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Hilkka Ijäs

GESTATIONAL DIABETES

METFORMIN TREATMENT, MATERNAL OVERWEIGHT AND LONG-TERM OUTCOME

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
FACULTY OF MEDICINE;
MEDICAL RESEARCH CENTER OULU;
OULU UNIVERSITY HOSPITAL

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Metformin treatment, maternal overweight and long-term outcome

Academic Dissertation to be presented with the assent of the Doctoral Training Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium 4 of Oulu University Hospital, on 28 August 2015, at 12 noon

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Abstract

Gestational diabetes mellitus (GDM) is defined as disturbed glucose metabolism first recognized during pregnancy. Untreated GDM increases the risk of obstetric and neonatal complications, such as fetal overgrowth (macrosomia). The first-line treatment of GDM includes diet therapy and the self-monitoring of blood glucose concentrations and, if needed, pharmacotherapy, which is most commonly accomplished with insulin. Oral anti-diabetic agents such as metformin have recently been under investigation. GDM increases the risk of developing overt diabetes, metabolic syndrome and cardiovascular diseases.

The aim of the present study was to investigate the effect of metformin vs. insulin therapy on pregnancy and neonatal outcome as well as on later growth and development of the infant and to investigate the independent and concomitant effects of GDM and maternal overweight/obesity on pregnancy outcome and maternal long-term risks.

In a randomized study of 100 women, metformin therapy was not associated with an increased risk of pregnancy or neonatal complications when compared with insulin treatment. However, 32% of the women treated with metformin needed additional insulin in the achievement of normoglycaemia. The need of additional insulin was associated with maternal obesity, an earlier need of pharmacotherapy and fasting hyperglycaemia in OGTT. Infants exposed to metformin were taller and heavier at the age of 18 months compared with infants exposed to insulin. There was no difference in the motor, social or linguistic development between these children when assessed at the age of 18 months.

In an epidemiological study of 24,565 pregnancies, normal-weight women with GDM did not have an increased risk of macrosomia or Caesarean delivery when compared with normal-weight women without GDM. GDM was an independent risk factor of neonatal morbidity, especially hypoglycaemia. Maternal overweight and obesity were independent risk factors of macrosomia and obesity was also an independent risk factor of Caesarean delivery and neonatal morbidity.

In a follow-up study (n = 116), women with a history of insulin-treated GDM had an increased risk of metabolic syndrome when compared with women without GDM 19 years after index pregnancy. However, maternal pre-pregnancy overweight as such was a stronger risk factor as regards the development of metabolic syndrome than previous GDM.

Keywords: gestational diabetes, long-term outcome, maternal overweight, metformin

Ijäs, Hilkka, Raskausdiabetes: metformiinihoito, äidin ylipainon merkitys ja pitkäaikaisennuste.
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Tiivistelmä

Raskausdiabetes on ensimmäisen kerran raskauden aikana ilmaantuva glukoosiaineenvaihdunnan häiriö. Hoitamattomana raskausdiabetes lisää raskaana olevan ja vastasyntyneen komplikaatioriskiä, erityisesti sikiön liiallista kasvua (makrosomiaa). Raskausdiabetestä hoidetaan ruokavaliolla, veren glukoosipitoisuuksien omaseurannalla sekä tarvittaessa lääkehoidolla, joka on useimmiten insuliinihoitoa. Muita diabeteslääkkeitä, kuten metformiinia, on tutkittu viime vuosina paljon. Raskausdiabetes lisää myöhemmällä iällä riskiä sairastua diabetekseen, metaboliseen oireyhtymään sekä sydän- ja verisuonisairauksiin.

Tämän tutkimuksen tarkoituksena oli selvittää metformiinihoidon tehoa ja turvallisuutta verrattuna insuliiniin raskausdiabeteksen hoidossa. Lisäksi selvitettiin raskausdiabeteksen ja ylipainon itsenäistä vaikutusta raskauskomplikaatioiden esiintyvyyteen sekä naisen myöhempään sairastuvuuteen.

Satunnaistetussa tutkimuksessa (n = 100) metformiini ei lisännyt vastasyntyneen makrosomian eikä vastasyntyneen tai raskauskomplikaatioiden riskiä verrattuna insuliiniin. Metformiinilla hoidetuista naisista 32% tarvitsi lisäksi insuliinia normaalin glukoositasapainon saavuttamiseksi. Lisäinsuliinin tarvetta ennustivat äidin lihavuus, varhainen lääkehoidon tarve sekä kohollaan olevat glukoosin paastoarvot sokerirasituksessa. Metformiinille altistuneet lapset olivat sekä pidempiä että painavampia 18 kuukauden iässä kuin insuliinille altistuneet lapset, mutta heidän motorisessa, sosiaalisessa tai kielellisessä kehityksessään ei ollut eroja.

Epidemiologisessa tutkimuksessa (n = 24,565) normaalipainoisen naisen raskausdiabetes ei lisännyt keisarileikkauksen tai sikiön makrosomian riskiä verrattuna normaalipainoisiin naisiin, joiden sokeriaineenvaihdunta oli normaali. Raskausdiabetes lisäsi itsenäisesti vastasyntyneen sairastavuuden ja hypoglykemian riskiä. Äidin ylipaino ja lihavuus lisäsivät itsenäisesti makrosomian riskiä ja lihavuus myös keisarileikkauksen ja vastasyntyneen sairastuvuuden riskiä.

Seurantatutkimuksessa (n = 116) insuliinihoidettujen raskausdiabeetikoiden riski sairastua 19 vuotta raskauden jälkeen myöhempään metaboliseen oireyhtymään oli lisääntynyt verrattuna terveisiin verrokkeihin. Raskautta edeltävä ylipaino oli vahvempi riskitekijä metabolisen oireyhtymän kehittymiselle kuin aiempi raskausdiabetes.

Asiasanat: metformiini, pitkäikaisennuste, raskausdiabetes, äidin ylipaino

To Timo, Eetu and Olli

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Oulu, May 2015 Hilkka Ijäs

Abbreviations

ADA	American Diabetes Association
AGA	appropiate for gestational age
BMI	body mass index
CI	confidence interval
CIMT	carotid intima-media thickness
GADA	glutamic acid decarboxylase autoantibody
GCT	glucose challenge test
GDM	gestational diabetes mellitus
Hba1c	glycated haemoglobin
GI	glycaemic index
HAPO	Hyperglycaemia and Adverse Pregnancy Outcome
HDL	high-density lipoprotein
IADPSG	International Association of Diabetes and Pregnancy Study Group
ICA	islet cell autoantibody
IDF	International Diabetes Federation
IGT	impaired glucose tolerance
IU	international unit
LDL	low-density lipoprotein
LGA	large for gestational age
MJ	megajoule
MetS (MS)	metabolic syndrome
NCEP	National Cholesterol Education Program Adult Treatment Panel III
NICU	neonatal intensive care unit
OGCT	oral glucose challenge test
OGTT	oral glucose tolerance test
OR	odds ratio
RCT	randomized controlled trial
RR	relative risk
SD	standard deviation
SGA	small for gestational age
TG	triglyceride
WHO	World Health Organization

List of original publications

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

I Ijäs H, Vääräsmäki M, Morin-Papunen L, Keravuo R, Ebeling T, Saarela T & Raudaskoski T (2011) Metformin should be considered in the treatment of gestational diabetes: a prospective randomized study. BJOG 118(7): 880–5.

II Ijäs H, Vääräsmäki M, Saarela T, Keravuo R & Raudaskoski T (2014) A follow-up of a randomized study of metformin and insulin in GDM: growth and development of the children at the age of 18 months. BJOG 2014; DOI: 10.1111/1471–0528.12964.

III Ijäs H, Koivunen S, Raudaskoski T., Kajantie E., Gissler M., Vääräsmäki M. Gestational diabetes and maternal obesity: independent and concomitant significance for perinatal outcome. Manuscript.

IV Ijäs H, Morin-Papunen L, Keränen AK, Bloigu R, Ruokonen A, Puukka K, Ebeling T, Raudaskoski T & Vääräsmäki M (2013) Pre-pregnancy overweight overtakes gestational diabetes as a risk factor for subsequent MS. Eur J Endocrinol 169(5): 605–11.

Contents

1 Introduction

Gestational diabetes mellitus (GDM) is defined as any degree disturbance of glucose metabolism with onset or first recognition during pregnancy (1, 2). This diagnosis includes both women who have had underlying undiagnosed diabetes before pregnancy and women whose glucose metabolism has been normal before pregnancy (3). The incidence of GDM varies worldwide from 1 to 25% according to the ethnic population and the criteria used in the diagnosis (4). In Finland, the incidence of GDM was 15% in 2013 (5).

Screening policies regarding GDM and the diagnostic criteria vary according to the different recommendations. According to Finnish Current Care Guidelines launched in 2008, all women, except those at very low risk, are recommended to be screened for GDM. It is recommended that screening for GDM should be performed by means of a 2-hour oral glucose tolerance test (OGTT) mainly at 24–28 gestational weeks (6).

The treatment of GDM improves pregnancy outcomes by reducing the incidence of macrosomia, pre-eclampsia and hypertensive disorders (7, 8). Diet therapy and self-monitoring of blood glucose concentrations are key factors in the treatment of GDM (9, 10). Approximately 13 to 15% of Finnish women with GDM need pharmacological therapy in addition to dietary modification in order to achieve normoglycaemia (5). Traditionally, insulin therapy has been the first-line medical treatment in GDM, but recently oral agents, especially metformin, have been under investigation (11).

Women with GDM are known to carry an almost eight-fold risk of subsequent diabetes mellitus later in life (12). In addition, GDM has been found to be associated with a later risk of metabolic syndrome (MetS) and cardiovascular diseases (13–17). The offspring of women with GDM have an increased risk of later obesity, diabetes and MetS (18).

The aim of the present study was to investigate the effect of metformin vs. insulin therapy on pregnancy and labour complications, neonatal outcome as well as later growth and development of the infant and to investigate the separate and concomitant effects of GDM and maternal overweight or obesity on pregnancy outcome and maternal long-term risks.

2 Review of the literature

2.1 Gestational diabetes mellitus

GDM is defined as a disturbance of glucose metabolism with a first recognition during pregnancy (1). The global incidence of GDM is increasing along with aging of the pregnant population, sedentary lifestyles and the growing proportion of overweight fertile-aged women. In the United States, almost one fifth of pregnant women are considered to have GDM (19).

2.2 Risk factors

Several risk factors are linked to the development of GDM. Maternal overweight is strongly associated with the risk of GDM (20, 21). The incidence of the condition increases along with maternal age, as the risk of GDM has been found to be increased seven- to tenfold in mothers older than 24 years in comparison with younger mothers (22). A history of GDM or a large-for-gestational-age (LGA) infant in a prior pregnancy increases the risk of developing GDM in subsequent pregnancies (23, 24). Other well-known risk factors include increased weight gain during pregnancy, a family history of type 2 diabetes, a history of unexplained fetal demise and suspected glucose intolerance before pregnancy (20, 24, 25). If glucose tolerance is normal during a first pregnancy, the incidence of GDM has been found to be low in subsequent pregnancies (26).

Insulin sensitivity during pregnancy is influenced by a woman's ethnic background, as, for example, women of Hispanic, Native American, African, Asian or Middle Eastern origin appear to be at greater risk of GDM than Caucasian women (27). Maternal height has been found to be inversely associated with the risk of GDM (28). In a recently published study and meta-analysis this inverse association between height and the risk of GDM was found in different races and ethnicities, with the strongest association among Asians (29).

2.2.1 Pathogenesis

During pregnancy, maternal carbohydrate, fat and protein metabolism changes in order to ensure fetal growth and development as well as maternal well-being. The most important regulator of maternal metabolism is insulin (30). Decreased

insulin sensitivity, or insulin resistance, is defined as a decreased biological response to a nutrient at a given concentration of insulin in the target tissue, such as liver, muscle or adipose tissue. Normally, maternal insulin sensitivity decreases by 50–60% with advancing gestation. This is a consequence of the increased maternal body fat content and the insulin-desensitizing effects of placental hormones, such as human placental lactogen (hPL), progesterone and cortisol as well as adipokines such as leptin and tumour necrosis factor-alpha (3, 31, 32). In normal pregnancy, decreased insulin sensitivity is compensated for by way of adequately increased insulin secretion. This is supposed to be due increased number of pancreatic β-cells resulting from hPL and prolactin secretion from the placenta and other circulating factors such as the hepatic growth factor (33–35).

Maternal glucose metabolism alters along with the changes in insulin sensitivity. In early pregnancy, maternal fasting glucose levels decrease and usually stabilize or begin to increase after 28 gestational weeks. Increased maternal plasma volume and fetoplacental glucose utilization are known to contribute in the decline in the fasting glucose levels (36).

Insulin resistance seems to be a major factor leading to GDM. Secondly, in GDM insulin secretion from the pancreatic β-cells is inadequate to meet the tissue demands for normal blood glucose regulation (31, 37). The genetics of GDM has reported to be similar to that of type 2 diabetes and there is evidence for clustering of type 2 diabetes in families with GDM. β-cell defect is highly hereditary and it has found to be one of the primary characteristics of GDM (38). Maternal hyperlipidaemia before pregnancy has been found to be a contributing factor in enhancing cytokine expression and resulting insulin resistance (31).

Metabolic dysfunction among women at risk of GDM is hypothesized to be already present before conception, as such women may have underlying insulin resistance or beta-cell dysfunction that potentiates the insulin resistance of pregnancy (34, 37). Women with GDM have been found to be more insulin resistant both before and after pregnancy compared with women without GDM (39, 40).

Undiagnosed diabetes and pregnancy

Undiagnosed pre-existing diabetes is associated with an increased risk of adverse pregnancy outcomes. Women with underlying diabetes during pregnancy are found to have 2.7-fold risk of congenital anomalies, 2.4-fold risk of pre-eclampsia and fourfold risk of perinatal death compared to women with GDM (41).

The incidence of type 2 diabetes is increasing worldwide, including young adults, leading to a growing amount of pregnancies complicated by this disturbance (42). It is estimated that about 30–50% of type 2 diabetes cases are undiagnosed and in pregnancy the diagnosis may be delayed until routine 24–28 gestational weeks screening of GDM is performed (43, 44). According to the International Association of Diabetes and Pregnancy Study Group (IADPSG), the criteria for overt diabetes in pregnancy are: fasting plasma glucose ≥ 7.0 mmol/l, glycated haemoglobin (Hba1c) ≥ 6.5% or random plasma glucose ≥ 11.1 mmol/l (45). Women with type 2 diabetes during pregnancy tend to be older, more obese, multiparous and have a shorter duration of diabetes than women with type 1 diabetes (46).

