Gestational diabetes mellitus – prevalence in southern Sweden and risk factors for subsequent diabetes

Ignell, Claes

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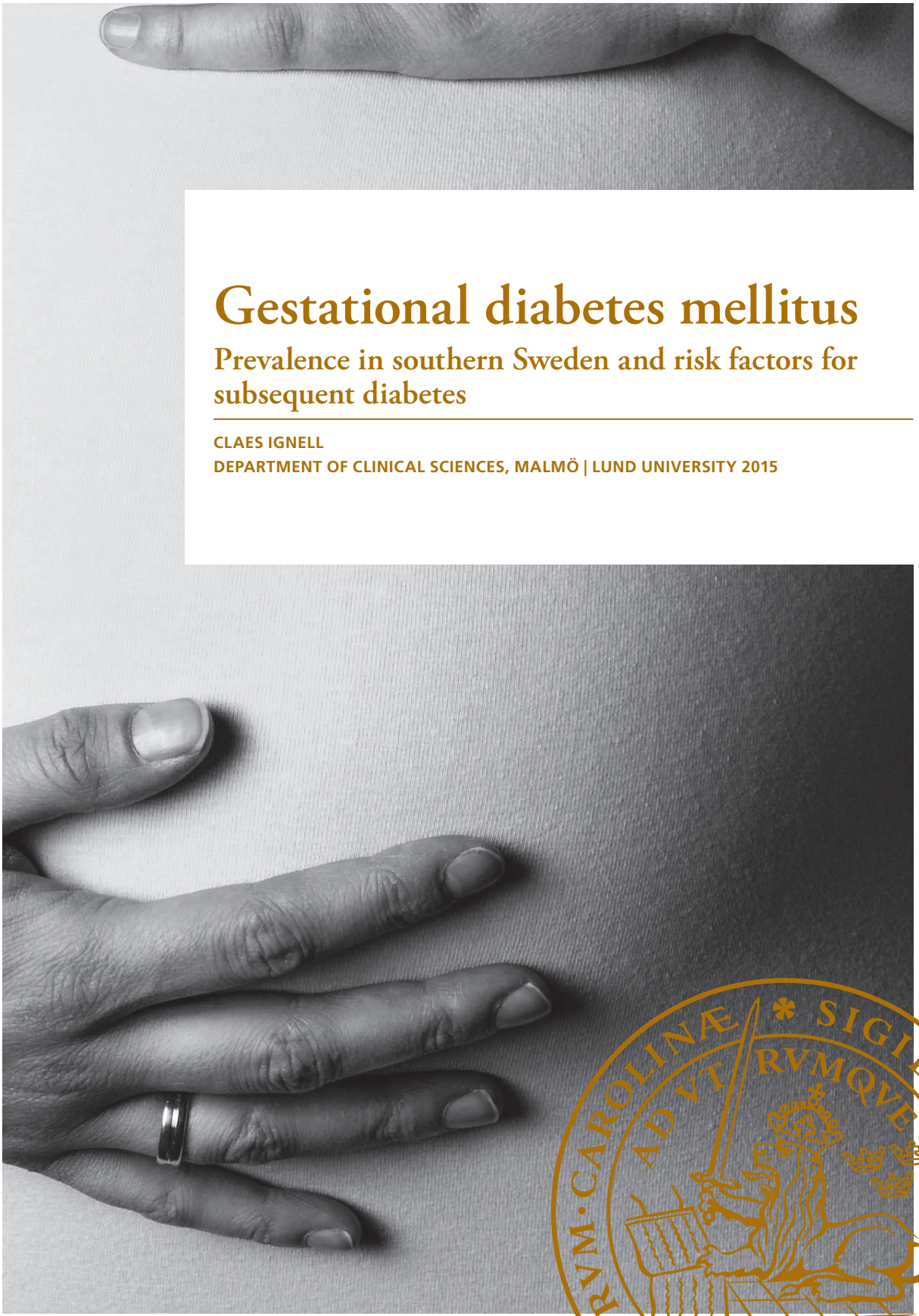

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CLAES IGNELL
DEPARTMENT OF CLINICAL SCIENCES, MALMÖ | LUND UNIVERSITY 2015

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LUND
UNIVERSITY

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Title and subtitle

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Abstract

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Results: Capillary glucose concentrations were found to be higher than venous glucose concentrations during oral glucose tolerance test (OGTT) after pregnancy (n = 55). Equivalence values for capillary glucose concentrations tended to be higher than those proposed by the WHO, but diagnostic disagreements mainly occurred close to the diagnostic cut-off limits.

In southern Sweden, defining GDM as a 2-h capillary plasma glucose concentration of ≥ 10.0 mmol/L during a universal 75-g OGTT, there was a 35% increase in GDM prevalence (p < 0.001) from 2003 (1.9%) to 2012 (2.6%) when assessed in a log-linear Poisson model during a period with stable diagnostic procedures.

1–2 years after pregnancy with GDM (n = 456), the increased frequency of diabetes in non-European women (17% vs. 4% in European women, p < 0.001) was associated with increased insulin resistance—related to higher body mass index (BMI) in Arab women, and higher insulin resistance relative to BMI in Asian women.

In logistic regression analysis, diabetes 5 years after GDM was associated with higher BMI at follow-up, non-European ethnicity, and higher OGTT 2-h glucose concentration in pregnancy (p < 0.0001). A prediction model based on these variables resulting in 86% correct classifications (n = 200), with an area under the receiver-operating characteristic curve of 0.91 (95% CI 0.86–0.95), was used in a function-sheet line diagram illustrating the individual effect of weight on diabetes risk.

Conclusions: Interconversion of results from capillary sampling and venous sampling is associated with uncertainty, but it may be suitable when translating results on a group basis. The prevalence of GDM in southern Sweden was 2.6% in 2012, with an upward trend. In women with GDM, insulin resistance was associated with subsequent diabetes, predicted by BMI, non-European ethnicity, and glucose tolerance during pregnancy.

Key words

Gestational diabetes, oral glucose tolerance test, prevalence, cohort studies, diabetes, sampling, ethnic groups, insulin secretion, insulin resistance, prognosis

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Front page:
"Pregnancy" by Tatiana Vbd, cropped by Claes Ignell, edited by Rasmus Malgerud Björgell, and available at: https://www.flickr.com/photos/kit4na/8570833723
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Back page:
A "selfie" from the 48th annual meeting of the European Association for the Study of Diabetes in Berlin 2012.

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The cure for boredom is curiosity.
There is no cure for curiosity.
Dorothy Parker

To Lisen, Jacob, Maja and Carl

Contents

Original papers

This doctoral dissertation thesis is based on the following papers, which are referred to in the text by their Roman numerals. The papers are appended at the end of the thesis.

I. Ignell C, Berntorp K. Evaluation of the relationship between capillary and venous plasma glucose concentrations obtained by the HemoCue Glucose 201+ system during an oral glucose tolerance test. Scand J Clin Lab Invest. 2011 Dec;71(8):670–5. Epub 2011 Oct 3.

II. Ignell C, Claesson R, Anderberg E, Berntorp K. Trends in the prevalence of gestational diabetes mellitus in southern Sweden, 2003–2012. Acta Obstet Gynecol Scand. 2014 Apr;93(4):420–4. Epub 2014 Mar 5.

III. Ignell C, Shaat N, Ekelund M, Berntorp K. The impact of ethnicity on glucose homeostasis after gestational diabetes mellitus. Acta Diabetol. 2013 Dec;50(6):927–34. Epub 2013 Jun 4.

IV. Ignell C, Anderberg E, Ekelund M, Berntorp K. Model for individual prediction of diabetes up to five years after gestational diabetes mellitus. Manuscript, submitted.

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Populärvetenskaplig sammanfattning

Graviditetsdiabetes (GDM) innebär att förhöjd glukosnivå i blodet (blodsocker) upptäckts hos en kvinna när hon är gravid. GDM behandlas med anpassad kost, fysisk aktivitet, och när det behövs även insulin, vilket tillsammans har visats motverka de ökade riskerna vid graviditet och förlossning för mamma och barn. Glukosnivåerna normaliseras nästan alltid efter förlossningen, men barnet behöver extra vård och övervakning. Kvinnor som haft GDM, och även deras barn, har ökad risk för att i framtiden utveckla diabetes – vilken kan minskas genom hälsosam livsstil.

Internationellt är venös provtagning standard för att mäta glukos, men eftersom kapillär provtagning är enklare att genomföra och analysera anger Världshälsoorganisationen gränsvärden för båda provtagningsmetoderna vid glukosbelastning. I relation till dessa gränsvärden, fann vi i vår studie på kvinnor fem år efter graviditet, att de kapillära värdena låg ytterligare något högre i relation till de venösa värdena än vad Världshälsoorganisationen anger. Det var dock god överenstämmelse mellan diagnoserna, och i de fall diagnoserna inte stämde låg värdena nära de diagnostiska gränsvärdena – där risken för feldiagnostik är som störst. Omräkningsekvationer togs fram för att kunna räkna om värden från kapillär provtagning till motsvarande venösa värden och vise versa. Utifrån storleken på omräkningsekvationernas säkerhetsintervall bedömdes ekvationerna kunna användas i studier och större grupper, men inte för enskilda individer.

Antalet kvinnor som diagnostiseras med GDM blir allt fler men ökningen varierar internationellt beroende på förekomsten av diabetes i befolkningen, folkgruppstillhörighet, ålder, förhållande mellan vikt och längd (BMI), samt hur hälso- och sjukvården undersöker kvinnorna under graviditeten. Vi visade i vår studie att förekomsten av GDM i Skåne och Blekinge, där mödrahälsovården erbjuder alla kvinnor glukosbelastning, ökade med 35 % från 2003 (1,9 %) till 2012 (2,6 %). Internationellt är det låga frekvenser, men det totala antalet kvinnor med GDM ökade med 64 % eftersom antalet förlossningar också ökade. Utifrån de uppgifter vi hade i studien kan vi inte svara på varför ökningen skett, men det kan vara förknippat med ökad förekomst av övervikt och ökad andel kvinnor från delar av världen där det är vanligare med diabetes. Socialstyrelsen har i år rekommenderat en anpassning av de diagnostiska gränsvärdena för GDM till de som föreslås av Världshälsoorganisationen 2013, vilket innebär en sänkning jämfört med idag och fler provtagningstidpunkter under glukosbelastningen. Införandet av dessa skulle innebära en ökning av andelen

kvinnor som diagnostiseras med GDM och därmed att fler kvinnor och deras väntande barn skulle få nytta av behandling.

Glukosnivåerna i kroppen styrs av hur glukos tas upp och lagras i levern och musklerna efter måltid, samt hur levern avger glukos till blodet mellan måltiderna. Bukspottkörtelns betaceller producerar insulin som sänker glukosnivån, men är beroende av kroppens känslighet för insulin. Känsligheten minskar (insulinresistens) när BMI blir högre och under graviditetens senare del. För att hålla glukosnivån normal behöver betacellerna då producera mer insulin. I vår studie hade kvinnor med GDM 1–2 år efter graviditet tecken till nedsatt insulinproduktion och ökad grad av insulinresistens – mest uttalat hos de som hade diabetes. Kvinnor med utom-europeiskt ursprung hade vid uppföljningen oftare diabetes, 17 % i jämförelse med 4 % av kvinnorna med europeiskt ursprung, och hade också ökad grad av insulinresistens. Hos kvinnor med arabiskt ursprung förklarades det av deras högre BMI. I jämförelse med kvinnor med europeiskt ursprung hade kvinnor med asiatiskt ursprung mer uttalad insulinresistens i förhållande till BMI – vid ursprung från vissa delar av Asien är det tidigare visat att hälsoriskerna ökar vid förhållandevis lägre BMI.

Fem år efter graviditetsdiabetes var risken att få diabetes starkt förknippad med högre BMI, utom-europeisk härkomst och högre glukoskoncentration vid glukosbelastningen under graviditet. Dessa tre faktorer kunde sammantaget med 86 % säkerhet förutse diabetes. Eftersom kroppsvikten var den viktigaste påverkbara riskfaktorn för diabetes tog vi fram ett diagram för att illustrera kvinnans individuella risk för diabetes i förhållande till hennes vikt – vilket i framtida studier kan visa sig vara värdefullt vid förebyggande samtal med kvinnor efter GDM.

Sammanfattningsvis har glukoskoncentrationer från kapillär och venös provtagning god diagnostisk överenstämmelse, men med viss osäkerhet i gränsvärdenas närhet och de är inte direkt utbytbara. Förekomsten av GDM i södra Sverige visar en stigande trend och uppnådde år 2012 2,6 %. I efterförloppet till GDM utvecklade kvinnor med utom-europeiskt ursprung oftare diabetes, vilket på olika sätt kunde hänföras till övervikt. Diabetesutveckling efter GDM kan med viss säkerhet förutses utifrån givna riskfaktorer, såsom BMI, utom-europeisk härkomst och den diagnostiska glukosnivån under graviditet.

Abbreviations

AUC	Area under the curve
ADA	American Diabetes Association
BMI	Body mass index
CI	Confidence interval
CV	Coefficient of variation
EASD	European Association for the Study of Diabetes
EBCOG	European Board & College of Obstetrics and Gynaecology
GDM	Gestational diabetes mellitus
GLT	Glucose load test
GNGT	Gestational normal glucose tolerance
HOMA-IR	Homeostasis model assessment of insulin resistance
IADPSG	International Association of the Diabetes and Pregnancy Study Groups
IDF	International Diabetes Federation
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
I/G30	Ratio of incremental insulin to glucose during the first 30 min of the OGTT
NGT	Normal glucose tolerance
OGTT	Oral glucose tolerance test
OR	Odds ratio
PI	Prediction interval
ROC	Receiver operating characteristic
SD	Standard deviation
WHO	World Health Organization

Background

Definitions

Diabetes is primarily defined by the level of hyperglycemia, with the following general categories (1, 2):

- Type 1 (insulin deficiency)
- Type 2 (progressive insulin secretory defect with the background of insulin resistance)
- Gestational diabetes mellitus (GDM), which is described below
- Specific types of diabetes with other causes (monogenic, disease of the pancreas, drug-induced).

