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GESTATIONAL DIABETES

**LONG-TERM, METABOLIC CONSEQUENCES
FOR THE MOTHER AND CHILD**

FACULTY OF MEDICINE,
INSTITUTE OF CLINICAL MEDICINE,
DEPARTMENT OF OBSTETRICS AND GYNECOLOGY,
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UNIVERSITY OF OULU;
NATIONAL INSTITUTE FOR HEALTH AND WELFARE,
DEPARTMENT OF CHILD AND ADOLESCENT HEALTH

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JATTA PIRKOLA

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Long-term, metabolic consequences for the mother
and child

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Abstract

Gestational diabetes (GDM) indicates increased risk for diabetes and the metabolic syndrome in women. Research on prenatal exposure to GDM as a risk factor for metabolic diseases is conflicting. Overweight (body mass index ≥ 25 kg/m²) is a strong risk factor for GDM and metabolic diseases; however, there are few published previous studies distinguishing the separate effects of overweight and GDM on the later risk for metabolic diseases in women and their children.

The present study evaluated pre-pregnancy overweight and GDM as determinants of long-term risk for diabetes and hypertension in women, and the metabolic consequences of prenatal exposures to maternal pre-pregnancy overweight and different types of maternal diabetes in children. The results are based on prospective, clinical data from Oulu University Hospital (n = 63 mothers and their children), and the Northern Finland Birth Cohort 1986 (NFBC 1986, n = 9,362 mothers and their 9,479 children).

Compared to normal-weight mothers with normal glucose tolerance in pregnancy, the NFBC 1986 mothers with simultaneous pre-pregnancy overweight and GDM had strikingly high risks for developing diabetes (hazard ratio, HR 47.2; 95% confidence interval 25.5–87.4) and hypertension (HR 9.2 [6.1–13.9]) twenty years after delivery. The risks for these diseases were elevated in mothers with pre-pregnancy overweight even when they had normal glucose tolerance during pregnancy (HR diabetes 12.6 [7.4–21.6], HR hypertension 2.9 [2.1–3.9]). GDM *per se* indicated increased risk only for diabetes (HR 10.6 [4.2–27.0]).

In the cohort from Oulu University Hospital, increased fasting insulin concentration (P = 0.04), first phase insulin response (P = 0.03), and homeostasis model value for insulin secretion (P = 0.008) were already observed at pre-school age in the offspring of mothers with Type 1 diabetes compared with offspring of mothers with GDM.

In the NFBC 1986 offspring, the prevalence of metabolic syndrome was 2.4% at age 16 years, using the International Diabetes Federation pediatric definition. Abdominal obesity, a waist girth over half one's length, defined approximately 85% of the adolescents with metabolic syndrome. The risks for overweight and abdominal obesity were high in those with prenatal exposure to both maternal pre-pregnancy overweight and GDM (odds ratio for overweight 4.1 [1.9–8.6], for abdominal obesity 3.8 [1.7–8.8]). In children of normal-weight women, prenatal exposure to GDM was not associated with increased risk of these outcomes.

Based on this study, preventing and reducing overweight in fertile age seems to be a key target for preventing metabolic diseases in women and their children.

Keywords: adolescent, body mass index, fetal programming, glucose tolerance test, insulin resistance, overnutrition, overweight, pregnancy, prospective studies, risk assessment

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Abbreviations

ACOG	American College of Obstetricians and Gynecologists
ADA	American Diabetes Association
AGA	appropriate for gestational age
ATP III	Adult Treatment Panel III
AUC	area under the curve
BMI	body mass index
CI	confidence interval
CSO	Central Statistical Office
DM	diabetes
EGIR	European Group for the Study of Insulin Resistance
ESC	European Society of Cardiology
FG	fasting blood glucose concentration
FPIR	first phase insulin response
GADA	auto-antibodies to glutamic acid decarboxylase
GCT	glucose challenge test
GDM	gestational diabetes
HAPO	study of Hyperglycemia and Adverse Pregnancy Outcome
HDL	high density lipoprotein concentration
HOMA-B	homeostasis model assessment value for insulin secretion
HOMA-IR	homeostasis model assessment value for insulin resistance
HOMA-S	homeostasis model assessment value for insulin sensitivity
HR	hazard ratio
IA-2A	insulinoma-associated antigen-2
ICA	auto-antibodies to islet cells
ICARUS	Islet Cell Antibody Register Users Study
ICD	International Classification of Diseases and Health Related Problems
IDF	International Diabetes Federation
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
IOTF	International Obesity Task Force
IVGTT	intravenous glucose tolerance test
IWC- GDM	Fifth International Workshop-Conference on Gestational Diabetes
LGA	large for gestational age
MAP	mean arterial pressure

MWC	maternity welfare centre
NDDG	National Diabetes Data Group
NFBC 1986	Northern Finland Birth Cohort 1986
NGT	normal glucose tolerance
NHANES	National Health and Nutrition Examination Survey
OAV	one abnormal value in oral glucose tolerance test
OGTT	oral glucose tolerance test
OR	odds ratio
SD	standard deviation
SGA	small for gestational age
TG	triglyceride concentration
T1DM	Type 1 diabetes
T2DM	Type 2 diabetes
USA	United States of America
WHO	World Health Organization

List of original publications

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

- I Pirkola J, Pouta A, Bloigu A, Miettola S, Hartikainen A-L, Järvelin M-R & Vääräsmäki M (2010) Pre-pregnancy overweight and gestational diabetes as determinants of subsequent diabetes and hypertension after 20-Year Follow-Up. *J Clin Endocrinol Metab* 95(2): 772–778.
- II Pirkola J, Vääräsmäki M, Leinonen E, Bloigu A, Veijola R, Tossavainen P & Knip M, Tapanainen P (2008) Maternal type 1 and gestational diabetes: postnatal differences in insulin secretion in offspring at preschool age. *Pediatr Diabetes* 9(6): 583–589.
- III Pirkola J, Tammelin T, Bloigu A, Pouta A, Laitinen J, Ruokonen A, Tapanainen P, Järvelin M-R & Vääräsmäki M (2008) Prevalence of metabolic syndrome at age 16 using the International Diabetes Federation paediatric definition. *Arch Dis Child* 93(11): 945–951.
- IV Pirkola J, Pouta A, Bloigu A, Hartikainen A-L, Laitinen J, Järvelin M-R & Vääräsmäki M (2010) Risks of Overweight and Abdominal Obesity at Age 16 Years Associated With Prenatal Exposures to Maternal Pre-Pregnancy Overweight and Gestational Diabetes Mellitus. *Diabetes Care* 33(5): 1115–1121.

Contents

- Abstract**
- Acknowledgements** **5**
- Abbreviations** **7**
- List of original publications** **9**
- Contents** **11**
- 1 Introduction** **13**
- 2 Review of the literature** **15**
 - 2.1 Gestational diabetes 15
 - 2.2 Establishing diagnosis of gestational diabetes 15
 - 2.2.1 Different screening strategies 15
 - 2.2.2 Screening tests 16
 - 2.2.3 Diagnostic criteria 17
 - 2.2.4 Recommendations for establishing diagnosis of gestational diabetes..... 18
 - 2.2.5 Hyperglycemia as a continuous trait..... 19
 - 2.3 Prevalence of gestational diabetes 20
 - 2.4 Gestational diabetes after delivery 20
 - 2.4.1 Postpartum screening 21
 - 2.4.2 Risk of diabetes 21
 - 2.4.3 Risk of metabolic syndrome 22
 - 2.4.4 Risk of cardiovascular disease..... 25
 - 2.4.5 Risks associated with hyperglycemia under the threshold of gestational diabetes 25
 - 2.5 Prenatal exposure to gestational diabetes..... 26
 - 2.5.1 Concepts associated with prenatal exposure to hyperglycemia 27
 - 2.5.2 Genetic and lifestyle factors 29
 - 2.5.3 Role of maternal diabetes type 30
 - 2.5.4 Long-term, metabolic consequences of prenatal exposure to GDM 31
 - 2.5.5 Long-term, metabolic consequences of prenatal exposure to hyperglycemia under the threshold of GDM..... 36
- 3 Aims of the study** **37**
- 4 Study populations and methods** **39**
 - 4.1 Health care in pregnancy..... 39

11

4.1.1	Screening and diagnosis of gestational diabetes.....	39
4.1.2	Treatment of pregnancies complicated by diabetes.....	39
4.2	Study populations.....	40
4.2.1	Clinical cohort from Oulu University Hospital.....	40
4.2.2	Northern Finland Birth Cohort 1986.....	41
4.3	Register-based data.....	46
4.4	Statistical methods.....	47
5	Results	49
5.1	Data attrition analyses.....	49
5.2	Risk of diabetes and hypertension in women with risk factors for gestational diabetes (paper I).....	49
5.3	Glucose metabolism at pre-school age in offspring with prenatal exposure to gestational diabetes (paper II).....	51
5.4	Prevalence of metabolic syndrome (paper III).....	52
5.5	Risks of overweight and abdominal obesity attributable to prenatal exposures to gestational diabetes and maternal overweight (paper IV).....	54
6	Discussion	57
6.1	Subjects and data quality.....	57
6.1.1	Clinical cohort from Oulu University Hospital.....	57
6.1.2	Northern Finland Birth Cohort 1986.....	57
6.2	Pre-pregnancy overweight and gestational diabetes as determinants of risk for subsequent diabetes and hypertension.....	59
6.3	Glucose metabolism at pre-school age in offspring with prenatal exposure to gestational diabetes.....	60
6.4	Prevalence of metabolic syndrome at age 16 years.....	60
6.5	Risks of overweight and abdominal obesity attributable to prenatal exposures to maternal pre-pregnancy overweight and gestational diabetes.....	61
6.6	Public health implications.....	62
6.7	Implications for future studies.....	63
7	Summary and conclusions	65
	References	67
	Original publications	83

1 Introduction

Pregnancy has been described as a transient excursion into the metabolic syndrome (1) and as a window to women's health (2). During pregnancy, metabolic adaptations are necessary to ensure the growth and development of the fetus and to meet the altered demands of the mother. In addition, the fetus and the mother are provided with adequate energy stores needed during labor and after birth (3). Glucose seems to be the major substrate for the human fetus throughout pregnancy, and glucose metabolism has thus been the subject of most studies on metabolism in pregnancy.

In general, during the second half of the pregnancy, insulin sensitivity decreases and insulin secretion increases. The relative insulin resistance in pregnancy stabilizes glucose input to the fetus. The characteristics of the changes in insulin sensitivity and secretion during pregnancy are not well known. The role of placental hormones seems to be crucial. Catalano (4) has suggested that decreased maternal insulin sensitivity during pregnancy may have been a reproductive asset when food supply was inadequate, but in the current society with an abundant nutrient supply and a sedentary lifestyle, decreased insulin sensitivity during pregnancy may manifest itself as hyperglycemia and increase the long-term risks of obesity and diabetes in both the mother and child.

By the year 1961 Pedersen had described the phenotype of the infant with prenatal exposure to maternal diabetes (i.e. hyperglycemia) as "Most conspicuous is obesity, the round cherub's cheeks, buried eyes, and short neck. Many infants have a plethoric appearance, reddened skin and an abundance of head hair". He suggested (5) that maternal hyperglycemia leads to fetal hyperinsulinemia and increased growth; a hypothesis that is still the basis of research on materno-fetal metabolism. There is now increasing evidence from animal and epidemiologic studies that prenatal exposure to a hyperglycemic environment can alter the growth trajectories and homeostatic regulatory mechanisms, causing lifelong changes resulting in increased risks for obesity and metabolic and cardiovascular diseases in the offspring (6–10).

The primary aim of this study was to evaluate the long-term, metabolic consequences of pre-pregnancy overweight and gestational diabetes for the mother and child.

2 Review of the literature

2.1 Gestational diabetes

Gestational diabetes (GDM) is defined as glucose intolerance with onset or first recognition during pregnancy (11). The diagnosis of GDM represents detection of a chronic metabolic abnormality (12). GDM is characterized by β -cell function insufficient to meet the increased insulin need due to pregnancy. Insufficient β -cell function in pregnancy results from the same causes as hyperglycemia in general: autoimmune diseases, monogenic causes and chronic insulin resistance due to various causes (13, 14).

2.2 Establishing diagnosis of gestational diabetes

The diagnostic criteria for GDM were originally based on a linear perception of high risk of subsequent Type 2 diabetes (T2DM), and set statistically (15). More than forty years after the publication of the original diagnostic criteria there still is no global consensus on screening strategy or diagnostic criteria for diagnosing GDM.

2.2.1 Different screening strategies

Screening is undertaken in order to detect individuals at risk for a disease. There are two main screening strategies for detecting the women at risk of developing GDM: universal and risk factor based screening (Figure 1). The universal screening strategy encompasses all pregnant women, and seems to result in higher detection rates of GDM (16). The outcome of risk factor based screening is influenced by the definition of the risk factors. Traditional risk factors for GDM include race (other than white), family history of T2DM, use of corticosteroids, high maternal age, pre-pregnancy overweight (body mass index $\text{BMI} \geq 25 \text{ kg/m}^2$), and previous GDM.

According to a recent survey, in the UK 82% of centers providing obstetric care routinely screen for GDM; 52% of them use a universal screening strategy (17). In the USA, 96% of obstetricians reported universal screening for GDM, 95% using the 50-g glucose challenge test (GCT), (18). In Finland, risk factor based screening was implemented from 1978 until 2008. In 2008, new, national Current

Care guidelines recommended screening all women, excepting only very low risk groups (19).