According to a recent review article, about 10% of cases of GDM are of autoimmune aetiology (47). Autoimmune diabetes is caused by the destruction of pancreatic β cells by immune-mediated mechanisms. Destruction is promoted by both genetic and environmental factors (48). Type 1 diabetes is characterised by the presence of various autoantibodies, including islet cell antibodies (ICAs), glutamic acid decarboxylase antibodies (GADAs) and antibodies to tyrosine phosphatase-like islet antigen (IA-2ab).

In GDM women, the prevalence of ICAs has been reported to vary from 1 to 15%, that of GADAs from 5 to 10% and that of IA-2ab from 0 to 6% (49). The prevalence of autoantibodies in women with GDM is highest in populations where the incidence of type 1 DM is high, e.g. in Finland (50). Pregnant women with autoantibodies are reported to have lower pre-pregnancy Body Mass Index (BMI), less weight gain and lower fasting insulin levels as well as greater need of insulin therapy during pregnancy compared with women with non-autoimmune GDM (51, 52).

One form of autoimmune diabetes which may become manifest during pregnancy is latent autoimmune diabetes in adults (LADA), which is characterised by the presence of GADAs. Such women require insulin treatment during pregnancy and are at risk of developing overt diabetes shortly after pregnancy (49, 50, 53).

Maturity-onset diabetes of the young (MODY), or monogenic diabetes, is present in approximately 5% of women with GDM. An autosomal dominant genetic mutation affecting pancreatic β cell function is present in MODY patients and there is a 50% risk of inheritance in their offspring. Diagnosis is usually made in childhood, youth or during gestation, because of the growing insulin resistance in pregnancy (54). MODY should be suspected if the mother has a strong family

history of diabetes. In MODY patients (MODY 3) the OGGT glucose values are similar to those of common form of GDM, or MODY patients (MODY 2) express fasting hyperglycaemia combined with a low increment of plasma glucose in an OGTT (55).

2.2.2 Screening and diagnosis

Diagnostic criteria and screening policies regarding GDM have varied over the time. The original diagnostic criteria of GDM were suggested by O'Sullivan and Mahan (1964) and were designed to identify pregnant women at an increased risk of subsequent type 2 diabetes (2, 56).

The diagnosis of GDM is generally based on abnormal OGTT results in pregnancy. The test is performed after an overnight fast and the first blood sample is taken before drinking the sugary drink containing 75g (or 100 g) of glucose. After the glucose load, 1-hour and 2-hour (and 3-hour) venous blood samples are taken (2). The diagnostic cut-off values vary according to different recommendations and are listed in Table 1.

Screening for GDM has often been based on historical and clinical risk factors in order to select mothers most likely to develop the condition. The risk factors associated with GDM have included a family history of diabetes, a previous large-for-gestational-age (LGA, birth weight $\geq 90^{th}$ percentile) neonate, maternal obesity, hypertension, glucosuria and age over 25 years (57).

The approach to GDM screening may also be universal, in which all mothers are screened. Both one- and two-step approaches are used. For example, in Northern America, a two-step approach with an oral glucose challenge test (OGCT) and an OGTT is the most widely used method. The OGCT involves a 50g glucose drink and a blood glucose measurement after one hour (58). Patients meeting or exceeding the OGCT screening threshold (1-hour glucose concentration $\geq$ 7.8 mmol/l) undergo an OGTT (4, 59). The one-step approach (an OGTT alone) is also widely used. In a randomized study in which one- and two-step approaches were compared, the prevalence of GDM was similar with both approaches, but the one-step approach was more expensive method than the two-step approach (60).

The American Diabetes Association (ADA) published a recommendation concerning detection and diagnostic criteria of GDM in 2003, according to which women with an average risk of GDM were recommended to be screened at 24–28 weeks of gestation. The very-low-risk population (age < 25 years, normal-weight,

member of an ethnic group with a low prevalence of GDM, no diabetes in first-degree relatives, no history of abnormal glucose tolerance or poor obstetric outcome) did not require glucose testing. According to this recommendation, one- or two-step approaches could be used. The diagnostic thresholds for GDM according to the ADA recommendations were 5.3 mmol/l for fasting, 10.0 mmol/l for 1-hour and 8.6 mmol/l for 2-hour samples in OGTT and the diagnosis was set if two or more of glucose values were equal or greater than a threshold value (61).

The Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study was designed to develop internationally agreed diagnostic criteria for GDM. The study involved a total of 25 505 women in nine countries with blinded OGTT result. The study showed a positive association between increasing maternal hyperglycaemia and both birth weight and a cord blood serum C-peptide level above the 90th percentile, reflecting fetal hyperinsulinaemia and hence an increased risk of neonatal hypoglycaemia. Positive associations were also found between increasing plasma glucose concentrations and primary Caesarean delivery, neonatal hypoglycaemia, premature delivery, shoulder dystocia or birth injury, treatment at a neonatal intensive care unit (NICU), hyperbilirubinaemia and pre-eclampsia. Maternal hyperglycaemia was linearly associated with adverse outcome (62).

The IADPSG, an international consensus group representing multiple obstetric and diabetes organizations held a conference in 2008 to establish recommendations for new diagnostic criteria of GDM according to the results of the HAPO study. The diagnostic criteria of GDM were based on an odds ratio (OR) of 1.75 times the mean for the following outcomes: increased neonatal body fat calculated from birth weight, length and flank skin fold as well as birth weight and cord serum C-peptide level above the 90th percentile. The cut-off values thus formed were 5.1 mmol/l for fasting, 10.0 mmol/l for 1-hour and 8.5 mmol/l for 2-hour plasma samples. If these criteria were used, 17.8% of the HAPO study population would be identified as having GDM. IADPSG recommends screening for all pregnant women at 24–28 gestational weeks. Women with strong risk factors are recommended to be screened as early as at their first prenatal visit by measuring fasting plasma glucose, Hba1c or a random plasma glucose sample and in the case of normal result screening at 24–28 gestational weeks should be performed (45, 63). New World Health Organization (WHO) recommendations were launched in 2014 and are equivalent to the IADPSG criteria (64).

A recent retrospective study concerned comparison of the prevalence and outcome of GDM in a Chinese population diagnosed by using the former ADA

criteria or the new IADPSG criteria (fasting glucose concentration ≥5.1 mmol/l). According to the ADA and IADPSG criteria, 11.7 versus 24.5% of the mothers were classified as having GDM, respectively. The cases diagnosed according to the ADA criteria were associated with an increased risk of adverse maternal and neonatal outcomes. Mothers meeting the IADPSG but not ADA criteria had an increased risks of gestational hypertension and infant admission to NICU, but when these outcomes were adjusted for maternal age and BMI, the risks were no longer increased. The study group concluded that the IADPSG criteria increased the prevalence of GDM by 200%, but among this population the risk of obstetric or neonatal morbidity was not increased (65).

In Finland, risk-factor-based-screening was in use before 2008 and the indications for screening are listed in Table 2. Since 2008, universal screening of GDM is recommended according to the new national Current Care Guidelines (Table 3). Finnish criteria for GDM are in line with ADA criteria (Table 1) (6). After this alteration of screening policy, the incidence of GDM has increased from 8 to 15% between 2006 and 2013 (66).

Universal screening has been found to reduce the risks of having LGA infants and hypertensive disorders of pregnancy, compared with no screening (67). On the other hand, according to a recent Cochrane review, evidence that screening for GDM improves maternal or infant health outcomes is insufficient and further studies are needed to determine which screening practices for GDM are the most profitable (58).

The data on the cost-effectiveness of GDM screening are limited. Two studies have reported cost-effectiveness in terms of maternal long-term health and later development of diabetes (68, 69). A recent study evaluating the cost-effectiveness of screening according to the IADPSG criteria revealed screening to be expensive but cost-effective by improving maternal and neonatal outcomes (70).

Table 1. Plasma glucose thresholds for the diagnosis of GDM according to different guidelines.

Organization	Year	Glucose challenge	0-hour value (mmol/l)	1-hour value (mmol/l)	2-hour value (mmol/l)	3-hour value (mmol/l)
O'Sullivan and Mahan (56)[b]	1964	100 g OGTT	5.0*	9.2*	8.1*	6.9*
NDDG** (71)[b]	1979	100 g OGTT	5.8	10.6	9.2	8.1
WHO (72) [a]	1999	75 g OGTT	7.0	Not required	7.8	
ADA (61) [b]	2003	75 g OGTT	5.3	10.0	8.6	
Canadian Diabetes Association (73) [b]	2008	75 g OGTT	5.3	10.6	8.9	
IADPSG (45) [a]	2008	75 g OGTT	5.1	10.0	8.5	
ACOG*** (74) [b]	2011	100 g OGTT	5.3	10.0	8.6	7.8
WHO (64) [a]	2014	75 g OGTT	5.1	10.0	8.5	

*values measured in whole blood

**National Diabetes Data Group

*** American Congress of Obstetricians and Gynecologists

[a] one value required for diagnosis [b] two or more values required for diagnosis

Table 2. Finnish screening guidelines for GDM before 2008.

Indications for screening	Cut-off values in OGTT
Age ≥ 40 years	0-hour 5.3 mmol/l
Overweight (BMI ≥ 25 kg/m²)	1-hour 10.0* or 11.0** mmol/l
Glucosuria or suspected fetal macrosomia in ongoing pregnancy	2-hour 8.7* or 9.6** mmol/l
Prior GDM	
Previous macrosomic infant (birth weight ≥ 4500g)	

*Venous plasma samples, **capillary plasma samples

Table 3. Finnish Current Care Guidelines for GDM screening(6)**.**

Early screening (12-16 weeks)	Universal screening (24-28 weeks)	Cut-off values in OGTT*
Prior GDM	All women except	0-hour 5.3
BMI ≥ 35kg/m²	normal weight nullipara ≤ 25	1-hour 10.0
Type 2 DM in 1st degree relatives	years without DM in first-degree	2-hour 8.6
Use of oral corticostreroids	relatives	
Polycystic ovary syndrome (PCOS)	normal weight multipara ≤ 40	
	years without a history of	
	macrosomic infant or GDM	

*one value required for diagnosis

2.3 Treatment of GDM

2.3.1 Self-monitoring of plasma glucose concentrations and efficacy of treatment of hyperglycemia

The treatment of GDM aims to reduce the risk of adverse neonatal outcomes such as macrosomia and birth injuries as well as the risk of pregnancy complications such as pre-eclampsia and hypertension (75). Treatment is based on self-monitoring of blood glucose concentrations, diet therapy and, if required, supplementation with pharmacological treatment. This treatment has been proven to be beneficial and to improve maternal and infant health outcomes (10, 76). On the other hand, the treatment of mild GDM has been found to be associated with an increased rate of delivery inductions and a need for treatment at a NICU (11).

Self-monitoring of glucose concentrations has been found to be a most effective way to monitor glucose balance and the need of pharmacological treatment (10).

According to Finnish Current Care Guidelines, after the diagnosis of GDM women receive dietary and lifestyle counselling and begin self-monitoring of capillary glucose concentrations twice weekly. Glucose concentrations are measured 5–7 times per day, fasting and one hour postprandial, target values being ≤ 5,5 mmol/l for fasting and ≤ 7.8 mmol/l for 1-hour postprandial (6).

The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) was designed to assess the effects of treatment of GDM on maternal and neonatal outcomes. Mothers were randomized to an intervention group with diet counselling and glucose self-monitoring, or to a control group with routine antenatal care. Insulin treatment was begun in 20% of the mothers in the

intervention group and 3% in the routine-care group. The rate of severe perinatal complications (defined as one or more of the following: death, shoulder dystocia, bone fracture, nerve palsy) was significantly lower in the intervention group than in the routine-care group (1 vs. 4%, $p = 0.01$). The rates of LGA infants (birth weight above 90th percentile) and macrosomia (birth weight $\geq$ 4000g) were significantly higher in the routine-care group than intervention group (22 vs. 13%, $p < 0.001$ and 21 vs. 10%, $p < 0.001$, respectively) (10).

A systematic review revealed that the treatment of GDM decreased the rates of shoulder dystocia and fetal macrosomia without increasing the rate of small-for-gestational-age (SGA) infants or perinatal loss. The authors concluded that treatment of GDM, including blood glucose control and special obstetric care, seems to lower the risks of some perinatal and neonatal complications (75).

2.3.2 Lifestyle interventions

Diet is the cornerstone in the management of GDM (77). It is aimed at maintaining sufficient energy intake for the mother and the fetus and ensuring glycaemic control of the mother. Diet treatment also reduces the need of pharmacotherapy and prevents excessive weight gain and complications such as macrosomia (6, 77).

Studies concerning nutritional treatment of GDM are scarce. According to a Cochrane Database review, the studies available are too small to draw conclusions as to the most beneficial diet treatment (78). A recently published systematic review and meta-analysis revealed a low glycaemic index (GI) diet to be associated with less frequent insulin use and lower birth weight than a total energy restriction diet or a low carbohydrate diet, without increasing the rates of SGA or LGA infants (79).

Dietary guidelines for GDM patients are based on the general nutritional recommendations for diabetes. Diet counselling performed by well-educated health care professionals should be provided for all women with GDM. They are recommended to have four regular meals and one to two snacks a day to meet the needs of pregnancy, and to avoid large carbohydrate loads. The daily energy intake should be between 7.5 and 8.4 megajoules (MJ) in normal-weight and between 6.7 and 7.5 MJ in overweight or obese mothers (6, 77). The appropriate weight gain in women with GDM remains controversial, but is dependent on an individual's BMI. In Finland, it is recommended that obese mothers should not gain any weight after the diagnosis of GDM (6).

Moderate exercise during pregnancy is assumed to have a beneficial effect on the glucose balance in GDM mothers. Physical activity appears to help in the achievement of glycaemic control and to limit the need of insulin in women with GDM by improving insulin sensitivity (80). Women who are physically active before and during pregnancy are found to have lower risk of developing GDM (81).

According to a Cochrane Database review which included 4 randomized controlled trials (RCTs) and 114 women with GDM, exercise intervention had no impact on the incidence of preterm delivery, macrosomia, stillbirth or congenital malformations, nor on the Apgar score of infants or the need of insulin treatment (82). One of these studies revealed that insulin requirements of overweight GDM women were lower and the need for insulin treatment appeared later in the exercise intervention group (83). However, women with GDM should be encouraged to be moderately intense in physical activity, if there is no medical or obstetric contraindication (77).

2.3.3 Insulin treatment

When dietary treatment proves to be insufficient in the achievement of normoglycaemia and the target glucose values in the self-monitoring are exceeded repeatedly, pharmacotherapy is indicated. Traditionally, the first-line pharmacological treatment of GDM has been insulin administration (11). Prior GDM, pre-pregnancy BMI > 30 kg/m² and GDM detected before 20 weeks of gestation have been reported to be associated with an increased need of insulin treatment in GDM (84).