In 1999, the World Health Organization (WHO) defined GDM as "carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy" (1). Thus, previously unrecognized diabetes is not excluded with this definition, which does not specify any upper limit of hyperglycemia. This is the definition used in the thesis.

However, in 2013 the WHO introduced the term "hyperglycemia first detected at any time during pregnancy", with the following categories (3):

- Diabetes mellitus in pregnancy (diagnosed by criteria for diabetes outside of pregnancy)
- Gestational diabetes mellitus (hyperglycemia below the thresholds for diabetes outside of pregnancy, but with risk of adverse pregnancy outcomes)

Adding women with known diabetes before pregnancy to this definition, the International Diabetes Federation (IDF) use the term "hyperglycemia in pregnancy" to describe the total burden of any glucose intolerance in pregnancy (4).

History

The Greek Apollonius of Memphis was the first to use the term "diabetes", meaning in Greek "to pass though" (dia – through, betes – to go), around 230 BC (5). However, the medical condition of "too great emptying of urine" was described earlier, around 1500 BC, in the Egyptian Ebers Papyrus. At that time, physicians in India used the term "honey urine", and later on the word "mellitus" (Greek for honey) was used to differentiate diabetes mellitus from diabetes insipidus (excessive thirst and urination, but with urine without any taste) (5). In 1922, insulin was used for the first time on a human, by Fredrick Banting and Charles Best at Toronto General Hospital. Mortality rates for women with diabetes known before pregnancy fell radically after the introduction of insulin (6).

GDM was first described in 1824, by Heinrich Bennewitz in Berlin. The thesis for his medical dissertation described a clinical case of a woman with recurrent glycosuria in three successive pregnancies (6). In 1909, John Withridge Williams, an obstetrician in Baltimore, reported differences in prognosis for women with early or late detection of glycosuria in pregnancy. Testing of carbohydrate metabolism in pregnancy by oral glucose tolerance test (OGTT) was described by Hurwitz and Jensen in 1946 (7). In a presentation that achieved high readership in 1953, the Belgian Joseph P. Hoet described glucose tolerance during and after pregnancy, increased rate of fetal loss in proportion to the degree of disordered glucose metabolism, and the inter-generational spectrum of obesity-hyperglycemia-diabetes being a consequence of heredity and the intrauterine environment (8). He used the terms "transitory diabetes of pregnancy" for GDM, and "metagestational diabetes" for subsequent diabetes.

Screening of all pregnant women by OGTT was first proposed in 1956, by Wilkerson and Remein (9): As a first step a 1-h 50-g OGTT was suggested, and if it was positive or if the woman had certain risk factors, it was to be followed by a 3-h 100-g OGTT. In 1961, John B. O'Sullivan introduced the term "gestational diabetes" for unsuspected, asymptomatic diabetes in pregnancy (10). In 1963, results of OGTT were presented in relation to the risk of future maternal diabetes, and diagnostic limits for GDM were set at two standard deviations above normal, corresponding to the prevalence of diabetes in the community (11). The "two-step strategy" with the O'Sullivan and Mahan criteria became the standard for decades (7). They are the basis of the currently used Carpenter/Coustan criteria from 1982. The updated criteria are adjusted for measurements of glucose concentration in plasma rather than blood and more specifically enzymatic glucose measurements (12).

The WHO criteria for GDM, from 1980 until 2006, were based on the "one-step strategy" criteria for the diagnosis of diabetes outside of pregnancy (1, 13-15), and were criticized for not taking physiological changes during pregnancy into account.

International workshops on GDM were held in 1979, 1984, 1990, 1997, and 2005 (16-20). During that time, the number of articles in PubMed indexed with "gestational diabetes mellitus" rose more than tenfold—from 39 to 443 per year—while "pregnancy" rose from 13,463 to 18,336 (http://www.ncbi.nlm.nih.gov/pubmed, accessed July 27, 2015). There were major advances in care of women with GDM, but global criteria for the screening and diagnosis were never achieved.

Where do we stand now?

In 2008 the results of the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study were published, based on pregnancy outcomes in 23,316 blinded participants from 15 centers in 9 countries who underwent a 75-g 2-h OGTT at 24–28 weeks of gestation (21). These data were used by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) in 2010 as a basis for new GDM diagnostic thresholds (22). This meant a paradigmatic shift: for the first time, diagnostic criteria were based on pregnancy outcomes. The proposed diagnostic thresholds are based on an odds ratio of 1.75 for birth weight ≥ the 90th percentile, cord C-peptide ≥ the 90th percentile, and percentage body fat ≥ the 90th percentile. In 2013, the WHO adopted these criteria with the aim of moving towards a universal standard recommendation for the diagnosis of GDM, stating that "treatment of GDM is effective in reducing macrosomia, large-for-gestational-age, shoulder dystocia, and pre-eclampsia/hypertensive disorders in pregnancy" (3).

In 2015, the Swedish National Board of Health and Welfare and the European Board & College of Obstetrics and Gynaecology proposed the use of these diagnostic thresholds of GDM (23, 24), while the American College of Obstetricians and Gynecologists still supports the use of the two-step procedure (25). In October 2015 at the world congress of the International Federation of Gynecology and Obstetrics (FIGO), the FIGO GDM Initiative expert committee is expected to present their viewpoint.

Pathophysiology of GDM

Glucose requirements rise throughout pregnancy with growing fetal and maternal demands (26). For these reasons, and due to an increasing plasma volume, fasting glucose normally falls and remains low during pregnancy. In the second and third trimesters, there are increasing levels of progesterone, cortisol, placentally derived human growth hormone, human placental lactogen, prolactin, leptin, and other

hormones (27, 28). In addition, tumor necrosis factor-α is secreted by the placenta and cytokines are secreted from adipose tissue, all of which contribute to postprandial insulin resistance, mainly in peripheral tissues (adipose tissue and skeletal muscle) (26). To maintain glucose homeostasis, a concomitant compensation in insulin production is required by the β-cells. Hyperplasia and hypertrophy of the β-cells have been attributed to placental hormones, such as prolactin and human placental lactogen (26). In the third trimester, hepatic insulin resistance—resulting in gluconeogenesis—contributes further to the demands on β-cells (26). There is usually an immediate decrease in insulin resistance after delivery, illustrating the role of the placental factors.

Most women with GDM have a reduction in insulin compensatory response (29, 30), and to a lesser extent increased insulin resistance (26). Due to the pathophysiological similarities with type-2 diabetes, GDM can be regarded as an early stage in the development of type-2 diabetes (31). In genome-wide association studies, genetic links between GDM and type-2 diabetes have been affirmed (26, 32, 33). Furthermore, metabolomics studies have suggested that there are overlapping patterns of metabolites in type-2 diabetes and GDM, while epigenetic studies and studies of the gut microbiome are continuously evolving (26, 34).

Risk factors for GDM and subsequent diabetes

Risk factors for GDM include previous GDM, previous macrosomia (> 90th percentile or ≥ 4,000 g; ≥ 4,500 in Sweden), obesity (BMI > 30 kg/m^2) , polycystic ovary syndrome, first-degree heredity of diabetes and high-risk ethnicity: Mediterranean, South Asian, African Black, North African, Caribbean, Middle Eastern, Hispanic (24). These are also risk factors for diabetes, and can be used as indicators for screening in early gestation, with the primary aim of detecting pregestational diabetes as recently proposed by the European Board & College of Obstetrics and Gynaecology (EBCOG) (24).

According to a recent meta-analysis, including 19,053 women, the rate of recurrence of GDM was 48% with a lower recurrence rate in primiparous women (40%) than in multiparous women (56%) (35). In a study from Seattle, delivery of a macrosomic infant (> 4,000 g) was associated with a threefold risk of GDM and a sixfold risk of pregestational diabetes in the pregnancy that followed (36). Parity is a variable that interacts with other risk factors, but after adjustments it has been shown to be associated with an increased risk of diabetes after the fourth delivery (37).

In a recent systemic review, obese women had a fourfold increased risk of GDM (38), and overweight women had double the risk, with a linear relationship between pre-pregnancy BMI and risk of GDM (39). The prevalence of GDM increases with age,

and is an important risk factor to adjust for when evaluating risks (4, 40). In a systemic review involving 4,982 women with polycystic ovary syndrome, an increased risk of GDM was reported in comparison with the 119,692 healthy controls (odds ratio (OR) = 3.4) (41). Such women have higher insulin resistance in relation to their BMI, in addition to an increased frequency of obesity and older age at pregnancy due to reduced fertility (42).

From a systematic review of 14 studies, Galtier *et al.*, reported ORs of 1.6 to 3.0 for a family history of type-2 diabetes and GDM (40), and recently first-degree heredity of diabetes was shown to be associated with GDM diagnosed either in early pregnancy or in late pregnancy by IADPSG criteria (43). It is also important to note that heritability of type-2 diabetes increases with the number and kind of family member(s) affected, with higher risks for siblings than for parents, while adoptive parents were not found to propose a risk, as described by Hemiminki *et al.* in a large study based on Swedish registries (44).

With increasing migration, it has become more important to assess ethnicity in relation to risk of gestational diabetes and subsequent diabetes. Ethnicity influences the prevalence of GDM and its progression to manifest diabetes postpartum, being higher in non-European populations (45-48). This may be partly explained by differences in insulin secretion and action (49-53). For the Asian population, especially the south Asian group, lower BMI thresholds in relation to risk of type-2 diabetes and cardiovascular disease have been suggested (54). In a previous study from our group, Arab women with GDM were found to be more insulin-resistant during pregnancy than Scandinavian women (55). However, these finding have been contradicted by others (49, 53).

While obesity is a strong, potentially modifiable risk factor for GDM, the corresponding evidence regarding tobacco use and socioeconomic factors is less convincing. However, a reduction in risk has been reported in relation to physical activity before and during pregnancy (40). Physical activity combined with dietary interventions during pregnancy to prevent GDM was recently reviewed by the Cochrane Institute, which stated that there was no clear evidence supporting these interventions (56). However, the possibility of drawing firm conclusions and of guiding future practice was limited due to variations in the trials concerning quality, interventions, populations, and use of outcome definitions. Recently, the IADPSG proposed universal coding of definitions of outcomes to facilitate comparison of findings between studies (57).

Risks associated with GDM

The intrauterine excess of nutrients and the enhanced insulin production that results from it both contribute to fetal growth (58). In a systematic review from 2012, Wendland *et al.*, described risks of GDM according to the criteria of the WHO from 1999 and the IADPSG. Significant risk ratios using the respective criteria were 2.2 and 1.4 for macrosomia, 1.4 and 1.2 for caesarean delivery, and 1.7 (both criteria) for large-for-gestational-age and pre-eclampsia (59).

In addition to hypertensive disorders during pregnancy, GDM is associated with increased levels of triglycerides and lower levels of high-density lipoproteins, and altogether a threefold increased risk of subsequent metabolic syndrome postpartum (28, 60). According to a review by Retnakaran *et al.*, following this, women with GDM also have an increased risk of cardiovascular disease, most markedly associated with hyperglycemia at 1 h during the postpartum OGTT (61, 62).

After delivery, the child has an increased risk of hypoglycemia, polycythemia, hyperbilirubinemia, respiratory distress syndrome, hypertrophic cardiomyopathia, and hypocalcemia (63). Studies have not only reported postpartum risks for the offspring, but also long-term risks similar to those of the mothers (64-66). The role of intrauterine hyperglycemia in programming the fetus was, however, recently questioned by Donovan and Cundy, who suggested that parental obesity as a confounder has not been taken into account (67).

The frequency of type-2 diabetes after GDM is more than sevenfold higher than in women with a normoglycemic pregnancy (risk ratio (RR) 7.4, 95% CI 4.8−11.5) (68). On the other hand, up to one-third of women with type-2 diabetes have a history of GDM (69). According to a systemic review by Kim *et al.*, the cumulative incidence of type-2 diabetes was reported to be 10% one year after GDM, and increased markedly during the first five years to 30% with an estimated lifetime risk of about 50–70% (70). Similar figures have been reported in previous studies from southern Sweden (71, 72).

Benefit of treatment for GDM

To estimate the effect of treating GDM on various adverse outcomes, Falavigna *et al.* conducted a systematic review (73). High-quality evidence was found for reducing fetal birth weight (≥ 4,000 g as well as > 90th percentile; number needed to treat (NNT) ~12), moderate-quality evidence was found for reducing pre-eclampsia and hypertensive disorders in pregnancy (NNT ~20), and low-quality evidence was found for reducing shoulder dystocia (NNT ~50). In addition to these advantages of GDM treatment, the WHO also pointed out that the risks of perinatal mortality, neonatal

intensive care admission, birth trauma, and caesarean section were reduced, although this did not reach statistical significance (3).

Diagnostic methods

Blood sampling and measurement of glucose concentration

Venous blood sampling is the international standard for measurement of plasma glucose concentration, while capillary measurements are regarded as being suitable for glucose monitoring and for diagnostic purposes in under-resourced countries (15). In 1999, the WHO provided diagnostic limits for both of these sampling sites, but without evidence for the differences (1). Capillary sampling and venous sampling have been evaluated in earlier studies, and most results have indicated no difference in the fasting state and higher capillary glucose concentrations after a glucose load (74-77).

