. 11-16.

ACOG Committee Opinion No. 650: Physical Activity and Exercise During Pregnancy and the Postpartum Period. 2015. *Obstetrics and gynecology,* **126**(6), pp. e135-42.

AKINCI, B., CELTIK, A., GENC, S., YENER, S., DEMIR, T., SECIL, M., KEBAPCILAR, L. and YESIL, S., 2011. Evaluation of postpartum carbohydrate intolerance and cardiovascular risk factors in women with gestational diabetes. *Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology,* **27**(5), pp. 361-367.

AKINCI, B., CELTIK, A., YENER, S. and YESIL, S., 2010. Prediction of developing metabolic syndrome after gestational diabetes mellitus. *Fertility and sterility,* **93**(4), pp. 1248-1254.

ALBAREDA, M., CABALLERO, A., BADELL, G., PIQUER, S., ORTIZ, A., DE LEIVA, A. and CORCOY, R., 2003. Diabetes and abnormal glucose tolerance in women with previous gestational diabetes. *Diabetes care,* **26**(4), pp. 1199-1205.

ALBAREDA, M., CABALLERO, A., BADELL, G., RODRIGUEZ-ESPINOSA, J., ORDONEZ-LLANOS, J., DE LEIVA, A. and CORCOY, R., 2005. Metabolic syndrome at follow-up in women with and without gestational diabetes mellitus in index pregnancy. *Metabolism: clinical and experimental,* **54**(8), pp. 1115-1121.

ALBERTI, K.G., ECKEL, R.H., GRUNDY, S.M., ZIMMET, P.Z., CLEEMAN, J.I., DONATO, K.A., FRUCHART, J.C., JAMES, W.P., LORIA, C.M., SMITH, S.C., Jr, INTERNATIONAL DIABETES FEDERATION TASK FORCE ON EPIDEMIOLOGY AND PREVENTION, HATIONAL HEART, LUNG, AND BLOOD INSTITUTE, AMERICAN HEART ASSOCIATION, WORLD HEART FEDERATION, INTERNATIONAL ATHEROSCLEROSIS SOCIETY and INTERNATIONAL ASSOCIATION FOR THE STUDY OF OBESITY, 2009. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation,* **120**(16), pp. 1640-1645.

ALBERTI, K.G., ZIMMET, P., SHAW, J. and IDF EPIDEMIOLOGY TASK FORCE CONSENSUS GROUP, 2005. The metabolic syndrome--a new worldwide definition. *Lancet,* **366**(9491), pp. 1059-1062.

ALBERTI, K.G. and ZIMMET, P.Z., 1998. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabetic medicine: a journal of the British Diabetic Association,* **15**(7), pp. 539-553.

AMERICAN DIABETES ASSOCIATION, 2018. 13. Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes-2018. *Diabetes care,* **41**(Suppl 1), pp. S137-S143.

AMERICAN DIABETES ASSOCIATION, 2018. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2018. *Diabetes care,* **41**(Suppl 1), pp. S13-S27.

AMERICAN DIABETES ASSOCIATION, 2017. 13. Management of Diabetes in Pregnancy. *Diabetes care,* **40**(Suppl 1), pp. S114-S119.

AMERICAN DIABETES ASSOCIATION, 2011. Diagnosis and classification of diabetes mellitus. *Diabetes care,* **34 Suppl 1**, pp. S62-9.

AMERICAN DIABETES ASSOCIATION, 2003. Gestational diabetes mellitus. *Diabetes care,* **26 Suppl 1**, pp. S103-5.

ANASTASIOU, E., LEKAKIS, J.P., ALEVIZAKI, M., PAPAMICHAEL, C.M., MEGAS, J., SOUVATZOGLOU, A. and STAMATELOPOULOS, S.F., 1998. Impaired endothelium-dependent vasodilatation in women with previous gestational diabetes. *Diabetes care,* **21**(12), pp. 2111-2115.

ANTIKAINEN, L., JAASKELAINEN, J., NORDMAN, H., VOUTILAINEN, R. and HUOPIO, H., 2018. Prepubertal Children Exposed to Maternal Gestational Diabetes Have Latent Low-Grade Inflammation. *Hormone research in paediatrics*, pp. 1-7.

ARODA, V.R., CHRISTOPHI, C.A., EDELSTEIN, S.L., ZHANG, P., HERMAN, W.H., BARRETT-CONNOR, E., DELAHANTY, L.M., MONTEZ, M.G., ACKERMANN, R.T., ZHUO, X., KNOWLER, W.C., RATNER, R.E. and DIABETES PREVENTION PROGRAM RESEARCH GROUP, 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. *The Journal of clinical endocrinology and metabolism,* **100**(4), pp. 1646-1653.

ASANO, R.Y., SALES, M.M., BROWNE, R.A., MORAES, J.F., COELHO JUNIOR, H.J., MORAES, M.R. and SIMOES, H.G., 2014. Acute effects of physical exercise in type 2 diabetes: A review. *World journal of diabetes,* **5**(5), pp. 659-665.

BALSELLS, M., GARCIA-PATTERSON, A., SOLA, I., ROQUE, M., GICH, I. and CORCOY, R., 2015. Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis. *BMJ (Clinical research ed.),* **350**, pp. h102.

BAO, W., YEUNG, E., TOBIAS, D.K., HU, F.B., VAAG, A.A., CHAVARRO, J.E., MILLS, J.L., GRUNNET, L.G., BOWERS, K., LEY, S.H., KIELY, M., OLSEN, S.F. and ZHANG, C., 2015. Long-term risk of type 2 diabetes mellitus in relation to BMI and weight change among women with a history of gestational diabetes mellitus: a prospective cohort study. *Diabetologia,* **58**(6), pp. 1212-1219.

BAPTISTE-ROBERTS, K., BARONE, B.B., GARY, T.L., GOLDEN, S.H., WILSON, L.M., BASS, E.B. and NICHOLSON, W.K., 2009. Risk factors for type 2 diabetes among women with gestational diabetes: a systematic review. *The American Journal of Medicine,* **122**(3), pp. 207-214.

BARKER, D.J. and OSMOND, C., 1986. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet (London, England),* **1**(8489), pp. 1077-1081.

BATTAGLIA, F.C. and LUBCHENCO, L.O., 1967. A practical classification of newborn infants by weight and gestational age. *The Journal of pediatrics,* **71**(2), pp. 159-163.

BATTARBEE, A.N., PALATNIK, A., ERNST, L.M. and GROBMAN, W.A., 2015. Association of Isolated Single Umbilical Artery With Small for Gestational Age and Preterm Birth. *Obstetrics and gynecology,* **126**(4), pp. 760-764.

BELLAMY, L., CASAS, J.P., HINGORANI, A.D. and WILLIAMS, D., 2009. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *Lancet,* **373**(9677), pp. 1773-1779.

BENHALIMA, K., JEGERS, K., DEVLIEGER, R., VERHAEGHE, J. and MATHIEU, C., 2016. Glucose Intolerance after a Recent History of Gestational Diabetes Based on the 2013 WHO Criteria. *PloS one,* **11**(6), pp. e0157272.

BERNSTEIN, J.A., QUINN, E., AMELI, O., CRAIG, M., HEEREN, T., LEE-PARRITZ, A., IVERSON, R., JACK, B. and MCCLOSKEY, L., 2017. Follow-up after

gestational diabetes: a fixable gap in women's preventive healthcare. *BMJ open diabetes research & care,* **5**(1), pp. e000445.

BERNTORP, K., ANDERBERG, E., CLAESSON, R., IGNELL, C. and KALLEN, K., 2015. The relative importance of maternal body mass index and glucose levels for prediction of large-for-gestational-age births. *BMC pregnancy and childbirth,* **15**, pp. 280.

BILLIONNET, C., MITANCHEZ, D., WEILL, A., NIZARD, J., ALLA, F., HARTEMANN, A. and JACQUEMINET, S., 2017. Gestational diabetes and adverse perinatal outcomes from 716,152 births in France in 2012. *Diabetologia,* **60**(4), pp. 636-644.

BJORSTAD, A.R., IRGENS-HANSEN, K., DALTVEIT, A.K. and IRGENS, L.M., 2010. Macrosomia: mode of delivery and pregnancy outcome. *Acta Obstetricia et Gynecologica Scandinavica,* **89**(5), pp. 664-669.

BLACK, M.H., SACKS, D.A., XIANG, A.H. and LAWRENCE, J.M., 2013. The relative contribution of prepregnancy overweight and obesity, gestational weight gain, and IADPSG-defined gestational diabetes mellitus to fetal overgrowth. *Diabetes care,* **36**(1), pp. 56-62.

BLICKSTEIN, I., 2004. Is it normal for multiples to be smaller than singletons? *Best practice & research. Clinical obstetrics & gynaecology,* **18**(4), pp. 613-623.

BO, S., MENATO, G., BOTTO, C., COTRINO, I., BARDELLI, C., GAMBINO, R., CASSADER, M., DURAZZO, M., SIGNORILE, A., MASSOBRIO, M. and PAGANO, G., 2006. Mild gestational hyperglycemia and the metabolic syndrome in later life. *Metabolic syndrome and related disorders,* **4**(2), pp. 113-121.

BO, S., VALPREDA, S., MENATO, G., BARDELLI, C., BOTTO, C., GAMBINO, R., RABBIA, C., DURAZZO, M., CASSADER, M., MASSOBRIO, M. and PAGANO, G., 2007. Should we consider gestational diabetes a vascular risk factor? *Atherosclerosis,* **194**(2), pp. e72-9.

BOERSCHMANN, H., PFLUGER, M., HENNEBERGER, L., ZIEGLER, A.G. and HUMMEL, S., 2010. Prevalence and predictors of overweight and insulin resistance in offspring of mothers with gestational diabetes mellitus. *Diabetes care,* **33**(8), pp. 1845-1849.

BONADONNA, R.C., GROOP, L., KRAEMER, N., FERRANNINI, E., DEL PRATO, S. and DEFRONZO, R.A., 1990. Obesity and insulin resistance in humans: a dose-response study. *Metabolism: clinical and experimental,* **39**(5), pp. 452-459.

BONAMY, A.K., PARIKH, N.I., CNATTINGIUS, S., LUDVIGSSON, J.F. and INGELSSON, E., 2011. Birth characteristics and subsequent risks of maternal cardiovascular disease: effects of gestational age and fetal growth. *Circulation,* **124**(25), pp. 2839-2846.

BONEY, C.M., VERMA, A., TUCKER, R. and VOHR, B.R., 2005. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. *Pediatrics,* **115**(3), pp. e290-6.

BOOMSMA, C.M., EIJKEMANS, M.J., HUGHES, E.G., VISSER, G.H., FAUSER, B.C. and MACKLON, N.S., 2006. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. *Human reproduction update,* **12**(6), pp. 673-683.

BOULET, S.L., ALEXANDER, G.R., SALIHU, H.M. and PASS, M., 2003. Macrosomic births in the United States: determinants, outcomes, and proposed grades of risk. *American Journal of Obstetrics and Gynecology,* **188**(5), pp. 1372-1378.