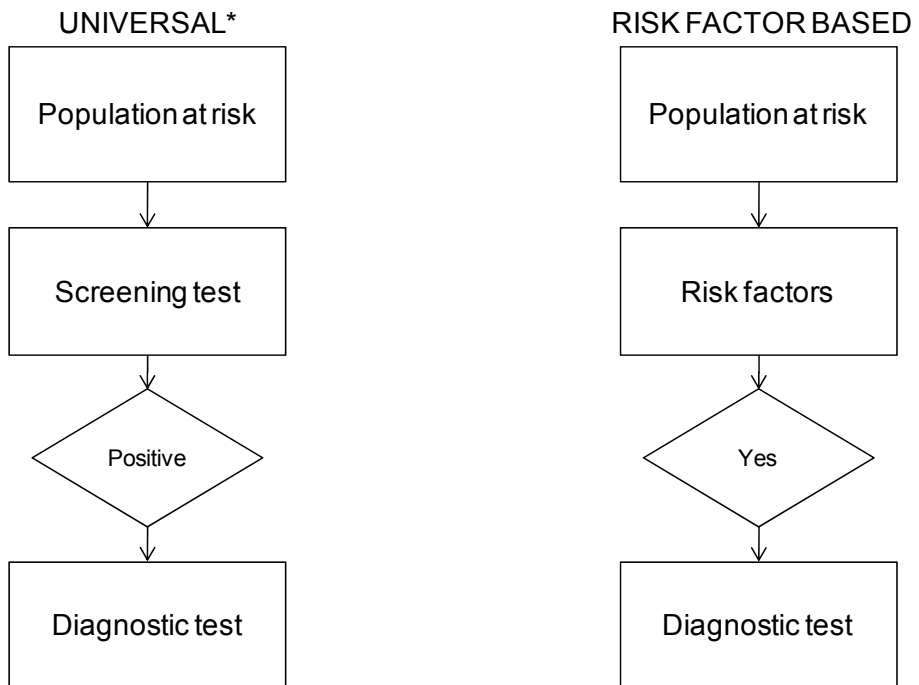


Fig. 1. Universal and risk factor based strategy for screening and diagnosing gestational diabetes. *ADA and Finnish Current Care guidelines (19, 20) recommend universal screening, excepting low-risk groups. Finnish Current Care guidelines recommend a one-step approach, i.e. omitting the screening test.

2.2.2 Screening tests

In the original study by O’Sullivan *et al.* (15), a 50-g GCT was used as a screening test. The cut-off value for performing a diagnostic oral glucose tolerance test (OGTT) was determined statistically to achieve acceptable degrees of sensitivity and specificity. Based on follow-up of six thousand women, Carpenter and Coustan (21) have further evaluated the cut-off values of the 50-g GCT. They concluded that a cut-off of 7.7 mmol/L at one hour postload results in 80–90% sensitivity and 15% screen positive women. Fasting glucose is an appealing alternative as a screening test for GDM; however, it seems that this method results in a relatively high rate of missed cases (19%, (22, 23).

There are no firm recommendations on screening for GDM, and there is no precise data available on the cost/benefit ratio for diagnosing GDM. Thus, it has been suggested that the selection of screening strategy should be population-specific, i.e. based on local, clinical considerations (24).

2.2.3 Diagnostic criteria

Diagnosis of GDM is based on 75-g or 100-g OGTT results. In the USA, the 100-g OGTT is most often used, whereas outside the USA the 75-g OGTT is more common (15, 24). It can be speculated that the lower load causes the patient less nausea and vomiting, and it requires a shorter testing time and is less expensive to perform.

The cut-off values in the OGTT were originally set statistically (15). In the USA, the National Diabetes Data Group (25) and Carpenter & Coustan criteria (21) are widely used (Table 1). Neiger and Coustan (26) have compared these criteria and suggested that the NDDG cut-offs are not sensitive enough to identify women requiring insulin during pregnancy or at risk for excessive fetal growth. Retnakaran *et al.* (27) have recently reported that the NDDG and Carpenter & Coustan criteria are similar in their ability to identify postpartum metabolic risk. Some diagnostic criteria for GDM are presented in Table 1.

Table 1. Some diagnostic criteria for gestational diabetes. NB: Blood and plasma glucose cut-off values are different.

Definition	Oral glucose load ^a	Plasma glucose cut-off values (mmol/L) postload				Diagnostic criteria ^b
		0 h	1 h	2 h	3 h	
O'Sullivan & Mahan (15)	100 g	5.0	9.2	8.1	6.9	2
National Diabetes Data Group (25)	100 g	5.8	10.6	9.2	8.0	2
Carpenter & Coustan (20, 21) ^c	100 g	5.3	10.0	8.6	7.8	2
Australasian Diabetes in Pregnancy Society (28)	75 g	5.5	NA	9.0	NA	1
WHO (29)	75 g	7.0	NA	7.8	NA	1
Canadian Diabetes Association (30)	75 g	5.3	10.6	8.9	NA	1
Jensen <i>et al.</i> 2003 (31)	75 g	6.1	NA	9.0	NA	1

^aThe OGTT should be performed in the morning after an overnight fast of at least 8 hours, but not more than 14 hours, and after at least 3 days of unrestricted diet (≥ 150 g carbohydrate/day) and physical activity. The subject should remain seated and should not smoke throughout the test.

^bNumber of abnormal values in the OGTT necessary for diagnosis

^csame cut-off values (at 2 hours) for the 75-g oral glucose load, recommended by the ADA and Finnish Current Care guidelines

2.2.4 Recommendations for establishing diagnosis of gestational diabetes

Establishing diagnosis of GDM is an issue of debate. The World Health Organization (WHO) recommends screening most pregnant women for GDM (32). In the USA, the American College of Obstetricians and Gynecologists recommends screening all pregnant women by patient history, clinical risk factors or a laboratory screening test (ACOG 2001); the American Diabetes Association states that low-risk women need not be screened with laboratory testing (20). The recommendations of the Fifth International Workshop-Conference on Gestational Diabetes in 2007 (IWC-GDM) for screening and diagnostic criteria of GDM (14) are shown below (Table 2). However, the United States Preventive Services Task Force Recommendation Statement in 2008 concluded that “current evidence is insufficient to assess the balance of benefits and harms of screening for GDM” (33).

A recent Canadian study has compared the costs of one- and two-step methods of screening and diagnosing GDM (34). This study suggests that the two-step method performed better in minimizing the cost for individual women

and the healthcare system without compromising diagnostic efficacy. In Finland, a one-step approach to screening and diagnosis of GDM is currently recommended. A 75-g oral glucose tolerance test (OGTT) with venous plasma cut-offs of 5.3, 10.0, and 8.6 mmol/L at fasting, 1 hour and 2 hours postload, respectively, is used as a screening test and to establish diagnosis. The diagnosis of GDM is set after one abnormal value in the OGTT (19).

Table 2. Recommendations of the Fifth International Workshop-Conference on Gestational Diabetes for screening and diagnosis of GDM (14).

Procedure	Timing	Description
GDM risk assessment	First prenatal visit	<ol style="list-style-type: none"> 1. Low risk if all following present <ul style="list-style-type: none"> -member of an ethnic group with a low prevalence of GDM -no known diabetes in first degree relatives -age<25 years -weight normal at birth and before pregnancy -no history of abnormal glucose metabolism / poor obstetric outcome 2. Average risk: Blood glucose testing at gestation week 24–28 3. High risk if one of the following present: Blood glucose testing as soon as feasible, if GDM not diagnosed repeat testing at gestation week 24–28 or any time the patient has symptoms or signs suggestive of hyperglycemia <ul style="list-style-type: none"> -severe obesity -strong family history of T2DM -previous GDM or impaired glucose metabolism -glucosuria
Blood glucose testing	Gestation week 24–28 unless otherwise indicated	<ol style="list-style-type: none"> 1. Two-step procedure: 50-g glucose challenge test (GCT) followed by a diagnostic oral glucose tolerance test (OGTT) in those meeting the threshold value 2. One-step procedure: diagnostic OGTT performed on all subjects
Establishing diagnosis	After blood glucose testing	Carpenter & Coustan criteria (please see Table 1) for OGTT cut-off values

2.2.5 Hyperglycemia as a continuous trait

In addition to diagnosing GDM, screening and glucose tolerance testing in pregnancy identify women with hyperglycemia that is under the threshold of GDM. There is increasing interest in investigating the risk of subsequent, aberrant glucose metabolism in these women, since they represent a potentially high-risk population that could easily be identified through current clinical practice. (35).

2.3 Prevalence of gestational diabetes

The prevalence of GDM depends on the screening strategy and diagnostic criteria used, and usually reflects the frequency of T2DM in the studied population ((36). The prevalence of GDM seems to be increasing worldwide; in a meta-analysis the estimates on the magnitude of the increase varied between 16–127% (37). In this meta-analysis, the study with best methodological value (38) estimated the relative increase in GDM prevalence in the USA between the years 1991–2000 to be 68% (%,(from 3.7% to 6.2%), %)with the highest proportional increase (from 1.4% to 2.7%) seen in the youngest age group (15–19 years). A recent study from the USA reported over 100% increase (from 1.9% to 4.2%) in GDM prevalence from 1989–1990 to 2003–2004 (39).

Maternal overweight (BMI ≥ 25 kg/m²) has been shown to be the strongest risk factor for GDM: in two meta-regression analyses, the odds ratios for developing GDM were 1.97–2.14 in overweight (BMI ≥ 25 kg/m²), 3.01–3.56 in obese (most studies BMI ≥ 30 kg/m²) and 5.55–8.56 in severely obese (BMI ≥ 35 –45 kg/m²) women compared with normal weight women (40, 41). In the Finnish obstetric population, the prevalence of overweight (BMI ≥ 25 kg/m²) increased from 18.8% in 1990 to 24.5% in 2000, and that of obesity (BMI 30 kg/m²) from 7.5% to 11.0% (42). During the same time period, the prevalence of GDM seems to have increased from 1.3% in 1991 (43) to 8.4% in 2006 (19), although different diagnostic criteria may influence the results: in the study by Hyvönen *et al.* (1991) the diagnosis of GDM was based on two abnormal values in the OGTT, whilst in the register-based data from the National Institute for Health and Welfare (former STAKES) the diagnosis was based on one abnormal value. In addition, when comparing prevalence figures, it must be remembered that the proportion of the population screened affects the prevalence estimates.

2.4 Gestational diabetes after delivery

Identifying women with GDM as a high-risk group for later disease offers clinicians an opportunity to alter the natural course of disease and to change women's health (44). The rationale for postpartum screening of women with GDM is to detect pre-existing and pregnancy-related abnormalities in glucose metabolism, to prevent or delay progression to T2DM and even reduce subsequent cardiovascular disease risk, and to minimize adverse pregnancy outcomes in subsequent pregnancies (45, 46).

The estimates of the recurrence rate of GDM vary between 30 and 84% and depend on the severity of the disease and follow-up time (47). Lower recurrence rates were found in non-Hispanic, white women, and a subsequent pregnancy within one year from the index pregnancy was associated with higher rates of GDM recurrence. GDM recurrence seems to indicate more severe insulin resistance, and it associates with later development of Type 2 diabetes (48).

2.4.1 Postpartum screening

Assessment of glucose metabolism by measuring fasting glucose has been shown to be inadequate in detecting aberrant glucose metabolism after GDM (45, 49). The IWC-GDM recommended measuring fasting plasma glucose 1–3 days after delivery and annually thereafter, and performing the 75-g OGTT early postpartum (6–12 weeks after delivery), 1 year postpartum and thereafter tri-annually (46). Inadequate, albeit rising, attendance rates for follow-up screening after GDM have been observed (49, 50). This may indicate that women with GDM, healthcare providers, or both, have not considered GDM as an early warning sign of later risk for Type 2 diabetes.

In Finland, Current Care guidelines (19) recommend performing the 75-g OGTT 6–12 weeks postpartum in women with insulin-treated GDM, 1 year postpartum in women with diet-treated GDM, and retesting thereafter according to test results and risk factors. Weight, waist girth, blood pressure and lipids should be measured at 1- to 3-year intervals, and information on a healthy diet and physical activity should be given.

2.4.2 Risk of diabetes

The risk factors for GDM and T2DM overlap (51, 52), and results of genetic studies suggest a shared ground for these diseases (53, 54). In the original study by O’Sullivan and Mahan the lifetime risk of (Type 2) diabetes exceeded 70% (55). Estimates of risk have varied in subsequent studies, probably due to differences in the proportion of women screened, diagnostic criteria and length of follow-up. In a meta-analysis from 1965 to 2002, the cumulative incidence of T2DM increased 5 years postpartum, but then seemed to plateau (51). In a recent meta-analysis including twenty cohort studies and over 675,000 women studied, women with GDM were consistently concluded to be at increased risk of

developing T2DM (RR 7.43) compared to those with a normoglycemic pregnancy (52).

Although genetic susceptibility to GDM is different to that of Type 1 diabetes (T1DM) part (5–10%) of the women with insulin-treated GDM have been estimated to develop T1DM (56). It has been suggested that there exists a distinct clinical entity, autoimmune gestational diabetes (57), as in these women autoimmune phenomena associated with T1DM present already during pregnancy or shortly thereafter (58, 59).

2.4.3 Risk of metabolic syndrome

The metabolic syndrome, or insulin resistance syndrome, is a distinctive constellation of risk factors for T2DM and cardiovascular disease described by Reaven in 1988 (60). As the key component of GDM is insulin resistance, it can be assumed that GDM is not only indicative of increased risk of later T2DM, but of the metabolic syndrome as well.