Several factors affect the measurement, including the sample material used (78, 79). Glucose measurements are based on enzymatic reactions involving glucose oxidase, glucose-1-dehydrogenase, or hexokinase (80). Hexokinase is used at central laboratories, and is stable also in hypoglycemic samples, while glucose oxidase is the classic method for point-of-care devices (78). The HemoCue Glucose system, which is widely used in Sweden for diagnostic purposes, measures glucose using photometric analysis and glucose-1-dehydrogenase, which is not as sensitive to oxygenation and hematocrit as glucose oxidase but can be interfered with by sugars other than β-D-glucose (80).

In 2004, routine glucose measurements in Sweden switched from whole blood to plasma glucose measurements, and a transformation factor of 1.11 was agreed on to comply with the International Federation of Clinical Chemistry and Laboratory Medicine system of reporting glucose (81). The unit for glucose concentration recommended by *Système International d'Unités* is mmol/L, and it can be converted to mg/dL by multiplying by a factor of 18.0182.

Screening of GDM and diagnostic procedures

GDM screening is not uniform internationally or in Sweden (24, 82). Universal screening can be performed using random tests for glycemia, or with glucose tolerance tests (24). Random glucose measurements and risk factor-based screening have a sensitivity to detect GDM of about 50% (82-85). Universal screening with a 75-g OGTT in the fasting state at weeks 24–28 of pregnancy is recommended for

diagnostic screening by the IADPSG, the American Diabetes Association (ADA), and the EBCOG, whereas the WHO has not acknowledged this "one-step procedure" and leaves it to future research (2, 3, 22, 24). On the basis of a consensus conference convened by the National Institutes of Health, Maryland, in 2013, the American College of Obstetricians and Gynecologists proposes a "two-step strategy". The first step is a non-fasting 50-g glucose load test, and if plasma glucose is ≥ 7.8 mmol/L at 1 h, a second step with a 100-g OGTT in the fasting state should be performed, with diagnostic thresholds according to Carpenter and Coustan, or the National Diabetes Data Group (25). The two-step procedure is supported by the ADA as an alternative to the one-step strategy (2). The different diagnostic criteria for screening and diagnosis of GDM are summarized in Table 1.

Table 1. Commonly used criteria for the diagnosis of GDM

		Lower limit in venous plasma (mmol/L)				
Organization, year	Tolerance test used	Fasting	1 h	2 h	3 h	Diagnosis
EASD, 1991	Fasting, 75-g OGTT	7.0	11.0	9.0		≥ 1 positive
WHO, 1999	Fasting, 75-g OGTT	7.0	-	7.8		≥ 1 positive
IADPSG, 2011	Fasting, 75-g OGTT	5.1	10.0	8.5		≥ 1 positive
ACOG, 2013†	Non-fasting 50-g GLT		7.8*			
Carpenter/Coustan†	Fasting 100-g OGTT	5.3	10.0	8.6	7.8	≥ 2 positive
NDDG†	Fasting 100-g OGTT	5.8	10.6	9.2	8.0	≥ 2 positive

*7.5 mmol/L in high-risk ethnic populations; some experts also recommend 7.2 mmol/L.
†The ACOG recommends a two-step screening, as described in the text.
GLT, glucose load test; NDDG, National Diabetes Data Group criteria.

The diagnostic thresholds for GDM that are mostly used in Sweden are based on the criteria of the Diabetic Pregnancy Study Group of the European Association for the Study of Diabetes (EASD) (82, 86). The basis for this was the WHO criteria of 1985, but the 2-h threshold was elevated arbitrarily because of a total of 32 women who exceeded the limit in a study involving 11 centers in Europe (86). When the universal OGTT was introduced for GDM screening in the county of Skåne in southern Sweden in 1992, both fasting and 2-h glucose concentrations were measured. However, after an initial study indicating that fasting glucose levels did not increase in normal pregnancies and had a low sensitivity in detecting GDM, the diagnosis of GDM has been solely based on the 2-h threshold value of the EASD criteria (87, 88). In recent years, most regions of Sweden have adopted the 2-h threshold value of the EASD criteria, and in some regions a fasting glucose threshold of 7.0 mmol/L as well (82). However, in most regions capillary glucose sampling is used and glucose values are reported as plasma glucose concentrations, corresponding to a fasting glucose threshold of 7.0 mmol/L and a 2-h glucose threshold of 10.0 mmol/L.

It should be noted that in the 2008 guidelines of the Swedish Society of Obstetrics and Gynecology (which did not fully support screening and treatment of GDM) the diagnosis of GDM also included a fasting glucose concentration to rule out diabetes by criteria used outside of pregnancy (89). Up to 2015, there has been no uniform national guideline for screening and diagnosis of GDM. As previously mentioned, the Swedish Board of Health and Welfare has now taken action on this issue and has adopted the new WHO and IADPSG thresholds for diagnosis of GDM, but leaves it to the local health authorities to specify the strategy for screening (23).

In addition to universal screening by 75-g OGTT in gestational weeks 24–28, the IADPSG recommends risk factor-based screening for unknown overt diabetes at the first prenatal visit (fasting plasma glucose ≥ 7.0 mmol/L, random venous plasma glucose ≥ 11.1 mmol/L, or HbA_{1c} ≥ 6.5%), which has been supported by the ADA and the EBCOG (2, 22, 24).

Prevalence of GDM

The prevalence of GDM in population-based studies has ranged from 1% to 22%, with an increasing trend in most racial/ethnic groups studied (40, 90). Prevalence of GDM differs in different populations, and is closely related to the prevalence of type-2 diabetes in a given population. Observed differences may very well be explained by differences in predisposing risk factors (40). The frequency of GDM is also influenced by the definition used and the screening activity for GDM, which makes it difficult to compare prevalence rates between populations (91). In 2000–2003, the prevalence of GDM in the county of Skåne, southern Sweden, was 1.9% (84).

Follow-up after GDM

As GDM is an important risk factor for type-2 diabetes and cardiovascular disease (62, 68), follow-up is important to promote a healthy lifestyle and to identify women who are in need of more intense preventive measures or treatment for postpartum diabetes (62). Intervention studies have shown that type-2 diabetes can be prevented by modification of lifestyle (92, 93), even in women with a history of GDM (94, 95). However, as there is poor compliance with recommended guidelines regarding follow-up (96), a major challenge in public healthcare is to identify individuals who have the highest risk (62, 97). Since HbA_{1c} is quick and easy to perform, it has been evaluated for postpartum follow-up, but it has shown low sensitivity in detection of diabetes and cannot replace OGTT (98-102).

Screening program for GDM in southern Sweden

In the counties of Blekinge and Skåne in southern Sweden, screening of GDM with OGTT is offered to all women in the twenty-eighth week of gestation, and also in gestational week 12 if there is a history of GDM in previous pregnancies or a first-degree relative with diabetes. These principles of the screening program were implemented in the whole region in 1995, and they were used unchanged during the recruitment period for the present study. The program has previously been shown to include more than 93% of the women, with 2% of the women not being able to perform the OGTT and less than 3% of the women refusing (84).

A standard 75-g OGTT is performed at the local antenatal clinic. The HemoCue blood glucose system (HemoCue AB, Ängelholm, Sweden) is used for immediate analysis of capillary glucose concentrations. To ascertain the quality of the individual testing, double sampling is used, with acceptance of a divergence of ≤ 0.3 mmol/L. The highest test result is regarded as the diagnostic value (84). If the degree of divergence is not acceptable, the equipment is checked and a second OGTT is offered.

The diagnostic criteria for GDM used in clinical practice are a slight modification of those recommended by the EASD, defining GDM as a 2-h capillary blood glucose concentration of ≥ 9.0 mmol/L (plasma glucose ≥ 10.0 mmol/L) (86). According to clinical routines, women with blood glucose concentrations of 7.8–8.9 mmol/L (plasma glucose 8.6–9.9 mmol/L) are offered a second OGTT within a week, and if the glucose levels are still in the intermediate range or lower, no more tests are offered.

Women diagnosed with GDM are referred to specialist antenatal care for intensified maternal and fetal surveillance. These women are given advice on diet and physical activity, and are closely monitored using self-tests for blood glucose. If treatment goals for glucose levels are not achieved, treatment with insulin is started. The intensified fetal surveillance involves more frequent checks by midwives and obstetricians, such as extended ultrasound examinations and cardiotocography.

Aims

The specific aims of the individual studies are given below.

I. Capillary and venous plasma glucose concentrations by the HemoCue 201+ system during an oral glucose tolerance test after pregnancy
   - Examine the relationship
   - Establish equations for conversion
   - Evaluate the correlation of diagnostic cut-off limits.

II. Prevalence of gestational diabetes in southern Sweden from 2003 to 2012
   - Determine the crude prevalence
   - Calculate the trend in prevalence.

III. Glucose homeostasis and ethnicity one to two years after pregnancy
   - Evaluate insulin resistance and insulin secretion after gestational diabetes
   - Describe these in relation to ethnic groups in southern Sweden
   - Investigate the impact of ethnicity and other risk factors for diabetes.

IV. Prediction of diabetes risk five years after pregnancy
   - Identify risk factors associated with diabetes after pregnancy
   - Evaluate models for prediction of diabetes after gestational diabetes
   - Apply the models in a tool to be used in clinical practice when counseling women after gestational diabetes.

Methods

I, III, IV. The Mamma Study

Subjects and study design

During the years 2003–2005, pregnant women in southern Sweden representing different glucose categories according to the OGTT were invited to take part in a five-year follow-up study, called the Mamma Study. The study design and the results of the 1- to 2-year follow-up have been described previously (103, 104).

Four of five delivery departments in the county of Skåne were included, covering 86% of all pregnancies in the region. The number of deliveries during the recruitment period was 32,716 and the estimated number of women with abnormal glucose tolerance during pregnancy was 1,600, as defined by their first-performed OGTT (104).

All the women were given verbal and written information about the study in connection with the OGTT at the local antenatal clinic, and they were finally invited to participate by the midwives at the delivery department. The women who accepted the invitation gave their written, informed consent.

The results of the OGTTs performed in pregnancy were identified, and the use of correct sampling technique was ensured. The studies described in this thesis used the diagnostic criteria for GDM proposed by the WHO in 1999 (1). The GDM group thus consisted of women with 2-hour blood glucose ≥ 7.8 mmol/L, corresponding to plasma glucose ≥ 8.6 mmol/L, calculated using a transformation factor of 1.11 as previously described (81). From the consent forms of each participating hospital, a control group was formed by selecting every twenty-fourth woman with a correct 2-h blood glucose value of < 7.8 mmol/L (plasma glucose < 8.6 mmol/L), indicating gestational normal glucose tolerance (GNGT). Information and a new consent form was sent with the invitation for follow-up. If no answer was received, two successive reminders were sent out.

Figure 1 is a flow chart of the study population. Altogether, 1,328 women with correct sampling technique during pregnancy were invited for follow-up. Of these, 636 women participated in the 1- to 2-year follow-up and 493 women participated in the 5-year follow-up, 468 of whom (127 GNGT, 341 GDM) had results from the previous follow-up.

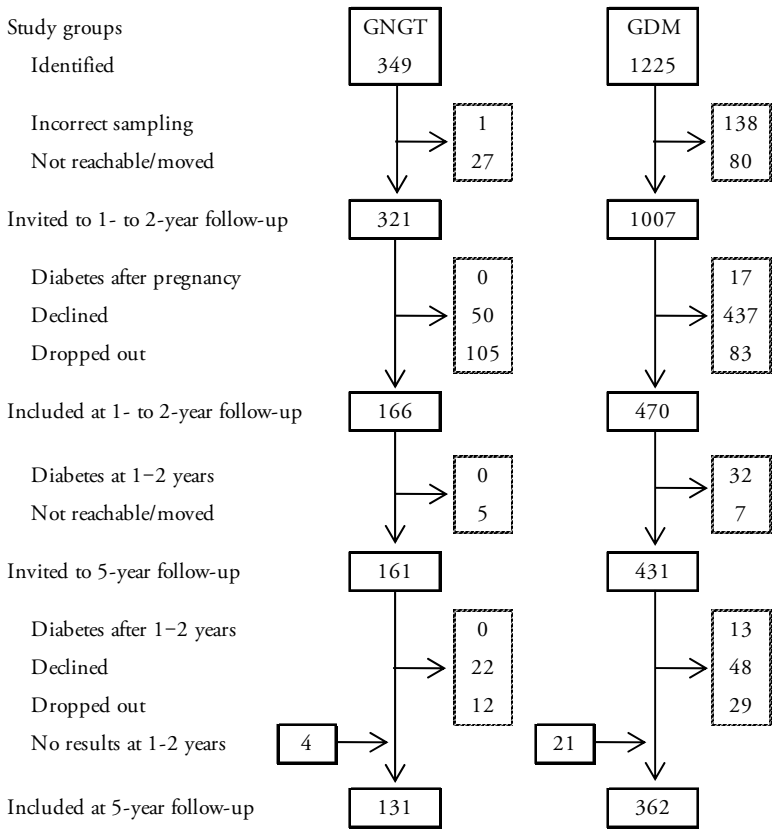

Figure 1. Flow chart of the study population of the Mamma Study. GDM was defined according to the WHO criteria of 1999.

Of the women who were invited for follow-up 1–2 years after their pregnancy, 17 had already been diagnosed with diabetes (all GDM). Furthermore, 520 of 1,007 (52%) of the women with previous GDM and 155 of 321 (48%) of the women with GNGT declined participation or dropped out. 32 women were diagnosed with diabetes at the first follow-up and 13 other women developed diabetes between the first and the second follow-up (all GDM). Non-participants at first follow-up, for whom the only descriptive data available were age, were previously reported to be significantly younger ($p < 0.05$) (104). Comparing the 341 women with previous GDM who attended both follow-up appointments with the 84 women (without any previous

diabetes diagnosis) who attended only the first one, there were no significant differences in clinical characteristics, such as ethnicity, first-grade diabetes heredity, age at delivery, 2-h glucose level during pregnancy, BMI, and glucose levels during the OGTT at the 1- to 2-year follow-up.