A four-times daily regimen of insulin has proven to be more effective than a two-times daily regimen in achieving glycaemic control in women with GDM (85). Fast-acting insulin before meals is administered to control postprandial hyperglycaemia and bedtime basal insulin to control fasting hyperglycaemia. Morning injection of basal insulin may improve glucose balance in some cases. Usually, insulin administration is initiated with small doses, which are increased at frequent intervals until the target values are met (77).

According to Finnish Current Care Guidelines, in the case of fasting hyperglycaemia in the self-monitoring, Neutral Protamine Hagedorn (NPH) insulin is administered in the evening and in the case of postprandial hyperglycaemia, insulin lispro or aspart is administered before meals. Even after the initiation of insulin, it is still necessary to continue with diet therapy (6).

Unlike human insulin, animal-sourced insulin has been found to cross the placenta as a result of antibody binding (86). However, it is maternal hyperglycaemia rather than maternal anti-insulin antibodies which influence birth weight (87). Insulin has been used during pregnancy for many decades without an increase in fetal complications (77).

There are few studies in which different types of insulin used during pregnancy have been compared in pre-gestational type 1 diabetic mothers. It has been suggested that better glucose balance is achieved with insulin analogues such as insulin aspart and insulin lispro than with human insulin (88–90). Administration of both insulin aspart and lispro (88, 89) as well as long-acting insulin analogues, such as detemir and glargine have proven to be safe during pregnancy (90). In conclusion, insulin analogues may lead to slightly better glycaemic control in type 1 diabetes than human insulin during pregnancy without evidence of a better perinatal outcome.

In women with GDM, several small randomized studies have shown rapid-acting insulin to be as effective as regular insulin with comparable pregnancy outcomes (91–94). There is a lack of evidence on the use of long-acting insulin analogues in the treatment of GDM and no randomized controlled studies have been published.

Insulin requirements usually increase along with gestational weeks because of the growing insulin resistance (95). Safe administration of insulin in pregnancy requires accurate counselling. Disadvantages of insulin therapy, such as the need of one to several subcutaneous injections daily, considerable costs, the risk of hypoglycaemia and increased appetite as well as weight gain, should not be ignored (96) (Table 5).

2.3.4 Metformin treatment

Metformin is a widely used anti-diabetic agent for type 2 diabetes belonging to biguanide drugs. It lowers blood glucose concentrations mainly by inhibiting gluconeogenesis in the liver and by increasing glucose uptake in skeletal muscle and adipocytes (97). The glucose-lowering effect is due to activation of liver kinase B1 adenosine monophosphate activated protein kinase (LKB1-AMPK) in insulin-sensitive tissues (98). Metformin does not cause hypoglycaemia or stimulate insulin production (99, 100). It improves especially hepatic insulin sensitivity and less muscle insulin sensitivity (101). Its use does not result in weight gain and today it is the first-line drug in type 2 diabetes (102).

Metformin crosses the placenta and its concentrations in the umbilical cord have been found to be comparable with concentrations in the maternal circulation (103–106). However, the rate of congenital malformations or other adverse fetal outcomes is not reported to be increased in women treated with metformin throughout pregnancy (107, 108).

Gastrointestinal side-effects are common adverse effect of metformin. The most serious adverse effect of metformin is metabolic acidosis with an increased lactate concentrations, which may occur both with therapeutic use and overdose of the substance. Lactic acidosis is a rare but potentially fatal condition with an estimated incidence of 0.03/1000 patient years and the symptoms may include neurological dysfunction, cardiac and respiratory failure, hypothermia, oliguria, acute renal failure and multisystem organ failure (109). The risk is higher among patients with liver or renal failure, alcohol consumption, cardiac and pulmonary diseases or sepsis (110). It is recommended that due to the risk of lactic acidosis, metformin should be discontinued before surgical operations (109).

Metformin in the treatment of type 2 diabetes during pregnancy

The earliest reports on metformin use during pregnancy are from studies published in 1979 and 1984. In these observational studies metformin treatment was not associated with an increased rate of adverse pregnancy outcome in women with type 2 diabetes when compared to insulin treatment (111, 112). Hellmuth and colleagues published a retrospective study on oral hypoglycaemic agents during pregnancy in diabetic women and found that women treated with metformin had higher incidences of pre-eclampsia and perinatal mortality than those treated with sulphonylurea, but the study has been criticized because of poor methodology (113). Later, a retrospective study revealed comparable maternal and fetal outcomes in pregnant women with type 2 diabetes treated with metformin, sulphonylurea or insulin (114). In an observational study in which metformin and insulin treatments were compared during pregnancy in women with type 2 diabetes, metformin was found to be associated with better glycaemic control throughout pregnancy (115).

A recent randomized study has been carried out in which metformin and insulin treatments were compared in 28 pregnant women with pre-existing type 2 diabetes or early gestational diabetes. Metformin treatment was associated with no risk of maternal hypoglycaemia, but 43% of the subjects treated with

metformin needed additional insulin. The investigators concluded that metformin is a good choice in pregnancies with overt diabetes or early GDM (116).

Metformin in the treatment of GDM

Four observational studies of metformin treatment in GDM have been carried out. Tertti *et al.* (2008) found that metformin was not associated with an increased risk of adverse perinatal outcomes when compared with diet treatment (117). In a study by Balani *et al.* (2009), metformin was associated with less maternal weight gain and better neonatal outcomes (less prematurity, neonatal jaundice and treatment at neonatal ward) in comparison with insulin (118). Goh *et al.* (2011) reported that metformin used for GDM in routine practice was associated with fewer adverse outcomes compared with insulin, but baseline differences between the treatment groups may have influenced the results (119). In the fourth observational study of women with GDM, metformin treatment was associated with a decreased need of additional insulin therapy and a lower incidence of macrosomia compared with dietary treatment (120).

Recently, the results of several randomized studies concerning comparison of metformin and insulin treatments in GDM have been published (121–126). These studies are listed in Table 4. According to the results of these studies, metformin treatment is not associated with an increased incidence of adverse pregnancy or perinatal outcome, such as macrosomia, neonatal hypoglycaemia and treatment at neonatal ward, compared with insulin treatment.

A meta-analysis of five RCTs revealed metformin to be comparable with insulin as regards glycaemic control and neonatal outcomes. The risk of pregnancy-induced hypertension was significantly lower (OR 0.52, 95% CI 0.30–0.90) and the risk of preterm deliveries (< 37 gestational weeks) was significantly higher (OR 1.74, 95% CI 1.13–2.68) in the metformin group than in the insulin group. Women in the metformin group gained significantly less weight than women in the insulin group. Fasting glucose levels in OGTT were significantly higher in women on metformin and supplemental insulin compared with in women on metformin only reflecting less severe disturbance of glucose metabolism in the latter group (127).

Table 4. RCTs concerning comparison of metformin and insulin treatment in cases of GDM.

Study	Year/Country	n (metf/ins)	Birth weight (g) (metf/ins)	Macrosomia % (metf/ins)	Neonatal hypoglycaemia % (metf/ins)	Treatment at neonatal ward % (metf/ins)	Additional insulin needed %
Moore *et al.* (121)	2007/USA	32/31	3452/3500	Not reported	0/6.5[5]	6.3/12.9	0
Rowan *et al.* (122)	2008/New Zealand and Australia	363/370	3372/3413	19.3/18.6[1]	3.3/8.1 (p < 0.01)[6]	18.7/21.1	46.3
Niromanesh *et al.* (123)	2012/Iran	80/80	3300/3400 (p < 0.01)	17.5/35.0[1] (p = 0.012)	3.8/2.5[5]	6.3/2.5	13.8
Mesdaghinia *et al.* (125)	2013/Iran	100/100	3512/3528	16/24[2]	10/15[5]	14/33 (p<0.01)	22.0
Tertti *et al.* (124)	2013/Finland	110/107	3604/3589	4.5/0.9[3]	16.5/16.8[7]	31.2/36.5	20.9
Spaulonci *et al.* (126)	2013/Brazil	47/47	3144/3238	0/6.5[4]	6.5/22.2 (p = 0.03)[8]	Not reported	26.1

[1]birth weight > 90th percentile, [2] birth weight > 95th percentile, [3]birth weight > 4500g or > 2SD, [4]birth weight ≥ 4000g

[5]not defined, [6]two or more neonatal glucose values < 2.6mmol/l, [7]required intravenous glucose, [8]neonatal glucose value < 2.2mml/l until age of 48h

Prenatal metformin exposure and offspring

The benefits of metformin treatment on pregnancy and neonatal outcomes have been well established in the studies mentioned above. The possible long-term consequences on the development and health of the offspring should also be taken into account. Up to now, few studies reporting the long-term outcomes of children prenatally exposed to metformin have been available. The Offspring Follow-Up study (MiG TOFU) concerned the overall growth and body composition of children born to GDM mothers at two years of age exposed to metformin or insulin *in utero* from gestational weeks 20 to 33 until delivery. The study revealed larger subscapular and biceps skin folds in children exposed to metformin, whereas total fat mass and growth did not differ between the groups. The authors interpreted this finding to represent a more favourable pattern of fat distribution later in life (128). In the same study, cord plasma lipid and C-reactive protein (CRP) concentrations did not differ significantly between the study groups suggesting that metformin treatment in GDM does not have adverse effect on neonatal metabolic status compared to insulin (129).

A cohort study of 126 children born to women with polycystic ovary syndrome (PCOS) undergoing metformin treatment before and during pregnancy revealed no adverse effects on the children's motor or social development when assessed up to the age of 18 months. The growth of the children did not differ in comparison with national gender-specific data (130).

A study by Carlsen *et al.* (2012) showed that the children of mothers with PCOS who were exposed to metformin *in utero* were significantly heavier than children in a placebo group when investigated at the age of one year (131). Prenatal metformin exposure was associated with increased sex-hormone binding globulin (SHBG) concentrations in umbilical cord when compared with those in the placebo group, which may indicate that newborns exposed to metformin *in utero* are more insulin resistant. The oestrogen and androgen levels did not differ significantly between the groups (132).

Tartarin and colleagues (2012) investigated the effects of metformin in human and murine testicular cells *in vitro*. Metformin was associated with decreased

testosterone secretion from the testicular cells from both origins. In an *in vivo* study on mice, metformin administration to pregnant mice reduced the size of the testes and the number of Sertoli cells in male offspring, compared with controls (133).

Metformin reduces insulin resistance and is associated with beneficial fat redistribution from visceral to subcutaneous deposits in adults (134). A recent experiment on mice revealed prenatal metformin exposure to be associated with increased body weight gain, a significant reduction in total body water content and an increase in mesenteric fat during a high-fat diet phase. In male offspring prenatal metformin exposure was associated with impaired glucose tolerance and elevated fasting glucose levels during a high-fat diet (135). The same study group has later demonstrated that prenatal exposure to metformin in the maternal high-fat diet mouse model decreased the adipose tissue accumulation in the female offspring and prevented disturbance in the glucose metabolism during the high-fat diet in the offspring of both genders. According to these studies it seems that maternal metabolic status during pregnancy is a key factor in determining how the prenatal metformin exposure affects on the offspring (136).

Rø *et al.* (2012) published a follow-up study of 25 children of women with PCOS randomized to metformin or placebo during pregnancy. There were no differences between the groups in height, weight or body composition measured at the age of 7–9 years. However, the children exposed to metformin had significantly higher fasting glucose concentrations than those exposed to placebo and there was a trend towards higher systolic blood pressure and lower LDL cholesterol concentrations in the metformin group (137).

Table 5. Potential benefits and harms of insulin and metformin treatments.

Insulin treatment	Metformin treatment
Benefits	Benefits
no placental pass	no risk of hypoglycaemia
effective	no weight gain
adjustable dosage	easy to administrate
Harms	low-cost
requires several daily injections	Harms
risk of hypoglycaemia	placental pass
weight gain	gastrointestinal symptoms
costly	lactate acidosis (rare)
poor compliance	possible long-term effects for the offspring

2.3.5 Glibenclamide treatment

Glibenclamide, also known as glyburide, is an oral hypoglycaemic agent belonging to sulphonylurea drugs, which acts by increasing the intracellular calcium content in pancreatic β-cells and enhancing insulin secretion. It stimulates insulin secretion independently of prevailing plasma glucose concentration and therefore its use in type 2 diabetes is associated with a considerable risk of hypoglycemia and weight gain (138, 139). Glibenclamide was withdrawn from the market in 2013 in Finland.

A randomized study of 404 GDM patients revealed no differences in glycaemic control or in perinatal complications such as birth weight above 90th percentile or over 4000 g, lung complications, hypoglycaemia and NICU treatment between glibenclamide- and insulin-treated mothers. The risk of maternal hypoglycaemia was lower with glibenclamide than with insulin and only 4% of the mothers treated with glibenclamide needed additional insulin. Glibenclamide was not detected in the cord serum of the infants (140). A secondary analysis of the study at issue showed that not treatment modality, but the severity of GDM, mean blood glucose concentrations, pregnancy weight gain and previous macrosomia were associated with an increased risk of adverse pregnancy outcome (141). It was later demonstrated that glibenclamide crosses the placenta and its use may be associated with a risk for neonatal hypoglycaemia. The concentrations of glibenclamide in the umbilical cord are about 70% of maternal serum concentrations (142).

Glibenclamide and insulin treatment in GDM were compared in a meta-analysis of nine studies with a total of 745 pregnant women on glibenclamide and

637 on insulin. No differences were found in the rates of macrosomia or LGA infants, birth weight, need of treatment at NICU or neonatal hypoglycaemia. However, not all of the studies included were randomized (143).

A recently published meta-analysis summarizing the short-term outcomes of treatment with glibenclamide, metformin or insulin in GDM revealed glibenclamide to be inferior to both insulin and metformin. The study included 15 RCTs, seven comparing glibenclamide with insulin, six comparing metformin with insulin and two comparing metformin with glibenclamide. Glibenclamide was associated with higher birth weight and more macrosomia and neonatal hypoglycaemia when compared with insulin, and more maternal weight gain, higher birth weight and more cases of macrosomia or LGA infants when compared with metformin. The authors concluded that glibenclamide should not be used in the treatment of GDM if metformin or insulin is available (144).

2.4 Short-term complications of GDM

2.4.1 Maternal complications

GDM increases the risk of hypertensive disorders during pregnancy (62). The risk of pregnancy-induced hypertension and pre-eclampsia is estimated to be two- to threefold compared with those with no glucose intolerance (145, 146).

Women with GDM have been found to have a twofold risk for Caesarean delivery (147). The HAPO study showed a linear association between maternal hyperglycaemia and Caesarean deliveries (62).

The risk of labour induction and post-partum haemorrhage have been found to be increased in women with GDM compared to non-GDM women (147).

