Screening for gestational diabetes mellitus
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Chapter 8

Gestational diabetes mellitus: treatment reduces the risk of complications

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Abstract

Recent studies show that higher blood glucose values after a 75-g oral glucose tolerance test in pregnancy are associated with higher rates of perinatal and maternal complications. Treatment of gestational diabetes mellitus (GDM) (or hyperglycemia in pregnancy) reduces the risk of complications. GDM is an asymptomatic condition. Screening is the only strategy to diagnose GDM in time, in order to provide treatment. Until recently, there was no uniformity concerning diagnostic strategy and treatment of GDM in the Netherlands, possibly due to lack of evidence on the risk of complications and the effectiveness of treatment. Results of several recent studies show that early detection and treatment of GDM are effective. By means of a more active screening and treatment policy it should be possible to reduce the perinatal and maternal complications as a result of GDM.
Introduction

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy and includes carbohydrate intolerance first developing in pregnancy, as well as pre-existing diabetes mellitus that has not been recognized before. Throughout the last years results of three large trials have been published that provide more clarity on the risk of complications and the effect of treatment of GDM. In this article we discuss the results of these trials. Furthermore we present the results of a national survey that we performed to determine current practices on screening and diagnostics of GDM in the Netherlands. We will discuss the results of survey in view of the recommendations from the renewed guideline “Diabetes and Pregnancy” issued by the Dutch Society of Obstetrics and Gynaecology (NVOG).

Criteria for GDM

Worldwide, and over the years there have been many different criteria for GDM all reflecting carbohydrate intolerance, albeit at different levels. The many different criteria preclude a sound comparison of research findings and extrapolation of study results. The lack of uniform criteria for GDM is amongst others founded by the fact that the original criteria for GDM established by O’Sullivan and Mahan in 1964, 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, focus has been directed more on perinatal and short-term maternal outcomes.

Pathophysiology of GDM

Placental hormones produced in pregnancy hamper normal carbohydrate metabolism. Corticotropin-releasing hormone, progesterone and human placental lactogen interfere with insulin receptors situated on various cells of the human body, making these cells less sensitive for insulin, resulting in relative insulin deficiency. To maintain maternal blood glucose levels within normal range, production of insulin by the beta-cells of the pancreas is increased. If this compensating mechanism is insufficient, GDM may occur.

Prevalence of GDM

The prevalence of GDM has increased over the last years and is estimated to be 2 to 9% depending on the population studied and the criteria for GDM that are applied. The prevalence of GDM in the Netherlands is estimated to be 2 to 4%. The prevalence of GDM is rising, mainly due to the rising epidemic of overweight and obesity and changes in lifestyle in developed countries.

Complications of GDM and treatment

Pre-existing diabetes mellitus type 1 and 2 are associated with maternal complications and adverse perinatal outcome. Various studies described that GDM is associated
with pregnancy complications too. In addition, women with GDM are at increased risk for diabetes mellitus type 2 in later life. Until recently however, exact risks associated with hyperglycemia in pregnancy less severe than overt diabetes mellitus were undecided. Moreover, the degree of carbohydrate intolerance at which the risk of specific complications increases was unspecified. In addition, before 2005 there was no evidence that treatment of GDM would reduce the risks of pregnancy complications. This has led to international but also national variety in the clinical practice of screening, diagnostics and treatment of GDM. We will discuss the results of three trials that have provided more clarity on the risk of complications and the effect of treatment of treatment of GDM.

**Risk of complications**

The ‘Hyperglycemia and adverse pregnancy outcome’ (HAPO)-study is an international cohort study that investigated the association between maternal blood glucose levels in pregnancy and the risk of adverse perinatal and maternal outcome. Aim of the study was to evaluate the association between the fasting, 1 hour and 2 hour plasma glucose value of the 75-g oral glucose tolerance test (OGTT) and various perinatal and maternal outcomes of pregnancy. Over 25,505 women with a singleton pregnancy underwent a 75-g oral glucose tolerance test (OGTT) between 24 and 32 weeks of gestation. Women with pre-existing diabetes mellitus were excluded. Primary outcomes of the study were birth weight above the 90th percentile for gestational age, primary caesarean delivery, clinical neonatal hypoglycemia, and cord-blood serum C-peptide level above the 90th percentile (fetal hyperinsulinemia). Secondary outcomes were premature delivery (< 37 weeks), shoulder dystocia or birth injury, need for intensive neonatal care, hyperbilirubinemia, and pre-eclampsia. Outcomes were adjusted for pre-specified confounders. Results from the HAPO study show positive associations between increasing levels of fasting, 1-hour, and 2-hour plasma glucose of the 75-g OGTT and the risk of virtually all perinatal and maternal primary and secondary outcomes after adjustment for confounders. Higher maternal blood glucose levels are significantly associated with adverse outcomes, even with glucose levels that are within the range that is considered as non-diabetic.