At the first follow-up appointment at the diabetes care unit 1–2 years after delivery, an OGTT was performed after overnight fasting in 470 women with previous GDM and in 166 women with normal glucose tolerance (NGT) during pregnancy. Venous samples were drawn at 0, 30, and 120 min to determine plasma glucose and serum insulin concentrations. Glucose concentration was measured in duplicate samples and the mean value was calculated. Weight and height were recorded and the BMI calculated. Information was obtained on first-grade diabetes heredity, earlier pregnancies, and ethnic affiliation. Based on the stated country of origin of at least three grandparents, women with previous GDM were grouped as being of European origin (n = 362) or of non-European origin (n = 94). The latter included subgroups of Arab women (n = 41: Egypt, Iraq, Lebanon, Morocco, Palestine, Somalia, and Syria), Asian women (n = 43: Afghanistan, China, India, Iran, Japan, Kurdistan, Pakistan, Philippines, South Korea, Taiwan, Thailand, Turkey, and Vietnam), and women of other origins (n = 10: Berber, Bolivia, Brazil, Chile, Colombia, Eritrea, Ghana, Israel, Uganda, and Uruguay). Using the definition described above, 14 women were unclassifiable.

The second and final follow-up appointment took place five years after the pregnancy and followed the same procedure as the 1- to 2-year follow-up, but the OGTT was performed with capillary blood sampling and only on fasting and at 2 h. Fifty-five consecutive non-smoking women were subject to both capillary and venous sampling after overnight fasting, and a standard 75-g OGTT performed by one specially trained laboratory assistant. A Venflon catheter (Becton Dickinson, Helsingborg, Sweden) was inserted into an antecubital vein. Duplicate blood samples were collected in cuvettes and analyzed. Immediately after that, glucose concentration was measured in duplicate samples of capillary blood from the third or fourth finger tip of the non-dominant hand, following the same procedure. Then, 75 g of anhydrous glucose dissolved in 300 mL water was given. The sampling and measurement procedures were then repeated after 30 min and 120 min.

Informed consent was obtained from all participants, and the study protocol was approved by the Ethics Committee of Lund University (LU 259-00).

Metabolic measurements

The HemoCue Glucose system (HemoCue AB, Ängelholm, Sweden) was used for immediate measurements of glucose concentrations (mmol/L) collected in 5 µl HemoCue Glucose cuvettes. After the switch to reporting of glucose concentration in plasma in 2004, the HemoCue Glucose 201+ Analyzer was used, converting blood

glucose concentrations to equivalent plasma glucose concentrations by using a factor of 1.11 (81, 105). The mean coefficient of variation of the duplicate samples performed in this study was 2.6% for venous analysis at first follow-up, and 2.5% for capillary samples at second follow-up. Analyses performed by one specially trained laboratory assistant in Study I had a mean CV of 1.8% from capillary sampling and 1.6% from venous sampling.

Serum insulin concentrations (mU/L) were measured with enzyme-linked immunosorbent assay (Dako, Glostrup, Denmark). The intra- and inter-assay CVs of this insulin assay were 5.1%–7.5% and 4.2%–9.3%, respectively.

Homeostasis model assessment was used to estimate insulin resistance (HOMA-IR), i.e. (fasting serum insulin × fasting plasma glucose) / 22.5 (106, 107). Insulin sensitivity was calculated from 1 / HOMA-IR. β-cell function was estimated using the insulinogenic index (I/G30), which is the ratio of the incremental insulin to glucose during the first 30 min of the OGTT, i.e. ($insulin_{30\ min}$ – $insulin_{0\ min}$) / ($glucose_{30\ min}$ – $glucose_{0\ min}$) (108). As insulin resistance modulates insulin secretion, the disposition index was used to adjust insulin secretion for the degree of insulin resistance, which is done by dividing I/G30 by HOMA-IR (50).

Statistical analysis

Study I

Data are presented as mean ± standard deviation (SD).

The statistical significance of the difference between mean capillary and venous glucose concentrations at each time interval was evaluated with Student's paired t-test. Correlations were estimated using the Pearson's test.

Results obtained for venous and capillary plasma glucose measurements were compared using the method of Bland and Altman, in which differences between paired measurements are plotted against the mean of each pair (109). The SD of the differences was multiplied by ± 1.96 to calculate the prediction interval (PI). Conversion equations were derived according to the method described for differences that were not constant (110).

To study the agreement between categories of glucose tolerance obtained by either capillary or venous glucose measurements, a cross-table was made. The overall indicator kappa (κ) was calculated. A value of 0 indicates that agreement is no better than chance, while values greater than 0.80 indicate very good agreement. Values between 0.61 and 0.80 can be taken to mean good agreement (111).

Study III

Data are presented as *n* (%) for categorical variables and as median (95% CI) for continuous variables. Indices, requiring log transformation due to skewedness, are presented as geometric means (95% CI).

Fisher's exact test was used to compare group frequencies and the Mann-Whitey U-test was used to compare differences between medians. Differences in geometric means were tested with analysis of variance (ANOVA), incorporating, where appropriate, age, non-European origin, first-degree diabetes heredity, number of deliveries, and interval to follow-up as covariates, with and without adjustment for BMI. Simple logistic regression analysis was used to calculate the OR (95% CI) for diabetes vs. after GDM.

Multivariable logistic regression analysis was used to show how known predictor variables affected the risk of developing diabetes vs. normal glucose tolerance after GDM. Variables tested for association with diabetes after GDM were age (years), BMI (kg/m^2), first-degree relative(s) with diabetes (yes/no), non-European, Arab or Asian origin (yes/no), and parity (which was best expressed as up to three deliveries at follow-up vs. more than three (≤ 3/> 3)). European origin was used as a reference for ethnic comparison. All logistic regression analyses were adjusted for time to follow-up (days).

Study IV

Data are presented as *n* (%) for categorical variables and as median (interquartile range) for continuous variables.

Fisher's exact test was used to compare group frequencies and the Mann-Whitney U-test was used to compare differences between medians. Simple logistic regression analysis was used to calculate R^2 by Nagelkerke, odds ratios (ORs), and 95% CI. Variables tested for associations with diabetes after GDM were non-European ethnicity (yes/no), first-grade diabetes heredity (yes/no), age at delivery (years), glucose concentrations during OGTT, interval to follow-up (years), BMI at follow-up (kg/m^2), and parity (which was best expressed as up to three deliveries at follow-up vs. more than three (≤ 3/> 3). Diagnosis in early gestation (yes/no) and insulin treatment during pregnancy (yes/no) were also analyzed but were not included in the final multivariable model.

Multivariable logistic regression analysis was done with either backward elimination of non-significant factors or forward addition of significant factors. The probability of diabetes (%) in the prediction model was calculated from the function: $F(t) = e^t / (1 + e^t)$, where t is represented by the equation from the final multivariable regression model (112). The performance of the prediction model was assessed with ROC curves, with calculations of AUC. The threshold for discrimination was calculated with the Youden index (113).

The current version of IBM SPSS Statistics for Windows (IBM Corporation, Armonk, NY, USA) was used for analysis, and two-sided *p*-values of less than 0.05 were considered statistically significant.

II. Prevalence and trend of GDM in southern Sweden

Subjects and study design

Data on numbers of deliveries and numbers of women with a diagnosis of GDM during the years 2003–2012 in southern Sweden (population 1,415,403 in 2012) were obtained from diagnostic registers of the delivery departments. GDM was defined according to clinical practice as a 2-h capillary blood glucose concentration of ≥ 9.0 mmol/L (plasma ≥ 10.0 mmol/L). In the county of Blekinge, the delivery department is situated in the city of Karlskrona, and the five delivery departments in the county of Skåne are located in Malmö, Lund, Ystad, Helsingborg, and Kristianstad. As women diagnosed with GDM in Ystad are referred to Lund for follow-up during pregnancy and with few exceptions deliver in Lund, Lund and Ystad were treated as one center. In the registers, GDM was coded according to the tenth revision of the International Classification of Diseases as diabetes mellitus arising in pregnancy (O24.4). Personal identification numbers were not revealed. References to year refer to the delivery year; screening and diagnosis may therefore have occurred in the previous calendar year. All women with one or more pregnancies during the study period who delivered live infant(s) or had stillbirth(s) after gestational week 21 were included.

Since the study was based on aggregated anonymous data, ethical approval and informed consent were not obtained.

Statistical analysis

The prevalence of GDM was estimated by dividing the number of women with GDM who gave birth during that year by the total number of women who gave birth that year. Poisson regression models were used to assess the effect of time (year) on the prevalence of GDM. Testing for trend was conducted by fitting year as a continuous variable in the log-linear Poisson model with the number of births as offset. Predicted prevalence and 95% CI are presented.

IBM SPSS Statistics 20 for Windows (IBM Corporation) was used for analysis, and two-sided *p*-values of less than 0.05 were considered to be statistically significant.

Results

I. Capillary and venous glucose levels during OGTT

The mean capillary and venous glucose concentrations obtained during the OGTT are given in Table 2. For two women, venous samples were missing in the fasting state and for three women venous samples were missing at 120 min post load. Capillary plasma glucose values were significantly higher than venous plasma glucose values at all the time points. However, the deviation between the samples was greatest in the non-fasting state.

Table 2. Capillary and venous plasma glucose concentrations during the OGTTs

Time interval, min	0	30	120
n	53	55	52
Capillary*	6.0 (0.7)	10.5 (1.7)	9.2 (1.9)
Venous*	5.8 (0.7)	8.7 (1.6)	7.7 (2.0)
Capillary-venous difference*	0.2 (0.3)	1.8 (1.0)	1.5 (0.7)
p	< 0.001	< 0.001	< 0.001

*Plasma glucose concentration (mmol/L). Data are mean (SD).
Differences between means were tested by Student's paired t-test.

The relationship between the capillary and venous plasma glucose concentrations at the different time points of the OGTT is shown in Figure 2, panels a–c. A high correlation was found during fasting (r = 0.93; $p < 0.001$), at 120 min post load (r = 0.94; $p < 0.001$), and to a lesser extent at 30 min post load (r = 0.81; $p < 0.001$).

The Bland-Altman difference plots are shown in Figure 3, panels a–c. Capillary glucose concentrations were consistently higher than venous glucose concentrations. Best agreement was found in the fasting state with data points clustered near the regression line, resulting in a narrow 95% PI. The 30-min glucose values showed the widest PI, reflecting a greater variation in differences between capillary and venous samples. Furthermore, the difference increased with increasing glucose concentration. In contrast, the regression line for the fasting and 120-min glucose values showed a negative slope with smaller differences between the methods with increasing glucose values.

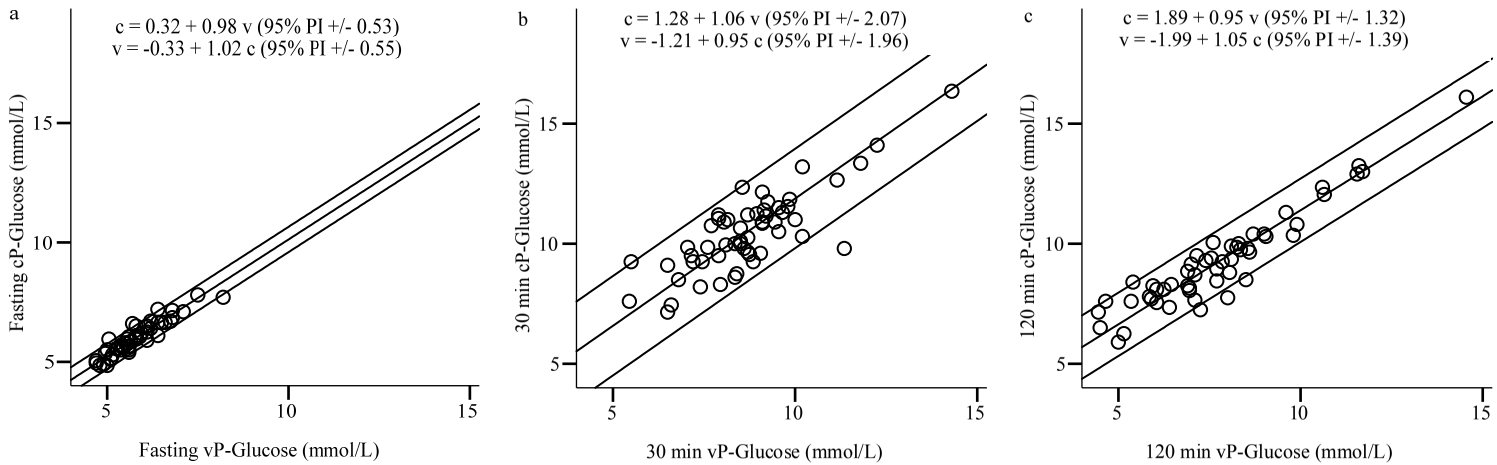

Figure 2. Scatter plots of capillary (c) and venous (v) plasma glucose concentrations during oral glucose tolerance test; panel a fasting (n = 53), panel b 30-min (n = 55), panel c 120-min (n = 52). Equations for conversions are given. Conversion lines and 95% PI are shown.