Various definitions for the metabolic syndrome in adults are used in research, making it difficult to compare results (Table 3). The traits studied are obesity, glucose and lipid metabolism, and blood pressure. The magnitude of the risk of metabolic syndrome after GDM seems to vary depending on the diagnostic criteria of GDM, the definition of the metabolic syndrome used, the length of follow-up after gestational diabetes and the population studied. The current studies are summarized in Table 4. The risk was found to be increased in 9/11 studies; amongst them one study from India, a country under epidemiologic transition (61). In the two largest studies to date, the risk of metabolic syndrome in women with a history of GDM was approximately three times higher (odds ratio, OR 3.2–3.4) than in women without GDM (62, 63).

Overweight is a strong risk factor for the development of metabolic syndrome. In the study by Albareda *et al.* (64), comprising women with GDM, the prevalence of metabolic syndrome was 44.2% in obese women compared to 2.9% in normal-weight women. In the study by Lauenborg *et al.* (62) these figures were 70.6% and 11.4%, respectively; and in the review by Vohr and Boney (9) the relative risk of metabolic syndrome in obese women with GDM was more than 5-fold compared to normal-weight women with GDM.

Some studies have reported individual components of the metabolic syndrome. In the study by Verma *et al.* (65) in the USA, systolic and diastolic blood pressure were higher in women with a history of GDM than in controls, and

a group effect on blood pressure was also observed. Similar results were found by Albareda *et al.* (64) and Lauenborg *et al.* (62) in Europe.

Table 3. Some definitions of the metabolic syndrome for adults.

Definition	Cut off values for components ^a				Criteria	
	Glucose metabolism (FG, mmol/L)	Central obesity (waist cm)	Dyslipidemia (TG, mmol/L) (HDL, mmol/L)			Hypertension (blood pressure, mmHg)
WHO (66)		Waist/hip 0.90/0.85	1.7	0.9/1.0	140/90	DM, IGT or IFG and 2 of 4, microalbuminuria
EGIR (67)	6.1	94/80	2.0	1.0	140/90	Insulin \geq 25 th percentile of nondiabetic population and 2 of 5
ATP III (68)	5.6	102/88	1.7	1.03/1.30	130/85	3 of 5
IDF (69)	5.6	Europe: 94/80, USA 102/88	1.7	1.03/1.29	130/85	Central obesity and 2 of 4

^aValues for males/females when applicable

ATP III=Adult Treatment Panel III, DM= diabetes mellitus, EGIR=European Group for the Study of Insulin Resistance, FG=fasting blood glucose concentration, HDL=high density lipoprotein concentration, IDF=International Diabetes Federation, IFG=Impaired fasting glucose, IGT=impaired glucose tolerance, TG=triglyceride concentration.

Table 4. Some studies on the prevalence of metabolic syndrome in women with a history of gestational diabetes.

Study	n GDM	n controls	Follow-up duration	Definition of metabolic syndrome ^a	Prevalence of metabolic syndrome
Verma <i>et al.</i> 2002, USA (65)	106	101 NGT	4–11 y	ATP III	27.2 vs. 8.2%
Bo <i>et al.</i> 2004, Italy (70)	81	25 OAV and 65 NGT	8.8/7.8/8.5 y	ATP III	21.0 vs. 16.0 vs. 4.6%
Albareda <i>et al.</i> 2005, Spain (64)	262	66 NGT	5 y	ATP III	2.9 vs. 1.8%
Lauenborg <i>et al.</i> 2005, Denmark (62)	481	481 diet-treated GDM and 1,000 background population	9.8 y	WHO, ATP III, EGIR	WHO: 38.8 vs. 13.4%; ATP III: 43.5 vs. 14.8%; EGIR: 32.4 vs. 11.1
Carr <i>et al.</i> 2006, USA (63)	332	663 NGT all with family history of T2DM	29.9 y	ATP III	86.6 vs. 73.5%
Tam <i>et al.</i> 2007, China (71)	68	136 NGT	8 y	IDF	7.5 vs. 8.1%
Ferraz <i>et al.</i> 2007, Brazil (72)	70	108 NGT	6.2 y	ATP III	1.7 vs. 1.5%
Di Cianni <i>et al.</i> 2007, Italy (73)	166	98 NGT	16 mo	ATP III	9 vs. 1%
Krishnaveni <i>et al.</i> 2007, India (61)	35	491 NGT	5 y	IDF	60 vs. 26%
Akinci <i>et al.</i> 2009, Turkey (74)	164	NGT	1–7 y	ATP III and IDF	14.9/ vs. 4.6% both definitions
Madarasz <i>et al.</i> 2009, Hungary (75)	68	39 NGT	4 y	WHO, ATP III, IDF	WHO: 30 vs. 0%; ATP III: 27 vs. 9%; IDF: 37 vs. 14%

^a please see Table 3 for definitions

NGT=normal glucose tolerance

2.4.4 Risk of cardiovascular disease

The studies on the risk of cardiovascular disease after a pregnancy complicated by GDM are few despite the fact that as early as in 1964 O'Sullivan identified women with a history of GDM to be at greater risk for hypertension, hyperlipidemia, electrocardiographic abnormalities and mortality (15). In the Genetics of Non-Insulin Dependent Diabetes Study, approximately 30 years after the index pregnancy, the prevalence of cardiovascular disease events was higher in women with a history of GDM (n=332) compared to normoglycemic controls, and the events had occurred at a younger age (63). This study comprised high-risk women (with first-degree relatives with Type 2 diabetes), and diagnosis of GDM was retrospective, based on self-reporting. Kim *et al.* (76) conducted a cross-sectional study of the participants of the Third National Health and Nutrition Examination Survey (NHANES 1988–1994), and concluded that in women without current diabetes the cardiovascular disease risk profile was similar regardless of a self-reported history of GDM (n=85, unaffected n=4,328). In a large, retrospective, population-based study from Canada the hazard ratio (HR) for cardiovascular disease events during a median follow-up of 11.5 years was 1.71 in women with previous GDM (n=8,191) compared with normoglycemic controls. In this study the risk of cardiovascular disease was prominent in the women who had developed Type 2 diabetes (77). This seems important, as in women with cardiovascular disease diabetes has been shown to exacerbate the risk of dying from myocardial infarction (78).

2.4.5 Risks associated with hyperglycemia under the threshold of gestational diabetes

Data on the risk of aberrant glucose metabolism in women with hyperglycemia under the threshold of GDM are starting to accumulate from different countries. The data from studies after pregnancy are summarized in Table 5. Studies by Retnakaran and Di Cianni (73, 79) have indicated that the timing of the single abnormal value on the 100-g OGTT has implications for metabolism after pregnancy; specifically, an abnormal fasting or 1-hour value seems to indicate more severe metabolic perturbation than abnormal 2- or 3-hour values. The studies on the risks of later metabolic diseases associated with hyperglycemia

under the threshold of GDM suggest that normal glucose metabolism in pregnancy conveys low susceptibility for later, abnormal glucose metabolism.

Table 5. Some studies on the risk of later abnormal glucose metabolism in women with hyperglycemia under the threshold of GDM during pregnancy.

Study	n	Follow-up	Outcome
Corrado <i>et al.</i> (80)	58 GDM vs. 66 OAV vs. 56 NGT	6.9 y	Abnormal glucose tolerance 34.5 vs. 28.7 vs.9.7%
Lee <i>et al.</i> 2008, Korea (81)	202 GDM vs. 96 OAV	6 y	Diabetes 29.2 vs. 8.4%
Vambergue <i>et al.</i> 2007, France (82)	466 GDM vs. 322 OAV vs. 221 NGT	6.8 y	Abnormal glucose tolerance 43.5 vs. 28.7 vs.8.3%
Carr <i>et al.</i> 2008, USA (83)	24,780 GCT performed, 6,222 OGTT performed, OAV 1253	8.8 y	Diabetes risk increases across GCT quartiles; OAV HR 2.06
Retnakaran <i>et al.</i> 2008, Canada (84)	91 OAV vs. 166 abnormal GCT vs. 93 NGT	3 mo	AUC glucose: 21.1 vs. 19.8 vs.18.0
Retnakaran <i>et al.</i> 2009, Canada (85)	15,381 abnormal GCT vs. 61,237 no referral for OGTT	6.4 y	Diabetes 5.4 vs.1.74 per 1,000 person-years, HR 2.56

AUC=area under the curve, GCT=glucose challenge test, HR=hazard ratio, NGT=normal glucose tolerance, OAV=one abnormal value in oral glucose tolerance test, OGTT=oral glucose tolerance test

2.5 Prenatal exposure to gestational diabetes

During pregnancy, maternal-fetal metabolism ensures the growth and development of the fetus and provides adequate energy stores for the immediate postnatal period (3). Glucose seems to be the major substrate of the fetus throughout pregnancy, and thus glucose has been the subject of most studies on metabolism in pregnancy, even though lipid and amino acid metabolism are important in determining fetal growth as well (3, 86, 87). Some concepts and possible pathophysiological mechanisms regarding prenatal exposure to hyperglycemia are presented below.

2.5.1 Concepts associated with prenatal exposure to hyperglycemia

Pedersen hypothesis

In 1952 Pedersen (88) postulated that maternal hyperglycemia leads to fetal hyperglycemia, which in turn evokes hyperinsulinemia in the fetus. The Pedersen hypothesis is still the basis of research on materno-fetal metabolism, and has been proven by several studies. Insulin is the main growth hormone for the fetus, and fetal hyperinsulinemia results in elevated weight and adiposity at birth (89). In addition to hyperglycemia, increasing maternal insulin resistance in pregnancy results in increased lipolysis and thus increased availability of free fatty acids as adipogenic substrates for the fetus (90). In 1984 Sparks (91) showed that the variability in weight between fetuses small for gestational age (SGA), appropriate for gestational age (AGA) and large for gestational age (LGA) is mainly due to the accretion of fat. More recently, Catalano *et al.* (4) have shown in neonates that prenatal exposure to GDM results in increased fat mass and proportion of body fat compared to infants of normoglycemic women, although there was no difference in birth weight. Interestingly, in a subpopulation analysis of neonates born AGA, the fat-free mass was smaller (2,832 vs. 2,919 g) in infants of women with GDM compared to infants of normoglycemic women. Similar results were found in infants born LGA (92).

Adipoinsular axis

Hyperinsulinemia during the fetal and early postnatal period seems to alter the complex neuroendocrine systems regulating body weight and metabolism (93, 94). In addition to insulin, offspring of mothers with GDM (and Type 1 diabetes) have elevated cord blood concentrations of leptin, a hormone secreted by the placenta and adipocytes (95, 96). Leptin concentration correlates with weight and adiposity at birth, and after birth insufficient leptin action associates with hyperphagia, decreased fat oxidation, increased tissue triglyceride levels, insulin resistance and obesity (97). The endocrine loop between leptin and insulin, linking the brain and endocrine pancreas, has been called the adipoinsular axis (97). It has been suggested that hyperleptinemia in the offspring of diabetic mothers is due to leptin resistance, where rising leptin concentrations are unable to control the increased fetal insulin secretion and adiposity caused by maternal hyperglycemia (98).

Fuel-mediated teratogenesis

In his Banting Lecture in 1980, Freinkel (99) presented his theory of fuel-mediated teratogenesis, suggesting that the concept of teratogenesis be extended to include alterations (in organ development) due to disturbances in maternal metabolism, occurring after organogenesis, and causing long-range effects upon anthropometric, metabolic and behavioral functions. It has been suggested that the theory of fuel-mediated teratogenesis might be expanded to include fetal overnutrition due to maternal obesity in pregnancy (100). Some studies have found support for the fetal overnutrition hypothesis (101, 102), whilst others have challenged the hypothesis (103, 104). Recently, abundant maternal nutrition due to excessive weight gain in pregnancy has also been postulated to be a cause of 'excess fuels' for the fetus (105, 106).

Developmental programming of health and disease

The association of low birth weight with cardiovascular disease later in life has been observed in several populations (107–110). Epidemiological studies and animal data have given rise to the concept of developmental programming of health and disease (110). Developmental programming can be defined as the phenomenon where a stimulus occurring during a critical window of development, i.e. the prenatal (and early postnatal) period, causes lifelong changes in the structure and function of the body (10, 111). Birth weight is the most extensively studied marker of the prenatal environment. In a meta-analysis, the relationship of birth weight and T2DM in later life was U-shaped, i.e. low and high birth weight associated with increased risk of disease (112). Low birth weight has been associated with an increased ratio of fat/lean mass at birth and later in life compared to those with higher birth weight (113, 114). The body composition in low birth weight infants is similar to that observed in infants of GDM mothers irrespective of birth weight (4, 92). In addition, programming of the hypothalamus-pituitary-adrenal axis may be on the pathway from small size at birth to increased risk of cardiometabolic diseases later in life (115, 116).

Vicious cycle

Already in 1976 Dörner *et al.* (117) found evidence for predominantly maternal (as opposed to paternal) transmission of T2DM. Based on studies on Pima Indians,

a population with endemic diabetes, Pettit *et al.* (118) have suggested that developmental programming of offspring adiposity and defective glucose metabolism due to prenatal exposure to hyperglycemia could lead to a vicious cycle of increasing overweight and metabolic diseases over each subsequent generation (Figure 2). Whether the vicious cycle operates in other populations than the Pima Indians is not known with certainty, as it has not yet been adequately investigated (8).