BREWER, M., KUECK, A. and RUNOWICZ, C.D., 2011. Chemotherapy in pregnancy. *Clinical obstetrics and gynecology,* **54**(4), pp. 602-618.

BROWN, J., ALWAN, N.A., WEST, J., BROWN, S., MCKINLAY, C.J., FARRAR, D. and CROWTHER, C.A., 2017. Lifestyle interventions for the treatment of women with gestational diabetes. *The Cochrane database of systematic reviews,* **5**, pp. CD011970.

BUCHANAN, T.A., METZGER, B.E., FREINKEL, N. and BERGMAN, R.N., 1990. Insulin sensitivity and B-cell responsiveness to glucose during late pregnancy in lean and moderately obese women with normal glucose tolerance or mild gestational diabetes. *American Journal of Obstetrics and Gynecology,* **162**(4), pp. 1008-1014.

BUTTE, N.F., 2000. Carbohydrate and lipid metabolism in pregnancy: normal compared with gestational diabetes mellitus. *The American Journal of Clinical Nutrition,* **71**(5 Suppl), pp. 1256S-61S.

CALLESEN, N.F., DAMM, J., MATHIESEN, J.M., RINGHOLM, L., DAMM, P. and MATHIESEN, E.R., 2013. Treatment with the long-acting insulin analogues detemir or glargine during pregnancy in women with type 1 diabetes: comparison of glycaemic control and pregnancy outcome. *The journal of maternal-fetal & neonatal medicine: the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians,* **26**(6), pp. 588-592.

CAMERON, A.J., BOYKO, E.J., SICREE, R.A., ZIMMET, P.Z., SODERBERG, S., ALBERTI, K.G., TUOMILEHTO, J., CHITSON, P. and SHAW, J.E., 2008. Central obesity as a precursor to the metabolic syndrome in the AusDiab study and Mauritius. *Obesity (Silver Spring, Md.),* **16**(12), pp. 2707-2716.

CARLSSON, S., 2019. Etiology and Pathogenesis of Latent Autoimmune Diabetes in Adults (LADA) Compared to Type 2 Diabetes. *Frontiers in physiology*, 10, pp. 320.

CARPENTER, M.W. and COUSTAN, D.R., 1982. Criteria for screening tests for gestational diabetes. *American Journal of Obstetrics and Gynecology,* **144**(7), pp. 768-773.

CARRINGTON, E.R., SHUMAN, C.R. and REARDON, H.S., 1957. Evaluation of the prediabetic state during pregnancy. *Obstetrics and gynecology,* **9**(6), pp. 664-669.

CASEY, B.M., LUCAS, M.J., MCINTIRE, D.D. and LEVENO, K.J., 1997. Pregnancy outcomes in women with gestational diabetes compared with the general obstetric population. *Obstetrics and gynecology,* **90**(6), pp. 869-873.

CATALANO, P.M., 2014. Trying to understand gestational diabetes. *Diabetic medicine: a journal of the British Diabetic Association,* **31**(3), pp. 273-281.

CATALANO, P.M., MCINTYRE, H.D., CRUICKSHANK, J.K., MCCANCE, D.R., DYER, A.R., METZGER, B.E., LOWE, L.P., TRIMBLE, E.R., COUSTAN, D.R., HADDEN, D.R., PERSSON, B., HOD, M., OATS, J.J. and HAPO STUDY COOPERATIVE RESEARCH GROUP, 2012. The hyperglycemia and adverse pregnancy outcome study: associations of GDM and obesity with pregnancy outcomes. *Diabetes care,* **35**(4), pp. 780-786.

CATALANO, P.M., TYZBIR, E.D., WOLFE, R.R., CALLES, J., ROMAN, N.M., AMINI, S.B. and SIMS, E.A., 1993. Carbohydrate metabolism during pregnancy in control subjects and women with gestational diabetes. *The American Journal of Physiology,* **264**(1 Pt 1), pp. E60-7.

CAUFRIEZ, A., FRANKENNE, F., HENNEN, G. and COPINSCHI, G., 1993. Regulation of maternal IGF-I by placental GH in normal and abnormal human pregnancies. *The American Journal of Physiology,* **265**(4 Pt 1), pp. E572-7.

CAUGHEY, A.B., CHENG, Y.W., STOTLAND, N.E., WASHINGTON, A.E. and ESCOBAR, G.J., 2010. Maternal and paternal race/ethnicity are both associated with gestational diabetes. *American Journal of Obstetrics and Gynecology,* **202**(6), pp. 616.e1-616.e5.

CHALLIER, J.C., BASU, S., BINTEIN, T., MINIUM, J., HOTMIRE, K., CATALANO, P.M. and HAUGUEL-DE MOUZON, S., 2008. Obesity in pregnancy stimulates macrophage accumulation and inflammation in the placenta. *Placenta,* **29**(3), pp. 274-281.

CHAMBERLAIN, C., MCLEAN, A., OATS, J., OLDENBURG, B., EADES, S., SINHA, A. and WOLFE, R., 2015. Low rates of postpartum glucose screening among indigenous and non-indigenous women in Australia with gestational diabetes. *Maternal and child health journal,* **19**(3), pp. 651-663.

CHELLAKOOTY, M., VANGSGAARD, K., LARSEN, T., SCHEIKE, T., FALCK-LARSEN, J., LEGARTH, J., ANDERSSON, A.M., MAIN, K.M., SKAKKEBAEK, N.E. and JUUL, A., 2004. A longitudinal study of intrauterine growth and the placental growth hormone (GH)-insulin-like growth factor I axis in maternal circulation: association between placental GH and fetal growth. *The Journal of clinical endocrinology and metabolism,* **89**(1), pp. 384-391.

CHENG, Y.W., CHUNG, J.H., KURBISCH-BLOCK, I., INTURRISI, M., SHAFER, S. and CAUGHEY, A.B., 2008. Gestational weight gain and gestational diabetes mellitus: perinatal outcomes. *Obstetrics and gynecology,* **112**(5), pp. 1015-1022.

CLAESSON, R., IGNELL, C., SHAAT, N. and BERNTORP, K., 2017. HbA1c as a predictor of diabetes after gestational diabetes mellitus. *Primary care diabetes,* **11**(1), pp. 46-51.

CLARK, H.D., GRAHAM, I.D., KAROVITCH, A. and KEELY, E.J., 2009. Do postal reminders increase postpartum screening of diabetes mellitus in women with gestational diabetes mellitus? A randomized controlled trial. *American Journal of Obstetrics and Gynecology,* **200**(6), pp. 634.e1-634.e7.

Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. National Diabetes Data Group. 1979. *Diabetes,* **28**(12), pp. 1039-1057.

CLAUSEN, T., BURSKI, T.K., OYEN, N., GODANG, K., BOLLERSLEV, J. and HENRIKSEN, T., 2005. Maternal anthropometric and metabolic factors in the first half of pregnancy and risk of neonatal macrosomia in term pregnancies. A prospective study. *European journal of endocrinology / European Federation of Endocrine Societies,* **153**(6), pp. 887-894.

CLAUSEN, T.D., MATHIESEN, E.R., HANSEN, T., PEDERSEN, O., JENSEN, D.M., LAUENBORG, J. and 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), pp. 340-346.

CLAUSEN, T.D., MATHIESEN, E.R., HANSEN, T., PEDERSEN, O., JENSEN, D.M., LAUENBORG, J., SCHMIDT, L. and DAMM, P., 2009. Overweight and the metabolic syndrome in adult offspring of women with diet-treated gestational diabetes mellitus or type 1 diabetes. *The Journal of clinical endocrinology and metabolism,* **94**(7), pp. 2464-2470.

CLAUSSON, B., LICHTENSTEIN, P. and CNATTINGIUS, S., 2000. Genetic influence on birthweight and gestational length determined by studies in offspring of twins. *BJOG: an international journal of obstetrics and gynaecology,* **107**(3), pp. 375-381.

COLBERG, S.R., SIGAL, R.J., FERNHALL, B., REGENSTEINER, J.G., BLISSMER, B.J., RUBIN, R.R., CHASAN-TABER, L., ALBRIGHT, A.L., BRAUN, B., AMERICAN COLLEGE OF SPORTS MEDICINE and AMERICAN DIABETES ASSOCIATION, 2010. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement executive summary. *Diabetes care,* **33**(12), pp. 2692-2696.

COMMITTEE ON PRACTICE BULLETINS-OBSTETRICS, 2018. ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. *Obstetrics and gynecology,* **131**(2), pp. e49-e64.

CORDERO, L., TREUER, S.H., LANDON, M.B. and GABBE, S.G., 1998. Management of infants of diabetic mothers. *Archives of Pediatrics & Adolescent Medicine,* **152**(3), pp. 249-254.

COSSON, E., CUSSAC-PILLEGAND, C., BENBARA, A., PHARISIEN, I., NGUYEN, M.T., CHIHEB, S., VALENSI, P. and CARBILLON, L., 2016. Pregnancy adverse outcomes related to pregravid body mass index and gestational weight gain, according to the presence or not of gestational diabetes mellitus: A retrospective observational study. *Diabetes & metabolism,* **42**(1), pp. 38-46.

CROWTHER, C.A., HILLER, J.E., MOSS, J.R., MCPHEE, A.J., JEFFRIES, W.S., ROBINSON, J.S. and AUSTRALIAN CARBOHYDRATE INTOLERANCE STUDY IN PREGNANT WOMEN (ACHOIS) TRIAL GROUP, 2005. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *The New England journal of medicine,* **352**(24), pp. 2477-2486.

CUSPIDI, C., SALA, C., PROVENZANO, F., TADIC, M., GHERBESI, E., GRASSI, G. and MANCIA, G., 2017. Metabolic syndrome and subclinical carotid damage: a meta-analysis from population-based studies. *Journal of hypertension*, **36**, pp. 23-30.

DAMM, P., KUHL, C., BERTELSEN, A. and MOLSTED-PEDERSEN, L., 1992. Predictive factors for the development of diabetes in women with previous gestational diabetes mellitus. *American Journal of Obstetrics and Gynecology,* **167**(3), pp. 607-616.

DASHE, J.S., MCINTIRE, D.D., LUCAS, M.J. and LEVENO, K.J., 2000. Effects of symmetric and asymmetric fetal growth on pregnancy outcomes. *Obstetrics and gynecology,* **96**(3), pp. 321-327.

DE ZEGHER, F., PEREZ-CRUZ, M., DIAZ, M., GOMEZ-ROIG, M.D., LOPEZ-BERMEJO, A. and IBANEZ, L., 2014. Less myostatin and more lean mass in large-born infants from nondiabetic mothers. *The Journal of clinical endocrinology and metabolism,* **99**(11), pp. E2367-71.

DEFRONZO, R.A., 2010. Insulin resistance, lipotoxicity, type 2 diabetes and atherosclerosis: the missing links. The Claude Bernard Lecture 2009. *Diabetologia,* **53**(7), pp. 1270-1287.

DEWEY, K., HEINIG, M., NOMMSEN, L., 1993. Maternal weight-loss patterns during prolonged lactation. *The American journal of clinical nutrition*, **58**(2):162-6.