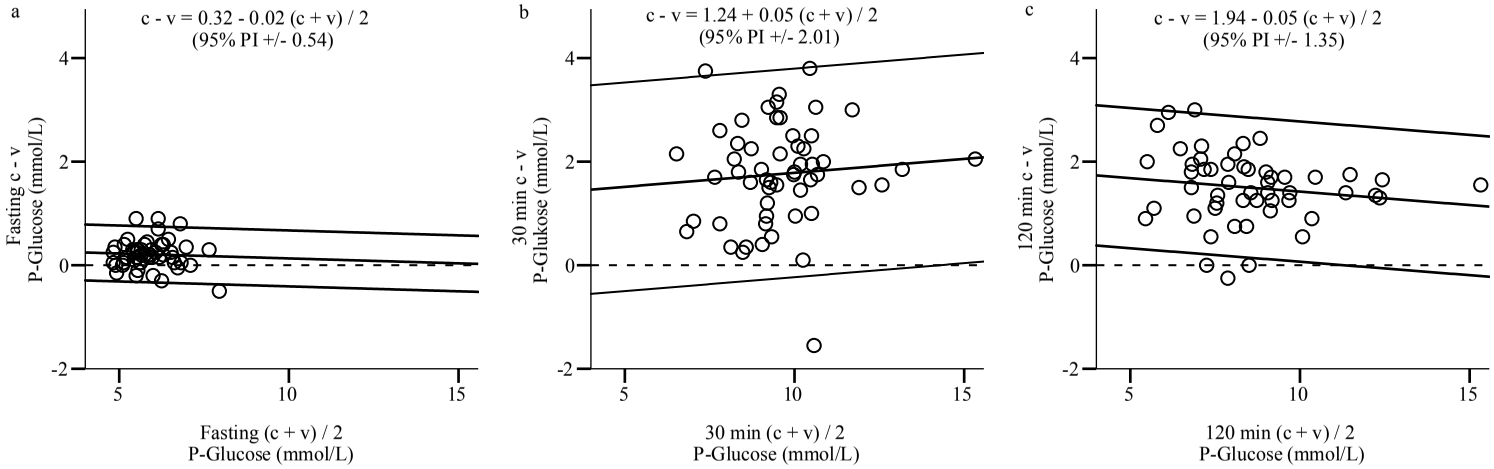

Figure 3. Bland-Altman plots of capillary and venous differences (c - v) versus capillary (c) and venous (v) mean ((c + v) / 2) of plasma glucose concentrations during oral glucose tolerance test; panel a fasting (n = 53), panel b 30-min (n = 55), panel c 120-min (n = 52). Equations for the regressions are given. Lines for the regressions and 95% PI are shown.

Equations were calculated for conversion between the two measurement methods, according to Carstensen (110). The equations, conversion lines, and 95% PI are shown in Figure 2. We tested the formulae to compare the equivalence values obtained in this study for venous and capillary plasma glucose concentrations with the corresponding equivalence values published by the WHO for the diagnosis of IGT and diabetes (1). In the fasting state, the capillary plasma glucose value equivalent to a venous plasma glucose of 7.0 mmol/L derived from this study was 7.2 mmol/L, as compared to the WHO value of 7.0 mmol/L. Similarly, for the venous 2-h post-load values of 7.8 mmol/L and 11.1 mmol/L, the capillary equivalence values were 9.3 mmol/L and 12.4 mmol/L, respectively, as compared to the WHO values of 8.9 mmol/L and 12.1 mmol/L. The differences were within the 95% PI.

The women with complete data (n = 50) were stratified by glucose tolerance status as having diabetes mellitus, IGT, or NGT according to the WHO 1999 criteria (WHO 1999) using either venous or capillary plasma glucose concentrations (Table 3). The consistency in classifying between capillary and venous glucose measurements was 82% (41/50) and κ was 0.70, indicating good agreement.

Table 3. Classifications of glucose tolerance status according to the WHO criteria of 1999 for capillary and venous plasma glucose concentrations

(n)	NGT (v)	IGT (v)	Diabetes (v)	Total (c)
NGT (c)	21	3	0	24
IGT (c)	5	14	0	19
Diabetes (c)	0	1	6	7
Total (v)	26	18	6	50

Complete data were available for 50 women.
c, capillary; v, venous.

All the women who were classified as having diabetes based on venous samples were also classified as having diabetes based on capillary samples. In the NGT category, five of 26 women were classified as having IGT by capillary glucose criteria. Their capillary 2-h glucose concentrations were in the range 9.0–10.0 mmol/L, as opposed to 7.0–7.7 mmol/L for venous samples (Figure 4). Of the women who were classified as having IGT by venous criteria, capillary concentrations indicated NGT in three (2-h capillary glucose concentrations in the range 7.8–8.8 mmol/L, as opposed to 8.0–8.5 for venous samples), and diabetes in one woman (2-h capillary glucose concentration 12.4 mmol/L, as opposed to 10.6 mmol/L in the venous sample).

It is important to note that the diagnoses differed mainly when glucose concentrations were close to the diagnostic limits, which is illustrated in Figure 4.

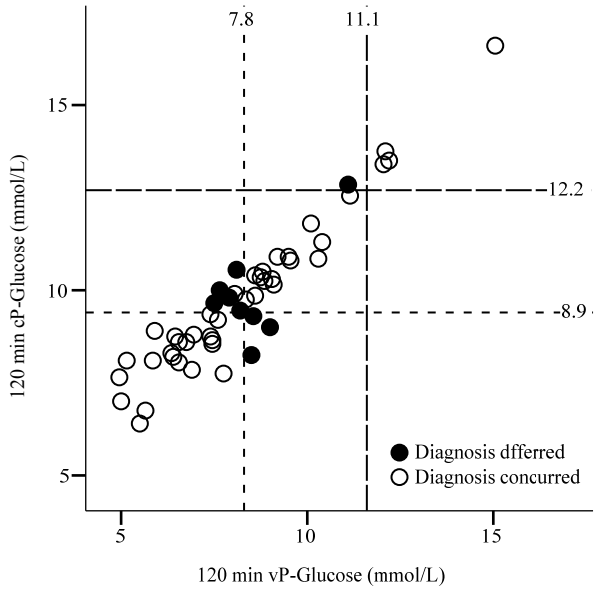

Figure 4. Capillary plasma glucose plotted against venous plasma glucose, measured at 2 h during OGTT, with indication of whether the diagnosis by WHO 1999 differed or concurred.

II. Prevalence and trend of GDM in southern Sweden

Of the 156,144 women who gave birth between January 1, 2003 and December 31, 2012, a total of 3,471 women (2.2%) were diagnosed with GDM in clinical practice (Table 4). Although there were some fluctuations in the prevalence of GDM diagnosed from one year to the next, an increasing trend was observed over the years: the average prevalence of GDM was 1.9% (789/42,285) during the first three years of the study period (2003–2005) as compared to 2.4% (1229/50,514) during the last three years (2009–2012). Whereas the prevalence of GDM differed between centers, there was a similar pattern of annual fluctuations.

When the effect of time on the prevalence of GDM was assessed in the log-linear Poisson model, a predicted overall increase in the prevalence of 35% was observed: 1.9% (95% CI 1.8–2.0) in 2003 and 2.6% (95% CI 2.4–2.7) in 2012 ($p < 0.0001$) (Figure 5).

Due to a simultaneous rise in birth rate, the number of women diagnosed with GDM increased by 64% during the corresponding time period, from 263 (95% CI 246–281) in 2003 to 431 (95% CI 407–457) in 2012 (Figure 5).

Table 4. Annual prevalence of gestational diabetes diagnosed in clinical practice, number of women diagnosed, and total number of deliveries in southern Sweden and at respective center, 2003–2012

	All women			Malmö			Lund-Ystad			Helsingborg			Kristianstad			Karlskrona		
	GDM		Births	GDM		Births	GDM		Births	GDM		Births	GDM		Births	GDM		Births
Year	%	*n*	*n*	%	*n*	*n*	%	*n*	*n*	%	*n*	*n*	%	*n*	*n*	%	*n*	*n*
2003	2.0	280	13 867	2.8	105	3705	2.0	84	4175	1.6	46	2857	1.1	19	1713	1.8	26	1417
2004	2.0	278	14 045	2.9	107	3707	1.7	74	4256	1.4	40	2873	1.8	31	1738	1.8	26	1471
2005	1.6	231	14 373	2.5	97	3837	1.5	67	4407	1.4	42	2899	0.8	14	1745	0.7	11	1485
2006	1.9	282	15 201	2.7	108	4057	1.6	74	4757	1.6	50	3034	1.7	30	1788	1.3	20	1565
2007	2.5	381	15 487	3.2	137	4282	2.2	104	4736	2.8	86	3119	1.8	33	1830	1.4	21	1520
2008	2.6	422	16 107	2.8	128	4539	2.7	135	4974	3.0	95	3218	1.6	30	1889	2.3	34	1487
2009	2.2	368	16 550	3.1	146	4702	2.0	100	4986	2.2	72	3347	1.2	23	1954	1.7	27	1561
2010	2.3	395	17 056	3.0	157	5194	1.9	97	5040	2.2	72	3311	1.7	33	1968	2.3	36	1543
2011	2.8	456	16 551	3.4	169	4991	2.7	131	4938	2.7	84	3141	1.9	38	2003	2.3	34	1478
2012	2.2	378	16 907	3.1	158	5148	2.2	108	5004	1.7	54	3242	1.5	31	2041	1.8	27	1472
Total	2.2	3471	156 144	3.0	1312	44 162	2.1	974	47 273	2.1	641	31 041	1.5	282	18 669	1.7	262	14 999
p_{trend}*	<0.0001			0.055			0.002			0.003			0.18			0.023		

**p*-values derived from Poisson regression models using the number of women with gestational diabetes as the outcome variable, year as a covariate variable, and the number of births as an offset.

This corresponds to an average increase in the prevalence of GDM of 3.4% per year and an average increase in the number of women diagnosed with GDM of 5.6% per year.

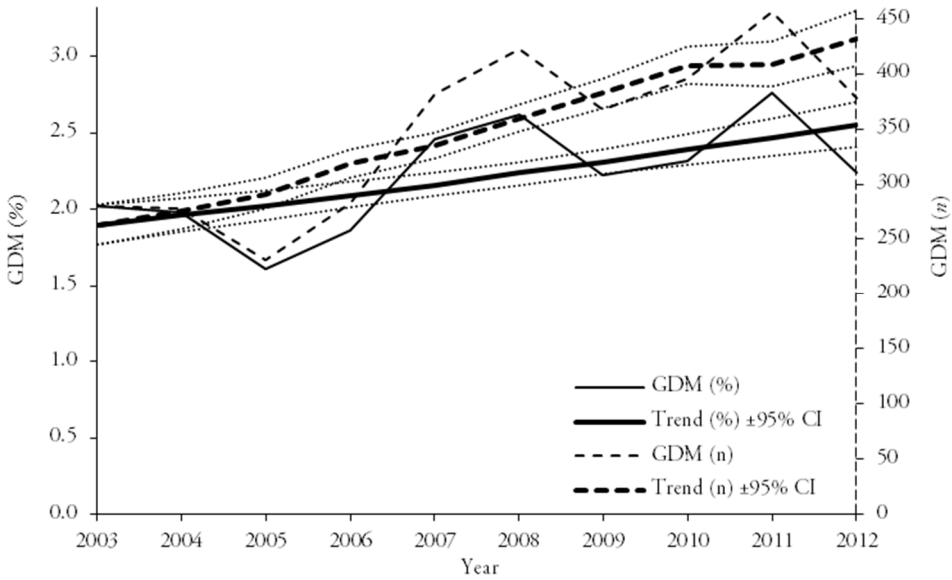

Figure 5. Southern Sweden, 2003–2012: annual prevalence (%), total number of women diagnosed with gestational diabetes mellitus in clinical practice (*n*), and respective upward trends calculated by Poisson regression.

III. Ethnicity and glucose homeostasis after GDM

Women with previous GDM were grouped according to glucose tolerance at follow-up. Of the 166 women with NGT during pregnancy, 133 also had NGT at follow-up and served as controls. Table 5 presents descriptive data of the study groups and results with adjustments for observed differences in demographic variables, with and without BMI as a covariate. Compared to the controls, HOMA-IR was increased after GDM in women with diabetes, even when adjusted for BMI. Increased HOMA-IR was also noted in women with IFG after GDM. β-cell function, measured as the insulinogenic index, was lower in women with previous GDM than in controls, and was related to glucose tolerance, being lowest in those who had diabetes. These differences were even more pronounced when adjusting the insulinogenic index for insulin resistance in the disposition index, which is illustrated in Figure 6.

Table 5. Descriptive data and results of the main outcome measures for controls and women after GDM, grouped according to glucose tolerance

	Controls	Women after GDM (n = 470)											
	(n=133)	NGT (n = 280)	p	p†	IFG (n = 54)	p	p†	IGT (n = 105)	p	p†	Diabetes (n = 31)	p	p†
Age, years	32 (31–33)	33 (32–34)	0.28		36 (33–37)	0.002		35 (34–36)	0.001		36 (32–39)	0.008	
BMI, kg/m^2	24.0 (23.0–25.4)	23.0 (22.7–23.7)	0.030		24.8 (24.0–27.0)	0.09		25.4 (24.5–26.9)	0.033		31.7 (28.8–35.4)	$< 10^{-5}$	
Non-European ethnicity	10 (7)	39 (14)	0.072		10 (19)	0.039		29 (28)	$< 10^{-4}$		16 (52)	$< 10^{-7}$	
First-grade diabetes heredity	18 (14)	76 (27)	0.001		25 (46)	$<10^{-5}$		42 (40)	$< 10^{-5}$		13 (42)	$< 10^{-3}$	
Deliveries > 3	4 (3)	11 (4)	0.78		6 (11)	0.066		14 (13)	0.006		4 (13)	0.041	
Time to follow-up, days	419 (410–436)	460 (438–483)	0.16		484 (429–523)	0.11		512 (481–551)	$< 10^{-4}$		525 (403-628)	0.064	
HOMA-IR*	1.3 (1.1–1.5)	1.4 (1.2–1.5)	0.77	0.84	1.9 (1.6–2.2)	0.021	0.029	1.6 (1.3–1.8)	0.11	0.55	3.2 (2.3-4.4)	$< 10^{-4}$	0.010
No. of samples available	101 (76)	200 (71)	0.35		38 (70)	0.46		72 (69)	0.24		25 (81)	0.65	
Insulinogenic index*	16.6 (14.1–19.6)	13.9 (12.7–15.3)	0.035	0.029	12.8 (9.9–16.6)	0.39	0.30	11.4 (9.9–13.2)	0.003	0.001	7.3 (5.5-9.9)	0.013	0.003
No. of samples available	88 (66)	191 (68)	0.74		33 (61)	0.61		69 (66)	1.0		21 (68)	1.0	
Disposition index*	13.2 (11.1–15.7)	10.2 (9.3–11.3)	0.010	0.007	6.9 (5.0–9.3)	0.013	0.022	7.8 (6.5–9.4)	$< 10^{-3}$	0.002	2.5 (1.8-3.6)	$< 10^{-7}$	$< 10^{-4}$
No. of samples available	86 (65)	187 (67)	0.74		33 (61)	0.74		65 (62)	0.69		21 (68)	0.84	

Data are median (95% CI) or n (%). All comparisons were performed vs. controls.