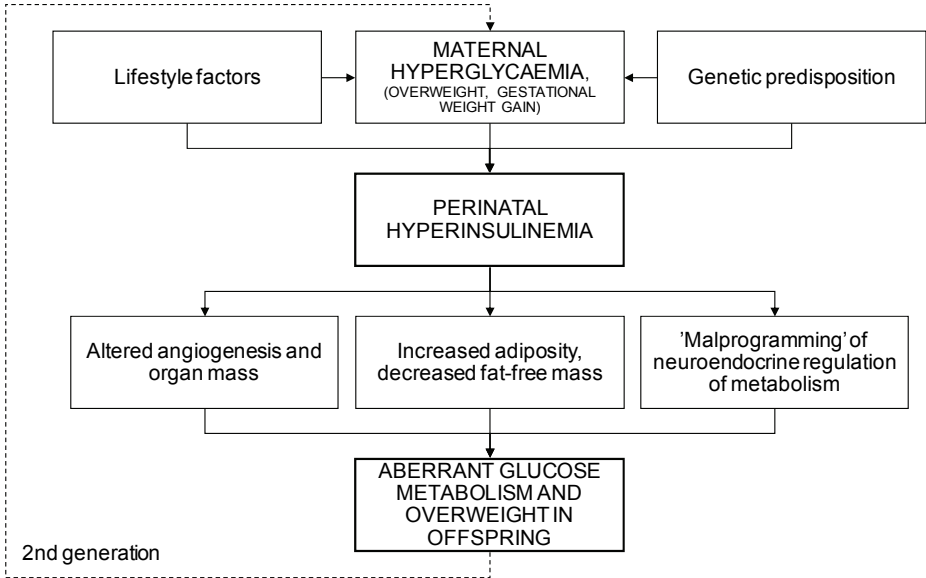


Fig. 2. Vicious cycle of transgenerational transmission of aberrant glucose metabolism and overweight (modified from Plagemann *et al.* (93)).

2.5.2 Genetic and lifestyle factors

Genetic and lifestyle factors have a strong influence on metabolic diseases. Obese parents may be genetically predisposed to obesity, and thus pass on the genes to their offspring. Since the advent of modern high-throughput genetic technologies (119), an impressive number of genetic variants with significant impact on the risk of metabolic diseases have been identified (120). However, these explain only a small proportion of the risk for obesity and metabolic disorders. Studies on the interaction between genetic predisposition and lifestyle behaviors, such as dietary intake and physical activity, have shown that appetite may be heritable

(121) and that the effects of genetic susceptibility to obesity may be modulated by physical activity (122). The genetic contribution to BMI has been postulated to be strong, especially in adolescence (123). Gender may also be important in the transmission of obesity-associated genes and behavior; a recent study has suggested that gender-assortative weight gain could be the key factor in the development of childhood obesity (124).

2.5.3 Role of maternal diabetes type

There is increasing evidence that prenatal exposure to maternal diabetes increases the long-term risks of abnormal glucose metabolism, obesity and metabolic disease in offspring (6–10). It has been demonstrated that the increased risks are in addition to genetic susceptibility (125, 126). However, controversy exists on whether the long-term, metabolic consequences of prenatal exposure to hyperglycemia are similar regardless of maternal diabetes type.

Animal models are not optimal for assessing the effects of prenatal exposure to maternal diabetes on offspring metabolism later in life, as the long-term metabolic effects seem to differ between species, probably due to differences in accumulation of fat during the fetal and neonatal period (4). Nevertheless, Susa *et al.* (127, 128) have studied the consequences of hyperinsulinemia during pregnancy in offspring of rhesus monkeys by subcutaneous injection of insulin in fetal tissue, and shown that hyperinsulinemia in pregnancy results in impaired insulin secretion in the offspring, resolving by 3 years of age. Human data from 63 infants aged 10–16 years in the Diabetes in Pregnancy Study showed that fetal hyperinsulinemia, assessed by amniotic fluid insulin concentration at 32–38 weeks gestation, is a strong predictor of obesity and impaired glucose tolerance (IGT) in childhood, irrespective of the type of maternal diabetes (pregestational, predominantly T1DM and GDM) (89, 129). Thus, it has been suggested that the effects of prenatal exposure to maternal diabetes are similar regardless of maternal diabetes type (8, 10).

There are, however, differences in the genetic background and in the defect responsible for hyperglycemia between the different types of diabetes. The timing of prenatal exposure to hyperglycemia is also different, as Type 1 and Type 2 diabetes are present before pregnancy, and thus exposure to hyperglycemia may be present from conception. In rodent models, prenatal exposure to mild hyperglycemia associates with normal weight or macrosomic pups and IGT in offspring, related to deficient insulin secretion (130–132). Prenatal exposure to

severe hyperglycemia associates with small size at birth and decreased insulin action in offspring (130, 133). Most human studies have found an excess of maternal transmission of T2DM (117, 134, 135); however, however it seems that for T1DM paternal transmission is stronger (136, 137). In the Pima Indian Study, offspring of mothers with diabetes diagnosed in pregnancy (i.e. GDM) were less often overweight and had lower postchallenge glucose concentration than offspring of mothers with diabetes diagnosed before pregnancy (i.e. Type 2 diabetes) (138). Plagemann *et al.* (139, 140) showed that stimulated insulin levels were lower and stimulated glucose levels higher, and BMI higher in offspring with prenatal exposure to GDM compared with those exposed to maternal T1DM. Clausen *et al.* (141) observed a higher prevalence of aberrant glucose metabolism (T2DM, IGT or impaired fasting glucose, IFG) in offspring of mothers with GDM compared with offspring of mothers with T1DM. Together, the studies suggest that the effects of prenatal exposure to diabetes may not be similar regardless of diabetes type.

2.5.4 Long-term, metabolic consequences of prenatal exposure to GDM

Data on long-term metabolic consequences of prenatal exposure to gestational diabetes started to accumulate at approximately the same time as data supporting the developmental origins of health and disease hypothesis. Below, the studies on long-term metabolic consequences of prenatal exposure to GDM are discussed according to the outcome(s) studied.

Risk of aberrant glucose metabolism

Prenatal exposure to GDM was associated with long-term risk of aberrant glucose metabolism in all but one of the studies (142). In order to design and implement preventive measures, it would be important to understand whether prenatal exposure to GDM predisposes to decreased insulin secretion and/or decreased insulin sensitivity. However, most existing human data are on prenatal exposure to Type 2 or Type 1 diabetes (126, 143, 144). Plagemann *et al.* (139) suggest that IGT in offspring of diabetic patients (T1DM and GDM) results from decreased insulin action, based on high insulin-to-glucose ratio in the OGTT at 0 and 2 hours postload. Malcolm *et al.* (142) found no difference in fasting insulin or glucose concentration between offspring of mothers with treated or

untreated/treated GDM. Clausen *et al.* (141) found elevated fasting glucose levels in the offspring of mothers with GDM. Vääräsmäki *et al.* (145) observed increased fasting glucose and decreased insulin sensitivity in the offspring of mothers with GDM compared with the offspring of mothers with no risk factors for GDM, even after adjustment for confounding factors including gender, birth weight and current BMI.

Risk of overweight and obesity

Prenatal exposure to GDM associated with increased risk of overweight in the majority of the studies (138, 140, 145–148). As maternal overweight is a strong risk factor for GDM (40, 41) and parental overweight seems to be related to overweight in children, probably via genetic and lifestyle influences as well as via the prenatal environment, it seems important that studies on the intergenerational effects of GDM should consider the influence of parental overweight. The studies on long-term metabolic consequences of prenatal exposure to GDM that have accounted for parental weight have yielded conflicting results: in the Pima Indian Study the children's risk for overweight was independent of maternal obesity (138, 149), and in the studies by Plagemann *et al.* (139, 140) no correlation was found between parental weight and relative weight of offspring. In five other studies (90, 150–153,) adjustment for parental weight attenuated the association of prenatal exposure to GDM with subsequent metabolic diseases (153), or parental obesity was a stronger predictor of offspring obesity than prenatal exposure to GDM (90, 150–152).

Risk of metabolic syndrome

As in adults, the lack of a uniform definition of metabolic syndrome in children and adolescents makes it difficult to compare results of different studies. In the Pima Indian Study (154), the Diabetes in Pregnancy Study (155) and in the study by Tam *et al.* (71), blood pressure was elevated in offspring with prenatal exposure to GDM. The prevalence of other components of the metabolic syndrome as well as the prevalence of the syndrome as an entity was found to be increased in the four other studies that evaluated these as outcomes (145, 146, 156). In the study by Boney *et al.* (156), prenatal exposure to GDM was a risk factor for metabolic syndrome at age 4–11 years only in those born large for gestational age (LGA). In the Mysore cohort prenatal exposure to GDM

associated with increased adiposity and cardiovascular risk markers, especially in girls (157). The two largest studies to date associated GDM with increased risk of metabolic syndrome in adolescence and young adulthood independently of birth weight (145, 146). The risk estimates in these studies were similar: the risk of metabolic syndrome in young adulthood was fourfold in children of mothers with GDM compared with the background population in the study by Clausen *et al.* (146), and the odds ratio for metabolic syndrome associated with prenatal exposure to GDM was 3.53 compared with children of mothers with no risk factors for GDM in the study by Väärasmäki *et al.* (145).

Difficulties in comparing results of studies on long-term metabolic consequences of prenatal exposure to GDM

Many of the studies on metabolic consequences of prenatal exposure to GDM are small in size and have follow-up periods extending only to prepubertal stage. The results are not easy to compare, as different screening and diagnostic criteria for GDM have been used, control groups are heterogeneous and outcomes are not consistently defined. Many studies have not assessed the influence of parental overweight. Some studies are summarized in Tables 6 and 7, which also illustrate the difficulties in comparing the studies.

Table 6. Some prospective studies on long-term metabolic consequences of prenatal exposure to gestational diabetes.

Study	Enrolment	n exposed to GDM	Control group	Follow-up	Outcomes	Adjustment for parental weight
Pima Indians of Arizona, USA (138, 149)	since 1965	68	541 born before maternal GDM diagnosis and 1326 NGT	15–19 y	Proportion desirable weight highest in those with prenatal exposure to GDM	Yes
Diabetes in Pregnancy Study, USA (7, 158)	1977–1983	88 GDM or T1DM	550 NGT	14–17 y	BMI and IGT prevalence highest in those with prenatal exposure to GDM	No
Malcolm <i>et al.</i> , Canada (142, 159)	1990–1995	25 vs. 46 ^a	none	9–11 y	IGT 0% vs. 8.7%, overweight 15.4% vs. 24.2%	No
Project Viva, USA (160)	1992–2002	51	152 IGT, 1035 NGT	3 y	SBP and sum of skinfolds higher in those with prenatal exposure to GDM	Yes
Catalano <i>et al.</i> , USA (90)	1990–1999	25	38 NGT	7–11 y	No differences in overweight, body composition or metabolic markers	Maternal pre-pregnancy BMI predicts overweight and percentage body fat
Northern Finland Birth Cohort (145)	1985–1986	96	3,709 no risk factors for GDM	16 y	OR for metabolic syndrome 3.53	Yes
Mysore Cohort, India (157)	1997–1998	35	479 NGT	5 and 9.5 y	Larger skinfolds, higher HOMA-IR and SBP	Yes

^aminimal treatment vs. tight glycemic control of GDM

Table 7. Some retrospective studies on long-term metabolic consequences of prenatal exposure to gestational diabetes.

Study	Children born	n exposed to GDM	Control group	Follow-up	Outcomes	Adjustment for parental weight
Plagemann <i>et al.</i> 1997, Germany (139, 140)	1980–1990	15	31 T1DM	5–9 y	IGT 20.0 vs. 17.4%; overweight 26.6 vs. 35.5%; obesity 13.3 vs. 25.8%	No correlation between parental and child overweight
Whitaker <i>et al.</i> 1998, USA (150)	1985–1986	63	159 GCT positive, OGTT normal vs. 45 GCT positive, no OGTT vs. 257 NGT	10 y	Obesity 19 vs. 14 vs. 16 vs. 24%	Prevalence of child obesity x 2 if parent obese
Vohr <i>et al.</i> 1999, Boney <i>et al.</i> , USA 2005 (151)(156)	1987–1989	42 and 52 ^a	43 and 42 NGT ^a	4–11 y	Overweight 35.2 vs. 4.3 vs. 5.0 vs. 20.5%; metabolic syndrome 50 vs. 21 vs. 29 vs. 18%	Maternal pre-pregnancy BMI and child birth weight predict BMI at age 7 y
Schaefer-Graf <i>et al.</i> 2002, Germany (152)	1995–2000	324	none	2.5–8.5 y	Overweight: normal weight parents 20.4 vs. one parent obese 34.1 vs. both parents obese 69.2%	Parental obesity predicts offspring obesity
Gillman <i>et al.</i> 2003, USA (153)	1982–1987	465	14416	9–14 y	At risk for overweight 17.1 vs. 14.2%; overweight 9.7 vs. 6.6%	Adjustment for maternal current BMI attenuated association
Hillier <i>et al.</i> , USA 2007 (147)	173 and 370 ^b	288 OAV vs. 999 GCT positive, OGTT normal vs. 7609 NGT	5–7 y	At risk of overweight: OR 1.22 GCT highest quartile vs. OR 1.28 OAV vs. OR 1.89 GDM not treated	Maternal hyperglycemia and childhood obesity related only in children born large for gestational age	
Lee <i>et al.</i> 2007, Korea (148)	1995–1997	202	96 OAV	3.8–8.9 y	BMI at age > 5 y 16.8 vs. 15.2 kg/m ²	Adjusted for maternal pre-pregnancy weight
Tam <i>et al.</i> 2008 (71)		63	101	8 y	Blood pressure 94/62 vs. 88/57; HDL-C 1.58 vs. 1.71	No
Clausen <i>et al.</i> 2008, 2009, Denmark (141, 146)	1978–1985	168	139 risk factors for GDM, normal OGTT vs. 160 T1DM vs. 128 background population	18–27 y	Aberrant glucose metabolism 21 vs. 12 vs. 11 vs. 4%; risk of overweight in GDM x 2, of metabolic syndrome x 4 vs. background population	No

^abirth weight large for gestational age and appropriate for gestational age, ^bnot treated and treated GDM

2.5.5 Long-term, metabolic consequences of prenatal exposure to hyperglycemia under the threshold of GDM

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study is a large, multinational, multiethnic study set out to clarify the risk of adverse pregnancy outcome associated with hyperglycemia under the threshold of GDM (35). In this study, maternal glucose concentrations showed a strong, linear association with fetal overgrowth, specifically adiposity at birth, and with fetal hyperinsulinemia (161). No long-term data of this study are available as yet. Previous, smaller studies in various populations have studied the short-term effects of maternal hyperglycemia on offspring and found similar results as in the HAPO study (162–168). However, there is a paucity of published reports on the long-term follow-up of offspring exposed to hyperglycemia under the threshold of GDM.