**Effect of treatment of GDM**

Two large randomised controlled trials evaluated the effect of treatment of GDM. The aim of the ‘Australian carbohydrate intolerance study in pregnant women’ (ACHOIS) was to evaluate if treatment of GDM reduced the risk of perinatal complications. Pregnant women with risk factors for GDM or women with an abnormal result of the 50-g glucose challenge test underwent a 75-g OGTT between 24 and 34 weeks of gestation. GDM was diagnosed if the venous plasma glucose level was < 7.8 mmol/L after overnight fasting and 7.8-11.0 mmol/L two hours after the OGTT. Women diagnosed with GDM were randomised (intervention group and control group). Women who were assigned to
the intervention group were frequently seen by a physician, performed self-monitoring of
blood glucose values four times a day, received individualised dietary advice and insulin
therapy if necessary. Women in the routine care group received regular obstetric care
(local protocol). Women in the routine care group and their physicians were unaware
of the diagnosis of glucose intolerance of pregnancy. A proportion of the women with
normal OGTT results were assigned to the routine care group to maintain blinding.
Thousand women were included. The rate of serious perinatal outcomes (composite
outcome: death, shoulder dystocia, bone fracture, and nerve palsy) among infants
was significantly lower in the intervention group than the routine care group (1 vs. 4%,
P=0.01). The number needed to treat to prevent one serious outcome was 34 (95%
confidence interval 20 - 103). Induction of labour was significantly more common in
the intervention group and more infants born to women in the intervention group were
admitted to the neonatal nursery. There was no difference in the rate of caeserean
sections (emergency or planned). Mean birth weight of infants born to women in the
intervention group was lower, and they were born at an earlier gestational age. Fewer
women in the intervention group received diagnosis of pre-eclampsia. Scores on mental
health status were in favor of women in the intervention group. The ACHOIS shows that
treatment of GDM (by means of dietary advice, blood glucose monitoring and insulin
therapy if required) reduces the rate of perinatal complications. This also leads to more
induction of labour in women with GDM and admittance of more infants to the neonatal
nursery, but not to higher rates of caeserean sections.

The second study on this subject aimed to evaluate if treatment of mild GDM would lead
to fewer perinatal and obstetric complications. Women with a singleton pregnancy
and an abnormal result on the 50-g glucose challenge test (glucose value of 7.5-11.1
mmol/l) underwent a 100-g OGTT between 24 and 31 weeks of gestation. “Mild
GDM” was diagnosed based on the results of the 100-g OGTT. Women with mild GDM
were randomised between an intervention group and a control group. Treatment in the
intervention group comprised regular self-monitoring of glucose values, dietary advice
and treatment with insulin if required. Women in the control group received standard
obstetric care (local protocol). A proportion of the women with normal OGTT results
were assigned to the routine care group to maintain blinding. Primary outcome was a
composite outcome of stillbirth or perinatal death and neonatal complications, including
neonatal hyperbilirubinemia, hypoglycemia, hyperinsulinemia, and birth trauma. There
were 958 women included in the study. There was no significant difference between
groups in incidence of the composite outcome (stillbirth or perinatal death and neonatal
complications, including neonatal hyperbilirubinemia, hypoglycemia, hyperinsulinemia,
and birth trauma). However, treatment of mild GDM was associated with reduced rates
of several pre-specified secondary outcomes, e.g. shoulder dystocia, caesarean delivery,
frequency of large-for-gestational-age infants and birth weight > 4000 g. Furthermore
treatment of GDM was associated with reduced rates of pre-eclampsia and gestational hypertension. Although women included in this trial had a milder degree of glucose intolerance than women included in the ACHOIS\textsuperscript{13}, results of this study show that treatment of mild GDM does not lead to a reduction of perinatal mortality, neonatal hypoglycemia, hyperbilirubinemia, hyperinsulinemia, and birth trauma. However, treatment of mild GDM does lead to reduced rates of shoulder dystocia, caesarean delivery, frequency of large-for-gestational-age infants, birth weight > 4000 g and gestational hypertension and pre-eclampsia.