Differences in medians were tested with the Mann-Whitney U-test. Frequency differences were tested using Fisher's exact test.

*Log-transformed in main analysis. Values are geometric means (95% CI). Differences were tested by ANOVA, adjusting for age, non-European ethnicity, first-degree diabetes heredity, number of deliveries, and time to follow-up.

†When also adjusting for BMI.

Table 6. Results of the OGTT for women after GDM, grouped according to ethnicity

	European	Non-European			Arab			Asian		
	(*n* =362)	(*n* = 94)	*p*	*p*†	(*n* = 41)	*p*	*p*†	(*n* = 43)	*p*	*p*†
Age, years	34 (33–34)	35 (33–36)	0.23		35 (31–38)	0.40		35 (32–37)	0.54	
BMI, kg/m^2	23.8 (23.0–24.0)	25.7 (24.5–27.7)	< 10^{-4}		28.0 (25.7–32.2)	< 10^{-6}		24.2 (23.4–25.5)	0.39	
Time to follow-up, days	462 (442–483)	538 (504–563)	< 10^{-4}		545 (504–685)	< 10^{-4}		506 (460–568)	0.11	
HOMA-IR*	1.5 (1.3–1.6)	2.0 (1.7–2.3)	0.001	0.033	2.1 (1.6–2.7)	0.004	0.65	1.9 (1.5–2.3)	0.046	0.016
No. of samples available	255 (70)	69 (73)	0.61		28 (68)	0.86		32 (74)	0.72	
Insulinogenic index*	12.6 (11.6–13.7)	12.7 (10.8–15.1)	0.79	0.91	14.0 (10.8–18.1)	0.32	0.61	12.7 (9.7–16.5)	0.91	0.90
No. of samples available	240 (66)	63 (67)	1.0		27 (66)	1.0		29 (67)	1.0	
Disposition index*	8.8 (7.9–9.7)	6.8 (5.5–8.4)	0.027	0.26	7.3 (5.3–10.0)	0.24	0.58	6.9 (5.1–9.4)	0.14	0.10
No. of samples available	235 (65)	60 (64)	0.9		25 (61)	0.61		29 (67)	0.87	

Arab and Asian women are included in the non-European group.
Data are median (95% CI) or *n* (%). All comparisons were performed against European women.
Differences in medians were tested with the Mann-Whitney U-test. Frequency differences were tested using Fisher's exact test.
*Log-transformed in main analysis. Values are geometric mean (95% CI). Differences were tested by ANOVA, adjusting for age and time to follow-up.
†When also adjusting for BMI.

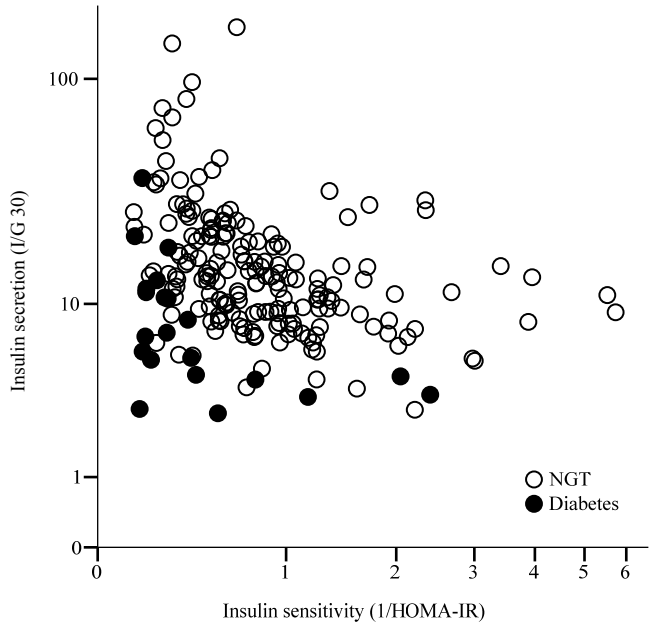

Figure 6. Insulin secretion plotted against insulin sensitivity for women after GDM with NGT and diabetes at one- to two-year follow-up. As women with diabetes had impaired insulin sensitivity and insulin secretion, they also had a lower disposition index, as indicated by their markers being closer to the origins of the coordinates.

Table 6 gives the results of the main outcome measures in women with previous GDM, grouped according to ethnicity. No differences were found between women from Western and Eastern Europe, and they were therefore grouped together. Non-European, Arab, and Asian origin was associated with higher HOMA-IR than European origin. Arab women were more overweight than European women, who had BMIs similar to those of Asian women. It is noteworthy that after adjustment for BMI, HOMA-IR did not differ significantly between Arab and European women, whereas the difference was more pronounced in Asian women. β-cell function, measured as the insulinogenic index, was unaffected by ethnicity. However, when adjusting for the degree of insulin resistance in the disposition index, non-European women showed lower estimates of β-cell function.

In this study, insulin resistance by HOMA-IR against BMI in a simple linear model had an R^2 of 34% ($p < 10^{-31}$). The rise in HOMA-IR relative to BMI, illustrated in Figure 7, was higher in Asian women than in European women, adjusting for age and interval to follow-up in multivariable regression analysis ($p = 0.021$).

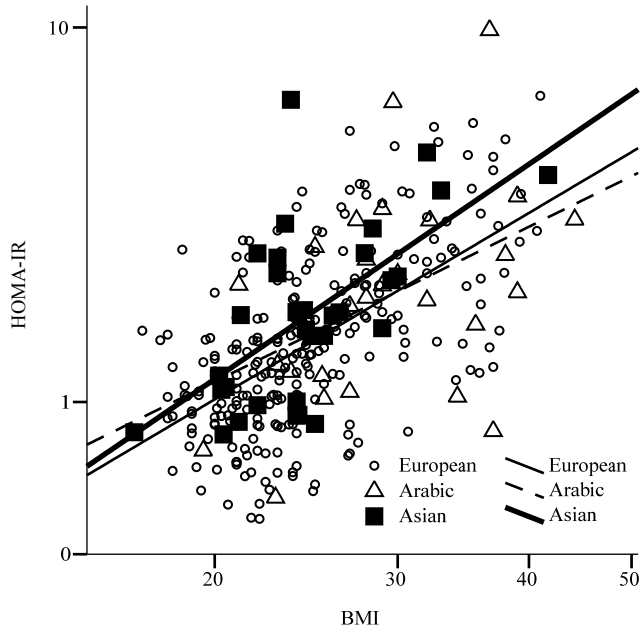

Figure 7. HOMA-IR plotted against BMI for women after GDM, according to ethnicity.

The frequency of diabetes after GDM was higher in all non-European groups than in European women. Among European women, 13 of 362 (4%) were diagnosed with diabetes, as compared to 16 of 94 non-European women (17%) ($p < 10^{-4}$). The corresponding numbers were 7 of 41 (17%) ($p = 0.002$) for Arab women and 6 of 43 (14%) ($p = 0.010$) for Asian women. In the Arab women, the diagnosis in three women was based on the fasting value alone, and that in four women was based on the 2-hour value alone. In the Asian women, the diagnosis in one woman was based on the fasting value alone, and that in five women was based on the 2-hour value alone.

The results of the logistic regression analyses are presented in Table 7. All analyses were adjusted for time to follow-up visit. Of the variables tested—using simple analyses—for any association with diabetes after GDM, BMI and the different categories of non-European ethnicity showed the highest associations. In the final multivariable model, in which all the selected predictors of diabetes development after GDM were assessed in separate analyses for the different ethnic groups, BMI showed the highest association. In addition, non-European and Asian origin showed significant associations, whereas Arab origin did not.

Table 7. Results of logistic regression analyses of variables tested for associations with diabetes after GDM

	Simple		Multivariable					
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Age, years	1.1 (1.0–1.2)	0.032	1.0 (0.9–1.2)	0.42	1.1 (0.9–1.2)	0.18	1.0 (0.9–1.2)	0.71
BMI, kg/m^2	1.2 (1.1–1.3)	< 10^{-7}	1.2 (1.1–1.2)	< 10^{-4}	1.1 (1.0–1.2)	0.004	1.1 (1.1–1.2)	0.002
Deliveries > 3	3.4 (1.0–11.5)	0.053	3.1 (0.7–15)	0.14	4.0 (0.7–24)	0.12	2.0 (0.3–14)	0.44
First-grade diabetes heredity	2.2 (1.0–4.9)	0.053	1.2 (0.4–3.2)	0.71	1.2 (0.4–3.9)	0.72	1.5 (0.4–4.8)	0.27
Non-European ethnicity	6.8 (3.0–15)	< 10^{-5}	5.0 (1.8–14)	0.002				
Arab ethnicity	10 (3.4–31)	< 10^{-4}			3.7 (0.9–15)	0.061		
Asian ethnicity	5.0 (1.7–15)	0.004					5.6 (1.5–21)	0.012

All variables were adjusted for time from delivery to follow-up. European ethnicity was used as reference.
Multivariable analyses were performed separately for each ethnic group.

IV. Prediction of diabetes up to five years after GDM

Altogether, 131 women with GNGT and 362 women with GDM had an OGTT five years postpartum (Table 8). None of the women with GNGT were diagnosed with diabetes at the one- to two-year follow-up or later, whereas in addition to the 45 women already diagnosed with diabetes, 28 other women with previous GDM were diagnosed with diabetes at the five-year appointment. Of the 72 women with IGT five years after GDM, 32 of them also had impaired fasting glucose (IFG).

Table 8. Diagnoses at the five-year follow-up

n (%)	GNGT	GDM
NGT	99 (76)	187 (52)
IFG	28 (21)	75 (21)
IGT	4 (3)	72 (20)
Diabetes	0	28 (8)
Total	131 (100)	362 (100)

Of the 362 women with previous GDM, 341 women had results from both visits (Table 9). Adding the 45 women already diagnosed with diabetes at one to two years or later, 72 of these 386 women (19%) had a diabetes diagnosis five years after GDM (by WHO 1999 criteria). Using the clinical 2-h cut-off limit of 10.0 mmol/L (EASD criteria), the corresponding numbers were 45 of 106 (42%).

Table 9. Diagnoses at one- to two-year follow-up versus five-year follow-up for women after GDM

		5 years				
		NGT	IFG	IGT	Diabetes	Total
1 to 2 years	NGT	139 (62)	46 (21)	30 (13)	9 (4)	224 (100)
	IFG	11 (26)	16 (37)	8 (19)	8 (19)	43 (100)
	IGT	25 (34)	9 (12)	30 (41)	10 (14)	74 (100)
	Total	175 (51)	71 (21)	68 (20)	27 (8)	341 (100)

In women with IFG or IGT at the one- to two-year OGTT, 18 of 117 (15%) had diabetes at the five-year OGTT, as compared to 9 of 224 (4%) for women with NGT. Using NGT as a reference, IFG or IGT at one- to two-year follow-up was

Table 10. Descriptive data from pregnancy and follow-up in relation to glucose category at five-year follow-up after GDM

	NGT (*n* = 187)	IFG (*n* = 75)	*p**	IGT (*n* = 72)	*p**	Diabetes (*n* = 28)	*p**
Non-European ethnicity	23 (13)	10 (15)	0.84	12 (18)	0.42	13 (48)	< 0.001
First-grade diabetes heredity	47 (28)	24 (36)	0.27	28 (44)	0.027	16 (62)	0.001
Age at delivery, years	32.1 (29.1–36.0)	32.3 (28.8–35.9)	0.99	34.6 (32.2–36.8)	0.002	35.4 (28.8–38.2)	0.060
Pregnancy							
2-h PG, mmol/L	9.3 (8.9–9.9)	9.3 (8.9–10.3)	0.43	9.5 (9.1–10.3)	0.083	10.1 (9.6–10.8)	< 0.001
Diagnosis in early gestation	8 (5.0)	5 (7.9)	0.53	7 (12)	0.13	6 (23)	0.006
Insulin treatment	12 (6.5)	7 (9.3)	0.44	8 (11)	0.20	6 (21)	0.018
1 to 2 years after pregnancy							
Interval to follow-up, years	1.3 (1.0–1.7)	1.2 (1.0–1.5)	0.15	1.4 (1.2–1.6)	0.12	1.4 (1.1–1.7)	0.68
Deliveries > 3	7 (4.0)	6 (8.5)	0.20	5 (7.2)	0.33	3 (10.7)	0.14
BMI, kg/m^2	23.0 (21.2–26.0)	24.1 (21.6–27.5)	0.010	24.4 (22.2–27.1)	0.011	27.0 (25.1–31)	$< 10^{-6}$
FPG, mmol/L	5.2 (4.9–5.6)	5.6 (5.2–6.0)	$< 10^{-4}$	5.3 (5.0–5.8)	0.12	5.7 (5.2–6.3)	< 0.001
2-h PG, mmol/L	5.8 (5.0–6.9)	6.4 (5.5–7.0)	0.043	7.4 (6.1–8.3)	$< 10^{-8}$	7.2 (6.9–8.5)	$< 10^{-6}$
5 years after pregnancy							
Interval to follow-up, years	5.1 (5.0–5.2)	5.1 (5.0–5.3)	0.95	5.1 (5.0–5.3)	0.39	5.2 (5.0–5.5)	0.28
Deliveries > 3	13 (7.0)	9 (12.0)	0.22	10 (13.9)	0.09	5 (18)	0.066
BMI, kg/m^2	23.4 (21.3–26.8)	25.0 (22.7–27.9)	0.005	25.8 (23.1–27.9)	0.001	28.0 (26.8–34.6)	$< 10^{-7}$
FPG, mmol/L	5.5 (5.3–5.8)	6.3 (6.2–6.5)	$< 10^{-35}$	6.0 (5.6–6.4)	$< 10^{-10}$	7.1 (6.8–7.2)	$< 10^{-15}$
2-h PG, mmol/L	7.4 (6.6–8.0)	7.7 (7.3–8.2)	0.003	9.7 (9.2–10.3)	$< 10^{-34}$	12.2 (9.5–12.7)	$< 10^{-13}$

Data given are *n* (%) or median (interquartile range).
*All comparisons were performed against NGT.