2.4.2 Neonatal complications

Undiagnosed and untreated GDM is associated with increased risks of maternal and perinatal complications. The main risk is fetal overgrowth (macrosomia), which increases the risk of delivery complications such as need of Caesarean delivery, shoulder dystocia, birth injuries and asphyxia as well as the risk of neonatal hypoglycaemia and respiratory distress syndrome (10, 148, 149). According to the hypothesis of "fuel-mediated teratogenesis", maternal glucose

crosses the placenta and leads to fetal hyperglycaemia and hyperinsulinaemia, which contribute to the acceleration of fetal growth (150).

Macrosomia is associated with increased perinatal morbidity (11). In a case-control study carried out by Langer *et al.*, subjects with untreated GDM had a two- to fourfold risk of macrosomia and shoulder dystocia, a two- to sevenfold risk of metabolic and respiratory complications and a fourfold risk for NICU admission than subjects with normal glucose tolerance or treated GDM (9). These risks can usually be avoided by effective treatment of GDM (10).

The neonates of GDM mothers suffer more often from respiratory distress syndrome than those of mothers without glucose disturbances (151). The risk is evident even in full-term infants born to women with GDM. The reason for this finding is not completely clear, but it has been suggested that hyperglycaemia and hyperinsulinaemia delay maturation of the fetal lungs (152, 153).

Neonatal hypoglycaemia is a significant health problem often leading to a need for intensive care. The reason for neonatal hypoglycaemia is that the enhanced insulin secretion of the fetus in response to maternal hyperglycaemia continues in the neonate a few days after delivery. Hypoglycemia is most commonly defined as newborn glucose concentration from < 2.0 mmol/l to 2.5mmol/l (154). Hypoglycaemia may be symptomless and the treatment of this condition is based on the clinical assessment, not solely on plasma glucose concentrations. The treatment includes fast-feed cycles and, when needed, intravenous glucose infusion (155).

The risk of hyperbilirubinaemia is also increased in the neonates of GDM mothers (148). Hyperbilirubinaemia contributes to newborn polycythaemia, which is a consequence of hyperglycaemia and leads to the rapid breakdown of red blood cells (156).

Disturbance of glucose metabolism in pregnancy is associated with an increased risk of congenital anomalies, such as cardiac malformations, caudal regression syndrome, neural tube defects and anomalies of genitourinary tract, when compared with that among non-diabetic women (156). Both undetected diabetes and GDM have found to increase the risk of congenital anomalies when compared with women without GDM (157). This finding may be partly due to maternal obesity (158). However, women with treated GDM seem to have even lower risk of perinatal death than women without diabetes, which may be due to more effective follow-up and treatment of the pregnancies (157).

2.5 Long-term consequences of GDM

2.5.1 Maternal risks

According to the literature, the recurrence rate of GDM varies from 30 to 84% whereas those without GDM in a previous pregnancy have a risk from 1 to 4% (26, 159-161). The most important risk factor of recurrent GDM is considered to be maternal weight before subsequent pregnancy, and excessive weight gain between pregnancies also increases the risk of recurrence (162).

Greater maternal pre-pregnancy BMI and higher weight gain after pregnancy have found to associate with the risk of future diabetes after GDM pregnancy (163, 164). It is suggested that women with GDM have less β-cell reserve and decreased insulin secretion and sensitivity already before pregnancy, which increases the risk of developing overt diabetes (3).

The worldwide prevalence of diabetes in adults was estimated to be 4.0% in 1995 and to rise to 5.4% by the year 2025 (165). The risk of future diabetes in women with GDM varies according to the length of follow-up and the ethnic population studied. In a review article of 28 studies with a follow-up times ranging from 6 weeks to 28 years post-partum, the cumulative incidence of diabetes ranged from 2.6 to over 70%. Fasting hyperglycaemia during pregnancy was found to be the most common risk factor associated with the future risk of diabetes (166). In a Finnish case-control study, 10% of women with GDM developed overt diabetes on average 6 years after the index pregnancy; 4.6% of them developed type 1 and 5.3% type 2 diabetes. The development of type 1 diabetes was associated with maternal age under 30 years, need for insulin treatment during the index pregnancy and the presence of ICAs and GADAs (50). Some studies concerning the risk of future diabetes in women with GDM are listed in Table 6.

In a meta-analysis of 20 studies, women with GDM were found to have a sevenfold risk of developing diabetes later in their life, compared with women with normal glucose tolerance during pregnancy (12). A systematic review revealed maternal pre-pregnancy BMI to be a strong risk factor of subsequent type 2 diabetes in women with prior GDM; for every 1kg increase in pre-pregnancy weight the odds of developing diabetes increased by 40%. Maternal body fat content was associated with diabetes risk more strongly than age, parity or a family history of diabetes (163).

Lifestyle changes including diet and exercise have been shown to decrease the later risk of diabetes in women with GDM. In a multi-centre randomized trial (Diabetes Prevention Program), 350 women with impaired glucose tolerance at baseline and having prior GDM were randomized to either an intensive lifestyle change targeting 7% reduction in weight, or a standard lifestyle and placebo or metformin treatment. The incidence of diabetes decreased by 53% in the GDM women with intensive lifestyle intervention and by 50% in the GDM women with metformin treatment (167).

Metabolic syndrome (MetS) is characterized by a cluster of factors including visceral obesity, insulin resistance, hypertension and dyslipidaemia, and this adverse metabolic profile predisposes individuals to subsequent type 2 diabetes and cardiovascular events (168). The definition of MetS varies according to the different organizations. Recently, International Diabetes Federation (IDF) and American Heart Association (AHA) representatives held discussions to standardize the definition of MetS and the criteria were: elevated waist circumference, elevated triglycerides, reduced high-density lipoprotein cholesterol (HDL-C), elevated blood pressure and elevated fasting glucose. The presence of any three of five risk factors constitutes a diagnosis of MetS (169). Several studies have indicated that a history of GDM increases the risk of MetS and cardiovascular diseases (CVDs) (13–17). Some studies on the risk of MetS in women with a history of GDM are listed in Table 7.

A 10-year follow-up revealed a 1.7-fold risk of future CVD in women with GDM compared with women without GDM. The increased CVD risk was attributable to subsequent development of type 2 diabetes (170). In a large prospective cohort study, GDM was found to be independently associated with an increased calculated 10-year CVD Framingham risk score, indicating increased future CVD risk (17). A recent study of women with cardiovascular events and matched controls showed prior GDM to be a useful marker of a raised CVD risk in overweight women (171).

Carotid intima-media thickness (CIMT) is the combined thickness of the intimal and medial layers of the carotid artery measured by ultrasound. Increased CIMT is a marker of subclinical atherosclerosis and a predictor of future clinical cardiovascular events such as stroke and coronary artery disease (172). Women with prior GDM appear to have increased CIMT compared with control women reflecting an increased risk of future cardiovascular events (173, 174). A recently published meta-analysis of studies on CIMT in GDM patients and controls

revealed an association between GDM and increased CIMT. This association already existed during pregnancy and was more evident in obese subjects (175).

The development of atherogenesis is affected by systemic low-grade inflammation, which is also a contributing factor in the development of type 2 diabetes and MetS (176, 177). Women with previous GDM have been demonstrated to have increased concentrations of markers of subclinical systemic inflammation, such as high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL6) and plasminogen activator inhibitor 1 (PAI-1) (178).

Table 6. Studies on the prevalence of diabetes in women with a history of GDM compared with those without GDM.

Study	Year/Country	n (GDM/no GDM)	Follow-up duration (years)	Prevalence of diabetes (%)
Damm *et al.* (179)	1994/Denmark	241/57	7.5	13.7 vs. 0
Albareda *et al.* (180)	2003/Spain	696/70	6.2	6.3 vs. 0
Järvelä *et al.* (50)	2006/Finland	435/435	6	9.9 vs. 0
Lee *et al.* (181)	2007/Australia	5470/783	2.2–8.6	20.0 vs. 7.4
Gunderson *et al.* (182)	2007/USA	166/2242	20	25.9 vs. 6.8
Feig *et al.* (183)	2008/Canada	21.823/637.341	5.2	13.2 vs. 1.0

Table 7. Studies on the prevalence of MetS in women with a history of GDM compared with those without GDM.

Study	Year/Country	n (GDM/no GDM)	Follow-up duration (years)	Prevalence of MetS (%)
Verma *et al.* (15)	2002//USA	106/101	4–11	27.2 vs. 8.2
Bo *et al.* (13)	2004/Italy	81/65	8–9	21.0 vs. 4.6
Albareda *et al.* (184)	2005/Spain	262/66	5	2.9 vs. 1.8
Lauenborg *et al.* (14)	2005/Denmark	481/1000	9.8	38.8 vs. 13.4
Akinci *et al.* (16)	2010/Turkey	164/65	1.7	14.9 vs. 4.6

2.5.2 Risks to offspring

The prenatal environment may affect the metabolism of the offspring through epigenetic mechanisms (185). According to the "Pedersen hypothesis" maternal

glucose crosses the placenta, leading to hyperglycaemia and hyperinsulinaemia of the fetus, which affects its' growth and development in the future (186).

Longitudinal studies among Pima Indians have demonstrated that prenatal exposure to diabetes and being either SGA or LGA at birth increases the risks of type 2 diabetes and hypertension in childhood (187–189). The significance of prenatal exposure to diabetic milieu is supported by the results of a study that revealed the risks of diabetes and overweight to be significantly higher in siblings born after the mother had developed type 2 diabetes than in those born before the mother's diagnosis (188). Association between maternal GDM and obesity with impaired glucose tolerance of the adolescent offspring have also been shown in a low-risk ethnic population (190, 191).

Boney *et al.* (2005) demonstrated that LGA (birth weight > 90th percentile) offspring of mothers with GDM have a significant risk of developing MetS when evaluated at the age of 6, 7, 9 and 11 years. In the same study, maternal obesity without glucose intolerance was also found to be a risk factor of childhood MetS (18). In adolescence, the offspring of mothers with GDM have markers of insulin resistance and MetS independently of birth weight, preterm birth or an overweight condition later on (191).

Clausen *et al.* (2008 and 2009) investigated the adult offspring of mothers with diet-treated GDM or type 1 diabetes compared with an unexposed reference group. The offspring of GDM mothers and type 1 diabetic mothers had an increased risk of type 2 diabetes and impaired glucose tolerance (OR 7.8, 95% CI 2.58–23.39 and OR 4.0, 95% CI 1.31–12.33, respectively), and their risk of being overweight was doubled (192). The risk of MetS in the offspring was increased fourfold in the case of maternal diet-treated GDM and doubled in connection with maternal type 1 diabetes. The risk of MetS increased along with the increasing level of maternal hyperglycaemia observed in OGTTs during pregnancy (193).

2.6 Maternal overweight

Maternal overweight and obesity is a growing health concern worldwide. For adults aged 20 years or older, overweight is commonly defined as a BMI of 25.0 to 29.9 kg/m², obesity as a BMI of 30.0–34.9 kg/m², severe obesity as a BMI of 35.0–39.9 kg/m², and morbid obesity as a BMI of 40.0 kg/m² or higher (194). BMI is calculated as weight (kilograms) divided by the square of height (meters) (195).

In the UK, approximately one in 20 pregnant women is considered to be obese (196) and in the Northern America, about 62% of the female population aged over 20 years are reported to be overweight and 33% obese (197). In Finland, the proportion of overweight and obese pregnant women has substantially increased in the 21st century. The prevalence of overweight mothers increased from 18.8 to 35.6% and the prevalence of obese mothers from 7.5 to 13.2% between 1990 and 2013 (66, 198).

Obese pregnant mothers and their newborns are reported to require significantly more intensive care than normal-weight mothers (199, 200). Increased maternal BMI is associated with increasing health service usage and healthcare costs because of the increased risk of complications in pregnancy and labour (200, 201).

2.6.1 Pregnancy and labour complications of maternal overweight

While the majority of women with GDM are either overweight or obese, studies concerning obesity-related risks on pregnancy outcome have not separately assessed the impact of overweight and hyperglycaemia. However, there has been some controversy as to whether or not overweight/obesity is an independent risk factor or whether the underlying hyperglycaemia contributes to adverse pregnancy outcomes (202).

Obesity leads to decreased insulin sensitivity, which contributes to several adverse pregnancy outcomes including the risk of maternal hypertensive and metabolic disorders and low-grade systemic inflammation. This phenomenon may be called MetS of pregnancy and is likely to resolve after delivery, though these women are known to have an underlying metabolic disorder (203). Obese pregnant women with normal glucose tolerance are reported to have higher daytime and nocturnal glucose profiles in continuous glucose monitoring compared with normal-weight women (204).

The risk of congenital neural tube, ventral wall and heart defects have been reported to be increased in the offspring of obese mothers (205, 206). However, contradictory findings have also been presented (207, 208). Ultrasonography in obese women is often suboptimal and the greater incidence of congenital malformations may partly be due to diagnostic difficulties.

Maternal overweight and obesity are associated with increased rates of GDM, hypertensive disorders, delivery complications and macrosomia (209). The HAPO

research group demonstrated that maternal obesity is independently associated with adverse pregnancy outcomes, including birth weight > 90th percentile (aOR 1.73, 95% CI 1.50–2.00), cord C-peptide concentrations > 90th percentile (aOR 1.77, 95% CI 1.49–2.11), primary Caesarean deliveries (aOR 1.51, 95% CI 1.33–1.71) and pre-eclampsia (aOR 3.91, 95% CI 3.31–4.62). The combination of GDM and obesity further increases these risks (210).

Compared to normal weight women, the risk of both elective and emergency Caesarean deliveries has found to be twofold in obese women (211). The increase in Caesarean deliveries in obese women may be partly related to the increased incidence of macrosomia and also to an increased risk of failure to progress in the first stage of labour (212, 213). In addition, obese women are found to have higher rates of delivery induction and failed inductions compared to normal weight women (214). The rates of operative vaginal deliveries, shoulder dystocia and third/fourth-degree lacerations have been found to be increased in obese nulliparous women compared with normal-weight women (214). Additionally, both regional and general anaesthesia are problematic in this population, as there may be difficulties in the placement of spinal or epidural anaesthetics or in the intubation of an obese mother (215).

A large Swedish population-based study revealed the risk of adverse pregnancy outcomes, such as hypertensive disorders, GDM, Caesarean delivery, stillbirth and LGA infants to be increased in women whose BMI increased by over 3 units between their first and second pregnancy compared with those with a BMI change of -1.0 to 0.9 units (216).

Maternal pre-pregnancy BMI has also been found to be independently associated with neonatal fat mass and percentage body fat (210). This finding is proposed to be related to metabolic changes, particularly insulin resistance of obese mothers (215). In obese women the combination of excessive fetal growth and functional limitations of the placenta to transfer sufficient amounts of oxygen to meet fetal requirements may lead to hypoxaemia and stillbirth (209). Several studies have shown an association between maternal obesity and stillbirth (216–219).