In the Early Bird Study (169), maternal fasting glucose measured at gestation week 28 (n=27) associated with birth weight, but not with weight or insulin resistance at the age of 8 years. Knight *et al.* (170) observed in 547 offspring of nondiabetic mothers that maternal prepregnancy BMI and fasting blood glucose measured at gestation week 28 correlated with offspring birth weight, but the effect of hyperglycemia resolved by 12 weeks of age, whilst the impact of maternal BMI continued until 2 years of age. Paternal BMI correlated with offspring weight from 12 weeks and with offspring BMI from 1 year onwards. Similar results were found by Ong *et al.* (171), who studied over 4,000,400 children of nondiabetic mothers from two cohorts. In this study, maternal hyperglycemia under the threshold of GDM associated with offspring birth weight and adiposity at birth, but this association disappeared by 3 months of age. Maternal prepregnancy BMI associated with offspring adiposity at 1 and 2 years. However, in two large, retrospective studies maternal hyperglycemia under the threshold of GDM increased the risk of aberrant glucose metabolism and overweight in offspring at age 5–7 years (147), and even in adulthood (141, 146). As the diagnostic criteria for GDM vary greatly, some of the studies reviewed earlier also present effects due to relatively mild glucose intolerance.

3 Aims of the study

Data from Oulu University Hospital and the Northern Finland Birth Cohort were used as follows:

1. To evaluate pre-pregnancy overweight and GDM, separately and concomitantly, as determinants of risk for subsequent diabetes and hypertension twenty years after delivery in women (I)
2. To assess insulin secretion and insulin resistance at pre-school age in offspring with prenatal exposure to GDM and T1DM compared with a control group of offspring of mothers with normal glucose tolerance during pregnancy (II)
3. To survey the prevalence of metabolic syndrome at age 16 years in a European, population-based birth cohort using the new IDF pediatric definition and compare this with prevalence estimated using the IDF adult definition and five other previously published definitions (III)
4. To estimate the risks of overweight and abdominal obesity at age 16 years associated with prenatal exposures to maternal pre-pregnancy overweight and GDM in offspring (IV)

4 Study populations and methods

The health care in pregnancy, including screening and diagnosis of gestational diabetes in the study populations are presented, followed by descriptions of the populations studied and methods used.

4.1 Health care in pregnancy

In Finland, cost-free, primary health care is offered to all pregnant women at maternity welfare clinics (MWC). Practically all pregnant women attend these clinics. When necessary, the women are treated in co-operation with the delivery hospital outpatient clinic.

4.1.1 Screening and diagnosis of gestational diabetes

During the study periods, GDM screening in the MWCs was based on assessment of risk factors, in accordance with national guidelines. A woman was considered at risk for GDM if at least one of the following risk factors was present: age over 40 years, BMI ≥ 25 kg/m², prior GDM, previous delivery of a macrosomic (birth weight > 4,500/4500 g) infant, glucosuria, and suspected fetal macrosomia in the current pregnancy (172). These women underwent glucose tolerance testing mainly at gestation week 26–28, performed after an overnight fast, conducted by administering a 2-hour, 75-gram oral glucose tolerance test (OGTT). In 1985–1986 the upper ranges of normal capillary blood glucose concentrations were 5.5, 11.0, and 8.0 mmol/L at fasting, 1 hour and 2 hours after the glucose load, respectively. In 1995–1997 the cut-off values for venous blood glucose concentrations were 4.8, 10.0, and 8.7 mmol/L. The diagnosis of GDM was set after one abnormal value during both study periods.

4.1.2 Treatment of pregnancies complicated by diabetes

At the delivery hospital outpatient clinic, the team caring for diabetic pregnant women comprised an endocrinologist, an obstetrician and a specialist nurse. Women with T1DM were registered in the outpatient clinic of the delivery hospital as soon as pregnancy was confirmed. They attended the hospital antenatal clinic at least every fourth week up to gestation week 32, and thereafter every 1–2 weeks. During the last weeks of pregnancy, the visits were twice a

week, or the women were hospitalized until delivery. Whilst at home, the women monitored their blood glucose values at least 2–3 days/week, according to a seven-point profile. The diabetologist checked the values and adjusted insulin dosage as required.

Women with GDM received dietary advice, were taught to monitor their blood glucose values at home and reported them to the specialist nurse once a week. Insulin therapy was initiated if fasting glucose concentration repeatedly exceeded 5.3 mmol/L and/or postprandial glucose repeatedly exceeded 6.7 mmol/L. Women requiring insulin therapy were monitored and treated as those with T1DM.

4.2 Study populations

The present study is based on data from two study populations, a clinical cohort from Oulu University Hospital (paper II) and the prospective, population-based Northern Finland Birth Cohort 1986 (NFBC 1986, papers I, III and IV).

4.2.1 Clinical cohort from Oulu University Hospital

Between 1 June 1995 and 31 May 1997, all mothers with T1DM or GDM delivering a singleton, full-term (\geq gestation week 37) infant at a tertiary level centre, Oulu University Hospital, were invited to take part in a study on prenatal exposure to hyperglycemia at delivery. Of the eligible mothers, 99 (29 with T1DM and 70 with GDM) and a control group of offspring of mothers unaffected by diabetes ($n=105$) gave their consent and were enrolled simultaneously.

Data collection, anthropometric measurements and laboratory analyses

Pregnancy, delivery and neonatal data were collected prospectively at the MWCs and the hospital, using standardized, national forms. The offspring (16 of mothers with T1DM, 22 of mothers with GDM, 25 of control mothers) were examined in 2000–2001 at age 3–6 years (mean 4.9 years).

In the clinical examination, anthropometric measurements [height and weight, waist circumference, thickness of three skin folds (biceps, triceps and subscapular)] were performed, and blood pressure was measured, fasting serum lipids and diabetes-associated auto-antibodies analyzed and a 60-min intravenous

glucose tolerance test (IVGTT) performed according to the Islet Cell Antibody Users Study (ICARUS) protocol (173, 174).

Plasma glucose and serum lipid concentration was measured by an automatic analyzer (Cobas Integra 700 Analyzer; Roche Diagnostics, Basel, Switzerland) using enzymatic, colorimetric methods and an enzymatic method with hexokinase, respectively. Serum insulin was measured using an enzyme-linked, immunosorbent assay (DakoCytomation Insulin; Dakocytomation Ltd., Ely, Cambridgeshire, UK) Auto-antibodies to islet cells (ICA) were detected with immunofluorescence, and auto-antibodies to glutamic acid decarboxylase (GADA) and insuloma-associated antigen-2 (IA-2A) were analyzed by radiobinding assays, as has previously been described (175).

Definitions

Maternal pre-pregnancy BMI was calculated as kg/m². Gestational weight gain was defined as weight at delivery minus pre-pregnancy weight. The weight and height values at age 3–6 years were converted to relative values based on a Finnish reference population (176). The first phase insulin response (FPIR) was calculated as the sum of the 1- and 3-minute insulin concentrations during the IVGTT. The homeostasis model assessment (HOMA) values were calculated using the validated calculator available at <http://www.dtu.ox.ac.uk> (177). The estimations of low-density lipoprotein concentrations were obtained using the Friedewald formula (178). Body fat percentage was estimated from skin fold thickness values using the Slaughter equation (179).

4.2.2 Northern Finland Birth Cohort 1986

The Northern Finland Birth Cohort 1986 (NFBC 1986) is an ongoing, population-based study comprising extensive data on parents and their children.

Data collection

All mothers resident in the two northernmost provinces of Finland, with an expected delivery date between July 1st 1985 and June 30th 1986, were eligible for the NFBC 1986 study; 99% (n=9,362, giving birth to 9,479 children) enrolled at the first antenatal visit in the MWCs. Data have been acquired prospectively since gestation week 12. Trained nurses helped mothers fill in two questionnaires at

MWCs. These questionnaires covered the early (data since 12–16th gestational week) and late pregnancy (after 24 weeks gestation including the perinatal period). A third questionnaire was filled in at the hospital by the attending midwives. The course of pregnancy and delivery, including complications and diseases, was further confirmed from patient records, as was the neonatal outcome. In 2000–2001, at offspring age 16 years, the adolescents and parents filled in a detailed postal questionnaire (response rates 80% and 76%, respectively), and the adolescents attended a clinical examination (participation rate 74%) performed by trained nurses.

Antenatal and birth data

Parental education and occupation, history of chronic disease, smoking habits, pre-pregnancy height and weight were recorded, and maternal height (to one decimal place in centimeters) wascentimetres) measured at the first antenatal visit. Maternal weight (to one decimal place in kilograms) and blood pressure (in mmHg, using a sphygmomanometer) were measured, and urine dipstick testing to detect glucosuria and proteinuria (≥ 0.3 g/L) was performed at the first and also at every subsequent visit at the MWCs. Gestational age was calculated from the last menstrual period, validated by clinical examination, and confirmed before gestation week 24 by ultrasound in 55% of the study population. Gestational age, weight and length at birth were recorded by the attending midwives at the delivery hospital.

Duration of maternal education was used as a measure for socioeconomic status, and classified as low/high with a cut-off at 9 years. Parity was dichotomized as nulliparous/parous. Maternal and paternal pre-pregnancy smoking was classified as smoker/non-smoker. Paternal diabetes was classified as yes/no. Pre-pregnancy body mass indexes (BMI) for mothers and fathers were calculated and classified as normal weight/overweight with a cut-off at 25 kg/m². Mean arterial pressure (MAP) after gestation week 36 was calculated using the formula $MAP = \text{diastolic blood pressure} + (\text{systolic blood pressure} - \text{diastolic blood pressure} / 3)$. Gestational hypertension was defined as systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg, and pre-eclampsia as proteinuria and blood pressure exceeding the aforementioned values after gestation week 20. The presence of risk factors for GDM and OGTT results in pregnancy were classified as follows: 1 no risk factors for GDM, 2 risk factor/s for GDM, diagnostic OGTT normal, 3 risk factor/s for GDM, OGTT not performed, 4 GDM.

In the women with GDM, the OGTT results were dichotomized as one/several abnormal values.

Offspring size at birth was classified as appropriate for gestational age (AGA) and small (SGA) and large (LGA) for gestational age according to plus/minus 2 standard deviations (SD) of the gender and gestational age-specific cohort distributions.

Data at offspring age 16 years

At the clinical examination of offspring, anthropometric measurements (height, weight, waist circumference at the level midway between the lowest rib margin and the iliac crest) were performed. Blood pressure was measured using an oscillometric pressure meter, Omron 705 CP, and if this failed, a mercury sphygmomanometer, taking two readings two minutes apart. Fasting blood samples for the analysis of glucose, insulin and lipids were drawn. Samples for serum insulin were stored at -20°C until analysis (within 7 days) by radioimmunoassay using commercial reagents (Pharmacia Diagnostics, Uppsala, Sweden). Plasma glucose and serum lipids were analyzed using an automatic analyzer (Cobas Integra 700, Roche Diagnostics, Basel, Switzerland) within 24 hours of sampling, at Oulu University Hospital laboratory.

Postal questionnaire data included family size and income and current parental weight. Family income/member/year was calculated as previously described (180). BMIs for parents were calculated and classified as in pre-pregnancy. In the offspring, overweight and obesity were defined using the International Obesity Task Force (IOTF) criteria (181). Abdominal obesity was defined as waist-to-height ratio ≥ 0.5 (182). Homeostasis model assessment values for insulin resistance (HOMA-IR) were defined from paired fasting and insulin levels using the validated calculator available at www.dtu.ox.ac.uk, based on a non-linear extension of the previously published formula $HOMA-IR = (FPI(mU/l) \times FPG(mmol/l))/22.5$ (177). Metabolic syndrome was defined using the IDF pediatric (183) and adult definitions (69), the ATP III adult definition and its pediatric modification, the age- and gender-specific criteria suggested by Jolliffe *et al.* (184). The hypertriglycemic waist phenotype was also used as a definition of the metabolic syndrome in adolescents (185). The definitions of the metabolic syndrome are summarized in Table 8.

Table 8. Definitions of the metabolic syndrome used in the present study.