Table 11. Descriptive data and results of simple regression analysis of variables tested for associations with diabetes up to five years after GDM

	A. After pregnancy						**B.** After IFG or IGT at 1–2 years		
	NGT at 1–2 years and 5 years	Diabetes at 1–2 years or later		Simple regression			Simple regression†		
	(*n* = 139)	(*n* = 73)	*p**	R^2	OR (95% CI)	*p*	R^2	OR (95% CI)	*p*
Non-European ethnicity	17 (13)	34 (51)	$< 10^{-7}$	0.21	7.09 (3.52–14.26)	**$< 10^{-7}$**	0.08	3.24 (1.02–10.31)	0.047
First-grade diabetes heredity	36 (27)	35 (54)	< 0.001	0.09	3.14 (1.69–5.84)	< 0.001	0.10	3.17 (1.11–9.05)	0.031
Age at delivery, years	31.9 (29.1–36.0)	35.4 (30.5–38.2)	0.004	0.06	1.10 (1.03–1.17)	0.005	0.12	1.15 (1.02–1.30)	**0.022**
Pregnancy									
2-h PG, mmol/L	9.3 (8.9–10.0)	10.1 (9.7–10.9)	$< 10^{-5}$	0.16	1.91 (1.41–2.58)	**$< 10^{-4}$**	0.35	4.32 (1.78–10.51)	**0.001**
Diagnosis in early gestation	8 (6.3)	16 (26)	< 0.001	0.10	5.24 (2.10–13.10)	< 0.001	0.19	-	1
Insulin treatment	7 (5.0)	21 (30)	$< 10^{-5}$	0.15	8.25 (3.30–20.64)	$< 10^{-5}$	0.17	6.00 (1.67–21.59)	0.006
1 to 2 years after pregnancy									
Interval to follow-up, years	1.3 (1.0–1.7)	1.4 (1.1–1.8)	0.31	<0.01	1.32 (0.80–2.20)	0.28	0.03	0.54 (0.19–1.57)	0.26
Deliveries > 3	5 (3.6)	11 (16)	0.004	0.06	5.08 (1.69–15.29)	0.004	0.13	10.00 (1.12–88.91)	0.039
BMI, kg/m^2	22.4 (20.8–24.7)	30.3 (25.8–35.4)	$< 10^{-15}$	0.40	1.28 (1.19–1.37)	**$< 10^{-10}$**	0.29	1.25 (1.10–1.41)	**0.001**
FPG, mmol/L	5.2 (4.9–5.5)	6.2 (5.5–6.8)	$< 10^{-16}$		NA		0.12	3.2 (1.20–8.2)	0.019
2-h PG, mmol/L	5.6 (4.8–6.3)	8.6 (7.0–11.2)	$< 10^{-20}$		NA		0.012	1.13 (0.82–1.5)	0.45
5 years after pregnancy									
Interval to follow-up, years	5.1 (5.0–5.2)	5.1 (5.0–5.3)	0.64	0.01	0.58 (0.25–1.34)	0.20	0.05	0.41 (0.11–1.50)	0.18
Deliveries > 3	6 (4.3)	7 (20)	0.005	0.07	5.54 (1.73–17.75)	0.004	0.04	2.50 (0.59–10.61)	0.21
BMI, kg/m^2	22.8 (20.9–25.9)	28.0 (26.7–35.1)	$< 10^{-9}$	0.35	1.30 (1.18–1.43)	$< 10^{-6}$	0.31	1.30 (1.10–1.53)	0.002
FPG, mmol/L	5.5 (5.2–5.8)	7.1 (6.7–7.2)	$< 10^{-16}$		NA			NA	
2-h PG, mmol/L	7.3 (6.6–8.1)	12.1 (9.3–12.6)	$< 10^{-11}$		NA			NA	

Data given are *n* (%) or median (interquartile range).*Comparisons performed against NGT at one to two years and five years. †Simple regression for diabetes after one to two years (*n* = 28) vs. NGT at five years (*n* = 36). Variables used in prediction models A and B are marked with bold *p*-values.

associated with an increased risk of diabetes up to five years postpartum (OR 5.1, 95% CI 2.5−10.4, $p < 10^{-5}$).

In Table 10, clinical data from pregnancy and follow-up are given in relation to glucose category at the five-year OGTT for women with previous GDM. Using NGT as a reference, women with diabetes were characterized by an increased frequency of non-European ethnicity, higher 2-h glucose level during pregnancy, higher BMI at both follow-up visits, and higher fasting and 2-h glucose levels during the OGTT one to two years postpartum. Similarly, women with IFG/IGT had higher BMI than women with NGT. Snuff was used in less than 1% of the women during pregnancy and follow-up, whereas 5% smoked during pregnancy (as compared to 9–10% during follow-up). There were no significant differences in the frequencies of tobacco use during pregnancy or follow-up between women with GNGT and women with GDM; nor were there any differences in the frequencies of smoking related to glucose tolerance at five-year follow-up.

To investigate which variables were associated with development of diabetes up to five years after GDM, women with NGT at one- to two-year follow-up and five-year follow-up were used as a reference (Table 11A). Of the variables tested for an association with diabetes in the multivariable analysis, ethnicity, 2-h glucose concentrations during pregnancy, and BMI at one- to two-year follow-up remained after backward elimination, while age at delivery and first-grade diabetes heredity were not significant in this study. Change in BMI between one- to two-year follow-up and five-year follow-up was not significantly associated with diabetes in multivariable analysis, when adjusting for BMI at the respective follow-up. One woman with a weight loss of 43% after pregnancy due to bariatric surgery and NGT at 5-year follow-up was considered to be an outlier, and was excluded from later analyses.

Variables remaining after backward elimination in the multivariable regression analysis were used when constructing a model for diabetes prediction after GDM, including results from 200 women (67 with diabetes, 133 with NGT). Accordingly, ethnicity (with 0 coding for European, and 1 coding for non-European, “E”), 2-h glucose concentration during pregnancy (“GP”), and BMI from the one- to two-year follow-up were used to generate model A for prognostication of diabetes risk (%) with NGT at one to two years and five years as reference: (Exp (1.919 × E + 0.703 × GP + 0.274 × BMI – 15.5)) / (1 + Exp (1.919 × E + 0.703 × GP + 0.274 × BMI – 15.5)) × 100. In this population, model A correctly prognosticated 86% of the women with diabetes after GDM, with an AUC of 0.91 (95% CI 0.86–0.95). A calculated optimal cut-off for diabetes risk of 36.4% yielded a sensitivity of 82.1% (Figure 8A), a specificity of 88.0%, a positive predictive value of 77.5%, and a negative predictive value of 90.7%.

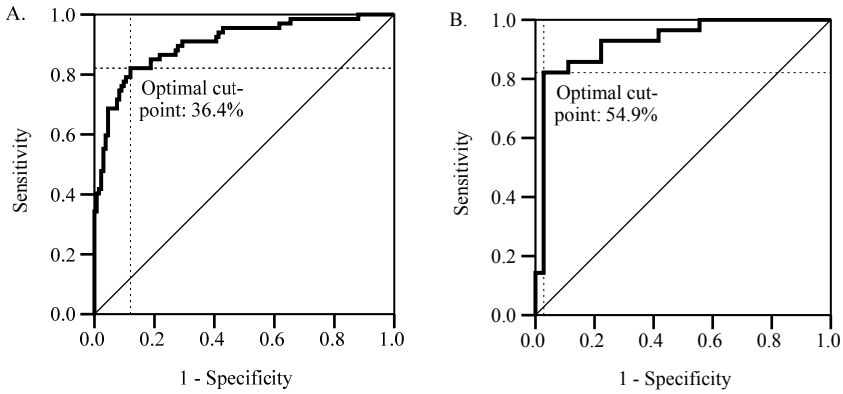

Figure 8. ROC curves for models A and B predicting diabetes up to five years after pregnancy, with calculated optimal cut-off limits indicated. A. Women after GDM (*n* = 200). B. The subgroup of women with IFG or IGT one to two years after GDM (*n* = 64).

Figure 9 illustrates the calculated risks of diabetes up to five years after GDM in relation to BMI at one- to two-year follow-up for each woman. With the idea of using analyzed follow-up data with the purpose of individual counseling of women after pregnancy with GDM, we designed a function-sheet with a line diagram relating possible weight to prognosticated risk of diabetes from model A. An individual example is shown in Figure 10.

To investigate determinants of diabetes or NGT five years after GDM in women classified as having IFG or IGT at one- to two-year follow-up, regression analyses were performed, adding significant variables in a forward strategy—as the quantity of women in this analysis was limited (Table 11B). Based on these findings, a prognostication model B was developed, resulting in 88% correct classifications in the 64 women included (28 with diabetes, 36 with NGT), with an AUC of 0.93 (95% CI 0.86–0.99). An optimal cut-off of 54.9% gave a sensitivity of 82.1%, a specificity of 97.2% (Figure 8B), a positive predictive value of 95.8%, and a negative predictive value of 87.5%. The prognostication of diabetes risk (%) with NGT as reference was calculated as (Exp (0.215 × AD + 2.156 × GP + 0.271 × BMI – 35.783) / (1+ Exp (0.215 × AD + 2.156 × GP + 0.271 × BMI – 35.783)) × 100, with "AD" representing age at delivery and "GP" representing 2-h plasma glucose concentration during pregnancy, and using BMI from the one- to two-year follow-up.

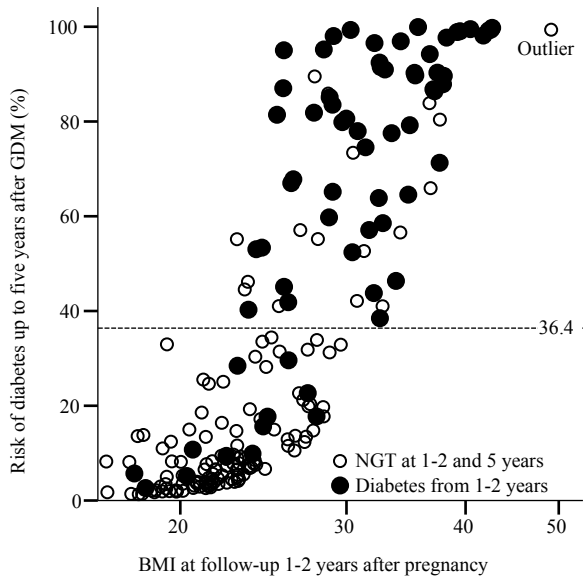

Figure 9. Risk of diabetes up to five years after GDM (model A) in relation to BMI at one- to two-year follow-up. Optimal cut-off based on the ROC curve is shown. The outlier, described in the text, was not included in the regression for the model.

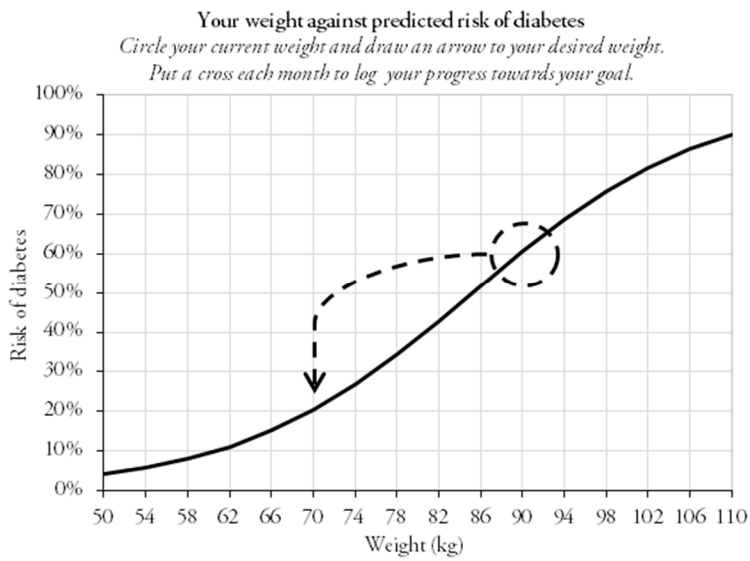

Figure 10. Line diagram representing an individually predicted risk of diabetes 5 years after GDM plotted against weight. This example illustrates the risk for a European woman with a height of 1.75 m, a 2-h OGTT capillary plasma glucose concentration of 11.2 mmol/L in pregnancy, and a current weight of 90 kg—resulting in a predicted 60% risk of diabetes with a constant weight and declining to a 20% risk with a weight loss of 20 kg.