DI CIANNI, G., LENCIONI, C., VOLPE, L., GHIO, A., CUCCURU, I., PELLEGRINI, G., BENZI, L., MICCOLI, R. and DEL PRATO, S., 2007. C-reactive protein and metabolic syndrome in women with previous gestational diabetes. *Diabetes/metabolism research and reviews,* **23**(2), pp. 135-140.

Diabeteksen ehkäisyn ja hoidon kehittämisohjelma, DEHKO 2000–2010. Tampere: Suomen Diabetesliitto 2000-2018.

KOSKI, S., KURKELA, O., ILANNE-PARIKKA, P., RISSANEN, P., 2018. Diabeteksen kustannukset Suomessa 2002-2011. Available: www.diabetes.fi/kustannustutkimus.

Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy: a World Health Organization Guideline. 2014. *Diabetes research and clinical practice,* **103**(3), pp. 341-363.

DORNHORST, A. and FROST, G., 2002. The principles of dietary management of gestational diabetes: reflection on current evidence. *Journal of human nutrition and dietetics: the official journal of the British Dietetic Association,* **15**(2), pp. 145-56; quiz 157-9.

EFSTRATIADIS, A., 1998. Genetics of mouse growth. *The International journal of developmental biology,* **42**(7), pp. 955-976.

EGGLESTON, E.M., LECATES, R.F., ZHANG, F., WHARAM, J.F., ROSS-DEGNAN, D. and OKEN, E., 2016. Variation in Postpartum Glycemic Screening in Women With a History of Gestational Diabetes Mellitus. *Obstetrics and gynecology,* **128**(1), pp. 159-167.

ESSER, N., PAQUOT, N. and SCHEEN, A.J., 2015. Inflammatory markers and cardiometabolic diseases. *Acta Clinica Belgica,* **70**(3), pp. 193-199.

EYDOUX, P., CHOISET, A., LE PORRIER, N., THEPOT, F., SZPIRO-TAPIA, S., ALLIET, J., RAMOND, S., VIEL, J.F., GAUTIER, E. and MORICHON, N., 1989. Chromosomal prenatal diagnosis: study of 936 cases of intrauterine abnormalities after ultrasound assessment. *Prenatal diagnosis,* **9**(4), pp. 255-269.

FARRAR, D., SIMMONDS, M., BRYANT, M., LAWLOR, D.A., DUNNE, F., TUFFNELL, D. and 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), pp. e0175288.

FARRAR, D., SIMMONDS, M., BRYANT, M., SHELDON, T.A., TUFFNELL, D., GOLDER, S., DUNNE, F. and LAWLOR, D.A., 2016. Hyperglycaemia and risk of adverse perinatal outcomes: systematic review and meta-analysis. *BMJ (Clinical research ed.),* **354**, pp. i4694.

FELDMAN, R.K., TIEU, R.S. and YASUMURA, L., 2016. Gestational Diabetes Screening: The International Association of the Diabetes and Pregnancy Study Groups Compared With Carpenter-Coustan Screening. *Obstetrics and gynecology,* **127**(1), pp. 10-17.

FERNANDEZ-REAL, J.M., BROCH, M., RICART, W., CASAMITJANA, R., GUTIERREZ, C., VENDRELL, J. and RICHART, C., 1998. Plasma levels of the soluble fraction of tumor necrosis factor receptor 2 and insulin resistance. *Diabetes,* **47**(11), pp. 1757-1762.

FERRARA, A., PENG, T. and KIM, C., 2009. Trends in postpartum diabetes screening and subsequent diabetes and impaired fasting glucose among women with histories of gestational diabetes mellitus: A report from the Translating Research Into Action for Diabetes (TRIAD) Study. *Diabetes care,* **32**(2), pp. 269-274.

FLORES-LE ROUX, J.A., SAGARRA, E., BENAIGES, D., HERNANDEZ-RIVAS, E., CHILLARON, J.J., PUIG DE DOU, J., MUR, A., LOPEZ-VILCHEZ, M.A. and PEDRO-BOTET, J., 2012. A prospective evaluation of neonatal hypoglycaemia in infants of women with gestational diabetes mellitus. *Diabetes research and clinical practice,* **97**(2), pp. 217-222.

FORHEAD, A.J. and FOWDEN, A.L., 2014. Thyroid hormones in fetal growth and prepartum maturation. *The Journal of endocrinology,* **221**(3), pp. R87-R103.

FRASER, A., NELSON, S.M., MACDONALD-WALLIS, C., CHERRY, L., BUTLER, E., SATTAR, N. and LAWLOR, D.A., 2012. Associations of pregnancy complications with calculated cardiovascular disease risk and cardiovascular risk factors in middle age: the Avon Longitudinal Study of Parents and Children. *Circulation,* **125**(11), pp. 1367-1380.

FREINKEL, N., 1980. Banting Lecture 1980. Of pregnancy and progeny. *Diabetes,* **29**(12), pp. 1023-1035.

FRUHBECK, G. and SALVADOR, J., 2000. Relation between leptin and the regulation of glucose metabolism. *Diabetologia,* **43**(1), pp. 3-12.

FULROTH, R., PHILLIPS, B. and DURAND, D.J., 1989. Perinatal outcome of infants exposed to cocaine and/or heroin in utero. *American Journal of Diseases of Children (1960),* **143**(8), pp. 905-910.

GAST, K.B., TJEERDEMA, N., STIJNEN, T., SMIT, J.W. and DEKKERS, O.M., 2012. Insulin resistance and risk of incident cardiovascular events in adults without diabetes: meta-analysis. *PloS one,* **7**(12), pp. e52036.

GASTALDELLI, A., NATALI, A., VETTOR, R. and CORRADINI, S.G., 2010. Insulin resistance, adipose depots and gut: interactions and pathological implications. *Digestive and liver disease: official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver,* **42**(5), pp. 310-319.

Gestational Diabetes. Current Care Guidelines. Working group set up by the Finnish Medical Society Duodecim, the Medical Advisory Board of the Finnish Diabetes Association and the Finnish Gynecological Association. 2013 -last update. Available online at: http://www.kaypahoito.fi/web/kh/suositukset/suositus?id=hoi50068 [9/6, 2018].

GETAHUN, D., FASSETT, M.J. and JACOBSEN, S.J., 2010. Gestational diabetes: risk of recurrence in subsequent pregnancies. *American Journal of Obstetrics and Gynecology,* **203**(5), pp. 467.e1-467.e6.

GOUESLARD, K., COTTENET, J., MARIET, A.S., GIROUD, M., COTTIN, Y., PETIT, J.M. and QUANTIN, C., 2016. Early cardiovascular events in women with a history of gestational diabetes mellitus. *Cardiovascular diabetology,* **15**, pp. 1-7.

GUNDERSON, E.P., JACOBS, D.R. Jr, CHIANG, V., LEWIS, C.E., FENG, J., QUESENBERRY, C.P. Jr and SIDNEY, S., 2010. Duration of lactation and incidence of the metabolic syndrome in women of reproductive age according to gestational diabetes mellitus status: a 20-Year prospective study in CARDIA (Coronary Artery Risk Development in Young Adults). *Diabetes,* **59**(2), pp. 495-504.

GUNN, J.K., ROSALES, C.B., CENTER, K.E., NUNEZ, A., GIBSON, S.J., CHRIST, C. and EHIRI, J.E., 2016. Prenatal exposure to cannabis and maternal and child health outcomes: a systematic review and meta-analysis. *BMJ open,* **6**(4), pp. e009986.

HAKKARAINEN, H., HUOPIO, H., CEDERBERG, H., PAAKKONEN, M., VOUTILAINEN, R. and HEINONEN, S., 2016. The risk of metabolic syndrome in women with previous GDM in a long-term follow-up. *Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology,* **32**, pp. 920-925.

HAKKARAINEN, H., HUOPIO, H., CEDERBERG, H., PAAKKONEN, M., VOUTILAINEN, R. and HEINONEN, S., 2015. Post-challenge glycemia during pregnancy as a marker of future risk of type 2 diabetes: a prospective cohort study. *Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology,* **31**(7), pp. 573-577.

HALL, J.G., PAULI, R.M. and WILSON, K.M., 1980. Maternal and fetal sequelae of anticoagulation during pregnancy. *The American Journal of Medicine,* **68**(1), pp. 122-140.

HAMMAMI, M., WALTERS, J.C., HOCKMAN, E.M. and KOO, W.W., 2001. Disproportionate alterations in body composition of large for gestational age neonates. *The Journal of pediatrics,* **138**(6), pp. 817-821.

HAN, S., MIDDLETON, P., SHEPHERD, E., VAN RYSWYK, E. and CROWTHER, C.A., 2017. Different types of dietary advice for women with gestational diabetes mellitus. *The Cochrane database of systematic reviews,* **2**, pp. CD009275.

HANDWERGER, S. and FREEMARK, M., 2000. The roles of placental growth hormone and placental lactogen in the regulation of human fetal growth and development. *Journal of pediatric endocrinology & metabolism: JPEM,* **13**(4), pp. 343-356.

HAPO STUDY COOPERATIVE RESEARCH GROUP, METZGER, B.E., LOWE, L.P., DYER, A.R., TRIMBLE, E.R., CHAOVARINDR, U., COUSTAN, D.R., HADDEN, D.R., MCCANCE, D.R., HOD, M., MCINTYRE, H.D., OATS, J.J., PERSSON, B., ROGERS, M.S. and SACKS, D.A., 2008. Hyperglycemia and adverse pregnancy outcomes. *The New England journal of medicine,* **358**(19), pp. 1991-2002.

HARTLING, L., DRYDEN, D.M., GUTHRIE, A., MUISE, M., VANDERMEER, B. and DONOVAN, L., 2013. Benefits and harms of treating gestational diabetes mellitus: a systematic review and meta-analysis for the U.S. Preventive Services Task Force and the National Institutes of Health Office of Medical Applications of Research. *Annals of Internal Medicine,* **159**(2), pp. 123-129.

HAUGUEL-DE MOUZON, S. and GUERRE-MILLO, M., 2006. The placenta cytokine network and inflammatory signals. *Placenta,* **27**(8), pp. 794-798.

HEDDERSON, M.M., WILLIAMS, M.A., HOLT, V.L., WEISS, N.S. and FERRARA, A., 2008. Body mass index and weight gain prior to pregnancy and risk of gestational diabetes mellitus. *American Journal of Obstetrics and Gynecology,* **198**(4), pp. 409.e1-409.e7.

HENRIKSEN, T., 2008. The macrosomic fetus: a challenge in current obstetrics. *Acta Obstetricia et Gynecologica Scandinavica,* **87**(2), pp. 134-145.

HERDER, C. and RODEN, M., 2011. Genetics of type 2 diabetes: pathophysiologic and clinical relevance. *European journal of clinical investigation,* **41**(6), pp. 679-692.

HILL, D.J., 1992. What is the role of growth hormone and related peptides in implantation and the development of the embryo and fetus. *Hormone research,* **38 Suppl 1**, pp. 28-34.