A positive association between maternal obesity and the risk of pre-eclampsia has been demonstrated in several studies (213, 220–222). A Norwegian population-based observational study revealed that women with late-onset pre-eclampsia delivering at term had an increased risk of LGA infants and the excess of LGA infants was attributable to maternal obesity but not GDM or diabetes (223).

Data on the association between maternal overweight or obesity and preterm birth (< 37 gestational weeks) is conflicting (224–226). Most studies show an increase in medically indicated preterm deliveries (227). A recent population-based study in Sweden showed an increased risk of spontaneous preterm delivery among overweight women. The highest risk was in women with severe obesity and the risk was particularly increased in cases of extremely preterm delivery (22–27 gestational weeks). The risk of medically indicated preterm delivery increased along with BMI, but when obesity-related disorders, such as hypertensive or diabetic disorders were excluded the risk was substantially reduced (225).

Obese women seem to have a more complicated puerperium: endometritis, post-partum haemorrhage, prolonged hospitalisation and wound infections appear to be more frequent in obese women (209). The risk of pregnancy-related thromboembolism is found to be increased in overweight and obese women (211).

2.6.2 Long-term consequences of maternal overweight

Maternal risks

Obesity increases the risks of type 2 diabetes and CVD (228). An overweight condition is a strong risk factor of GDM and together they are associated with future risks of diabetes and MetS (14, 184). In a follow-up study by Pirkola *et al.* (2010) pre-pregnancy overweight alone and with concomitant GDM was an essential risk factor as regards later development of diabetes and hypertension. GDM with normal pre-pregnancy weight predicted future diabetes, but not hypertension (229).

Offspring risks

Childhood obesity is an increasing health concern. It is defined as a BMI $\geq 95^{th}$ percentile of the BMI-for-age growth charts in children and adolescents aged 2-19 years. The prevalence of childhood and adolescent obesity is reported to be 16.9% in the U.S. and 12–36% in Europe (230, 231).

Maternal metabolism affects on fetal programming *in utero* and may have long-term metabolic consequences in the offspring by way of epigenetic mechanisms. Infants born SGA have been found to be at an increased risk of

future overweight and development of MetS (232). High birth weight is also associated with obesity in adolescents and adults for at least 25 years (233). Both maternal obesity and hyperglycaemia have been reported to be associated with metabolic disturbances and obesity of the offspring (234). The current epidemic of obesity and related disorders seems to begin as early as *in utero* along with fetal overgrowth and adiposity (215).

The results of a recent review do not support earlier evidence that prenatal exposure to hyperglycaemia alone increases the risk of obesity and diabetes in the offspring. Parental obesity is considered to be an even more important risk factor as regards the later development of obesity or diabetes of the offspring than exposure to maternal hyperglycaemia (235). In a longitudinal cohort study, maternal pre-pregnancy overweight was an independent risk factor of offspring overweight and abdominal obesity at the age of 16 years and concomitant maternal GDM further increased the risk. GDM in normal-weight mothers was not associated with an increased risk of offspring overweight (236).

Children born to obese mothers have been found to be obese at the age of two years twice as often as children of normal-weight mothers (237). A high maternal pre-pregnancy BMI, excessive gestational weight gain and high offspring birth weight have been found to correlate with overweight and abdominal obesity in the offspring (238, 239). However, the retrospective cohort studies are unable to demonstrate the influence of current lifestyle on the risk of obesity and MetS.

The increased prevalence of childhood and adolescent obesity is related to increased rates of type 2 diabetes and MetS. Impaired glucose tolerance was found in 25% of obese children aged 4–10 years and in 21% of obese adolescents in a multiethnic cohort study (240). Boney *et al.* have published a longitudinal cohort study of the offspring of women with and without GDM. Maternal GDM was not an independent risk factor of offspring MetS, but the risk was increased when LGA status and maternal GDM were combined, both being equal predictors of future MetS (18). Moreover, a cohort study carried out by Patel *et al.* demonstrated high maternal pre-pregnancy BMI to be a significant predictor of current wheezing and physician-diagnosed asthma in adolescent offspring (241).

3 Aims of the present study

The main aim of the present study was to investigate the effect of metformin on pregnancy outcome as an alternative to insulin in the treatment of GDM and to compare the neonatal outcomes as well as later growth and development of the children exposed to metformin or insulin *in utero*. In addition, this study was aimed at investigation of the separate and concomitant effects of GDM and maternal overweight or obesity on pregnancy outcomes and maternal long-term risks.

The specific aims of this study were:

1. To investigate the efficacy of metformin in the prevention of fetal macrosomia and its influence on neonatal outcome in comparison with insulin (Study I).
2. To compare the growth and development of children prenatally exposed to metformin or insulin up to the age of 18 months (Study II).
3. To investigate the independent and concomitant effects of maternal GDM and overweight or obesity on pregnancy and neonatal outcome (Study III).
4. To evaluate the incidence of MetS and its' components, carotid intima-media thickness and serum levels of inflammatory markers in women with a history of insulin-treated GDM compared with women without GDM 19 years after the index pregnancy (Study IV).

4 Materials and methods

The clinical part of this study was carried out in the department of Obstetrics and Gynecology, Oulu University Hospital in 2005–2013. The Study I was a randomized, controlled study conducted 2005–2009 and the Study II was a follow-up of the Study I. The study IV was a clinical case-control study. Written informed consent was obtained from the participants. The studies were approved by the Ethics Committee of the Northern Ostrobothnia Hospital District and the Study I also by Finnish National Agency of Medicines. The Study I was registered at Clinicaltrials.gov, NCT01087866; http://clinicaltrials.gov/ct2/show/NCT01087866.

The Study III was a register-based retrospective study, in which Finnish Medical Birth Register (MBR) data were used. MBR data includes detailed information on the course and complications of pregnancy, delivery and perinatal health of the newborn and since 2004, the MBR has included information on whether an OGTT was performed, whether the result was abnormal and whether insulin treatment was initiated during pregnancy. MBR does not include information on possible initiation of metformin treatment.

4.1 Studies I and II

4.1.1 Study subjects and design

During the study period risk-factor based screening of GDM at 24–28 gestational weeks was organized by maternity welfare clinics. A diagnosis of GDM was set after one or more abnormal values in OGTT (Table 2).

After the diagnosis of GDM the women received dietary and lifestyle counselling at primary care. Self-monitoring of glucose concentrations were measured before breakfast and one and a half hours after the main meals. The target fasting glucose concentration was < 5.3 mmol/l and postprandial < 6.7 mmol/l. Pharmacological treatment was considered if glucose concentrations rose above the target levels at least twice.

The inclusion criteria of the study were singleton pregnancy, in which GDM was diagnosed at 12–34 weeks of gestation and the mother was unable to maintain their glucose balance with dietary treatment. Exclusion criteria were pre-eclampsia (blood pressure above 140/90 mmHg and proteinuria over 0.3 g per day after 20 weeks of gestation), essential hypertension requiring antihypertensive

medication or fetal growth restriction (fetal growth < 5 percentile for gestational age). A total of 100 patients were randomized. Randomization was made using opaque numbered sealed envelopes containing a randomization code generated manually in blocks of ten. The flowchart of the study is presented in Figure 1.

In the Study II, a questionnaire concerning growth and development of the child was sent to the women who participated in Study I. The questionnaire was returned by 45/47 mothers in the metformin group and by 48/50 mothers in the insulin group, the response rate being 96%. The flowchart of the Study II is presented in Figure 2.

4.1.2 Methods and outcomes

Before initiating medication, normal renal and liver functions were ensured by determining the serum concentrations of ASAT and ALAT, electrolytes and creatinine after an overnight fast, and level of HbA_1c was also measured by using standard laboratory methods.

Metformin (Diformin retard® 750 mg, Leiras Finland) was initiated at a dose of 750 mg once daily for the first week, twice daily for the second week, and three times daily from the third week onwards. Medication was discontinued if significant side effects, such as diarrhea occurred. If normoglycaemia was not achieved with the maximal daily dose of metformin in one to two weeks, supplemental insulin was added. Insulin treatment was accomplished according to the hospitals' guidelines: long-acting human NPH insulin (Protaphane®, Novo Nordisk, Denmark) was used to normalize fasting glucose concentrations and rapid-acting insulin analog (Humalog®, Eli Lilly, USA) was used to normalize postprandial concentrations. The women continued the self-monitoring of blood glucose concentrations and reported values to the nurse. During delivery, glucose monitoring was performed by the midwife and the women were treated with an intravenous glucose infusion and, when needed, short-acting human insulin (Actrapid®, Novo Nordisk, Denmark) according to the hospitals' guidelines.

During pregnancy, the women were followed at the hospitals' outpatient maternity clinics at four-week intervals from 12 to 32 weeks, at two-week intervals from 32 to 36 weeks and once to twice weekly after 36 weeks of gestation. Maternal weight gain was recorded and fetal growth and well-being was assessed by ultrasonography at every prenatal visit. Level of HbA_{1c} was measured at randomization, two weeks after the initiation of medication and

monthly thereafter. Delivery induction was considered at 40 gestational weeks at the latest. A post-partum visit was scheduled approximately 8 weeks after delivery.

The primary outcome was the incidence of macrosomia defined as birth weight over 4000g, or LGA, defined as birth weight above the mean plus two standard deviations (+2SD) using the Finnish sex-specific charts adjusted for gestational age (242). Secondary outcomes included neonatal complications such as admission to NICU, neonatal hypoglycaemia requiring intravenous glucose treatment, hyperbilirubinaemia treated by means of phototherapy, and birth injuries (clavicular fracture or brachial nerve injury). Apgar scores and cord artery pH were recorded. Maternal outcomes included need of supplemental insulin in the metformin group, incidence of premature deliveries before 37 gestational weeks, hypertensive complications of pregnancy, weight gain during pregnancy and mode of delivery.

In the Study II, questionnaire was completed by a trained nurse at the child welfare clinic and it included data on height, weight and head circumference (HC) at the ages of 6, 12 and 18 months, as well as motor, social and linguistic development as assessed by a doctor at 18 months of age.

The check-up at 18 months of age included examination of vision, consisting of corneal light reflex and red reflex examination with an ophthalmoscope, Hirschberg and cover tests in the assessment of strabismus and pinch grip to test eye-hand co-ordination. Evaluation of motor function included the capacity to stand and walk without support, normal pinch grip and co-ordination of the upper limbs. The social, emotional and language development of the child was evaluated by testing the response to spoken commands and by the ability to enunciate understandable words and make reciprocal contact.

The weight and height percentiles of the children at different ages were calculated using recently updated Finnish growth reference software (243). The numbers of children growing above the 95^{th} percentile or below the 5^{th} percentile lines were recorded. Weight-for-length (i.e. percentage difference from median weight of the children of same length) was calculated by using the same software. According to Finnish Current Care Guidelines concerning childhood obesity, a weight-for-length percentage of 10 to 20% was defined as overweight and over 20% as obesity (244). To evaluate body composition, the ponderal index (PI) was calculated as 1 000 000x weight in kilograms divided by height in centimetres cubed (kg/cm^3).

The primary outcomes were weight and height of the children at the ages of 6, 12 and 18 months. The secondary outcomes included motor, social and linguistic

development of the children up to the age of 18 months as well as the body composition of the children defined by PI and the incidence of overweight and obesity defined by weight-for-length.

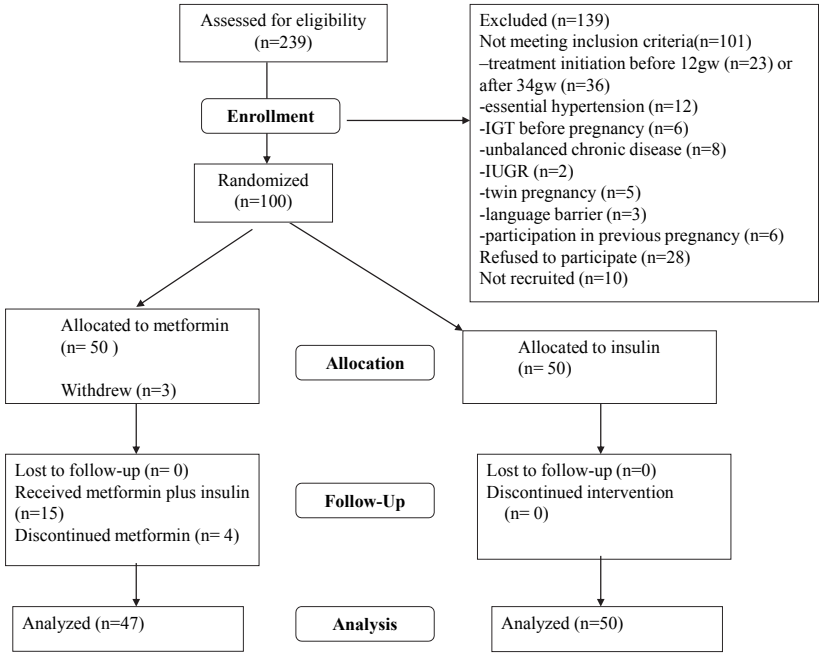

Fig. 1. Flowchart of Study I

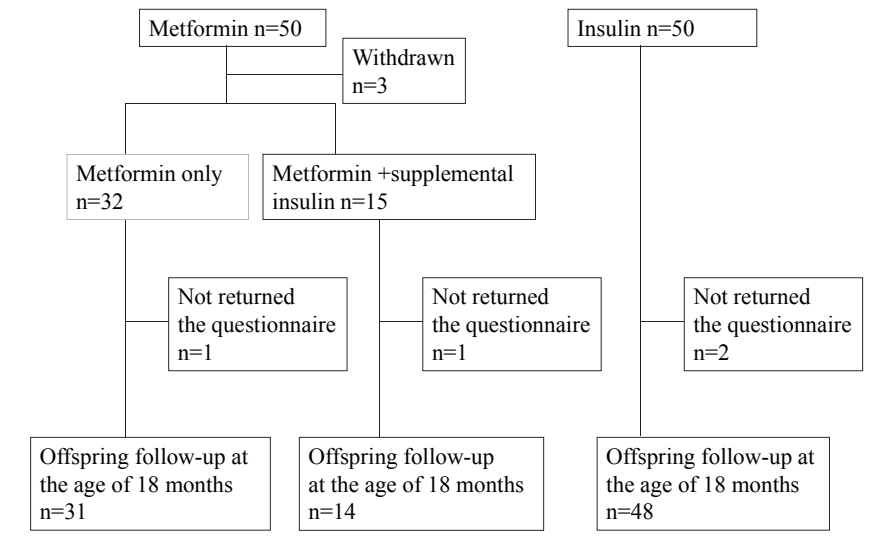

Fig. 2. Flowchart of Study II

4.2 Study III

4.2.1 Study subjects

The study population consisted of all women who delivered in 2009 in Finland and had a singleton pregnancy and an OGTT performed during pregnancy (n = 24 565). The screening and treatment of GDM were performed according to the Finnish Current Care Guidelines (Table 3). The use of oral anti-diabetic agents was not recommended by the guideline (6). The women were divided into two groups according their OGTT results (normal or abnormal) and both groups were further divided into subgroups according to their pre-pregnancy BMI: normal-weight (BMI $\leq$ 24.9 kg/m²), overweight (BMI 25.0–29.9 kg/m²) and obese (BMI $\geq$ 30 kg/m²). The flowchart of the Study III is presented in Figure 3.