Definition	Cut-offs for components ^a					Criteria
	Glucose metabolism (FG, mmol/L)	Central obesity (waist, cm)	Dyslipidemia		Hypertension (blood pressure mmHg)	
			(TG, mmol/L)	(HDL, mmol/L)		
IDF definitions (69, 183, 184)						
Pediatric ^b	5.6	87.5/80.0	1.7	1.03	130/85	Central obesity and 2 criteria of 4
Age-specific	5.6	91.8/77.7	1.59/1.46	1.03/1.27	M: 128/82 F: 128/84	
Adult						
Europe	5.6	94/80	1.7	1.03	130/85	Central obesity and 2 criteria of 4
USA	5.6	102/88	1.7	1.03	130/85	
ATP III definitions(68, 184, 186)						
Pediatric	6.1	98.1/92.7	1.24	1.03	90th percentile ^c	
Age-specific	5.6	100.6/85.2	1.59/1.46	1.03/1.27	M: 128/82 F: 128/84	3 criteria of 5
Adult	5.6	102/88	1.7	1.03/1.30	130/85	
Hypertriglycemic waist (185)	87.5/82.0	1.30/1.31				2 criteria of 2

^aValues for males/females (M/F) when applicable

^bOver 90th percentile of the population studied or adult cut off if lower

^cover 90th percentile of the population studied

ATP III=Adult Treatment Panel III, FG=fasting blood glucose, HDL=high density lipoprotein concentration, IDF=International Diabetes Federation, TG=triglyceride concentration

Study groups

For the study evaluating risks of later diabetes and hypertension in women with risk factors for GDM (paper I), the mothers with T1DM (n=27), chronic hypertension (n=209), a multiple pregnancy (n=115), OGTT not performed despite indications during pregnancy (n=1876) or data missing (most often on pre-pregnancy BMI n=651) were excluded. A variable of the determinants of risk was formed from pre-pregnancy overweight, the susceptibility for GDM, and OGTT results in pregnancy as follows: (1) normal-weight women with GDM

(n=70); (2) overweight women with GDM (n=54); (3) normal-weight (n=768) and (4) overweight (n=250) women with risk factors for GDM but normal OGTT results; and (5) women with no risk factors for GDM (n=5341). To assess the effect of current overweight, the study population was assorted in a similar way, substituting pre-pregnancy overweight with overweight in 2000–2001, 16 years after the index pregnancy.

The study surveying the prevalence of the metabolic syndrome using different definitions (paper III) included offspring born from singleton pregnancies who had participated in the clinical examination at age 16 years and had complete data on all variables used to define metabolic syndrome (n=5,665).

For the study estimating the risks of overweight and abdominal obesity associated with prenatal exposures to GDM and maternal overweight (paper IV) the classification of prenatal exposure was the same as the classification of determinants of risk described for paper I. This study included offspring born from singleton pregnancies who had participated in the clinical examination. Excluded were those who had a mother or father with diabetes before pregnancy (n=73), a mother who had not undergone OGTT during pregnancy despite indications (n=1,942), and those who had not participated in the clinical follow-up examination or had incomplete data on the outcome variables (n=3,020).

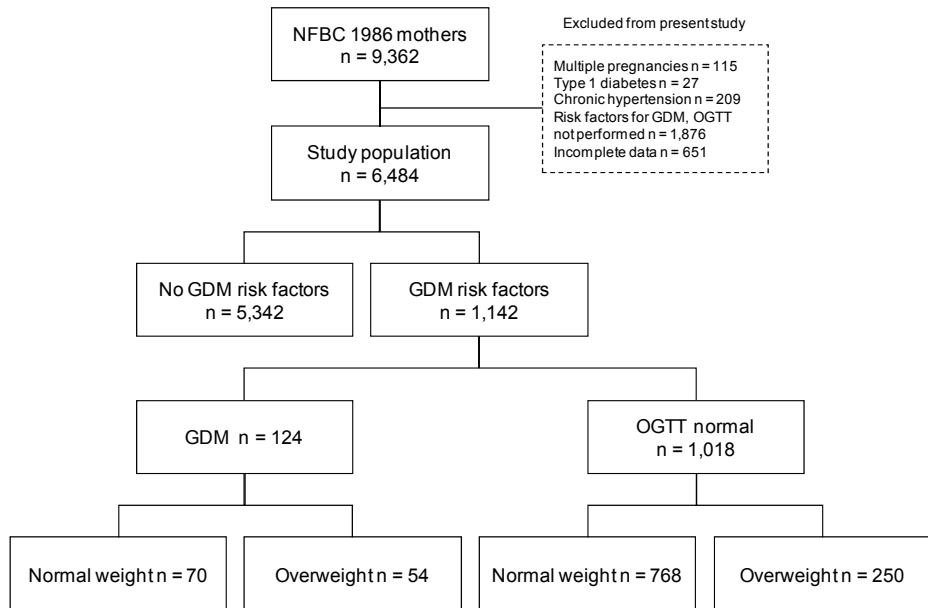


Fig. 3. Flow chart of the NFBC 1986 mothers (I, published by permission from The Endocrine Society).

4.3 Register-based data

Data on clinical diagnoses of diabetes and hypertension were based on hospital discharge data, on receiving reimbursement for medication used to treat the disease and on death certificates. Data from the National Institute for Health and Welfare, the Social Insurance Institution of Finland, and Statistics Finland were obtained for the period 1985–2006. The diagnosis codes in the hospital discharge data and in the data on reimbursement for medical expenses were based on the International Classification of Diseases and Health Related Problems, ICD 8, ICD 9 and ICD 10. The codes used for diabetes were 250 (ICD 8 and ICD 9) and E10, E11, E14 (ICD 10), and for hypertension 400-404 (ICD 8), 401-405 (ICD 9) and I10, I11, I15 (ICD 10). Women were considered to have developed diabetes and/or hypertension if they had a discharge or death certificate diagnosis of the disease and/or received reimbursement for drugs to treat the disease(/s).

4.4 Statistical methods

Data were analyzed with SPSS for Windows 14.0 and 15.0 (SPSS Inc, Chicago, Illinois, USA), R ((187), and CIA v 2.1 (188). Normally distributed data are presented as means and 95% confidence intervals (CI). Logarithmic transformation was used for skewed variables to achieve normality; these data are presented as geometric means and 95% CI. Analysis of variance was used for comparisons between study groups and analysis of covariance for adjusted comparisons. Categorical data are presented as percentage (%). Pearson's chi-square test was used to evaluate differences between groups for categorized variables.

When evaluating the later risks of diabetes and hypertension in women with risk factors for GDM (paper I), Kaplan-Meier time-to-event curves were created to graphically evaluate the proportional hazards assumption and to estimate cumulative incidence of diabetes and hypertension. The unadjusted proportional hazard ratios (HR) of the outcomes for the determinants of risk were estimated using Cox regression analyses.

Logistic regression analysis was used to evaluate the independent associations of prenatal exposure variables with offspring overweight and abdominal obesity (paper IV). To create the adjusted regression models, variables with a statistically significant odds ratio (OR) in the unadjusted analyses were entered simultaneously. All two-way interactions between predictors were tested for and found to be non-significant.

5 Results

5.1 Data attrition analyses

In the clinical cohort from Oulu University Hospital, there were no statistically significant differences in gestational age at birth, birth weight or length between those lost to follow-up and those participating in the clinical examination (paper I). In the NFBC 1986, data attrition analyses revealed no differences in demographic or clinical characteristics (e.g. maternal education, child birth weight) between those with missing data and the study populations (papers I, III, and IV).

5.2 Risk of diabetes and hypertension in women with risk factors for gestational diabetes (paper I)

The prevalence of GDM was 1.9%, and risk factors for GDM but normal glucose tolerance in pregnancy were observed in 15.7% of the study population. Pre-pregnancy overweight was present in 43.5% of the women with GDM and in 24.6% of the women with a normal OGTT. Diagnosis of GDM was based on one abnormal value in the OGTT in 81.0% of the normal-weight women with GDM and in 66.7% of the overweight women with GDM. The characteristics of the study population, assorted according to risk factors for GDM, OGTT results and pre-pregnancy weight, are shown in Table 9.

Kaplan-Meier time-to-event curves are shown in Figure 4. Twenty years after delivery, the cumulative incidence of treated diabetes and hypertension in the whole study population was 1.3 % and 7.5%, respectively. Compared to normal-weight women with normal glucose tolerance in pregnancy, the women with simultaneous pre-pregnancy overweight and GDM had strikingly high risks for developing diabetes (hazard ratio, HR 47.24) and hypertension (HR 9.16) twenty years after delivery. The risks for these diseases were elevated in women with pre-pregnancy overweight even when they had normal glucose tolerance during pregnancy (hazard ratio diabetes 12.63, hypertension 2.86). GDM *per se* indicated increased risk only for diabetes (hazard ratio 10.61).

Table 9. Characteristics of the NFBC 1986 mothers assorted according to pre-pregnancy weight and glucose metabolism in pregnancy.

Characteristic	Pre-pregnancy weight and glucose metabolism in pregnancy						No risk factors for GDM
	Risk factors for GDM present			OGTT normal			
	normal weight	overweight	normal weight	normal weight	overweight	overweight	
number	70	54	768	250	5342		
Age (y)**	27.0 (25.6, 28.5)	31.8 (30.0, 33.7)	27.0 (26.7, 27.4)	28.6 (27.9, 29.3)	26.6 (26.4, 26.7)		
Height (m)	1.63 (1.62, 1.65)	1.62 (1.61, 1.64)	1.64 (1.63, 1.64)	1.63 (1.62, 1.64)	1.63 (1.63, 1.63)		
Weight (kg)**	56.6 (55.0, 58.2)	79.5 (76.2, 82.9)	56.7 (56.3, 57.2)	76.7 (75.4, 78.0)	55.8 (55.6, 56.0)		
% Nulliparous**	41.4	14.8	37.5	28.8	37.0		
% Pre-pregnancy smoker*	15.9	13.2	16.8	19.6	21.2		
OGTT 0 h (mmol/L)**	4.9 (4.6, 5.1)	5.2 (4.9, 5.4)	4.2 (4.2, 4.2)	4.3 (4.3, 4.4)	NA		
OGTT 1 h (mmol/L)**	9.1 (8.7, 9.6)	9.9 (9.4, 10.4)	7.4 (7.3, 7.5)	7.7 (7.5, 7.9)	NA		
OGTT 2 h (mmol/L)**	8.5 (8.1, 8.8)	7.9 (7.5, 8.4)	5.6 (5.5, 5.7)	5.8 (5.7, 6.0)	NA		
% OAV**	81.0	66.7	NA	NA	NA		
MAP after gw 36**	91 (89, 94)	99 (96, 102)	93 (93, 95)	97 (96, 99)	92 (92, 93)		
%Gestational hypertension**	1.4	5.9	4.1	5.4	2.7		
% Pre-eclampsia**	1.4	3.9	2.1	3.3	1.7		
BMI in 2000–2001 (kg/m ²)**	23.6 (22.6, 24.6)	30.9 (29.5, 32.4)	24.3 (24.0, 24.5)	31.5 (30.7, 32.4)	23.7 (23.6, 23.8)		
%Overweight in 2000–2001**	35.3	100.0	39.0	93.5	31.2		

Data are geometric means (95% confidence interval) for continuous variables, percentage for categorical variables

Difference between groups assessed using analysis of variance for continuous variables, chi-square test for categorical variables

*P for difference between groups <0.05

**P for difference between groups <0.001

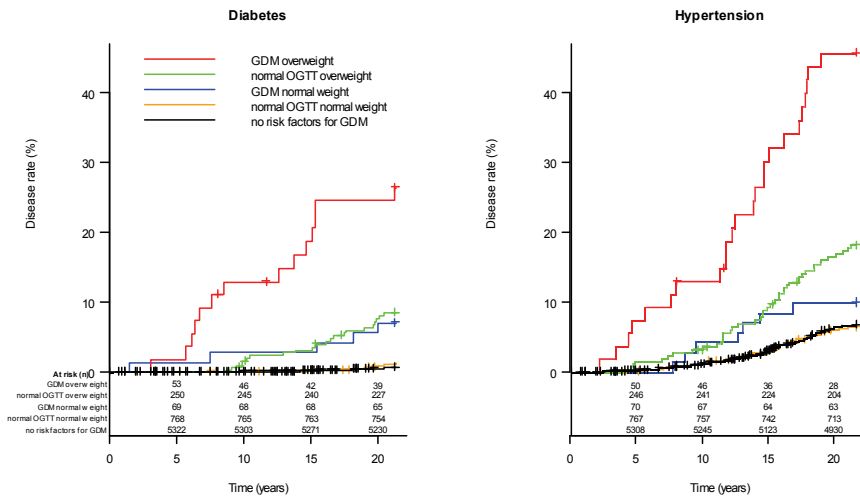


Fig. 4. Time-to-event data for diagnoses of diabetes and/or hypertension after delivery in the NFBC 1986 mothers (I, published by permission from The Endocrine Society).

5.3 Glucose metabolism at pre-school age in offspring with prenatal exposure to gestational diabetes (paper II)

In the clinical cohort from Oulu University Hospital, the mothers with GDM were older, had a greater pre-pregnancy BMI and gained less weight during pregnancy than mothers with T1DM or controls (Table 10). There were no statistically significant differences in relative weight, relative height, percentage body fat, waist circumference, blood pressure or fasting serum lipids between offspring with prenatal exposure to gestational diabetes or T1DM or offspring of control mothers at the follow-up examination at a mean age of 4.9 years (Table 10). The offspring of mothers with T1DM had higher fasting serum insulin concentrations (38.4 vs. 25.5 pmol/L, $P=0.04$) FPIR (373.2 vs. 271.5 pmol/L, $P=0.03$), and HOMA-B (83.6 vs. 58.2, $P=0.01$) than offspring of mothers with GDM. When adjusted for maternal pre-pregnancy BMI, birth weight, age, and relative weight at examination, FPIR remained increased in offspring of mothers with T1DM compared with the other study groups ($P=0.04$). When adjusted for maternal weight gain instead of maternal pre-pregnancy BMI, the differences between study groups in glucose regulation parameters attenuated to statistical non-significance.

Table 10. Characteristics of the clinical cohort from Oulu University Hospital.

