Screening for gestational diabetes mellitus
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Chapter 1

General introduction
Gestational diabetes mellitus: a metabolic disorder of pregnancy

Gestational diabetes mellitus (GDM) is a common metabolic disorder of pregnancy. It is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy. It includes new-onset carbohydrate intolerance as well as pre-existing diabetes mellitus that has not been recognised before pregnancy (predominantly diabetes mellitus type 2). GDM comprises carbohydrate intolerance that continues to exist after pregnancy as well as carbohydrate intolerance that subsides after pregnancy.

Pathophysiology
Placental hormones produced in pregnancy hamper normal carbohydrate metabolism. Corticotropin-releasing hormone, progesterone, oestradiol, and human placental lactogen interfere (directly or indirectly) with insulin receptors that are situated on various cells of the human body, making these cells less sensitive for insulin. Decreased insulin sensitivity leads to diminished entry of glucose into the cells and thus hyperglycemia. This is a physiological process emerging in the second trimester of pregnancy, enabling the growing fetus adequate glucose supply. To maintain maternal blood glucose levels within the normal range, production of insulin by the beta-cells of the pancreas is increased. If this mechanism is insufficient, GDM may occur. It is unclear why some women develop GDM while others do not. In non-pregnant obese individuals, elevated levels of free fatty acids lead to decreased insulin sensitivity. In case of pregnancy, insulin sensitivity decreases even further, potentially leading to hyperglycemia. Another suggested mechanism is autoimmunity. A small subgroup of women with GDM carries markers of humoral autoimmunity against pancreatic beta-cells. Autoimmunity against pancreatic beta-cells in otherwise asymptomatic women may become manifest in pregnancy as insulin resistance is increased due to interference of placental hormones with the insulin receptors.

Criteria for GDM
Over the years there have been many different criteria for GDM all reflecting carbohydrate intolerance, albeit at different levels. Original criteria for GDM were established by O’Sullivan and Mahan in 1964. These criteria were initially selected to identify women at risk for developing diabetes mellitus (type 2) in the future, and did not reflect the risk for complications during pregnancy and delivery. In recent years, the focus has been more directed on perinatal and short-term maternal outcomes.

The reference test to diagnose GDM is the oral glucose tolerance test (OGTT). With this test a glucose solution containing 75 g or 100 g of glucose is ingested after overnight fasting. Before and after administration of the glucose containing solution, plasma glucose values are measured. As various threshold values are applied to classify the
results of the OGTT as abnormal, (international) comparison of the prevalence of GDM is complicated.\textsuperscript{9-12} Common criteria to define the OGTT as abnormal are criteria set by the World Health Organisation (WHO) and the American Diabetes Association (ADA) (Table 1).\textsuperscript{1,6}

**Epidemiology**

The prevalence of GDM depends on the criteria that are used. Furthermore, women with specific ethnic background (e.g. women from Asia, the Caribbean, and the Middle East) are at increased risk for GDM. Probably genetic differences, access to health care and dietary habits play a role.\textsuperscript{13} In the USA and Canada the prevalence of GDM is reported to be between 2.5 and 10%, depending on ethnicity of the population studied.\textsuperscript{14} In a number of Asian countries (e.g. India) GDM is reported in up to 15% of all pregnancies.\textsuperscript{15} In the Netherlands prevalence is estimated to vary between 2 and 4%. Worldwide the prevalence of GDM is rising, mainly due to the rising epidemic of overweight and obesity.\textsuperscript{4,16,17} Other risk factors for GDM reported in the literature are: family history of diabetes mellitus, increasing maternal age, obstetric history (previous GDM or offspring with birth weight >90\textsuperscript{th} percentile), multiple pregnancy and polycystic ovarian syndrome.\textsuperscript{14}