Discussion

I. Capillary and venous glucose levels during OGTT

In the present study, capillary plasma glucose concentrations were higher than their venous counterpart at all measured time points of the OGTT, including fasting glucose measurements. This is in line with the results of Kruijshoop *et al.* (77), but it contrasts with some other studies—as well as proposed equivalence values by the WHO in 1999, with no differences in the fasting state (1, 74-76, 114, 115). In agreement with previous reports, the differences were of greater magnitude after glucose ingestion and were most pronounced at 30 min, coincident with the peak of the glucose curve (74-77, 115). The difference at 2 h during the OGTT was greater than what has been reported from some previous studies, using glucose hexokinase methods (74-77). A study using the HemoCue system for capillary glucose measurement and the glucose oxidase method for venous measurement, reported a 2-h difference similar to ours when taking the 11% difference between glucose concentrations in blood and plasma into account (81, 114).

It is generally believed that capillary glucose measurements are less reproducible than venous measurements (79). In a study by Bhavadharini *et al.*, the intra-assay and inter-assay coefficients of variation for venous blood glucose ranged from 0.78% to 1.68%, while the mean coefficient of variation for capillary samples was 4.2% (115). However, Kruijshoop *et al.* reported coefficients of variation that were similar to ours (77). The fact that one specially trained laboratory assistant handled all blood samples during the OGTT in the present study probably contributed to our finding of low intra-individual coefficients of variation for both capillary glucose measurements and venous glucose measurements.

The reported PIs for capillary versus venous glucose concentrations in the present study at fasting were almost identical to those in two previous studies that were larger (114, 116), while the PI at the 2-h time point of the OGTT was double that reported by Colaguiri *et al.* (114). In contrast, the PIs of the differences in the Bland-Altman plots reported by both Bhavadharini *et al.* and Kruijshoop *et al.* were more than double those of ours, both in the fasting state and post load (77, 115). However, these studies used different methods for analysis of glucose concentrations in capillary and venous samples. In our study, all analyses were performed using an identical method, which was a methodological strength, even though a central laboratory method was

not used. Carstensen *et al.* reported an overall wider PI than the mean of ours, assuming similar relationships at all measured time points of the OGTT (0, 30, 60, and 120 min). As the relationships differ in the fasting state and after glucose ingestion according to our results, being of greater magnitude after load, a wider PI could be expected when post-load measurements predominate in the model.

The slope of the regression line in the fasting state was similar to that reported by Stahl *et al.* and Colaguiri *et al* (114, 116), and the slope at 2 h was similar to that reported by Eriksson *et al.* and Colaguiri *et al* (75, 114). However, the intercept of the regression line differed between the studies. Since these earlier studies used simple regression to establish conversion equations and not Bland-Altman diagrams, as recommended by Carstensen in 2010, the findings of the above-mentioned studies are not completely comparable (110).

Capillary equivalence values of both our study and that by Colaguiri *et al.*, were within the 95% PI of the capillary diagnostic limits proposed by the WHO in 1999 (1). Although there is an uncertainty associated with derived equivalence values, it is interesting to note that the capillary plasma glucose concentration of 10.0 mmol/L used in most parts of Sweden as the diagnostic limit for GDM, had an equivalence value of 8.5 mmol/L using our conversion equation—the level recommended by IADPSG and affirmed by the WHO in 2013 (3, 22). For diagnostic purposes, it is important to note that OGTT as such has a rather low reproducibility, especially for 2-h glucose levels in the intermediate range (117-119), emphasizing the need for re-testing of women with glucose concentrations close to the diagnostic limits. Since insulin resistance continuously increases during the first part of the third trimester, re-testing is also indicated from clinical signs of GDM (such as accelerated fetal growth or polyhydramnios).

II. Prevalence and trend of GDM in southern Sweden

The crude prevalence of GDM in southern Sweden was estimated to be 2.6% in 2012, which was in line with most reports at the time from northern Europe (2% to 6%), but low from an international standpoint (< 1% to 28%) (85, 91). The data can be regarded as being valid, as the register was partially manually controlled, and the data were in line with numbers reported to the Swedish Medical Birth Register (http://www.socialstyrelsen.se/). If the detection rates of the screening procedures are taken into account (83, 84), with southern Sweden offering all women OGTT and most other parts of Sweden relying on random glucose measurements, the reported figures can be seen as an updated indicator of the prevalence in the whole nation. A recent review, based on 47 studies and with adjustments to account for differences in heterogeneity in screening methods and glucose cut-off values, estimated the global prevalence of hyperglycemia in pregnancy as defined by the IADPSG criteria (4). In

2013, the global prevalence was 16.9%, ranging from 6.3% to 36.7% in Europe, and from 5.2% to 40.4% globally (4). The result illustrates possible effects of policy change in the diagnosis of hyperglycemia in pregnancy.

The 35% upward trend in the prevalence of GDM during the years 2003−2012, corresponding to an average annual increase of 3.4% per year, was in line with previously reported trends in Caucasian women, though varying in other populations from 0.5% to 8.3% (40). As there was a concomitant rise in birth rate during the study period, the number of women diagnosed with GDM increased by 64%. In clinical practice, and at the levels of policy-making and resource allocation, it is just as important to focus on numbers as to focus on prevalence rates.

As this study was limited to crude numbers for the prevalence of GDM, associations with risk factors for GDM could not be analyzed. According to national statistics, the mean age and mean BMI of pregnant women in the region were relatively constant during the study period (http://www.socialstyrelsen.se/). However, the percentage of women with BMI ≥ 30 kg/m^2 increased from 10% to 12%, and the percentage of women of childbearing age with a non-Swedish background increased from 26% to 41% (first-generation or second-generation immigrants; http://www.scb.se/). The composition of the immigrant population is another important factor to consider, with an increasing proportion of women from high-risk countries.

III. Ethnicity and glucose homeostasis after GDM

The finding that women with previous GDM, irrespective of glucose tolerance status, had impaired β-cell function in relation to their level of insulin resistance after pregnancy is well supported by other studies (30, 52, 120-122). Furthermore, this impairment was most pronounced in women with diabetes. It has previously been demonstrated in hyperglycemic clamp studies that subjects with IFG are mainly characterized by hepatic insulin resistance, while subjects with IGT are mainly characterized by muscle insulin resistance (123). When adjusting for the prevailing degree of insulin resistance, subjects in both of these pre-diabetic glucose categories have been shown to have a marked decrease in first-phase insulin response (123, 124). In our study, this was reflected by an increased HOMA-IR in women with IFG after GDM, and by a decrease in disposition index in both pre-diabetic groups. The OGIS method by Mari *et al.* might have been useful to demonstrate muscle insulin resistance, as it correlates with the glucose clamp assessing total glucose disposal (postprandial insulin sensitivity), but requires samples from 90 min (125). A strength of the study was that β-cell function was assessed using the insulinogenic index (I/G30), which is a more dynamic index to estimate early insulin secretion from than HOMA-β, which is based only on fasting samples and which has been used in some studies (52, 108).

In the present study, non-European women had higher insulin resistance than European women, as determined by HOMA-IR. In Arab women, this apparent difference was eradicated by adjustment for their higher BMI but it was strengthened in Asian women. Our results conflict with the results of a previous study from our group, which found Arab women to be more insulin-resistant even after adjustment for BMI (55). However, that study was based on a smaller material of pregnant women and used a higher cut-off to define GDM. Mørkrid *et al.* reported results similar to ours in a study performed during early gestation—with women from the Middle East and Asia being more insulin-resistant than European women. The difference in HOMA-IR was not apparent after adjustment for BMI in Middle Eastern women, but it was still apparent in Asian women (53). In general, Asian women have a lower BMI (1.3 kg/m^2) than European women of the same age with the same proportion of body fat and with the same risk of cardiovascular disease (54). By analogy with this, our study and previous studies (49, 126), demonstrated a steeper rise in insulin resistance with BMI in Asian women. Furthermore, one must also consider that the term "Asian ethnicity" includes subgroups with different body compositions (54). If the number of Asian women in our study had been greater, further analysis of subgroups might have proven valuable, as done by Mørkrid *et al.* (53).

IV. Prediction of diabetes up to five years after GDM

Of the women in the cohort who attended both follow-up appointments after GDM, 42% were diagnosed with subsequent diabetes five years after their pregnancy with GDM (modified EASD criteria). This is a higher frequency than previously reported from our area by Ekelund *et al.*, who found a diabetes prevalence of 30% five years after GDM (72). However, due to the high rate of drop-out from the present study, the figure is unreliable and should be interpreted with caution.

In women with previous GDM, BMI, non-European ethnicity, and the 2-h glucose concentration of the OGTT during pregnancy were the factors most closely associated with diabetes up to 5 years after pregnancy. In women with IFG or IGT at one- to two-year follow-up, age replaced non-European ethnicity as a more significant factor in multivariable analysis. These variables, included in the proposed models, might well be accompanied or replaced by other risk factors in repeated studies in other populations, although higher glucose concentration during pregnancy and higher BMI after pregnancy appear to be explicit risk factors for future diabetes (72, 127-129). Higher age, first-grade diabetes heredity, and parity > 3 were less stable predictors, which might be attributed to significant confounding with non-European ethnicity in this population. However, an Austrian group assessing risk factors for diabetes manifestation up to ten years after GDM did not observe any effect of non-

European origin (98). When using broader ethnic classifications, caution is warranted, as considerable differences can exist even within apparently well-defined populations (54).

A limitation of the study was the rather low overall participation rate in the one- to two-year follow-up; for this reason, we refrained from analyzing total rate of diabetes following GDM (104). Studies have repeatedly shown poor compliance with recommended guidelines in clinical practice, and women fail to attend the postpartum visit, even in the research setting (96). Nevertheless, 85% of eligible women from the first follow-up took part in the five-year follow-up, and it is a strength that their previously recorded data from the one- to two-year follow-up was not significantly different from the data from those who declined participation or dropped out. The participation rate at the first-follow-up might have been improved if follow-up had been performed at the regular maternal care visit three months after delivery, which would also have been valuable since early conversion to type-2 diabetes is not uncommon (70, 128).

The cut-off points identified concerning prediction of diabetes risk, resulting in high predictive values for both models, may not be good enough to be used by clinicians for them to refrain from further follow-up. For this purpose, completing the models with other variables might prove to be effective (72, 127-132). Nevertheless, both prediction models performed well, with large proportion of correct classifications, and should encourage validation in other populations in future studies.

The method of motivational interviewing has been shown to be useful when counseling to encourage weight loss (133). The concept of using a prediction model in a function-sheet line diagram to illustrate an individualized risk in relation to a modifiable risk factor may prove to be a useful tool when motivating women to adopt a healthy lifestyle, and may increase compliance to follow-up.

Conclusions

I. Capillary glucose concentrations were higher than venous glucose concentrations throughout the OGTT, the differences being greatest in the non-fasting state at the peak level of the glucose curve.

Based on established equations for non-constant differences, equivalence values for capillary glucose concentrations tended to be higher than the corresponding diagnostic limits proposed by the WHO.

Diagnostic disagreements occurred primarily with glucose concentrations close to the diagnostic cut-off limits.

Derived equivalence values are associated with uncertainties when used for diagnostic purposes on an individual basis, but they could be suitable when translating results on a group basis.

II. The calculated prevalence of GDM in southern Sweden increased from 1.9% in 2003 to 2.6% in 2012, with an average annual increase of 3.4%.

III. One to two years after pregnancy, insulin secretion in relation to insulin resistance was lower in women with previous GDM than in women with normal glucose tolerance during pregnancy.

Women of non-European origin were characterized by increased insulin resistance—related to increased BMI in Arabic women and to a higher level of insulin resistance relative to BMI in Asian women.

BMI was the most important risk factor for diabetes development after GDM. In addition, Asian origin was identified as a significant risk factor, whereas Arab origin was not.

IV. Higher BMI, non-European ethnicity, and higher 2-h glucose concentration during pregnancy were important predictors of diabetes development one to five years after GDM.

The proposed prediction models of diabetes one to five years after GDM performed well in the study, but need to be validated.

The concept of using a function-sheet line diagram to illustrate an individualized risk in relation to a modifiable risk factor is proposed as a model when counseling women after GDM.

Reflections for future work

Capillary glucose screening has been used in Sweden for many years, and it is regarded as being effective and more convenient for—and acceptable to—patients. If capillary sampling is to be continued, a large-scale study in pregnant women will be needed to establish conversion algorithms for proposed new diagnostic thresholds for GDM. The study should preferably involve several centers that are representative of all regions of the country and it should also include a repeated OGTT to evaluate intra-individual variation. It would also be desirable to compare results from reference laboratory methods of glucose analysis to those obtained on the more convenient glucometers that are recommended for diagnostic use.

In future studies, glucose disposal indices based on multiple time points during the OGTT could give a better understanding of ethnic differences between subgroups of the population.

With the increasing number of risk factors and a change to proposed new diagnostic thresholds, the prevalence of GDM can be expected to increase substantially (134). It and the prevalence of subsequent diabetes will be important to evaluate in relation to diagnostic methods, care given, adverse outcomes, and cost-effectiveness (135, 136). To facilitate this, the Swedish Pregnancy Register should include data on all separate glucose concentrations during the OGTT in pregnancy, as well as other risk factors, such as pregnancy weight and ethnicity (137, 138). Cooperation with the Swedish National Diabetes Register is a further possibility to gain access to data and information on conversion to manifest diabetes. With the increasing amount of proper data available, using prediction models during and after pregnancy might prove to be justified at both the individual level and the societal level—for motivational purposes, and to direct the use of resources (139).

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Gestational diabetes mellitus

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The studies were conducted 2010 to 2015:
I. Capillary and venous glucose concentrations
II. Prevalence and trend of gestational diabetes
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