HILL, D.J. and MILNER, R.D., 1985. Insulin as a growth factor. *Pediatric research,* **19**(9), pp. 879-886.

HOD, M., KAPUR, A., SACKS, D.A., HADAR, E., AGARWAL, M., DI RENZO, G.C., CABERO ROURA, L., MCINTYRE, H.D., MORRIS, J.L. and DIVAKAR, H., 2015. The International Federation of Gynecology and Obstetrics (FIGO) Initiative on gestational diabetes mellitus: A pragmatic guide for diagnosis, management, and care. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics,* **131 Suppl 3**, pp. S173-211.

HOMKO, C., SIVAN, E., CHEN, X., REECE, E.A. and BODEN, G., 2001. Insulin secretion during and after pregnancy in patients with gestational diabetes mellitus. *The Journal of clinical endocrinology and metabolism,* **86**(2), pp. 568-573.

HORNBERGER, L.K., 2006. Maternal diabetes and the fetal heart. *Heart (British Cardiac Society),* **92**(8), pp. 1019-1021.

HU, G., LINDSTROM, J., JOUSILAHTI, P., PELTONEN, M., SJOBERG, L., KAAJA, R., SUNDVALL, J. and TUOMILEHTO, J., 2008. The increasing prevalence of metabolic syndrome among Finnish men and women over a decade. *The Journal of clinical endocrinology and metabolism,* **93**(3), pp. 832-836.

HUNT, K.J. and SCHULLER, K.L., 2007. The increasing prevalence of diabetes in pregnancy. *Obstetrics and gynecology clinics of North America,* **34**(2), pp. 173-99, vii.

HUOPIO, H., CEDERBERG, H., VANGIPURAPU, J., HAKKARAINEN, H., PAAKKONEN, M., KUULASMAA, T., HEINONEN, S. and LAAKSO, M., 2013. Association of risk variants for type 2 diabetes and hyperglycemia with gestational diabetes. *European journal of endocrinology / European Federation of Endocrine Societies,* **169**(3), pp. 291-297.

HUOPIO, H., HAKKARAINEN, H., PAAKKONEN, M., KUULASMAA, T., VOUTILAINEN, R., HEINONEN, S. and CEDERBERG, H., 2014. Long-term changes in glucose metabolism after gestational diabetes: a double cohort study. *BMC pregnancy and childbirth,* **14**, pp. 296.

HYVÖNEN, K., 1991. *Gestaatiodiabeteksen esiintyvyys ja seulonta.*, University of Kuopio, Department of Obstetrics and Gynecology.

IJAS, H., MORIN-PAPUNEN, L., KERANEN, A.K., BLOIGU, R., RUOKONEN, A., PUUKKA, K., EBELING, T., RAUDASKOSKI, T. and VAARASMAKI, M., 2013. Pre-pregnancy overweight overtakes gestational diabetes as a risk factor for subsequent metabolic syndrome. *European journal of endocrinology / European Federation of Endocrine Societies,* **169**(5), pp. 605-611.

ILANNE-PARIKKA, P., ERIKSSON, J.G., LINDSTROM, J., HAMALAINEN, H., KEINANEN-KIUKAANNIEMI, S., LAAKSO, M., LOUHERANTA, A., MANNELIN, M., RASTAS, M., SALMINEN, V., AUNOLA, S., SUNDVALL, J., VALLE, T., LAHTELA, J., UUSITUPA, M., TUOMILEHTO, J. and FINNISH DIABETES PREVENTION STUDY GROUP, 2004. Prevalence of the metabolic syndrome and its components: findings from a Finnish general population sample and the Diabetes Prevention Study cohort. *Diabetes care,* **27**(9), pp. 2135-2140.

INSTITUTE OF MEDICINE (US) AND NATIONAL RESEARCH COUNCIL (US) COMMITTEE TO REEXAMINE IOM PREGNANCY WEIGHT GUIDELINES, 2009.

INTERACT CONSORTIUM, SCOTT, R.A., LANGENBERG, C., SHARP, S.J., FRANKS, P.W., ROLANDSSON, O., DROGAN, D., VAN DER SCHOUW, Y.T., EKELUND, U., KERRISON, N.D., ARDANAZ, E., ARRIOLA, L., BALKAU, B., BARRICARTE, A., BARROSO, I., BENDINELLI, B., BEULENS, J.W., BOEING, H., DE LAUZON-GUILLAIN, B., DELOUKAS, P., FAGHERAZZI, G., GONZALEZ, C., GRIFFIN, S.J., GROOP, L.C., HALKJAER, J., HUERTA, J.M., KAAKS, R., KHAW, K.T., KROGH, V., NILSSON, P.M., NORAT, T., OVERVAD, K., PANICO, S., RODRIGUEZ-SUAREZ, L., ROMAGUERA, D., ROMIEU, I., SACERDOTE, C., SANCHEZ, M.J., SPIJKERMAN, A.M., TEUCHER, B., TJONNELAND, A., TUMINO, R., VAN DER, A.D.L., WARK, P.A., MCCARTHY, M.I., RIBOLI, E. and WAREHAM, N.J., 2013. The link between family history and risk of type 2 diabetes is not explained by anthropometric, lifestyle or genetic risk factors: the EPIC-InterAct study. *Diabetologia,* **56**(1), pp. 60-69.

INTERNATIONAL ASSOCIATION OF DIABETES AND PREGNANCY STUDY GROUPS CONSENSUS PANEL, METZGER, B.E., GABBE, S.G., PERSSON, B., BUCHANAN, T.A., CATALANO, P.A., DAMM, P., DYER, A.R., LEIVA, A., HOD, M., KITZMILER, J.L., LOWE, L.P., MCINTYRE, H.D., OATS, J.J., OMORI, Y. and SCHMIDT, M.I., 2010. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes care,* **33**(3), pp. 676-682.

ISOMAA, B., ALMGREN, P., TUOMI, T., FORSEN, B., LAHTI, K., NISSEN, M., TASKINEN, M.R. and GROOP, L., 2001. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes care,* **24**(4), pp. 683-689.

JAMES-TODD, T.M., KARUMANCHI, S.A., HIBERT, E.L., MASON, S.M., VADNAIS, M.A., HU, F.B. and RICH-EDWARDS, J.W., 2013. Gestational age, infant birth weight, and subsequent risk of type 2 diabetes in mothers: Nurses' Health Study II. *Preventing chronic disease,* **10**, pp. E156.

JARVELA, I.Y., JUUTINEN, J., KOSKELA, P., HARTIKAINEN, A.L., KULMALA, P., KNIP, M. and TAPANAINEN, J.S., 2006. Gestational diabetes identifies women at risk for permanent type 1 and type 2 diabetes in fertile age: predictive role of autoantibodies. *Diabetes care,* **29**(3), pp. 607-612.

JUNG, U.J. and CHOI, M.S., 2014. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. *International journal of molecular sciences,* **15**(4), pp. 6184-6223.

KABEYA, Y., GOTO, A., KATO, M., TAKAHASHI, Y., MATSUSHITA, Y., INOUE, M., MIZOUE, T., TSUGANE, S., KADOWAKI, T. and NODA, M., 2013. History of

having a macrosomic infant and the risk of diabetes: the Japan public health center-based prospective diabetes study. *PloS one,* **8**(12), pp. e84542.

KATON, J., REIBER, G., WILLIAMS, M.A., YANEZ, D. and MILLER, E., 2012. Hemoglobin A1c and postpartum abnormal glucose tolerance among women with gestational diabetes mellitus. *Obstetrics and gynecology,* **119**(3), pp. 566-574.

KAUTZKY-WILLER, A., PRAGER, R., WALDHAUSL, W., PACINI, G., THOMASETH, K., WAGNER, O.F., ULM, M., STRELI, C. and LUDVIK, B., 1997. Pronounced insulin resistance and inadequate beta-cell secretion characterize lean gestational diabetes during and after pregnancy. *Diabetes care,* **20**(11), pp. 1717-1723.

KEW, S., YE, C., SERMER, M., CONNELLY, P.W., HANLEY, A.J., ZINMAN, B. and RETNAKARAN, R., 2011. Postpartum metabolic function in women delivering a macrosomic infant in the absence of gestational diabetes mellitus. *Diabetes care,* **34**(12), pp. 2608-2613.

KHOURY, M.J., ERICKSON, J.D., CORDERO, J.F. and MCCARTHY, B.J., 1988. Congenital malformations and intrauterine growth retardation: a population study. *Pediatrics,* **82**(1), pp. 83-90.

KIM, C., LIU, T., VALDEZ, R. and BECKLES, G.L., 2009. Does frank diabetes in first-degree relatives of a pregnant woman affect the likelihood of her developing gestational diabetes mellitus or nongestational diabetes? *American Journal of Obstetrics and Gynecology,* **201**(6), pp. 576.e1-576.e6.

KIM, C., NEWTON, K.M. and KNOPP, R.H., 2002. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. *Diabetes care,* **25**(10), pp. 1862-1868.

KIM, S.H., 2015. Maturity-Onset Diabetes of the Young: What Do Clinicians Need to Know? *Diabetes & metabolism journal*, 39(6), pp. 468-477.

KIM, S.Y., SHARMA, A.J., SAPPENFIELD, W., WILSON, H.G. and SALIHU, H.M., 2014. Association of maternal body mass index, excessive weight gain, and gestational diabetes mellitus with large-for-gestational-age births. *Obstetrics and gynecology,* **123**(4), pp. 737-744.

KIRPICHNIKOV, D., MCFARLANE, S.I. and SOWERS, J.R., 2002. Metformin: an update. *Annals of Internal Medicine,* **137**(1), pp. 25-33.

KITAJIMA, M., OKA, S., YASUHI, I., FUKUDA, M., RII, Y. and ISHIMARU, T., 2001. Maternal serum triglyceride at 24--32 weeks' gestation and newborn weight in

nondiabetic women with positive diabetic screens. *Obstetrics and gynecology,* **97**(5 Pt 1), pp. 776-780.

KOLTERMAN, O.G., INSEL, J., SAEKOW, M. and OLEFSKY, J.M., 1980. Mechanisms of insulin resistance in human obesity: evidence for receptor and postreceptor defects. *The Journal of clinical investigation,* **65**(6), pp. 1272-1284.

KOPONEN, P., BORODULIN, K., LUNDQVIST, A., SÄÄKSJÄRVI, K., JÄÄSKELÄINEN, T., KOSKELA, T., KOSKINEN, S., 2019. FinTerveys -tutkimuksen perustulokset. Available: www.terveytemme.fi/finterveys

KOSKI, S., KURKELA, O., ILANNE-PARIKKA, P., RISSANEN, P., 2018. Diabetes lukuina 2018:1. Available: www.diabetes.fi/kustannustutkimus.

KRAMER, C.K., CAMPBELL, S. and RETNAKARAN, R., 2019. Gestational diabetes and the risk of cardiovascular disease in women: a systematic review and meta-analysis. *Diabetologia,* **62**(6), pp. 905-914.