**Clinical relevance**

Pre-existing diabetes mellitus type 1 and 2 are associated with maternal complications and adverse perinatal outcome (such as congenital anomalies).\textsuperscript{18,19} When we started the studies described in this thesis, the association between GDM and the risk of pregnancy complications had been described in various studies, however it seemed less explicit than in overt diabetes. As high concentrations of glucose in women with GDM result in increased fetal insulin production, and fetal hyperinsulinemia leads amongst others to macrosomia, most reported adverse outcome associated with GDM in the literature was fetal overgrowth, with related complications such as caesarean section.\textsuperscript{20}

In 2008 the results of the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study were published. In this study the association between hyperglycemia in pregnancy (less severe than pre-existing diabetes) and adverse maternal and pregnancy outcomes was evaluated.\textsuperscript{21} Higher levels of blood glucose after a 75-g OGTT were associated

| Table 1. Various criteria for gestational diabetes mellitus (GDM) |
|----------------------|----------|----------|----------|----------|
|                      | OGTT     | Fasting value | 1 hour value | 2 hour value | 3 hour value |
| World Health Organisation \textsuperscript{a} | 75 g     | > 7.0 mmol/l | -          | ≥ 7.8 mmol/l | -          |
| American Diabetes Association \textsuperscript{b} | 75 g     | ≥ 5.3 mmol/l | ≥ 10.0 mmol/l | ≥ 8.6 mmol/l | -          |
| American Diabetes Association \textsuperscript{b} | 100 g    | ≥ 5.3 mmol/l | ≥ 10.0 mmol/l | ≥ 8.6 mmol/l | ≥ 7.8 mmol/l |

OGTT = Oral glucose tolerance test; \textsuperscript{a} Diagnosis of GDM if fasting value > 7.0 mmol/L or 2 hour value ≥ 7.8 mmol/L; \textsuperscript{b} Diagnosis of GDM if two out of three of four values exceed threshold value.
with increased risk of primary caesarean section, clinical neonatal hypoglycemia, preterm delivery, preeclampsia and shoulder dystocia. Women with GDM also have an increased risk of developing GDM in their next pregnancy. Moreover, the risk of developing diabetes type 2 in the future is increased. This risk may be as high as 50%, and is highest in women who need insulin treatment in pregnancy, and in women with obesity. Children of women with GDM have an increased risk for childhood and adult metabolic problems, such as obesity and diabetes mellitus type 2.

**Effect of treatment**

Results of two large randomised controlled trials have shown that treatment of GDM with dietary and lifestyle advices, and insulin if required, is associated with a significant reduction of pregnancy complications compared to routine obstetric care, indicating a beneficial effect of treatment of GDM.

**Background of the research described in this thesis**

When we started the studies described in this thesis, there was considerable debate on the relevance of screening for GDM. Internationally but also nationwide various criteria for GDM were used and different strategies for the diagnostic work-up were applied. This was mainly due to lack of evidence on the association between hyperglycemia in pregnancy and pregnancy complications. The beneficial effect of treatment at the time was established in one randomised controlled trial. Throughout the period this thesis was written, the association between maternal hyperglycemia and pregnancy complications became clear from the HAPO study. Also, results of another randomised controlled trial on the effect of treatment of GDM were published. Although the need for a uniform diagnostic strategy was there for a long time, results of the above mentioned studies emphasised this need even more.

The OGTT can be used as a diagnostic test for GDM in women with symptoms, e.g. suspected macrosomia or polyhydramnios. Often women with GDM however, have no specific symptoms or signs. In asymptomatic women, GDM can only be detected if some form of glucose screening is performed. In current clinical practice various tests and strategies are used. Frequently used tests are random glucose measurement, fasting glucose measurement and a glucose challenge test (blood glucose measurement one hour after ingestion of 50 g of glucose). There is no agreement on which screening test is most appropriate, since estimates of accuracy and costs of the tests reported in the literature vary. There is also discussion on which women should be tested. International expert groups have recommended selective screening based on risk factors for GDM. Opponents of this selective screening strategy criticise the use of risk factors, since this strategy fails to identify over one-third of cases of GDM, and therefore they advocate universal screening. Studies that have evaluated risk factor based screening often included a selection of risk factors and did not combine these risk factors in a quantitative
manner (i.e. risk scoring system or a prediction model), thereby possibly overlooking the diagnostic value of risk factors in the selection of women at risk for GDM.