Characteristic	Mothers with diabetes		Controls
	T1DM	GDM	
number	16	22	25
Mothers			
Age at delivery (y)*	27.6 (25.4, 30.1)	32.9 (30.2, 35.9)	30.2 (28.5, 32.1)
Height (cm)	163 (159, 166)	164 (161, 166)	166 (164, 169)
Pre-pregnancy weight (kg)	63.3 (56.1, 71.5)	67.3 (62.6, 72.4)	61.2 (56.9, 65.9)
Pre-pregnancy BMI (kg/m ²)*	23.9 (21.3, 26.8)	25.1 (23.4, 26.9)	22.1 (20.9, 23.4)
Gestational weight gain (kg)*	14.2 (11.4, 17.8)	9.2 (6.7, 12.7)	14.1 (12.2, 16.4)
Family history of diabetes (%)*	18.9	18.2	8.0
Children			
Males (%)	31.3	40.9	44.0
Age at examination (y)*	4.23 (3.83, 4.67)	4.67 (4.38, 4.98)	5.53 (5.38, 5.68)
Height (cm)*	104.9 (102.0, 107.9)	109.2 (106.8, 111.6)	115.8 (113.4, 118.4)
Relative height (SD)	0.6 (0.3, 1.1)	0.7 (0.5, 1.1)	0.9 (0.6, 1.5)
Weight (kg)*	17.4 (16.0, 18.9)	18.4 (17.4, 19.3)	20.7 (19.2, 22.4)
Relative weight (%)	102 (96–108)	98 (95, 101)	99 (95, 104)
Waist (cm)	50.6 (48.7, 52.6)	52.4 (51.0, 53.8)	53.2 (51.2, 55.4)
Percentage body fat	15.5 (13.6, 17.6)	14.1 (12.8, 15.5)	13.9 (12.4, 15.6)
SBP (mmHg)	101 (98–105)	98 (95, 100)	101 (98, 105)
DBP (mmHg)	59 (54, 63)	57 (55, 59)	60 (58, 62)

Data are geometric means (95% confidence interval) for continuous variables, percentage for categorical variables. *P for difference between groups<0.05

5.4 Prevalence of metabolic syndrome (paper III)

The clinical and biochemical characteristics and prevalence of metabolic syndrome using different definitions of the NFBC 1986 adolescents studied are shown in Table 11. The observed overall prevalence estimate of the metabolic syndrome by the IDF pediatric definition was 2.4%, whereas the IDF adult definition yielded a lower prevalence estimate of 1.7%. The prevalence estimate of the metabolic syndrome was higher in males compared with females by all definitions used. The subjects with the syndrome were taller than those without the syndrome (males 177.5 vs. 174.6 cm, $P<0.001$; females 165.6 vs. 163.8 cm,

P=0.001). Abdominal obesity (waist-to-height ratio > 0.5) identified almost 85% of the adolescents (84.2% of males and 84.8% of females) with metabolic syndrome by the new IDF pediatric criteria. There were no differences in BMI, waist circumference, or HOMA-IR between the subgroups defined using different definitions of the metabolic syndrome (IDF pediatric, IDF age-specific, IDF adult, ATP pediatric, and hypertriglycemic waist definition). The group with hypertriglycemic waist phenotype had lower fasting glucose concentration and systolic blood pressure compared with groups defined using other definitions of the metabolic syndrome.

Table 11. Characteristics and prevalence of the metabolic syndrome in the NFBC 1986 children.

Characteristic	Males	Females
number	2,862	2,803
Height (cm)	174.8 (174.5, 175.0)	163.8 (163.6, 164.1)
Weight (kg)	63.8 (63.4, 64.2)	56.4 (56.1, 56.7)
BMI (kg/m ²)	20.9 (20.8, 21.0)	21.0 (20.9, 21.1)
Waist circumference (cm)	75.3 (75.0, 75.6)	71.5 (71.0, 71.8)
SBP (mmHg)	121 (120, 121)	110 (109, 110)
DBP (mmHg)	68 (68, 69)	67 (66, 67)
Glucose (mmol/L)	5.3 (5.3, 5.3)	5.0 (5.0, 5.0)
Insulin (pmol/L)	67.1 (65.9, 68.4)	67.8 (66.8, 68.8)
Total cholesterol (mmol/L)	4.02 (4.00, 4.05)	4.36 (4.33, 4.39)
HDL-cholesterol (mmol/L)	1.29 (1.28, 1.30)	1.46 (1.45, 1.47)
LDL-cholesterol (mmol/L)	2.12 (2.10, 2.14)	2.23 (2.21, 2.25)
Triglyceride (mmol/L)	0.74 (0.73, 0.75)	0.77 (0.76, 0.78)
HOMA-IR	1.26 (1.24, 1.28)	1.26 (1.24, 1.28)
Metabolic syndrome (%)		
IDF definitions (69, 183, 184)		
Pediatric	3.5 (2.9, 4.3)	1.2 (0.8, 1.7)
Age-specific	3.1 (2.5, 3.9)	3.2 (2.6, 3.9)
Adult		
Europe	2.2 (1.7, 2.8)	1.2 (0.8, 1.7)
USA	1.4 (1.0, 1.9)	0.6 (0.4, 1.0)
ATP definitions (68, 184, 186)		
Pediatric	3.3 (2.7, 4.1)	0.8 (0.5, 1.2)
Age-specific	3.5 (2.8, 4.2)	2.2 (1.7, 2.8)
Adult	3.1 (2.5, 3.8)	1.5 (1.1, 2.0)
Hypertriglycemic waist (185)	3.8 (3.1, 4.5)	2.5 (2.0, 3.1)

Data are geometric means (95% confidence interval) for continuous variables, percentage (95% confidence interval) for prevalence

5.5 Risks of overweight and abdominal obesity attributable to prenatal exposures to gestational diabetes and maternal overweight (paper IV)

The characteristics of the study population, assorted according to maternal GDM and/or pre-pregnancy overweight, are shown in Table 12. The prevalence of overweight (defined using the IOTF criteria) in the whole study population at age 16 years was 12.7% (14.5% in males, 11.0% in females) and that of abdominal obesity (waist-to-height ratio ≥ 0.5) 8.3% (8.0% in males, 8.6% in females). The risks associated with prenatal exposure to maternal overweight and GDM simultaneously were high (overweight OR 4.05; abdominal obesity OR 3.82). Even in offspring of mothers without GDM, the risks associated with prenatal exposure to maternal overweight were greater for both outcomes (overweight OR 2.56; abdominal obesity OR 2.60). No statistically significant risks for overweight and abdominal obesity were associated with prenatal exposure to GDM in the offspring of normal-weight women. These results were adjusted for parental pre-pregnancy smoking, paternal overweight, gender and size at birth.

Table 12. Characteristics of the NFBC 1986 mothers, fathers and children assorted according to mothers' pre-pregnancy overweight and glucose metabolism in pregnancy.

Characteristic	Mothers' pre-pregnancy overweight and glucose metabolism in pregnancy					
	Gestational diabetes (GDM)			No risk factors for GDM		
	Normal weight	Overweight	OGTT normal	Normal weight	Overweight	OGTT normal
Mothers						
Age (y)**	27.4 (25.8, 29.1)	34.8 (32.8, 36.9)	27.2 (26.8, 27.7)	29.4 (28.5, 30.3)	26.9 (26.7, 27.0)	21.0 (20.9, 21.1)
Pre-pregnancy BMI (kg/m ²)**	21.2 (20.7, 21.8)	29.0 (28.1, 29.9)	21.3 (21.1, 21.5)	28.9 (28.4, 29.5)	21.0 (20.9, 21.1)	36.6
Nulliparous (%)**	41.3	9.1	37.2	24.0	18.3	4.4
Smoker (%)	14.6	11.4	14.3	14.6	18.3	18.3
Education <9 y (%)**	2.2	20.0	5.1	9.3	4.4	4.4
Fathers						
BMI (kg/m ²)**	24.3 (23.4, 25.1)	26.7 (25.3, 28.1)	23.8 (23.6, 24.1)	24.2 (23.8, 24.6)	23.7 (23.6, 23.8)	28.3
Overweight (%)**	38.1	56.7	32.0	36.0	28.3	37.8
Smoker (%)	42.9	31.3	35.8	38.4	37.8	37.8
Children						
Newborn						
Weight (kg)**	3.67 (3.53, 3.82)	3.70 (3.49, 3.92)	3.69 (3.64, 3.74)	3.78 (3.68, 3.88)	3.48 (3.46, 3.40)	49.5
Male (%)	55.1	60.0	52.1	55.8	49.5	2.2
SGA (%)	0	0	0.6	1.9	2.2	0.4
LGA (%)*	2.0	8.6	6.2	10.4	0.4	0.4
Age 16 years						
BMI (kg/m ²)**	21.0 (20.5, 21.0)	22.7 (21.3, 24.1)	20.7 (20.5, 21.0)	21.0 (20.5, 21.0)	20.7 (20.6, 20.8)	72.6 (72.4, 72.9)
Waist (cm)**	74.6 (72.1, 77.3)	77.4 (73.1, 82.0)	72.9 (72.3, 73.6)	74.6 (72.1, 77.3)	72.6 (72.4, 72.9)	11.7
Overweight (%)**	8.2	40.0	13.5	27.9	11.7	11.7
Abdominal obesity (%)**	8.2	26.7	9.1	19.5	7.5	7.5

Data are geometric means (95% confidence interval) for continuous variables, percentage for categorical variables

Difference between groups assessed using analysis of variance for continuous variables, chi-square test for categorical variables

*P for difference between groups <0.05

**P for difference between groups <0.001

6 Discussion

6.1 Subjects and data quality

The validity of the data and the strengths and limitations of the present study are discussed in this section.

6.1.1 Clinical cohort from Oulu University Hospital

The data can be considered valid, as the study population was highly homogeneous in terms of ethnicity, and any bias of the study population is unlikely because of the free-of-charge maternal care attended by almost all pregnant women. The diagnosis and treatment of diabetes was standardized, and the prospective data on pregnancies and deliveries were compiled in a standardized manner. The control group was older than offspring of T1DM and GDM. It is, however, unlikely that this has affected the results, as all the children were pre-pubertal and there were no differences in relative height or weight. One limitation, however, is the small sample resulting in relatively low statistical power.

6.1.2 Northern Finland Birth Cohort 1986

The NFBC 1986 provides prospective long-term data on a general population-based cohort. To date, this is the most comprehensive follow-up cohort of prenatal exposure to GDM. All participants were European, living in the same area during the same time period and similarly followed up. Data collection was prospective, with validated methods. The exceptionally high retention rate (74% participation rate in follow-up examination at age 16 years) adds further to the value of the NFBC 1986. In addition to distinguishing between the effects of GDM and overweight, the extensive data enabled accounting for several confounding factors, even paternal variables.

Finnish registers containing data on health care are demonstrably comprehensive and reliable (189). However, when evaluating the results, it must be remembered that the outcomes were based on register data on having a diagnosis of diabetes and/or hypertension. Though the combination of different registers to achieve catchment of diseases should be optimal, only the women

with diagnosed and, in most cases, treated disease were included, i.e., all the women who can control their disease by lifestyle are not included in the present study. In addition, diabetes and hypertension may be present for years before being diagnosed: in a previous, population-based study of Finnish middle-aged subjects, only 37.2% of those with diabetic blood glucose values were aware of the condition (190). Thus, it is likely that the cumulative incidence of diabetes and hypertension are to some extent underestimated in the present study. However, we find no reason to expect that the number of undiagnosed women would differ between study groups, and consequently the risk estimates should not be affected (biased).

In the present study, diabetes types occurring after delivery could not be differentiated; T2DM is assumed to be predominant. It is probable that T1DM is diagnosed relatively soon after delivery, and the later increase in cumulative incidence is due to T2DM (58).

In the NFBC 1986, screening for GDM was risk factor based, and the diagnosis of GDM was made after one abnormal value. In addition, a relatively large number of women did not undergo GDM screening despite indications. Thus, some women with GDM may have gone undetected, and women with relatively mild disturbances in glucose metabolism are included in the GDM group. Despite that, clear differences in later risk for diabetes and hypertension were found between women with and without GDM in the index pregnancy, and also between offspring of these groups.

Maternal hyperglycemia, irrespective of its etiology, has been postulated to have similar long-term effects on the offspring (8, 10). However, the genetic factors contributing to the predisposition to metabolic disturbances in offspring and the timing of prenatal exposure to hyperglycemia are not identical in the offspring of mothers with different types of diabetes. As the data comparing long-term consequences of prenatal exposures to different diabetes types in humans are limited, the results of the present study are comparable only with studies on prenatal exposure to GDM.

Finally, the study groups for determinants of later risk for diabetes and hypertension, and risk of overweight and abdominal obesity attributable to prenatal exposures were quite small; however, as the differences observed were statistically significant and clinically plausible, we consider the results highly relevant.

6.2 Pre-pregnancy overweight and gestational diabetes as determinants of risk for subsequent diabetes and hypertension

The risk of subsequent diabetes indicated by GDM is well established (51, 52, 55). Recent studies suggest that even mild glucose intolerance during pregnancy indicates an increased risk for later, aberrant glucose metabolism (Table 5). In our study, pre-pregnancy overweight emerged as an essential risk factor for subsequent metabolic disorders. Both GDM and pre-pregnancy overweight, occurring independently, indicated an increased risk for diabetes, but the risk was strikingly high in women with simultaneous pre-pregnancy overweight and GDM.

Previous studies report hypertension after GDM mainly as a component of the metabolic syndrome (62, 73). To our knowledge, there are no previous studies on the risk of chronic hypertension after GDM. In the present study the risk for hypertension was not increased by GDM *per se*. Pre-pregnancy overweight indicated an increased risk for subsequent hypertension, but as for diabetes, the risk for hypertension was strikingly high in the women with simultaneous pre-pregnancy overweight and GDM.