KRAMER, C.K., SWAMINATHAN, B., HANLEY, A.J., CONNELLY, P.W., SERMER, M., ZINMAN, B. and RETNAKARAN, R., 2014. Each degree of glucose intolerance in pregnancy predicts distinct trajectories of beta-cell function, insulin sensitivity, and glycemia in the first 3 years postpartum. *Diabetes care,* **37**(12), pp. 3262-3269.

KUZMICKI, M., TELEJKO, B., SZAMATOWICZ, J., ZONENBERG, A., NIKOLAJUK, A., KRETOWSKI, A. and GORSKA, M., 2009. High resistin and interleukin-6 levels are associated with gestational diabetes mellitus. *Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology,* **25**(4), pp. 258-263.

KWIK, M., SEEHO, S.K., SMITH, C., MCELDUFF, A. and MORRIS, J.M., 2007. Outcomes of pregnancies affected by impaired glucose tolerance. *Diabetes research and clinical practice,* **77**(2), pp. 263-268.

KYLIN, E.S., 1923. Hypertonie-Hyperglykämie-Hyperurika miesyndrom. *Zentralblatt für Innere Medizin,* (44), pp. 105.

LANDON, M.B., SPONG, C.Y., THOM, E., CARPENTER, M.W., RAMIN, S.M., CASEY, B., WAPNER, R.J., VARNER, M.W., ROUSE, D.J., THORP, J.M. Jr, SCISCIONE, A., CATALANO, P., HARPER, M., SAADE, G., LAIN, K.Y., SOROKIN, Y., PEACEMAN, A.M., TOLOSA, J.E., ANDERSON, G.B. and EUNICE KENNEDY SHRIVER NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT MATERNAL-FETAL MEDICINE UNITS NETWORK,

2009. A multicenter, randomized trial of treatment for mild gestational diabetes. *The New England journal of medicine,* **361**(14), pp. 1339-1348.

LARSSON, G., SPJUTH, J., RANSTAM, J., VIKBLADH, I., SAXTRUP, O. and ASTEDT, B., 1986. Prognostic significance of birth of large infant for subsequent development of maternal non-insulin-dependent diabetes mellitus: a prospective study over 20-27 years. *Diabetes care,* **9**(4), pp. 359-364.

LAUENBORG, J., GRARUP, N., DAMM, P., BORCH-JOHNSEN, K., JORGENSEN, T., PEDERSEN, O. and HANSEN, T., 2009. Common type 2 diabetes risk gene variants associate with gestational diabetes. *The Journal of clinical endocrinology and metabolism,* **94**(1), pp. 145-150.

LAUENBORG, J., HANSEN, T., JENSEN, D.M., VESTERGAARD, H., MOLSTED-PEDERSEN, L., HORNNES, P., LOCHT, H., PEDERSEN, O. and DAMM, P., 2004. Increasing incidence of diabetes after gestational diabetes: a long-term follow-up in a Danish population. *Diabetes care,* **27**(5), pp. 1194-1199.

LAUENBORG, J., MATHIESEN, E., HANSEN, T., GLUMER, C., JORGENSEN, T., BORCH-JOHNSEN, K., HORNNES, P., PEDERSEN, O. and DAMM, P., 2005. The prevalence of the metabolic syndrome in a danish population of women with previous gestational diabetes mellitus is three-fold higher than in the general population. *The Journal of clinical endocrinology and metabolism,* **90**(7), pp. 4004-4010.

LAURINI, R., LAURIN, J. and MARSAL, K., 1994. Placental histology and fetal blood flow in intrauterine growth retardation. *Acta Obstetricia et Gynecologica Scandinavica,* **73**(7), pp. 529-534.

LEAN, M., HAN, T., SEIDELL, J., 1998. Impairment of health and quality of life inpeople with large waist circumference. *Lancet*, **351**(9106), pp. 853-6.

LEHTORANTA, L., VUOLTEENAHO, O., LAINE, V.J., KOSKINEN, A., SOUKKA, H., KYTO, V., MAATTA, J., HAAPSAMO, M., EKHOLM, E. and RASANEN, J., 2013. Maternal hyperglycemia leads to fetal cardiac hyperplasia and dysfunction in a rat model. *American journal of physiology. Endocrinology and metabolism,* **305**(5), pp. E611-9.

LEKVA, T., BOLLERSLEV, J., NORWITZ, E.R., AUKRUST, P., HENRIKSEN, T. and UELAND, T., 2015. Aortic Stiffness and Cardiovascular Risk in Women with Previous Gestational Diabetes Mellitus. *PloS one,* **10**(8), pp. e0136892.

LEVITZKY, Y.S., PENCINA, M.J., D'AGOSTINO, R.B., MEIGS, J.B., MURABITO, J.M., VASAN, R.S. and FOX, C.S., 2008. Impact of impaired fasting glucose on

cardiovascular disease: the Framingham Heart Study. *Journal of the American College of Cardiology,* **51**(3), pp. 264-270.

LILLIOJA, S., MOTT, D.M., SPRAUL, M., FERRARO, R., FOLEY, J.E., RAVUSSIN, E., KNOWLER, W.C., BENNETT, P.H. and BOGARDUS, C., 1993. Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus. Prospective studies of Pima Indians. *The New England journal of medicine,* **329**(27), pp. 1988-1992.

LINNE, Y., BARKELING, B. and ROSSNER, S., 2002. Natural course of gestational diabetes mellitus: long term follow up of women in the SPAWN study. *BJOG: an international journal of obstetrics and gynaecology,* **109**(11), pp. 1227-1231.

LOBNER, K., KNOPFF, A., BAUMGARTEN, A., MOLLENHAUER, U., MARIENFELD, S., GARRIDO-FRANCO, M., BONIFACIO, E. and ZIEGLER, A.G., 2006. Predictors of postpartum diabetes in women with gestational diabetes mellitus. *Diabetes,* **55**(3), pp. 792-797.

LOBO, T.F., TORLONI, M.R., GUEUVOGHLANIAN-SILVA, B.Y., MATTAR, R. and DAHER, S., 2013. Resistin concentration and gestational diabetes: a systematic review of the literature. *Journal of reproductive immunology,* **97**(1), pp. 120-127.

LOWE, W.L. Jr, LOWE, L.P., KUANG, A., CATALANO, P.M., NODZENSKI, M., TALBOT, O., TAM, W.H., SACKS, D.A., MCCANCE, D., LINDER, B., LEBENTHAL, Y., LAWRENCE, J.M., LASHLEY, M., JOSEFSON, J.L., HAMILTON, J., DEEROCHANAWONG, C., CLAYTON, P., BRICKMAN, W.J., DYER, A.R., SCHOLTENS, D.M., METZGER, B.E. and HAPO FOLLOW-UP STUDY COOPERATIVE RESEARCH GROUP, 2019. Maternal glucose levels during pregnancy and childhood adiposity in the Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study. *Diabetologia,* **62**(4), pp. 598-610.

LOWE, W.L. Jr, SCHOLTENS, D.M., LOWE, L.P., KUANG, A., NODZENSKI, M., TALBOT, O., CATALANO, P.M., LINDER, B., BRICKMAN, W.J., CLAYTON, P., DEEROCHANAWONG, C., HAMILTON, J., JOSEFSON, J.L., LASHLEY, M., LAWRENCE, J.M., LEBENTHAL, Y., MA, R., MARESH, M., MCCANCE, D., TAM, W.H., SACKS, D.A., DYER, A.R., METZGER, B.E. and HAPO FOLLOW-UP STUDY COOPERATIVE RESEARCH GROUP, 2018. Association of Gestational Diabetes With Maternal Disorders of Glucose Metabolism and Childhood Adiposity. *Jama,* **320**(10), pp. 1005-1016.

LOZOFF, B., JIMENEZ, E., HAGEN, J., MOLLEN, E. and WOLF, A.W., 2000. Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. *Pediatrics,* **105**(4), pp. E51.

LU, J., ZHANG, S., LI, W., LENG, J., WANG, L., LIU, H., LI, W., ZHANG, C., QI, L., TUOMILEHTO, J., CHEN, J., YANG, X., YU, Z. and HU, G., 2019. Maternal gestational diabetes is associated with offspring's hypertension. *American journal of hypertension*, **32**(4), pp. 335-342.

LUDWIG, D.S. and CURRIE, J., 2010. The association between pregnancy weight gain and birthweight: a within-family comparison. *Lancet (London, England),* **376**(9745), pp. 984-990.

LUNDE, A., MELVE, K.K., GJESSING, H.K., SKJAERVEN, R. and IRGENS, L.M., 2007. Genetic and environmental influences on birth weight, birth length, head circumference, and gestational age by use of population-based parent-offspring data. *American Journal of Epidemiology,* **165**(7), pp. 734-741.

LUO, Z.C., NUYT, A.M., DELVIN, E., AUDIBERT, F., GIRARD, I., SHATENSTEIN, B., CLOUTIER, A., COUSINEAU, J., DJEMLI, A., DEAL, C., LEVY, E., WU, Y., JULIEN, P. and FRASER, W.D., 2012. Maternal and fetal IGF-I and IGF-II levels, fetal growth, and gestational diabetes. *The Journal of clinical endocrinology and metabolism,* **97**(5), pp. 1720-1728.

MA, R.C., TUTINO, G.E., LILLYCROP, K.A., HANSON, M.A. and TAM, W.H., 2015. Maternal diabetes, gestational diabetes and the role of epigenetics in their long term effects on offspring. *Progress in biophysics and molecular biology,* **118**(1-2), pp. 55-68.

MADARASZ, E., TAMAS, G., TABAK, G.A., SZALAY, J. and KERENYI, Z., 2008. Metabolic syndrome after pregnancy complicated with gestational diabetes: four-year follow-up. *Orvosi hetilap,* **149**(18), pp. 831-838.

MAGED, A.M., MOETY, G.A., MOSTAFA, W.A. and HAMED, D.A., 2014. Comparative study between different biomarkers for early prediction of gestational diabetes mellitus. *The journal of maternal-fetal & neonatal medicine: the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians,* **27**(11), pp. 1108-1112.

MAGNUS, P., 1984. Causes of variation in birth weight: a study of offspring of twins. *Clinical genetics*, **25**(1):15-24.

MÄNNISTÖ, S., LAATIKAINEN, T., HARALD, K., BORODULIN, K., JOUSILAHTI, P., KANERVA, N., PELTONEN, M. and VARTIAINEN, E., 2015. Työikäisten ylipainon ja lihavuuden kasvu näyttää hidastuneen: kansallisen FINRISKI-terveystutkimuksen tuloksia. *Laakarilehti,* **70**(14-15), pp. 969.

MANRIQUE, C., LASTRA, G. and SOWERS, J.R., 2014. New insights into insulin action and resistance in the vasculature. *Annals of the New York Academy of Sciences*, **1311**, pp. 138-150.

MARQUETTE, G.P., KLEIN, V.R. and NIEBYL, J.R., 1985. Efficacy of screening for gestational diabetes. *American Journal of Perinatology,* **2**(1), pp. 7-9.