Summary of background
Worldwide the prevalence of GDM is rising. Hyperglycemia in pregnancy is associated with maternal and pregnancy complications. Treatment of GDM reduces the risk of pregnancy complications. The question remains what is the best strategy to identify women with GDM?

Aim of this thesis
The aim of this thesis was to evaluate various screening strategies for GDM. We wanted to explore accuracy measures of three individual screening tests, and the potential of using risk factors and patient characteristics. Furthermore, we wanted to assess costs associated with the various strategies, in order to obtain an adequate and cost-effective strategy to timely detect women with GDM.

Specific research questions were
1. What is the current policy on the (diagnostic) work-up of GDM in the Netherlands?
2. Which test has the best accuracy to screen for GDM?
3. Is it possible to estimate the risk of GDM for individual patients?
4. Can we use risk indicators to improve (cost-)effectiveness of screening?
5. What is the most cost-effective strategy to prevent complications from GDM?

Outline of the thesis
This thesis comprises three parts: In the first part we assess the accuracy of three different screening tests for GDM. In the second part we focus on the use of individual patient characteristics and on risk factors to predict GDM. In the third part clinical practice in the Netherlands and costs and effects of various screening strategies are evaluated.

In chapter 2 we report the results of a comparison of the performance of two screening tests for GDM. Accuracy measures of the random glucose test and the 50-g glucose challenge test were compared with data from a prospective cohort of 1301 women. All women underwent a 50-g glucose challenge test as well as random glucose measurement between 24 and 28 weeks of gestation with the 75-g OGTT as gold standard. We assessed the performance of the tests by their discriminative capacities (Q2).

In chapter 3 we describe the results of a systematic review of the literature to assess the accuracy of the random glucose test as a screening test for GDM (Q2).

In chapter 4 we describe the results of a systematic review of the literature and meta-analysis to obtain summary estimates of accuracy measures of the 50-g glucose challenge test for GDM using a bivariate approach (Q2).
In chapter 5 we report on the accuracy of fasting glucose measurement for the detection of GDM. With a systematic review of the literature and bivariate meta-analysis we estimated summary estimates of accuracy measures and assessed the ability of the test as screening test for GDM (Q2).

In chapter 6 we present results of a validation study in which we evaluated a clinical scoring system for GDM. To validate the scoring system we used data from a prospective cohort study comprising 1266 women. Performance of the scoring system was evaluated in terms of calibration and discriminative ability. We compared the efficiency of a screening strategy derived from the scoring system with conventional screening (Q3 and Q4).

In chapter 7 we describe the construction and internal validation of a clinical prediction model based on medical history and patient characteristics to estimate the risk of GDM in individual women. We constructed the prediction model with multiple logistic regression analysis with data from a prospective cohort study and evaluated its performance with internal validation (Q3 and Q4).

In chapter 8 we give an overview of the literature on the increased risk of perinatal complications associated with GDM, and on the effect of treatment of GDM. In this chapter we also report the results of a survey among gynaecologists and midwives to assess current policy and clinical practice regarding detection and treatment of GDM in the Netherlands (Q1).

In chapter 9 costs and effects of various strategies to detect GDM are evaluated in a model based economic evaluation. A detailed cost-effective analysis was performed calculating incremental costs per prevented perinatal complication (Q5).

In chapter 10 we summarise and discuss the results of this thesis and evaluate their implications for clinical practice and for future research.

In chapter 11 we summarise and discuss the results of this thesis and evaluate their implications for clinical practice and for future research in Dutch.
References