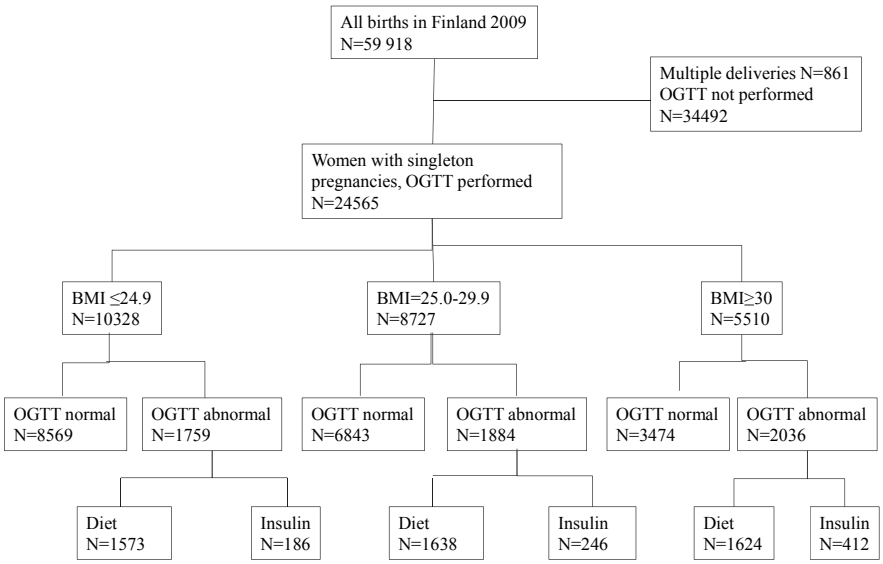

Fig. 3. Flowchart of Study III

4.2.2 Methods and outcomes

Pre-pregnancy BMI was calculated as the individual's pre-pregnancy weight (kg) divided by the square of the height (m). The primary outcomes included the incidence of macrosomia defined as large for gestational age (LGA, birth weight over mean +2SD) (242), the rate of Caesarean delivery and perinatal morbidity defined as need for treatment at a neonatal ward.The secondary outcomes were the rates of perinatal loss, premature deliveries (i.e. delivery before 37+0 gestational weeks), neonatal hypoglycaemia and delivery inductions as well as the 5-minute Apgar scores of the neonates.

4.3 Study IV

4.3.1 Study subjects

The primary study group consisted of 127 women with insulin-treated GDM who gave birth at Oulu University Hospital between 1988 and 1993. During this period, risk factor-based GDM screening was performed with an OGTT (Table 2). After the diagnosis of GDM, the patients received dietary and lifestyle counselling and began self-monitoring of glucose concentrations. According to the treatment guidelines in 1988-1993, insulin therapy was begun if blood glucose concentrations repeatedly exceeded the target levels (5.3 mmol/l when fasting and 6.7 mmol/l at 1.5 h after a meal).

The healthy control women (n = 127) were selected from the delivery log and were matched for age (± 2 years), parity (primiparous, 1–3 and > 3 deliveries), and year of delivery. All participants were asked to complete a detailed postal questionnaire including obstetric history and data on current diseases (medically treated diabetes, hypertension, and dyslipidaemia); the response rate was 81%. A total of 116 women (52.5%) were willing to attend clinical examinations (Figure 4).

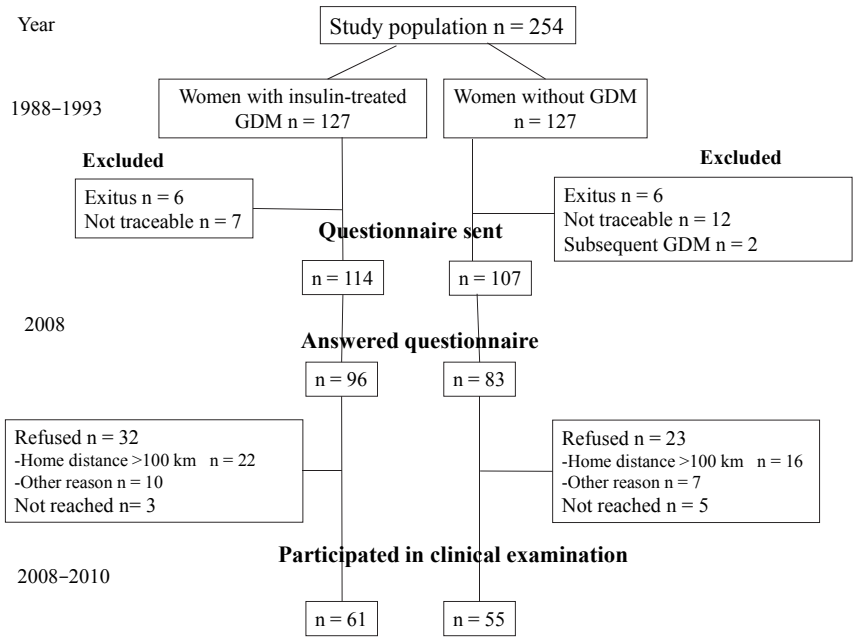

Fig. 4. Flowchart of Study IV

4.3.2 Methods and outcomes

Clinical examinations of the women was performed by a trained nurse (Table 8). Blood pressure was measured twice using an automatic device (AND UA-767) after 5-min rest in the sitting position. The average of the two measurements was used in the analysis.

Carotid intima-media thickness (CIMT) was measured by an experienced radiologist using a high-resolution B-mode ultrasonographic equipment (iU22, Philips Ultrasound, Bothell, WA, USA) with a 3–9-MHz linear-array transducer. The right common carotid artery was scanned (1 cm proximal to the dilatation of the carotid bulb) and the image was focused on the posterior wall. A minimum of 3 measurements were taken over a 1-cm length in a plaque-free area. The far wall of the carotid artery was analysed using an offline automatic computerized analysing system (Philips Qlab quantification software). The limits of normal and

abnormal CIMT values were defined according to Simon *et al.*, who have reported the distribution of normal values of CIMT according to age and gender. Abnormally increased CIMT was considered as a value above the 75th upper percentile in each age category (245).

A venous blood sample was drawn from an antecubital vein after an overnight fast of 10 to 12 hours. A 2-h 75-g OGTT, with fasting and 2-h values of plasma glucose and insulin, was performed among those without pre-existing diabetes. In the those with diabetes, only fasting glucose and insulin concentrations were measured. The serum lipid profile was assessed, and serum levels of hsCRP, PAI-1, leptin, and adiponectin were measured (Table 8).

Table 8. Clinical and laboratory examinations of the Study IV.

Clinical examinations	Laboratory tests
Weight	OGTT or fasting glucose
Height	Total cholesterol
BMI	Low-density lipoprotein cholesterol (LDL-C)
Waist circumference	High-density lipoprotein cholesterol (HDL-C)
Hip circumference	Triglycerides
Waist-hip-ratio (WHR)	High sensitivity CRP (hsCRP)
Blood pressure	Plasminogen activator-inhibitor-1 (PAI-1)
CIMT	Adiponectin
	Leptin

Plasma glucose and insulin concentrations were determined by using an automatic chemical analyser (Cobas Integra 700, Roche Diagnostics, Switzerland). Total cholesterol, LDL-C, HDL-C, and TG were analysed by using an automatic chemical analyser (Advia 1800, Siemens Healthcare Diagnostics, Terrytown, NY, USA); levels of hsCRP, were analysed by immunonephelometry (BN ProSpec, Siemens Healthcare Diagnostics, Marburg, Germany); those of PAI-1, by enzyme immunoassay (Diagnostica Stago, France); and those of adiponectin and leptin, by radioimmunoassay (Millipore Corporation, MA, USA).

Finnish Current Care Guidelines criteria were used in the diagnoses of impaired glucose tolerance (IGT), diabetes (Table 9), hypertension and dyslipidaemia (246-248). Blood pressure ≥ 140/90 mmHg was considered mildly elevated and ≥ 160/100 mmHg considerably elevated. The criteria for dyslipidaemia was a serum LDL-C concentration ≥ 3.0 mmol/l, TGs ≥ 2.0 mmol/l or HDL-C ≤ 1.0 mmol/l or a combination thereof. Metabolic syndrome was defined according to NCEP (Updated 2001) criteria (249) (Table 10).

Table 9. Diagnostic criteria of IGT and diabetes in 2-h 75-g OGTT according to Finnish Current Care Guidelines(246)**.**

Definition	Fasting glucose	2-hour glucose
IGT	6.1–6.9 mmol/l	7.8–11.0 mmol/l
Diabetes	≥ 7.0 mmol/l	> 11.0 mmol/l

Table 10. Diagnostic criteria of metabolic syndrome in women according to NCEP(249)**.**

At least three of the following	Definition
Central obesity	Waist circumference ≥ 88 cm
Dyslipidaemia	Triglycerides ≥ 1.7 mmol/l or HDL ≤ 1.29 mmol/l
Blood pressure	≥ 135/85 mmHg
Fasting plasma glucose	≥ 5.6 mmol/l

4.4 Statistical methods

In Study I, power calculations were made knowing that the rate of macrosomia in cases of untreated GDM is two- to fourfold higher than in non-diabetic women or after effective treatment of GDM (9). The incidence of newborns weighing over 4000g in women with insulin-treated GDM was 29.3% in our hospital in 2004. Our presumption was that metformin is less effective than insulin in preventing fetal macrosomia. Calculation of sample size was carried out to detect a 30 percent unit difference in the rate of macrosomia between the study groups. A two-sided test with 80% power and significance level 0.05 gave a sample size of 50 women in each group. In the Study I, intention to treat analysis was performed, as the subjects with metformin and supplemental insulin were analyzed in the metformin group. Additional analyses were made by comparing women with only metformin and metformin with supplemental insulin.

Analyses of all four studies were performed with SPSS for Windows software (versions 16.0–22.0; SPSS Inc.). Comparisons between two groups were carried out by using Student's *t*-test for continuous variables with a normal distribution and by using the Mann-Whitney *U*-test for continuous variables with a non-normal distribution. For categorial variables, Fisher's exact test was used according to the expected frequencies. Two-tailed tests were used for all analyses and $p < 0.05$ was regarded as being statistically significant.

Multivariate analyses in Study II were performed with children's weight and overweight or obesity at the age of 18 months as dependent variables and maternal pre-pregnancy BMI and treatment option as predictive variables.

In Study III, logistic regression was used to calculate risk ratios and 95% confidence intervals concerning the risk of development of outcomes associated with GDM, BMI and mode of treatment. Normal-weight women with normal glucose tolerance were used as a reference group.

In Study IV, the study subjects were divided into four subgroups according to their GDM status and pre-pregnancy BMI (< 25.0 kg/m^2 or ≥ 25.0 kg/m^2) in order to assess the significance of pre-pregnancy overweight. One-way ANOVA was used to compare the four groups. Logistic regression analysis was performed with MetS as the dependent variable and the following predictive variables: pre-pregnancy BMI, GDM, pre-eclampsia, and chronic hypertension during pregnancy.

5 Results

5.1 Metformin versus insulin in the treatment of GDM (Study I)

The baseline characteristics (age, parity, BMI, glucose concentrations in OGTT, gestational age at randomization) of the women on metformin or insulin therapy did not differ (original publication I, Table 1, page 884).

The mean weight gain of the women during pregnancy did not differ between the insulin (9.2 $\pm$ 5.5 kg) and metformin (8.6 $\pm$ 3.3 kg) groups (p = 0.5). The incidence of hypertensive complications was similar, while four women in both study groups had mild pre-eclampsia.

The mean gestational age at delivery was similar in both groups (Table 11). There were three spontaneous premature deliveries at 31, 33 and 36 gestational weeks in the insulin group (6.0%) and one at 36 gestational weeks in the metformin group (2.1%) (p = 0.3). The incidences of both vacuum extraction deliveries and cesarean sections were significantly higher in the metformin group compared with the insulin group (p = 0.04) (Table 11).

The mean birth weight of the newborns, and the incidences of LGA infants or neonatal complications did not differ significantly between the study groups (Table 11). There were two clavicular fractures after shoulder dystocia in the insulin group. No perinatal deaths occurred in this trial.

5.1.1 Need of supplemental insulin

Metformin treatment was converted to insulin treatment in one study subject after three weeks of therapy because of elevated levels of liver enzymes and in one subject the metformin dose was reduced to 1500mg/d because of diarrhoea. Fifteen women of 47 (31.9%) did not achieve normoglycaemia with metformin and needed supplemental insulin treatment. After starting supplemental insulin three of the women discontinued use of metformin because of gastrointestinal side-effects. The characteristics of the women on metformin only and on metformin with supplemental insulin are listed in Table 12. The mean birth weight of their neonates was significantly higher in the supplemental insulin group than in the metformin-only group. The mean amount of insulin needed before delivery was 30 IU (range 5–169 IU) in women randomized to insulin treatment and 43 IU (range 2–72 IU) in the metformin and supplemental insulin group (p = 0.05).

Table 11. Outcomes in the metformin- and insulin-treated groups.

Outcome	Metformin n = 47	Insulin n = 50	RR (95% CI)	p-value
GA at delivery (weeks)	38.9 ± 1.8	39.3 ± 1.1		0.153
Spontaneous vaginal delivery	22 (46.8)	36 (72.0)	0.7 (0.46–0.92)	0.011
Labor induction	24 (51.0)	26 (52.0)	1.0 (0.67-1.45)	0.960
Caesarean delivery	18 (38.3)	10 (20.0)	1.9 (0.99–3.31)	0.047
Birth weight (g)	3712 ± 432	3558 ± 593		0.145
Birth weight ≥ 4000 g	9 (19.1)	11 (22.0)	0.9 (0.40-1.91)	0.729
LGA infants	4 (8.5)	5 (10.0)	0.9 (0.24–2.98)	0.801
Neonatal hypoglycaemia	4 (8.5)	7 (14.0)	0.7 (0.23–1.89)	0.439
Treatment at neonatal ward	7 (14.9)	11 (22.0)	0.7 (0.29–1.60)	0.368

Data are mean ± SD or n (%), RR = Relative Risk, CI = Confidence Interval

GA = Gestational age

Table 12. Baseline characteristics and neonatal outcome in the metformin group.