MATHIESEN, E.R., KINSLEY, B., AMIEL, S.A., HELLER, S., MCCANCE, D., DURAN, S., BELLAIRE, S., RABEN, A. and INSULIN ASPART PREGNANCY STUDY GROUP, 2007. Maternal glycemic control and hypoglycemia in type 1 diabetic pregnancy: a randomized trial of insulin aspart versus human insulin in 322 pregnant women. *Diabetes care,* **30**(4), pp. 771-776.

MEIGS, J.B., CUPPLES, L.A. and WILSON, P.W., 2000. Parental transmission of type 2 diabetes: the Framingham Offspring Study. *Diabetes,* **49**(12), pp. 2201-2207.

MELCZER, Z., BANHIDY, F., CSOMOR, S., TOTH, P., KOVACS, M., WINKLER, G. and CSEH, K., 2003. Influence of leptin and the TNF system on insulin resistance in pregnancy and their effect on anthropometric parameters of newborns. *Acta Obstetricia et Gynecologica Scandinavica,* **82**(5), pp. 432-438.

METZGER, B.E., BUCHANAN, T.A., COUSTAN, D.R., DE LEIVA, A., DUNGER, D.B., HADDEN, D.R., HOD, M., KITZMILLER, J.L., KJOS, S.L., OATS, J.N., PETTITT, D.J., SACKS, D.A. and ZOUPAS, C., 2007. Summary and recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes care,* **30 Suppl 2**, pp. S251-60.

MIAKOTINA, O.L., DEKOWSKI, S.A. and SNYDER, J.M., 1998. Insulin inhibits surfactant protein A and B gene expression in the H441 cell line. *Biochimica et biophysica acta,* **1442**(1), pp. 60-70.

MILLER, H.C., 1946. The effect of diabetic and prediabetic pregnancies on the fetus and newborn infant. *The Journal of pediatrics,* **29**(4), pp. 455-461.

MOKDAD, A.H., FORD, E.S., BOWMAN, B.A., DIETZ, W.H., VINICOR, F., BALES, V.S. and MARKS, J.S., 2003. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *Jama,* **289**(1), pp. 76-79.

MOLEDA, P., HOMA, K., SAFRANOW, K., CELEWICZ, Z., FRONCZYK, A. and MAJKOWSKA, L., 2013. Women with normal glucose tolerance and a history of gestational diabetes show significant impairment of beta-cell function at normal insulin sensitivity. *Diabetes & metabolism,* **39**(2), pp. 155-162.

MORREALE DE ESCOBAR, G., OBREGON, M.J. and ESCOBAR DEL REY, F., 2004. Role of thyroid hormone during early brain development. *European journal of endocrinology,* **151 Suppl 3**, pp. U25-37.

MOSES, R., DAVIS, W., RODGERS, D., MEYER, B. and CALVERT, D., 1997. The metabolic profile of glucose tolerant women who have had large for gestational age babies. *The Australian & New Zealand Journal of Obstetrics & Gynaecology,* **37**(2), pp. 177-180.

NATIONAL COLLABORATING CENTRE FOR WOMEN'S AND CHILDREN'S HEALTH (UK), 2015. Diabetes in Pregnancy: Management of Diabetes and Its Complications from Preconception to the Postnatal Period. London: National Institute for Health and Care Excellence (UK).

NEERHOF, M.G., 1995. Causes of intrauterine growth restriction. *Clinics in perinatology,* **22**(2), pp. 375-385.

NGUYEN, N.T., NGUYEN, X.M., LANE, J. and WANG, P., 2011. Relationship between obesity and diabetes in a US adult population: findings from the National Health and Nutrition Examination Survey, 1999-2006. *Obesity Surgery,* **21**(3), pp. 351-355.

NIELSEN, K.K., KAPUR, A., DAMM, P., DE COURTEN, M. and BYGBJERG, I.C., 2014. From screening to postpartum follow-up - the determinants and barriers for gestational diabetes mellitus (GDM) services, a systematic review. *BMC pregnancy and childbirth,* **14**, pp. 41.

NOCTOR, E., CROWE, C., CARMODY, L.A., SAUNDERS, J.A., KIRWAN, B., O'DEA, A., GILLESPIE, P., GLYNN, L.G., MCGUIRE, B.E., O'NEILL, C., O'SHEA, P.M., DUNNE, F.P. and ATLANTIC-DIP INVESTIGATORS, 2016. Abnormal glucose tolerance post-gestational diabetes mellitus as defined by the International Association of Diabetes and Pregnancy Study Groups criteria. *European journal of endocrinology,* **175**(4), pp. 287-297.

O'SULLIVAN, J.B. and MAHAN, C.M., 1964. Criteria for the Oral Glucose Tolerance Test in Pregnancy. *Diabetes,* **13**, pp. 278-285.

OUNSTED, M., MOAR, V.A. and SCOTT, A., 1985. Risk factors associated with small-for-dates and large-for-dates infants. *British journal of obstetrics and gynaecology,* **92**(3), pp. 226-232.

OVESEN, P.G., JENSEN, D.M., DAMM, P., RASMUSSEN, S. and KESMODEL, U.S., 2015. Maternal and neonatal outcomes in pregnancies complicated by gestational

diabetes. a nation-wide study. *The journal of maternal-fetal & neonatal medicine: the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians,* **28**(14), pp. 1720-1724.

PARRA-SAAVEDRA, M., CROVETTO, F., TRIUNFO, S., SAVCHEV, S., PEGUERO, A., NADAL, A., PARRA, G., GRATACOS, E. and FIGUERAS, F., 2013. Placental findings in late-onset SGA births without Doppler signs of placental insufficiency. *Placenta,* **34**(12), pp. 1136-1141.

PEDERSEN, J., 1952. *Diabetes and Pregnancy: Blood Sugar of Newborn Infants.*, Copenhagen, Denmark, Danish Science Press.

PEDERSEN, A.L.W., TERKILDSEN MAINDAL, H. and JUUL, L., 2017. How to prevent type 2 diabetes in women with previous gestational diabetes? A systematic review of behavioural interventions. *Primary care diabetes,* **11**(5), pp. 403-413.

PERSSON, M., FADL, H., HANSON, U. and PASUPATHY, D., 2013. Disproportionate body composition and neonatal outcome in offspring of mothers with and without gestational diabetes mellitus. *Diabetes care,* **36**(11), pp. 3543-3548.

PETERS, R.K., KJOS, S.L., XIANG, A. and BUCHANAN, T.A., 1996. Long-term diabetogenic effect of single pregnancy in women with previous gestational diabetes mellitus. *Lancet (London, England),* **347**(8996), pp. 227-230.

PETRY, C.D., EATON, M.A., WOBKEN, J.D., MILLS, M.M., JOHNSON, D.E. and GEORGIEFF, M.K., 1992. Iron deficiency of liver, heart, and brain in newborn infants of diabetic mothers. *The Journal of pediatrics,* **121**(1), pp. 109-114.

PETTITT, D.J., OSPINA, P., KOLACZYNSKI, J.W. and JOVANOVIC, L., 2003. Comparison of an insulin analog, insulin aspart, and regular human insulin with no insulin in gestational diabetes mellitus. *Diabetes care,* **26**(1), pp. 183-186.

PHILIPS, A.F., DUBIN, J.W., MATTY, P.J. and RAYE, J.R., 1982. Arterial hypoxemia and hyperinsulinemia in the chronically hyperglycemic fetal lamb. *Pediatric research,* **16**(8), pp. 653-658.

PICON, M.J., MURRI, M., MUNOZ, A., FERNANDEZ-GARCIA, J.C., GOMEZ-HUELGAS, R. and TINAHONES, F.J., 2012. Hemoglobin A1c versus oral glucose tolerance test in postpartum diabetes screening. *Diabetes care,* **35**(8), pp. 1648-1653.

PIHKALA, J., HAKALA, T., VOUTILAINEN, P. and RAIVIO, K., 1989. Characteristic of recent fetal growth curves in Finland. *Duodecim; laaketieteellinen aikakauskirja,* **105**(18), pp. 1540-1546.

PIRKOLA, J., POUTA, A., BLOIGU, A., HARTIKAINEN, A.L., LAITINEN, J., JARVELIN, M.R. and VAARASMAKI, 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), pp. 1115-1121.

PIRKOLA, J., POUTA, A., BLOIGU, A., MIETTOLA, S., HARTIKAINEN, A.L., JARVELIN, M.R. and VAARASMAKI, M., 2010. Prepregnancy overweight and gestational diabetes as determinants of subsequent diabetes and hypertension after 20-year follow-up. *The Journal of clinical endocrinology and metabolism,* **95**(2), pp. 772-778.

POSTON, L., CALEYACHETTY, R., CNATTINGIUS, S., CORVALÁN, C., UAUY, R., HERRING, S., GILLMAN, MW., 2016. Preconceptional and maternal obesity: epidemiology and health consequences. *The lancet. Diabetes & endocrinology,* **4**(12), pp. 1025-1036.

POYHONEN-ALHO, M.K., TERAMO, K.A., KAAJA, R.J. and HIILESMAA, V.K., 2005. 50 gram Oral Glucose Challenge Test Combined with Risk Factor-Based Screening for Gestational Diabetes. *European journal of obstetrics, gynecology, and reproductive biology,* **121**(1), pp. 34-37.

PUHKALA, J., KINNUNEN, T.I., VASANKARI, T., KUKKONEN-HARJULA, K., RAITANEN, J. and LUOTO, R., 2013. Prevalence of metabolic syndrome one year after delivery in Finnish women at increased risk for gestational diabetes mellitus during pregnancy. *Journal of pregnancy,* **2013**, pp. 139049.

QIAO, Q., LAATIKAINEN, T., ZETHELIUS, B., STEGMAYR, B., ELIASSON, M., JOUSILAHTI, P. and TUOMILEHTO, J., 2009. Comparison of definitions of metabolic syndrome in relation to the risk of developing stroke and coronary heart disease in Finnish and Swedish cohorts. *Stroke,* **40**(2), pp. 337-343.

RADAELLI, T., VARASTEHPOUR, A., CATALANO, P. and HAUGUEL-DE MOUZON, S., 2003. Gestational diabetes induces placental genes for chronic stress and inflammatory pathways. *Diabetes,* **52**(12), pp. 2951-2958.

RAIKO, J.R., VIIKARI, J.S., ILMANEN, A., HUTRI-KAHONEN, N., TAITTONEN, L., JOKINEN, E., PIETIKAINEN, M., JULA, A., LOO, B.M., MARNIEMI, J., LEHTIMAKI, T., KAHONEN, M., RONNEMAA, T., RAITAKARI, O.T. and

JUONALA, M., 2010. Follow-ups of the Cardiovascular Risk in Young Finns Study in 2001 and 2007: levels and 6-year changes in risk factors. *Journal of internal medicine,* **267**(4), pp. 370-384.

RANHEIM, T., HAUGEN, F., STAFF, A.C., BRAEKKE, K., HARSEM, N.K. and DREVON, C.A., 2004. Adiponectin is reduced in gestational diabetes mellitus in normal weight women. *Acta Obstetricia et Gynecologica Scandinavica,* **83**(4), pp. 341-347.