In the published study we used population-attributable fractions of risk to illustrate the impact of GDM and pre-pregnancy overweight on the subsequent risks of diabetes and hypertension on population level. In retrospect, it can be argued that the population-attributable fraction of risk is not an appropriate measure, since our study population was limited first by gender (only women) and further by excluding those women with no data on glucose metabolism in pregnancy. The reported figures are true for this population, but may not be applicable in other settings.

Overweight is increasing among women of the fertile age – a recent Finnish study showed a substantial increase in the proportion of overweight (18.8% to 24.5%) and obese (7.5% to 11%) parturients from the year 1990 to 2004 (42). Similar data have been reported from the USA (191). In our study population, pre-pregnancy overweight was retained twenty years after pregnancy, and approximately one third of the women with normal weight before the index pregnancy became overweight during follow-up. The observed, alarmingly high risks of diabetes and hypertension associated with concomitant pre-pregnancy overweight and GDM warrant public health attention. Further preventive measures, i.e. weight control, are urgently needed in the high-risk groups identified.

6.3 Glucose metabolism at pre-school age in offspring with prenatal exposure to gestational diabetes

Even though the genetic predisposition and timing of exposure to hyperglycemia are different in the offspring of mothers with T1DM and GDM, data comparing the effects of prenatal exposure to maternal T1DM and GDM are limited. Silverman *et al.* (158) found no difference in the prevalence of IGT between offspring with prenatal exposure to T1DM and GDM. Plagemann *et al.* (139) observed lower stimulated blood glucose and higher stimulated insulin in offspring with prenatal exposure to T1DM, compared with offspring with prenatal exposure to GDM. Clausen *et al.* (141) found adult offspring of mothers with GDM to be at higher risk of diabetes and pre-diabetes than offspring of mothers with T1DM. In the present study, offspring of mothers with T1DM had increased insulin secretion compared with offspring of mothers with GDM already at preschool age. This is in line with the results of Plagemann *et al.*, and supports the notion that the metabolic consequences of prenatal exposure to diabetes are different for different types of (maternal) diabetes.

The association of gestational weight gain with offspring weight later in life has emerged recently (105, 106). In our study, the mothers with GDM gained the least weight during pregnancy. The differences between study groups were attenuated to non-significant when adjusting for gestational weight gain. We speculate that the low weight gain of women with GDM was a factor protecting against adverse effects of prenatal exposure to hyperglycemia. In addition, the mothers with GDM received intensive education and monitoring during pregnancy, which may have affected the diet and lifestyle of the whole family, and thus the glucose metabolism of the offspring in a favorable way, especially at pre-school age.

6.4 Prevalence of metabolic syndrome at age 16 years

Our study is the first report on the prevalence of metabolic syndrome in adolescents using the IDF pediatric definition published in 2007 (183). This is also the first report on the prevalence of the metabolic syndrome in adolescents from a European, general-population based cohort. The observed overall prevalence estimate of the metabolic syndrome by the IDF pediatric definition was 2.4%. The IDF adult definition yielded a lower prevalence estimate of 1.7%.

This is interesting, as the IDF suggests age 16 – the age of the subjects in this study – as a cut point between the pediatric and adult definition (69).

Previous large-scale, population-based data on the prevalence of metabolic syndrome are mainly from North America (184, 186, 192–194). We observed a lower prevalence of metabolic syndrome in our cohort compared with these previous reports. This, as well as the lower prevalence observed using the IDF adult definition, is probably due to the differences in waist circumference cut-offs between different definitions. As the cut-offs are higher for adults and in the North American populations, the observed prevalence are lower. The cut-offs derive from percentiles of cohort distributions, and thus reflect higher waist circumference in the adult and North American pediatric population compared with the NFBC 1986.

Obesity is the main component of the metabolic syndrome in children (195). In the NFBC 1986, the IDF pediatric definition of metabolic syndrome was not met by any normal-weight males, whereas in obese males, the prevalence was 44.2%. It has been suggested that the simple message “keep your waist circumference less than half your height” could decrease health risks related to obesity (182). Our results strongly support this, as a waist-to-height ratio over 0.5 defined 85% of the adolescents with metabolic syndrome by the IDF pediatric definition.

6.5 Risks of overweight and abdominal obesity attributable to prenatal exposures to maternal pre-pregnancy overweight and gestational diabetes

Previous studies assessing overweight of children with prenatal exposure to GDM have not always acknowledged maternal overweight. The results of studies that have accounted for maternal overweight are conflicting. Four studies have found an independent association between prenatal exposure to maternal GDM and offspring overweight (89, 140, 148, 196). The results from the Pima Indian Study (118), an indigenous population with endemic diabetes, may not be generalized to other populations; two other studies were retrospective and lacked a control group of mothers with normal glucose tolerance (140, 148). Five studies have found that prenatal exposure to GDM was not independently associated with offspring obesity (90, 150, 151, 153, 197); one was questionnaire-based (153), and one lacked a control group of mothers with normal glucose tolerance (197). A recent study by Catalano *et al.* (90) suggests that maternal pre-pregnancy overweight is

the strongest predictor of childhood obesity, independent of maternal glucose metabolism during pregnancy, or offspring birth weight.

In the present study, the risks of overweight (OR 4.05) and abdominal obesity (OR 3.82) associated with prenatal exposure to overweight and GDM simultaneously were high. In children of mothers with normal glucose tolerance in pregnancy, the risks associated with prenatal exposure to overweight were quite high for both outcomes (overweight OR 2.56, abdominal obesity OR 2.60). No statistically significant risks for overweight and abdominal obesity were found to be associated with prenatal exposure to GDM in the offspring of normal-weight women. Given the well-known health risks related to overweight and abdominal obesity and the rising prevalence of both pre-pregnancy overweight and GDM, the results of the present study call for urgent public health attention.

6.6 Public health implications

The increasing prevalence of diseases related to insulin resistance, i.e. overweight including obesity and T2DM, is one of the most alarming public health challenges worldwide (198). Gestational diabetes can be considered a continuum of these diseases, providing an opportunity for early identification of women and their children at high risk of developing metabolic disorders. There is no global consensus on screening for GDM; however, GDM screening as well as weight monitoring are part of maternal healthcare in most developed countries. These practices can be reflected through the WHO guidelines for screening, which were published in 1968, but are still applicable today (199). Screening for GDM and weight monitoring in pregnancy fulfill many of these criteria. However, there are no uniform screening and diagnostic criteria for GDM. The treatment of GDM is well established, but there is a lack of consensus on who to treat, and the effects of treatment on the long-term health of mothers and their children are controversial.

Data are scarce on preventing the long-term, metabolic consequences of GDM, suggesting that lifestyle intervention may be effective in preventing diabetes in women with a history of GDM (200). This is supported by data from middle-aged people, which show that lifestyle interventions can prevent progression from glucose intolerance to T2DM (201, 202) and development of metabolic syndrome in overweight subjects (190).

The results of the few studies on the effect of treatment of gestational diabetes on the next generation are not consistent: In the Australian Carbohydrate

Intolerance in Pregnancy Study, treatment of GDM vs. routine care decreased the risk of adverse perinatal outcomes as well as also the cord blood concentrations of insulin and leptin, suggesting that treatment of GDM may affect the malprogramming of the adipoinular axis *in utero* (203, 204). However, at age 4–5 years, no differences in BMI were observed between children of the treatment and routine care groups (94 vs. 105 children) (205). The results of the Canadian study by Malcolm *et al.* (142) were similar: tight glycemic control during pregnancy (vs. minimal intervention) did not affect glucose metabolism or overweight in offspring at pre-school age. However, in the study by Hillier *et al.* (147) the risk of childhood obesity was attenuated in the offspring of mothers with diagnosed and treated GDM compared with the offspring of mothers with untreated hyperglycemia of, lesser degrees (positive GCT or OAV in OGTT).

In the USA, the short-term costs of GDM have been estimated to be USD 3,305 during pregnancy and USD 209 during the first year of life of the offspring (206). There are few published reports available on the cost-effectiveness regarding prevention of long-term consequences of GDM in women and their children. As screening for GDM and maternal weight monitoring are part of current clinical practice in most countries, it can be speculated that a high-risk population of young women and their newborn children could easily be identified at low cost. The possible prevention and early detection of metabolic diseases could have major public health implications.

6.7 Implications for future studies

Based on the present study, accentuated insulin resistance during pregnancy, identified as GDM or overweight, indicates increased, long-term risk for metabolic diseases in the mother and child (Figure 5). The mechanisms involved are not yet clear-cut. The roles of genetic variation, the perinatal environment, and later lifestyle factors in determining the long-term risk of metabolic diseases are an intriguing subject of further studies. Advances in genotyping and computational technologies facilitate holistic assessment of large amounts of data and enable a thorough understanding of the determinants of metabolic diseases, which may ultimately lead to novel treatment or intervention strategies.

The results of this study suggest that maternal healthcare providers could have an excellent opportunity to influence the future health of women and children. However, further studies on designing, implementing and evaluating interventions are necessary to evaluate the public health value of the findings

presented in preventing metabolic diseases. The HAPO study will provide international data on the long-term consequences of maternal hyperglycemia as a continuous trait, but the follow-up has only recently started. In Finland, the FinnGeDi study, which has also just started, will provide information on identifying the mothers and children at highest risk of adverse short- and long-term consequences of hyperglycemia in pregnancy, including GDM. In addition, the FinnGeDi study aims to design and evaluate strategies to prevent the long-term, adverse metabolic consequences of hyperglycemia in pregnancy in both mother and child.

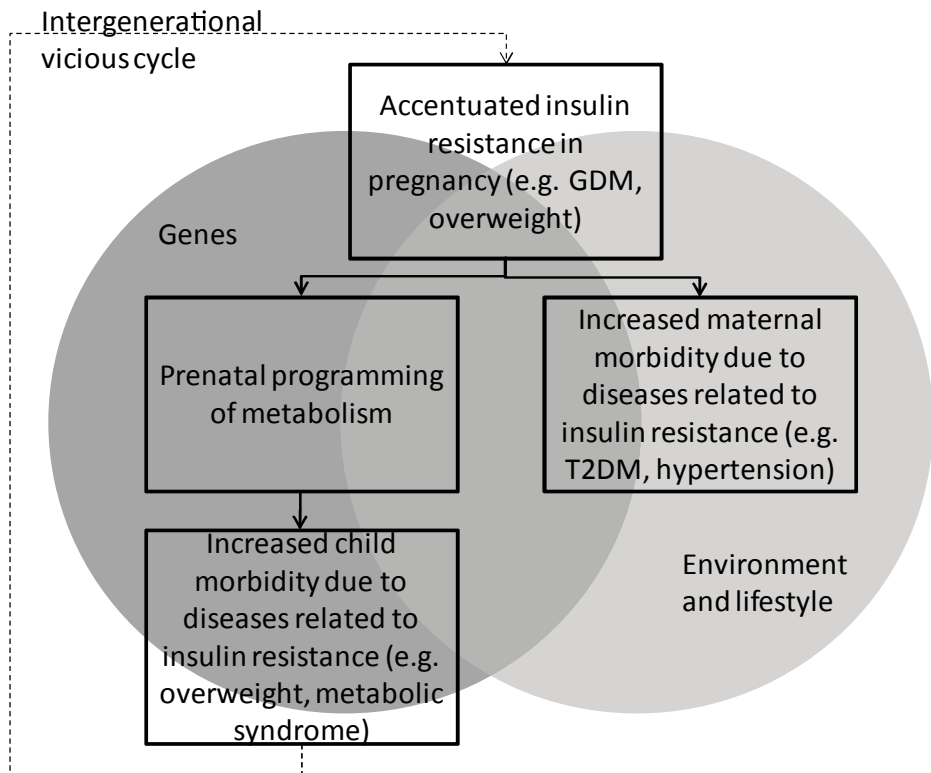


Fig. 5. Intergenerational vicious cycle of insulin resistance.

7 Summary and conclusions

The purpose of the present study was to evaluate the significance of maternal pre-pregnancy overweight and glucose metabolism in pregnancy on the future risks of diabetes and hypertension, and to assess the long-term risks of aberrant glucose metabolism and overweight associated with prenatal exposures to maternal overweight and different diabetes types.

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

1. Pre-pregnancy overweight emerges as an essential risk factor for subsequent diabetes and hypertension in women. The risks of these diseases are alarmingly high in women with concomitant pre-pregnancy overweight and GDM.
2. Prenatal exposure to T1DM results in increased insulin secretion compared with prenatal exposure to GDM already at pre-school age. Gestational weight gain seems to influence the effects of prenatal exposure to different diabetes types.
3. The prevalence of the metabolic syndrome in a contemporary European cohort, at age 16 years, is lower than observed in reports from North America. At the recommended cut-off age between the IDF pediatric and adult definition, the pediatric definition gives a higher prevalence estimate than the adult definition. Abdominal obesity, a waist girth over half one's length, defines 85% of the adolescents with metabolic syndrome.
4. Prenatal exposure to concomitant maternal overweight and GDM conveys high risk for overweight and abdominal obesity in adolescence. Pre-pregnancy maternal overweight is a risk factor for these outcomes even in children of mothers with normal glucose tolerance in pregnancy. In offspring of normal-weight women, the risk of overweight or abdominal obesity is not increased by prenatal exposure to GDM.

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- I Pirkola J, Pouta A, Bloigu A, Miettola S, Hartikainen A-L, Järvelin M-R & Väärasmäki M (2010) Pre-pregnancy overweight and gestational diabetes as determinants of subsequent diabetes and hypertension after 20-Year Follow-Up. *J Clin Endocrinol Metab* 95(2): 772–778.
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