Outcome	Metformin only n = 32	Metformin with additional insulin n = 15	p-value
BMI* (kg/m^2)	29.6 ± 5.3	35.7 ± 7.2	0.002
OGTT 0h glucose (mmol/l)	5.0 ± 0.5	6.1 ± 1.1	0.001
OGTT 2h glucose (mmol/l)	8.0 ± 1.8	8.7 ± 2.2	0.310
GA at randomization (weeks)	31 ± 3.1	26 ± 5.9	0.001
Birth weight (g)	3615 ± 417	3919 ± 400	0.022

Data are mean ± SD

* at first antenatal visit, GA = Gestational age

5.2 Follow-up of children exposed to metformin or insulin (Study II)

The gestational age and the mean birth weight of the neonates were similar in both groups, but there was a statistically significant difference in the length of the neonates between the groups (metformin 50.8 vs. insulin 49.9 cm, p = 0.047).

At the post-partum follow-up visit, the BMI of the mothers did not differ significantly between the metformin and insulin groups (30.4 vs. 29.9 kg/m²) and

67% of mothers who had been on metformin and 62% of mothers on insulin breast-fed their infants. There was no significant difference between the groups according to mode of feeding (totally breast- or bottle-fed, or combined).

Weight, height and PI of the children aged 6 and 12 months are presented in the Table 13. There was no significant difference in the proportions of overweight, obese or underweight infants (determined by weight-for-length) between the groups. There was a tendency to a higher rate of overweight at the age of 18 months in metformin-exposed children, but the difference was not statistically significant (22.2 vs. 12.5%, RR 1.78, 95% CI 0.70–4.49). Mean HC was similar in both groups at every time point.

The occurrence of any mild motor or linguistic developmental delay at the age of 18 months was rare and similar in both groups.

After adjustment for maternal pre-pregnancy BMI the mean weight at the age of 18 months was 12.0kg (95% CI 11.6–12.5) vs. 11.3kg (95% CI 10.9–11.8) in the metformin and insulin groups, respectively. In multivariate regression analysis, maternal pre-pregnancy BMI was associated with the weight of the children at the age of 18 months so that one unit increase in maternal BMI increased the weight of the child by 0.096 kg (95% CI 0.040–0.150kg, p = 0.001). One unit increase in maternal BMI caused a significant increase in the estimated risk of the child being overweight (OR 1.13, 95% CI 1.03–1.25, p = 0.013) or obese (OR 1.27, 95% CI 1.05–1.55, p = 0.014) at the age of 18 months. Metformin-exposure was also associated with higher weight at this time point so that insulin exposure decreased the weight by 0.709kg (95% CI -1.37– -0.05kg, p = 0.036).

Table 13. Growth of children exposed to metformin or insulin at the ages of 12 and 18 months.

Outcome	Metformin n = 45	Insulin n = 48	p-value
12 months measurements			
Weight (kg)	10.5 ± 1.5	9.8 ± 1.3	0.035
Height (cm)	76.9 ± 3.3	75.6 ± 3.1	0.062
PI (kg/m^3)	23.0 ± 2.5	22.8 ± 2.0	0.617
18 months measurements			
Weight (kg)	12.1 ± 1.9	11.3 ± 1.5	0.040
Height (cm)	83.9 ± 3.6	82.2 ± 3.1	0.023
PI (kg/m^3)	20.4 ± 2.1	20.3 ± 1.7	0.895

Data are mean ± SD

PI = ponderal index

5.3 Independent and concomitant effects of GDM and overweight/obesity on pregnancy outcome (Study III)

In 2009, there were 59 057 singleton deliveries in Finland. The mean age of the mothers was 30.0 years, the mean pre-pregnancy BMI 24.3 kg/m^2 and the rate of primiparity 42%. The incidence of an abnormal OGTT result during pregnancy was 9.6%.

OGTTs were performed among 24 565 (42%) mothers and GDM was diagnosed in 23% of them (n = 5,679). Of all the tested women, 10,328 (42.0%) were of normal-weight, 8,727 (36%) were overweight, and 5,510 (22%) were obese. The probability of GDM increased along with weight. The proportion of mothers requiring insulin treatment was 14.9%. Obese mothers were most likely to be treated with insulin.

5.3.1 Macrosomia

The risk of macrosomia was not increased in normal-weight women with GDM, when normal-weight women without GDM were taken to be the reference group (RR 1.18, 95% CI 0.86–1.60). In women with normal OGTT results, both overweight and obesity were associated with an increased risk of macrosomia, with RRs of 1.21 (95% CI 1.00–1.48) for overweight women and 1.60 (95% CI 1.29–1.99) for obese women. Concomitant GDM further increased the risk, with RRs of 1.90 (95% CI 1.48–2.44) for overweight GDM women and 2.86 (95% CI 2.31–3.53) for obese GDM women (Table 14).

5.3.2 Caesarean delivery

GDM or overweight alone were not associated with an increased rate of Caesarean section, but in women with both conditions, the rate was increased (RR 1.32, 95% CI 1.19–1.46). Among obese women, the risk of Caesarean delivery was increased with or without GDM, with RRs of 1.58 (95% CI 1.45–1.73) and 1.23 (95% CI 1.13–1.34), respectively (Table 14).

When only primiparous women were analysed, the risk of Caesarean delivery was slightly increased in normal-weight GDM women (RR 1.19, 95% CI 1.04–1.37) and overweight women without GDM (RR 1.14, 95% CI 1.04–1.25). Obesity without GDM was associated with an increased risk of Caesarean delivery (RR 1.34, 95% CI 1.20–1.49). When overweight or obesity occurred

together with GDM, the risk of Caesarean delivery further increased, with RRs of 1.41 (95% CI 1.23–1.62) and 1.71 (95% CI 1.51–1.93), respectively.

5.3.3 Neonatal morbidity

GDM was associated with a nine- to tenfold risk of neonatal hypoglycaemia in all BMI groups, but the risk was also increased (1.4-fold) in obese mothers with normal glucose tolerance. The risk of treatment of the infant in a neonatal ward among women with GDM increased along with the BMI category, with RRs of 1.36 (95% CI 1.19–1.61) for normal-weight women, 1.51 (95% CI 1.31–1.75) for overweight women and 1.99 (95% CI 1.75–2.25) for obese women. Among women without GDM, maternal obesity was a risk factor as regards treatment in a neonatal ward (RR 1.33, 95% CI 1.18–1.50). GDM was associated with an increased risk of preterm delivery in all BMI groups (Table 14).

Table 14. Relative risk of adverse pregnancy outcome according to pre-pregnancy BMI and OGTT results.

	BMI ≤24.9 n = 10328		BMI 25.0–29.9 n = 8727		BMI ≥ 30 n = 5510	
OGTT status	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
n (%)	8569 (83.0)	1759 (17.0)	6843 (78.4)	1884 (21.6)	3474 (63.0)	2036 (37.0)
Preterm delivery	1	1.28 (1.01-1.62)	0.88 (0.75-1.05)	1.38 (1.10-1.73)	1.11 (0.91-1.35)	1.52 (1.23-18.7)
Caesarean delivery	1	1.10 (0.98-1.23)	1.04 (0.97-1.12)	1.23 (1.19-1.46)	1.23 (1.13-1.34)	1.58 (1.45-1.73)
Macrosomia	1	1.18 (0.86-1.60)	1.21 (1.00-1.48)	1.90 (1.48-2.44)	1.60 (1.29-1.99)	2.86 (2.31-3.53)
Neonatal hypoglycaemia	1	8.73 (7.06-10.80)	1.10 (0.86-1.42)	9.35 (7.60-11.51)	1.38 (1.03-1.85)	10.54 (8.61-12.89)
Neonatal morbidity*	1	1.36 (1.19-1.61)	1.06 (0.96-1.18)	1.51 (1.31-1.75)	1.33 (1.18-1.50)	1.99 (1.75-2.25)

Data are RR (95% CI)

*Treatment at a neonatal ward

5.4 Independent and concomitant effects of GDM and pre-pregnancy overweight on maternal long-term outcome (Study IV)

5.4.1 Index pregnancy

During the index pregnancy, the mean age of the women was 35.9 vs. 33.7 years in the study group and control group, respectively (p = 0.067). Pre-pregnancy BMI was significantly higher in GDM women than in controls (27.1 vs. 24.5 kg/m², p = 0.004, respectively). Smoking was rare in both groups (6.6 vs. 5.8%, p = 0.163, respectively). The diagnosis of GDM in the study group was set at a median of 26 (range: 6–39) gestational weeks.

5.4.2 Current outcome

During the clinical examination performed on average 19 years (range 16–21) after the index pregnancy, the mean ages of the GDM and control women did not differ between the groups (52.8 vs. 51.7 years, p = 0.386). Neither was there a difference in menopause status, as 62% of the GDM women and 60% of the control women were postmenopausal (p = 0.850). Women with a history of GDM smoked more often than women in the control group (21 vs. 7%, p = 0.038). The self-reported incidences of diabetes, chronic hypertension, and medically treated dyslipidaemia were significantly higher among the GDM women than the controls, 56 vs. 2% (p < 0.001), 54 vs. 31% (p = 0.015) and 48 vs. 20% (p = 0.003), respectively.

During the clinical examination, the mean BMI was similar in both groups (Table 15), and 65.6% and 76.4% of the GDM and control women were overweight, respectively.

In clinical examinations, six new diagnoses of diabetes were set in the GDM group and two in the control group, increasing the prevalence of diabetes to 65.6 and 5.5% in these groups, respectively. In addition, seven and six cases of IGT were found, respectively. When the previously diagnosed and new cases were summarized, the total prevalence of dyslipidaemia in the GDM and control groups was 61 and 60%, respectively. Women in the GDM group had a significantly lower mean LDL-C concentration than control women, and this

difference remained significant after the exclusion of women with medication for dyslipidaemia (after exclusion, 2.6 vs. 3.2 mmol/l, respectively, p = 0.03).

The incidence of MetS was significantly higher in the GDM group than in the control group (Table 15). The groups did not differ in terms of the concentrations of systemic inflammation markers.

Women in the GDM group had significantly greater mean value of CIMT than the control women and CIMT was more often considered abnormal (Table 15). When excluding smokers, the difference in CIMT between the groups remained significant (0.63 vs. 0.56 mm, respectively, p = 0.003).

Table 15. Current clinical and laboratory parameters among women with prior insulin-treated GDM and controls examined 19 years after the index pregnancy.

Outcome	GDM n = 61	Control n = 55	RR (95% CI)	p-value
BMI (kg/m²)	28.7 ± 5.9	29.2 ± 5.9		0.678
Waist circumference (cm)	94.4 ± 14.9	94.4 ± 14.2		0.990
Waist-hip ratio	0.92 ± 0.07	0.90 ± 0.06		0.165
MetS	38 (62.3)	17 (30.9)	1.8 (1.3-2.6)	0.001
CIMT (mm)	0.67 ± 0.29	0.56 ± 0.08		0.007
Abnormal CIMT	43 (64.2)	17 (37.0)	1.7 (1.1-2.6)	0.004

Data are mean ± SD or n (%), RR = relative risk, CI = confidence interval

CIMT = carotid intima-media thickness

5.4.3 Effect of pre-pregnancy overweight

To assess the significance of pre-pregnancy overweight, both groups were divided into two subgroups according to pre-pregnancy BMI (< 25 kg/m² or ≥ 25 kg/m²). Three women in the control group were excluded because of missing pre-pregnancy weight data. The prevalence of MetS was 85.7% in overweight GDM women, 66.7% in overweight control women, 30.8% in normal-weight GDM women and 11.8% in normal-weight control women (p < 0.001) (Table 16).

Logistic regression analysis showed pre-pregnancy overweight to be the strongest factor predicting subsequent MetS. A one-unit increase in pre-pregnancy BMI was associated with a 1.5-fold increase in the estimated risk of MetS. Previous insulin-treated GDM was associated with a 3.5-fold increase in the estimated risk of MetS. When control women of normal pre-pregnancy weight (BMI < 25 kg/m²) were taken to be the reference group, the aOR for MetS was

3.3 (95% CI 0.9–12.7) for GDM women of normal pre-pregnancy weight, 15.0 (95% CI 3.6–62.8) for control women with pre-pregnancy overweight and 45.0 (95% CI 10.0–184.1) for GDM women with pre-pregnancy overweight.

Table 16. Comparison between the pre-pregnancy BMI groups

	GDM		Control		
Outcome	BMI < 25	BMI ≥ 25	BMI < 25	BMI ≥ 25	p-value
Pre-pregnancy BMI*	22.9 ± 1.5	30.4 ± 4.9	22.0 ± 1.6	28.7 ± 2.2	< 0.001
Current BMI*	25.0 ± 3.1	31.8 ± 6.1	26.1 ± 3.1	34.4 ± 5.7	< 0.001
MetS	8 (30.8)	30 (85.7)	4 (11.8)	12 (66.7)	< 0.001
CIMT**	0.60 ± 0.14	0.72 ± 0.36	0.56 ± 0.08	0.58 ± 0.08	0.022
Abnormal CIMT	14 (53.8)	29 (85.3)	16 (48.5)	8 (47.1)	0.002

Group 1 = GDM + BMI < 25 26, Group 2 = GDM + BMI ≥ 25 36, Group 3 = Control + BMI < 25 34, Group 4 = Control + BMI ≥ 25 17

Data are mean ± SD or n (%), p-value between groups, * kg/m², **mm

6 Discussion

6.1 Effect of metformin on pregnancy and neonatal outcome

In the present study, the incidence of adverse pregnancy and neonatal outcomes was not increased in women treated with metformin compared with women treated with insulin. The incidence of LGA infants/macrosomia and the mean birth weight of the newborns were similar with metformin and insulin treatments, the results being in line with those of most RCTs (121–126). However, a study by Niromanesh *et al.* (2012) revealed a significantly lower incidence of macrosomia and lower mean birth weight with women treated with metformin versus insulin (123). It is noteworthy that the definition of macrosomia/LGA vary between studies, which may impact on the incidences of those outcomes.

In this study, the frequency of neonatal hypoglycaemia was slightly but non-significantly higher in the insulin group than in the metformin group. In the MiG trial and a study by Spaulonci *et al.*, the incidence of severe neonatal hypoglycaemia was significantly higher in the insulin- than in the metformin-treated groups (122, 126), but other RCTs have not shown such a difference (121, 123–125). This may be partly due to different guidelines on diagnosis and treatment of hypoglycaemia. Overall, metformin treatment does not seem to increase the risk of neonatal complications and it may even decrease the risk of neonatal hypoglycaemia in comparison with insulin.