RATNER, R.E., CHRISTOPHI, C.A., METZGER, B.E., DABELEA, D., BENNETT, P.H., PI-SUNYER, X., FOWLER, S., KAHN, S.E. and DIABETES PREVENTION PROGRAM RESEARCH GROUP, 2008. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. *The Journal of clinical endocrinology and metabolism,* **93**(12), pp. 4774-4779.

RAYANAGOUDAR, G., HASHI, A.A., ZAMORA, J., KHAN, K.S., HITMAN, G.A. and 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), pp. 1403-1411.

REAVEN, G.M., 1988. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes,* **37**(12), pp. 1595-1607.

REINBLATT, S.L., MORIN, L. and MELTZER, S.J., 2006. The importance of a postpartum 75 g oral glucose tolerance test in women with gestational diabetes. *Journal of obstetrics and gynaecology Canada: JOGC = Journal d'obstetrique et gynecologie du Canada: JOGC,* **28**(8), pp. 690-694.

REIS, J.P., LORIA, C.M., SORLIE, P.D., PARK, Y., HOLLENBECK, A. and SCHATZKIN, A., 2011. Lifestyle factors and risk for new-onset diabetes: a population-based cohort study. *Annals of Internal Medicine,* **155**(5), pp. 292-299.

RETNAKARAN, R., QI, Y., CONNELLY, P.W., SERMER, M., ZINMAN, B. and HANLEY, A.J., 2010. Glucose intolerance in pregnancy and postpartum risk of metabolic syndrome in young women. *The Journal of clinical endocrinology and metabolism,* **95**(2), pp. 670-677.

RETNAKARAN, R., QI, Y., SERMER, M., CONNELLY, P.W., HANLEY, A.J. and ZINMAN, B., 2008. Glucose intolerance in pregnancy and future risk of pre-diabetes or diabetes. *Diabetes care,* **31**(10), pp. 2026-2031.

RETNAKARAN, R. and SHAH, B.R., 2017. Role of Type 2 Diabetes in Determining Retinal, Renal, and Cardiovascular Outcomes in Women With Previous Gestational Diabetes Mellitus. *Diabetes care,* **40**(1), pp. 101-108.

RETNAKARAN, R. and SHAH, B.R., 2009. Mild glucose intolerance in pregnancy and risk of cardiovascular disease: a population-based cohort study. *CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne,* **181**(6-7), pp. 371-376.

RIDKER, P.M., 2003. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. *Circulation,* **107**(3), pp. 363-369.

RIDKER, P.M., HENNEKENS, C.H., BURING, J.E. and RIFAI, N., 2000. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *The New England journal of medicine,* **342**(12), pp. 836-843.

ROBERT, M.F., NEFF, R.K., HUBBELL, J.P., TAEUSCH, H.W. and AVERY, M.E., 1976. Association between maternal diabetes and the respiratory-distress syndrome in the newborn. *The New England journal of medicine,* **294**(7), pp. 357-360.

ROBITAILLE, J. and GRANT, A.M., 2008. The genetics of gestational diabetes mellitus: evidence for relationship with type 2 diabetes mellitus. *Genetics in medicine: official journal of the American College of Medical Genetics,* **10**(4), pp. 240-250.

RONO, K., MASALIN, S., KAUTIAINEN, H., GISSLER, M., RAINA, M., ERIKSSON, J.G. and LAINE, M.K., 2019. Impact of maternal income on the risk of gestational diabetes mellitus in primiparous women. *Diabetic medicine: a journal of the British Diabetic Association*, 36(2), pp. 214-220.

ROSENBERG, T.J., GARBERS, S., CHAVKIN, W. and CHIASSON, M.A., 2003. Prepregnancy weight and adverse perinatal outcomes in an ethnically diverse population. *Obstetrics and gynecology,* **102**(5 Pt 1), pp. 1022-1027.

SAARI, A., SANKILAMPI, U., HANNILA, M.L., KIVINIEMI, V., KESSELI, K. and DUNKEL, L., 2011. New Finnish growth references for children and adolescents aged 0 to 20 years: Length/height-for-age, weight-for-length/height, and body mass index-for-age. *Annals of Medicine,* **43**(3), pp. 235-248.

SALAFIA, C.M., MINIOR, V.K., PEZZULLO, J.C., POPEK, E.J., ROSENKRANTZ, T.S. and VINTZILEOS, A.M., 1995. Intrauterine growth restriction in infants of less

than thirty-two weeks' gestation: associated placental pathologic features. *American Journal of Obstetrics and Gynecology,* **173**(4), pp. 1049-1057.

SANKILAMPI, U., HANNILA, M.L., SAARI, A., GISSLER, M. and DUNKEL, L., 2013. New population-based references for birth weight, length, and head circumference in singletons and twins from 23 to 43 gestation weeks. *Annals of Medicine,* **45**(5-6), pp. 446-454.

SARAMIES, J., KEINÄNEN-KIUKAANNIEMI, S., KOIRANEN, M., JOKELAINEN, J., MEYER-ROCHOW, VB., TIMONEN, M., 2006. Late pregnancy blood pressure in nulliparas and subsequent abnormal glucose tolerance. *Diabetes research and clinical practice*, **71**(2), pp. 220-4.

SCHELLONG, K., SCHULZ, S., HARDER, T. and PLAGEMANN, A., 2012. Birth weight and long-term overweight risk: systematic review and a meta-analysis including 643,902 persons from 66 studies and 26 countries globally. *PloS one,* **7**(10), pp. e47776.

SCHWARTZ, N., NACHUM, Z. and GREEN, M.S., 2016. Risk factors of gestational diabetes mellitus recurrence: a meta-analysis. *Endocrine,* **53**(3), pp. 662-671.

SCHWARTZ, N., QUANT, H.S., SAMMEL, M.D. and PARRY, S., 2014. Macrosomia has its roots in early placental development. *Placenta,* **35**(9), pp. 684-690.

SEIDMAN, D.S., EVER-HADANI, P., STEVENSON, D.K., SLATER, P.E., HARLAP, S. and GALE, R., 1988. Birth order and birth weight reexamined. *Obstetrics and gynecology,* **72**(2), pp. 158-162.

SHAH, B.R., LIPSCOMBE, L.L., FEIG, D.S. and LOWE, J.M., 2011. Missed opportunities for type 2 diabetes testing following gestational diabetes: a population-based cohort study. *BJOG: an international journal of obstetrics and gynaecology,* **118**(12), pp. 1484-1490.

SHAH, B.R., RETNAKARAN, R. and BOOTH, G.L., 2008. Increased risk of cardiovascular disease in young women following gestational diabetes mellitus. *Diabetes care,* **31**(8), pp. 1668-1669.

SHANKLIN, D.R., 1970. The influence of placental lesions on the newborn infant. *Pediatric clinics of North America,* **17**(1), pp. 25-42.

SHIELDS, B.M., KNIGHT, B.A., HILL, A., HATTERSLEY, A.T. and VAIDYA, B., 2011. Fetal thyroid hormone level at birth is associated with fetal growth. *The Journal of clinical endocrinology and metabolism,* **96**(6), pp. E934-8.

SHU, X.O., HATCH, M.C., MILLS, J., CLEMENS, J. and SUSSER, M., 1995. Maternal smoking, alcohol drinking, caffeine consumption, and fetal growth: results from a prospective study. *Epidemiology (Cambridge, Mass.),* **6**(2), pp. 115-120.

SMITH, C.A., 1947. Effects of maternal under nutrition upon the newborn infant in Holland (1944-1945). *The Journal of pediatrics,* **30**(3), pp. 229-243.

SOLOMON, C.G., WILLETT, W.C., CAREY, V.J., RICH-EDWARDS, J., HUNTER, D.J., COLDITZ, G.A., STAMPFER, M.J., SPEIZER, F.E., SPIEGELMAN, D. and MANSON, J.E., 1997. A prospective study of pregravid determinants of gestational diabetes mellitus. *Jama,* **278**(13), pp. 1078-1083.

SPJUTH, J., LARSSON, G., NILSSON-EHLE, P., SCHERSTEN, B. and ASTEDT, B., 1993. Can the birth of a large infant predict risk for atherosclerotic vascular disease in the mother? *Diabetologia,* **36**(2), pp. 117-120.

STANCÁKOVÁ A, JAVORSKÝ M, KUULASMAA T, HAFFNER SM, KUUSISTO J, LAAKSO M, 2009. Changes in insulin sensitivity and insulin release in relation to glycemia and glucose tolerance in 6,414 Finnish men. *Diabetes*, **58**(5), pp. 1212-21.

STANCAKOVA, A. and LAAKSO, M., 2016. Genetics of Type 2 Diabetes. *Endocrine development*, 31, pp. 203-220.

STUEBE, A.M., RICH-EDWARDS, J.W., WILLETT, W.C., MANSON, J.E. and MICHELS, K.B., 2005. Duration of lactation and incidence of type 2 diabetes. *Jama,* **294**(20), pp. 2601-2610.

SUSSMAN, J.B., KENT, D.M., NELSON, J.P. and HAYWARD, R.A., 2015. Improving diabetes prevention with benefit based tailored treatment: risk based reanalysis of Diabetes Prevention Program. *BMJ (Clinical research ed.),* **350**, pp. h454.

TAM, W.H., MA, R.C., YANG, X., KO, G.T., LAO, T.T., SAHOTA, D.S., CHAN, M.H., LAM, C.W., COCKRAM, C.S. and CHAN, J.C., 2013. Prediction of women's long-term cardiometabolic risks using glycemic indices during pregnancy. *The journal of obstetrics and gynaecology research,* **39**(2), pp. 484-491.

TAM, W.H., MA, R.C.W., OZAKI, R., LI, A.M., CHAN, M.H.M., YUEN, L.Y., LAO, T.T.H., YANG, X., HO, C.S., TUTINO, G.E. and CHAN, J.C.N., 2017. In Utero Exposure to Maternal Hyperglycemia Increases Childhood Cardiometabolic Risk in Offspring. *Diabetes care,* **40**(5), pp. 679-686.

TANASE-NAKAO, K., ARATA, N., KAWASAKI, M., YASUHI, I., SONE, H., MORI, R. and OTA, E., 2017. Potential protective effect of lactation against

incidence of type 2 diabetes mellitus in women with previous gestational diabetes mellitus: A systematic review and meta-analysis. *Diabetes/metabolism research and reviews,* **33**(4).

TEHRANI, F.R., HASHEMI, S., HASHEMINIA, M. and AZIZI, F., 2012. Follow-up of women with gestational diabetes in the Tehran Lipid and Glucose Study (TLGS): a population-based cohort study. *The journal of obstetrics and gynaecology research,* **38**(4), pp. 698-704.

TERTTI, K., LAINE, K., EKBLAD, U., RINNE, V. and RONNEMAA, T., 2014. The degree of fetal metformin exposure does not influence fetal outcome in gestational diabetes mellitus. *Acta Diabetologica,* **51**(5), pp. 731-738.

The national Institute for Health and Welfare, Finland. Finnish Medical Birth Register. 2012. Available: http://www.thl.fi/en/statistics/parturients.

The national Institute for Health and Welfare, Finland. Finnish Medical Birth Register. 2016. Available: http://www.thl.fi/en/statistics/parturients.