In our study, the incidence of preterm delivery was low and similar in both groups, the risk being slightly lower in women with metformin treatment, which is probably coincidental. The two relevant meta-analyses published revealed metformin treatment to be associated with an increased risk of preterm delivery (127, 144). The rate of Caesarean deliveries was significantly higher in metformin-treated than in insulin-treated women in our study. This finding is also presumed to be coincidental and due to small sample size, as it is not probable that metformin treatment has had an influence on the course of delivery.

In the present study we did not find any difference in the weight gain or in the rate of pre-eclampsia in women treated with metformin or insulin. Meta-analyses have revealed that metformin treatment was associated with lower maternal weight gain and a lower incidence of pregnancy-induced hypertension in comparison with insulin treatment (127, 144). In addition, the more recent systematic review and meta-analysis revealed metformin treatment to be

associated with lower postprandial blood glucose concentrations of the mother and less severe neonatal hypoglycaemia in comparison with insulin (144).

6.2 Need of supplemental insulin in women on metformin

In this study, 32% of the women on metformin treatment needed additional insulin to achieve normoglycaemia. In other RCTs, the need of additional insulin has varied from 14 to 46%. A systematic review and meta-analysis of six RCTs revealed the average need of additional insulin with metformin to be 38% (144).

According to the results of our study, the need of additional insulin in metformin-treated women associated with greater BMI, fasting hyperglycaemia in OGTT and earlier need of pharmacological intervention. In a study by Tertti *et al.*, the need of additional insulin was associated with higher age, earlier abnormal OGTT results and an earlier need of pharmacotherapy in pregnancy and in a study by Spaulonci, it was associated with early gestational age at diagnosis and higher mean pre-treatment glucose levels (124, 126). A meta-analysis carried out by Gui *et al.* revealed significantly higher fasting blood glucose concentrations in women who needed supplemental insulin compared to women with metformin only (127). In addition, in the study of Tertti *et al.*, the need of supplemental insulin associated with higher $HbA1_c$ and fructosamine concentrations at randomization indicating a higher level of hyperglycaemia among these patients (124). These findings indicate that in more serious forms of GDM, metformin alone is insufficient to ensure the glycaemic control of mothers and additional insulin is often needed. However, in those patients the use of metformin may possibly delay the need of insulin administration and decrease the amount of insulin needed.

In our study, the newborns of mothers on metformin and supplemental insulin had a significantly higher mean birth weight when compared with the metformin-only group. The LGA rate was 20% in the metformin plus supplemental insulin group, 3% in the metformin-only group and 10% in the insulin-only group. The differences did not reach statistical significance, probably because of the small sample size. It is likely that the women who needed supplemental insulin had more severe disturbances in their glucose metabolism. Glycaemic control among these women was also unsatisfactory over a longer period, which may accelerate the growth of the fetus before the achievement of normoglycaemia.

6.3 Outcomes of children prenatally exposed to metformin or insulin

Our results showed metformin-exposed children to be significantly taller and heavier at the age of 18 months than insulin-exposed children. However, mean PI did not differ significantly between the groups, indicating similar body adiposity. There was a tendency towards a higher rate of overweight at the age of 18 months in the metformin group, but the difference did not reach statistical significance, which may be due to small study population. The clinical significance of this finding is unclear. In the MiG TOFU study by Rowan *et al.* (2011), there was no difference at the age of two years in the height or weight of children exposed to either metformin or insulin *in utero*. The study revealed larger subscapular and biceps skin folds in children exposed to metformin, whereas the total fat mass of the children did not differ between the groups. The authors interpreted this finding to be a more favourable fat distribution in metformin-exposed than in insulin-exposed children (128). In the study carried out by Carlsen *et al.* (2012) 199 children of mothers with PCOS who were exposed to metformin or placebo in utero were investigated at the age of one year. Children exposed to metformin were found to be significantly heavier than those in the placebo group, but the height of the infants was not reported (131). The results of the studies made in women with GDM or PCOS are not completely comparable, because in PCOS-studies, metformin-exposure has begun already from the conception and continued through pregnancy and it has been compared to placebo, not to insulin.

Both maternal obesity and hyperglycaemia have been reported to be associated with metabolic disturbance and obesity of the offspring, but the role of pharmacological treatment of GDM in the child's future growth and metabolism has not been separately investigated (18, 234). Glycaemic control during pregnancy probably has more influence on the subsequent growth of the offspring than the mode of treatment, at least according to the similar short-term neonatal outcomes in metformin versus insulin studies.

In the present study there were no differences in the motor, social or linguistic development of the metformin- or insulin-exposed children, when assessed at the age of 18 months. This is in accordance with the results of a cohort study of 126 children born to PCOS women with metformin treatment during pregnancy where no adverse effects on the children's growth or motor and social development were found when assessed up to the age of 18 months (130). However, in the study of

Glueck *et al.* and ours, sample sizes are too small to detect differences between the groups in rare conditions, such as developmental delays.

6.4 Separate and concomitant effects of GDM and maternal overweight/obesity on pregnancy outcome

Many investigators reporting the influence of maternal overweight or obesity on pregnancy outcomes have not considered the effect of GDM. Recently, maternal obesity was shown to be an independent risk factor of macrosomia (210, 250, 251). In our study, the risk of macrosomia was increased 1.2-fold in overweight women and 1.6-fold in obese women without GDM, confirming the findings in these studies.

In our study, normal-weight mothers with treated GDM had similar rates of macrosomia and Caesarean delivery as normal-weight women confirmed to be normoglycaemic by way of OGTTs. On the contrary, in the HAPO study, GDM in normal-weight women was associated with an increased risk of macrosomia (210). The reason for this difference may be connected with the study protocol in the HAPO investigation, as the women did not receive optimal treatment for mild GDM because of the blinded OGTT results in the study. Our results support those reported by Crowther *et al.* (10), demonstrating that through optimal treatment and follow-up of GDM, the outcomes of GDM women are comparable to those of the background population.

Overweight and obesity have been shown to increase the risk of Caesarean delivery both with and without accompanying GDM (252, 253). The HAPO study group demonstrated an increased risk of primary Caesarean section in obese women (210). Our study demonstrated a 1.2-fold increased risk of Caesarean delivery in obese glucose-tolerant mothers, and when only primiparous women were included, a similar risk extended to overweight mothers. Concomitant GDM further increased the risk in both groups, in line with the results of previous studies (210, 252, 254).

In our study, the infants of GDM mothers were nine- to tenfold more likely to have hypoglycaemia than infants in the reference group. They also had a 1.4- to twofold increased risk of being admitted to a neonatal ward. This is consistent with previous literature, including the HAPO study (62). The increased rate of neonatal ward treatment may be explained by the need to follow and treat neonates with hypoglycaemia, as blood glucose concentrations of symptomless

neonates are followed up routinely when the mother is known to have GDM. In addition, an Apgar score of < 7 was more frequent in normal-weight and obese, but not overweight, women with GDM, which may reflect an asphyxia-related need for follow-up in a neonatal ward.

In the HAPO study, maternal obesity was independently associated with an increase in cord C-peptide concentrations, reflecting hyperinsulinaemia of the newborn and hence, an increased risk of neonatal hypoglycaemia (210). In line with the results of the HAPO study, our study showed maternal obesity to be an independent risk factor of neonatal hypoglycaemia. This finding may be explained by the fact that obese pregnant women without a diagnosis of GDM have been reported to have higher daytime and nocturnal glucose profiles upon continuous glucose monitoring despite a controlled diet in comparison with normal-weight women both early and late gestation. In addition, the same study found fasting insulin, C-peptide, free fatty acids (FFAs) and triglycerides to be significantly higher in obese than normal weight women (204).

In our study, maternal overweight or obesity was not associated with an increased risk of preterm delivery; on the contrary, GDM was associated with an increase in the rate of prematurity. This may be a result of medically indicated preterm deliveries. The incidence of preterm deliveries was low; between 3.2–5.6% in our study population. The results of previous studies on the association between maternal overweight or obesity and preterm delivery are conflicting and most show an increase in medically indicated preterm delivery (224–227). A recent population-based study in Sweden revealed an increased risk of spontaneous preterm delivery in obese women, with the highest risk in extremely obese mothers with extremely preterm deliveries. There was also an increase in medically indicated preterm deliveries, but when diabetes and hypertensive disorders were excluded, the risk was substantially decreased (225).

6.5 Separate and concomitant effects of GDM and pre-pregnancy overweight on long-term maternal outcome

The risk of subsequent diabetes has been reported to be increased at least sevenfold in women with GDM compared with healthy controls (12) and the prevalence of diabetes has varied from 2.6 to 70% in studies with follow-up of six weeks to 20 years (166). In our study, after 19 years of follow-up, the incidence of diabetes was 65.6 versus 1.8%, that of hypertension 54.1 versus 30.9% and that of

dyslipidaemia 47.5 versus 20.0% in women with previous insulin-treated GDM in comparison with controls, respectively.

The prevalence of MetS in our study was 62 versus 31% in women with previous GDM compared with controls at mean age of 52 years. It was higher than in previous studies, where the rates at 2–11 years after pregnancy have been reported to be 3–39% in GDM women and 1–13% in controls (13–16, 184). The higher incidence of MetS in our study after a longer period of follow-up may represent a continuum of metabolic disease and it may also be affected by transition to the menopausal state (255, 256). Another plausible explanation for the high proportion of cases of MetS in our study is that we included only GDM women who required insulin treatment during pregnancy. In accordance with our results, previous studies have revealed that the requirement of insulin to achieve normoglycaemia in GDM is associated with an increased rate of subsequent morbidity, especially diabetes (50). The high prevalence of single components of MetS (diabetes, hypertension, or dyslipidaemia) that do not yet meet the full criteria of this disturbance suggests a further increased prevalence of MetS in future.

In logistic regression analysis, pre-pregnancy overweight was the strongest independent risk factor as regards subsequent MetS in the present study. In other follow-up studies the pre-pregnancy BMI of the study subjects has not been reported. Our results are in agreement with those of a previous cohort study in which pre-pregnancy overweight was found to be an essential risk factor of subsequent diabetes and hypertension (229).

Increased CIMT has been reported to reflect a higher risk of cardiovascular events in women with a history of GDM (173, 174, 257). In the present study, the women with previous insulin-treated GDM exhibited significantly increased CIMT, and the proportion of abnormal CIMT values was also significantly higher among them. This was seen in GDM women regardless of pre-pregnancy weight class and it was also independent of smoking status. Our findings support the concept of an increased CVD risk in women with a history of GDM. The results of a recent meta-analysis included our findings and it was concluded that GDM was associated with increased CIMT, the relationship being stronger in the overweight GDM population and beginning at the time of pregnancy and remaining significant for years afterwards (175).

6.6 Clinical implications

In the short term, metformin with or without additional insulin has proven to be a safe and effective alternative to insulin in GDM, as also found in our study. In a meta-analysis, metformin was even superior to insulin in terms of maternal weight gain, postprandial blood glucose concentrations and pregnancy-induced hypertension. It was associated with a lower incidence of neonatal hypoglycaemia, but a higher incidence of preterm delivery. In addition, metformin seems to be more acceptable to women with GDM despite its gastrointestinal side-effects (144). Metformin is more cost-effective than insulin and it may be more easily available, for example in low-income countries.

The only reason to avoid the use of metformin in the treatment of GDM is because of its possible long-term effects on the offspring. Metformin reduces insulin resistance and is associated with beneficial fat redistribution from visceral depots to subcutaneous deposits in adults (134). Rowan *et al.* suggested that fetuses exposed to metformin in utero might have improved insulin action, which may also lead to more beneficial fat distribution and insulin-sensitivity later in life (128). Recent animal studies in mice revealed metformin exposure *in utero* to affect the expression of several metabolic genes and pathways at neonatal age (135, 136). Firstly, when metformin was administered to dams on a regular diet, the offspring were predisposed to diet-induced obesity (135). Secondly, metformin administration to dams during a high fat diet resulted beneficial effects in fat mass accumulation and glucose tolerance in the offspring (136). In our study and in a study by Carlsen *et al.*, children prenatally exposed to metformin were of greater weight than children exposed to insulin or placebo (131). These results might indicate that prenatal metformin exposure may have impact on hormonal and metabolic environment of the fetus and the importance of environmental factors on fetal growth and metabolism should not be ignored. In a recently published study, both birth weight and infant weight strongly associate with overweight in later life (239). Further studies are needed to investigate the body composition by using precise methods and the insulin sensitivity of offspring exposed to metformin and/or insulin prenatally.

Women with a history of GDM have an increased risk of future diabetes, MetS and CVD. GDM is often accompanied by an overweight condition and the results of our study indicate that maternal overweight or obesity is an independent risk factor of both adverse pregnancy outcome and future risk of MetS. Lifestyle guidance before and during pregnancy should therefore be extended not only to

mothers with GDM but also to overweight mothers with normal glucose tolerance. Pregnancy is the most favourable phase of life to influence a woman's lifestyle and with intervention it could be possible to cut the disadvantageous continuum between overweight mothers and offspring.

7 Summary and conclusions

The first aim of the present study was to investigate the safety and effectiveness of metformin compared with insulin in the treatment of GDM and the impact of treatment on growth and development of children by the age of 18 months. The second aim was to evaluate the separate and concomitant effect of GDM and maternal overweight/obesity on pregnancy outcome and the mothers' subsequent health.

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

I In the short term, metformin is a safe and effective alternative to insulin in the treatment of GDM. However, approximately one third of metformin-treated mothers need additional insulin to maintain sufficient control of glycemia. Greater BMI, fasting hyperglycaemia in OGTT and earlier need of pharmacological intervention associate with the need of additional insulin in metformin-treated subjects.

II Children prenatally exposed to metformin are heavier at the age of 12 months and both taller and heavier at the age of 18 months than children exposed to insulin, but their degree of adiposity defined by PI is similar. Prenatal exposure to metformin does not increase the risk of adverse motor, social or linguistic development of the offspring by the age of 18 months when compared with insulin.

III GDM in normal-weight women is not related to an increased risk of macrosomia or Caesarean delivery compared with that in normal-weight women without GDM. However, GDM increases the risk of neonatal morbidity, especially hypoglycaemia. Maternal overweight and obesity are independently associated with the risk of macrosomia and maternal obesity is an independent risk factor of Caesarean delivery and neonatal morbidity. Concomitant GDM further increases these risks.

IV Women with a history of insulin-treated GDM have a twofold increased risk of future MetS compared with controls without GDM. Additionally, they exhibit a significantly higher degree of CIMT than controls, indicating an increased risk of cardiovascular events. However, the strongest risk factor predicting future MetS risk is pre-pregnancy overweight, not GDM, and the risk is highest when both of these factors are combined.

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