THORPE-BEESTON, J.G., NICOLAIDES, K.H., SNIJDERS, R.J., FELTON, C.V. and MCGREGOR, A.M., 1991. Thyroid function in small for gestational age fetuses. *Obstetrics and gynecology,* **77**(5), pp. 701-706.

TOVAR, A., CHASAN-TABER, L., EGGLESTON, E. and OKEN, E., 2011. Postpartum screening for diabetes among women with a history of gestational diabetes mellitus. *Preventing chronic disease,* **8**(6), pp. A124.

TUOMI, T., SANTORO, N., CAPRIO, S., CAI, M., WENG, J. and GROOP, L., 2014. The many faces of diabetes: a disease with increasing heterogeneity. *Lancet (London, England),* **383**(9922), pp. 1084-1094.

TUOMILEHTO, J., LINDSTROM, J., ERIKSSON, J.G., VALLE, T.T., HAMALAINEN, H., ILANNE-PARIKKA, P., KEINANEN-KIUKAANNIEMI, S., LAAKSO, M., LOUHERANTA, A., RASTAS, M., SALMINEN, V., UUSITUPA, M. and FINNISH DIABETES PREVENTION STUDY GROUP, 2001. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *The New England journal of medicine,* **344**(18), pp. 1343-1350.

UNNIKRISHNAN, R., PRADEEPA, R., JOSHI, S.R. and MOHAN, V., 2017. Type 2 Diabetes: Demystifying the Global Epidemic. *Diabetes,* **66**(6), pp. 1432-1442.

VAGUE, J., 1947. Not Available. *La Presse medicale,* **55**(30), pp. 339.

VAN DE VOORDE, J., PAUWELS, B., BOYDENS, C. and DECALUWE, K., 2013. Adipocytokines in relation to cardiovascular disease. *Metabolism: clinical and experimental,* **62**(11), pp. 1513-1521.

VAN RYSWYK, E.M., MIDDLETON, P.F., HAGUE, W.M. and CROWTHER, C.A., 2016. Women's views on postpartum testing for type 2 diabetes after gestational diabetes: Six month follow-up to the DIAMIND randomised controlled trial. *Primary care diabetes,* **10**(2), pp. 91-102.

VAN VLIET-OSTAPTCHOUK, J.V., NUOTIO, M.L., SLAGTER, S.N., DOIRON, D., FISCHER, K., FOCO, L., GAYE, A., GOGELE, M., HEIER, M., HIEKKALINNA, T., JOENSUU, A., NEWBY, C., PANG, C., PARTINEN, E., REISCHL, E., SCHWIENBACHER, C., TAMMESOO, M.L., SWERTZ, M.A., BURTON, P., FERRETTI, V., FORTIER, I., GIEPMANS, L., HARRIS, J.R., HILLEGE, H.L., HOLMEN, J., JULA, A., KOOTSTRA-ROS, J.E., KVALOY, K., HOLMEN, T.L., MANNISTO, S., METSPALU, A., MIDTHJELL, K., MURTAGH, M.J., PETERS, A., PRAMSTALLER, P.P., SAARISTO, T., SALOMAA, V., STOLK, R.P., UUSITUPA, M., VAN DER HARST, P., VAN DER KLAUW, M.M., WALDENBERGER, M., PEROLA, M. and WOLFFENBUTTEL, B.H., 2014. The prevalence of metabolic syndrome and metabolically healthy obesity in Europe: a collaborative analysis of ten large cohort studies. *BMC endocrine disorders,* **14**, pp. 9.

VARNER, M.W., RICE, M.M., LANDON, M.B., CASEY, B.M., REDDY, U.M., WAPNER, R.J., ROUSE, D.J., TITA, A.T., THORP, J.M., CHIEN, E.K., SAADE, G.R., PEACEMAN, A.M., BLACKWELL, S.C., VANDORSTEN, J.P. and EUNICE KENNEDY SHRIVER NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT (NICHD) MATERNAL-FETAL MEDICINE UNITS (MFMU) NETWORK, 2017. Pregnancies After the Diagnosis of Mild Gestational Diabetes Mellitus and Risk of Cardiometabolic Disorders. *Obstetrics and gynecology,* **129**(2), pp. 273-280.

VERMA, A., BONEY, C.M., TUCKER, R. and VOHR, B.R., 2002. Insulin resistance syndrome in women with prior history of gestational diabetes mellitus. *The Journal of clinical endocrinology and metabolism,* **87**(7), pp. 3227-3235.

VIANA, L.V., GROSS, J.L. and AZEVEDO, M.J., 2014. Dietary intervention in patients with gestational diabetes mellitus: a systematic review and meta-analysis of randomized clinical trials on maternal and newborn outcomes. *Diabetes care,* **37**(12), pp. 3345-3355.

VILJANEN, H., 2013. *Raskausdiabeteksen diagnostiikka ja kriteerien muutoksen merkitys raskausdiabeteksen esiintyvyydelle Pohjois-Savon sairaanhoitopiirin alueella. Pro Gradu.* University of Eastern Finland.

VOIGT, M., ROCHOW, N., JAHRIG, K., STRAUBE, S., HUFNAGEL, S. and JORCH, G., 2010. Dependence of neonatal small and large for gestational age rates on maternal height and weight--an analysis of the German Perinatal Survey. *Journal of perinatal medicine,* **38**(4), pp. 425-430.

VORA, N. and BIANCHI, D.W., 2009. Genetic considerations in the prenatal diagnosis of overgrowth syndromes. *Prenatal diagnosis,* **29**(10), pp. 923-929.

WHITE, P., 1949. Pregnancy complicating diabetes. *The American Journal of Medicine,* **7**(5), pp. 609-616.

WIDNESS, J.A., TERAMO, K.A., CLEMONS, G.K., VOUTILAINEN, P., STENMAN, U.H., MCKINLAY, S.M. and SCHWARTZ, R., 1990. Direct relationship of antepartum glucose control and fetal erythropoietin in human type 1 (insulin-dependent) diabetic pregnancy. *Diabetologia,* **33**(6), pp. 378-383.

WOLSTENHOLME, J., ROONEY, D.E. and DAVISON, E.V., 1994. Confined placental mosaicism, IUGR, and adverse pregnancy outcome: a controlled retrospective U.K. collaborative survey. *Prenatal diagnosis,* **14**(5), pp. 345-361.

WORLD HEALTH ORGANIZATION, 2017-last update, Diabetes. Available: http://www.who.int/mediacentre/factsheets/fs312/en/ [10/3, 2017].

WORLD HEALTH ORGANIZATION, 2016-last update, Obesity and Overweight fact sheet no 311. Available: http://www.who.int/mediacentre/factsheets/fs311/en/

WOULDES, T.A., BATTIN, M., COAT, S., RUSH, E.C., HAGUE, W.M. and ROWAN, J.A., 2016. Neurodevelopmental outcome at 2 years in offspring of women randomised to metformin or insulin treatment for gestational diabetes. *Archives of disease in childhood. Fetal and neonatal edition*, **101**(6), pp. F488-F493.

WRITING GROUP MEMBERS, MOZAFFARIAN, D., BENJAMIN, E.J., GO, A.S., ARNETT, D.K., BLAHA, M.J., CUSHMAN, M., DAS, S.R., DE FERRANTI, S., DESPRES, J.P., FULLERTON, H.J., HOWARD, V.J., HUFFMAN, M.D., ISASI, C.R., JIMENEZ, M.C., JUDD, S.E., KISSELA, B.M., LICHTMAN, J.H., LISABETH, L.D., LIU, S., MACKEY, R.H., MAGID, D.J., MCGUIRE, D.K., MOHLER, E.R.,3rd, MOY, C.S., MUNTNER, P., MUSSOLINO, M.E., NASIR, K., NEUMAR, R.W., NICHOL, G., PALANIAPPAN, L., PANDEY, D.K., REEVES, M.J., RODRIGUEZ, C.J., ROSAMOND, W., SORLIE, P.D., STEIN, J., TOWFIGHI, A., TURAN, T.N., VIRANI,

S.S., WOO, D., YEH, R.W., TURNER, M.B., AMERICAN HEART ASSOCIATION STATISTICS COMMITTEE and STROKE STATISTICS SUBCOMMITTEE, 2016. Executive Summary: Heart Disease and Stroke Statistics--2016 Update: A Report From the American Heart Association. *Circulation,* **133**(4), pp. 447-454.

XIANG, A.H., TAKAYANAGI, M., BLACK, M.H., TRIGO, E., LAWRENCE, J.M., WATANABE, R.M. and BUCHANAN, T.A., 2013. Longitudinal changes in insulin sensitivity and beta cell function between women with and without a history of gestational diabetes mellitus. *Diabetologia,* **56**(12), pp. 2753-2760.

XU, H., SIMONET, F. and LUO, Z.C., 2010. Optimal birth weight percentile cut-offs in defining small- or large-for-gestational-age. *Acta Paediatrica (Oslo, Norway: 1992),* **99**(4), pp. 550-555.

XU, Y., SHEN, S., SUN, L., YANG, H., JIN, B. and CAO, X., 2014. Metabolic syndrome risk after gestational diabetes: a systematic review and meta-analysis. *PloS one,* **9**(1), pp. e87863.

YILDIRIM, Y., TINAR, S., ONER, R.S., KAYA, B. and TOZ, E., 2006. Gestational diabetes mellitus in patients receiving long-term corticosteroid therapy during pregnancy. *Journal of perinatal medicine,* **34**(4), pp. 280-284.

YOGEV, Y., XENAKIS, E.M. and LANGER, O., 2004. The association between preeclampsia and the severity of gestational diabetes: the impact of glycemic control. *American Journal of Obstetrics and Gynecology,* **191**(5), pp. 1655-1660.

YU, Z., HAN, S., ZHU, J., SUN, X., JI, C. and GUO, X., 2013. Pre-pregnancy body mass index in relation to infant birth weight and offspring overweight/obesity: a systematic review and meta-analysis. *PloS one,* **8**(4), pp. e61627.

YURA, S., SAGAWA, N., ITOH, H., KAKUI, K., NUAMAH, M.A., KORITA, D., TAKEMURA, M. and FUJII, S., 2003. Resistin is expressed in the human placenta. *The Journal of clinical endocrinology and metabolism,* **88**(3), pp. 1394-1397.

HEIDI HAKKARAINEN

Gestational diabetes (GDM) is a common hyperglycemic state that occurs during pregnancy. Women with GDM are at risk for later development of type 2 diabetes (T2DM), metabolic syndrome (MetS) and cardiovascular diseases. The aim of this thesis was to define the incidence of T2DM and MetS in women according to the degree of hyperglycemia during pregnancy. The impact of a large-for-gestational-age newborn on the later risk of maternal T2DM and MetS in women with and without GDM was also explored.

UNIVERSITY OF
EASTERN FINLAND

uef.fi

**PUBLICATIONS OF
THE UNIVERSITY OF EASTERN FINLAND**
Dissertations in Health Sciences

ISBN 978-952-61-3133-7
ISSN 1798-5706