**Summary of literature**

The studies described above show that higher glucose values in pregnancy are associated with a number of important perinatal and maternal outcomes. Treatment of (mild) GDM reduces the rate of serious perinatal complications (composite outcome: death, shoulder dystocia, bone fracture, and nerve palsy), pre-eclampsia and delivery of large-for-gestational-age infants and birth weight > 4000 g.

**Screening policy in the Netherlands**

In 2006 the Dutch multidisciplinary guideline “Diabetes and Pregnancy” was published. The guideline recommended to perform either a random glucose measurement or a fasting glucose measurement at the first pregnancy check up in order to detect hyperglycemia that already exists early in pregnancy (unknown pre-existing diabetes mellitus). Screening in the second trimester was not recommended because at the time there was insufficient evidence for screening in the second trimester to be effective.\textsuperscript{17} In view of the results of the above-mentioned trials the latter recommendation was reconsidered. In the guideline of the Dutch Society of Obstetrics and Gynaecologists (NVOG) issued in 2010 screening in the second trimester is recommended.\textsuperscript{18} It is recommended to perform screening in the first and second trimester in women with risk factors for GDM (history of GDM, BMI >30kg/m\textsuperscript{2}, previous macrosomic baby, first degree relative with DM, certain ethnicities, history of (unexplained) perinatal death, polycystic ovary syndrome). The screening test recommended for the first trimester is a random or fasting glucose measurement. The test recommended in the second trimester is the 75-g OGTT.\textsuperscript{18} If women had gestational diabetes in a previous pregnancy it is recommended to perform a 75-g OGTT in the 16\textsuperscript{th} week of pregnancy.

**Survey**

Because we suspected a large variability in the screening, diagnosis, and management of women with GDM, we performed a national survey to determine current policy on GDM in the Netherlands. We performed this survey before 2010, so in the period before the new Dutch NVOG guideline was issued. The survey was web-based (www.questionpro.com) and comprised questions on screening and treatment of GDM. For all Dutch hospitals with an obstetric department (n=93) one gynaecologist received an invitation by email to participate in the survey. Furthermore we randomly invited 129 midwives.
Table 1. Policy on screening in the Netherlands (midwives and gynaecologists) before 2010.

<table>
<thead>
<tr>
<th></th>
<th>Gynaecologists n (%)</th>
<th>Midwives n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening 1st trimester</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>46 (67.6)</td>
<td>75 (81.5)</td>
<td>121 (75.6)</td>
</tr>
<tr>
<td>No</td>
<td>22 (32.4)</td>
<td>17 (18.5)</td>
<td>39 (24.4)</td>
</tr>
<tr>
<td>Screening 2nd trimester</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>36 (52.9)</td>
<td>60 (65.2)</td>
<td>96 (60.0)</td>
</tr>
<tr>
<td>No</td>
<td>32 (47.1)</td>
<td>32 (34.8)</td>
<td>64 (40.0)</td>
</tr>
<tr>
<td>Screening 2nd trimester</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All women</td>
<td>15 (41.7)</td>
<td>21 (35.0)</td>
<td>36 (37.5)</td>
</tr>
<tr>
<td>Women with risk factors</td>
<td>21 (58.3)</td>
<td>39 (65.0)</td>
<td>60 (62.5)</td>
</tr>
<tr>
<td>Methods of screening in 2nd trimester</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting glucose measurement</td>
<td>17 (47.2)</td>
<td>28 (46.7)</td>
<td>45 (46.9)</td>
</tr>
<tr>
<td>Random glucose measurement</td>
<td>29 (80.6)</td>
<td>45 (75.0)</td>
<td>74 (77.1)</td>
</tr>
<tr>
<td>Challenge test with 50 g glucose</td>
<td>9 (25.0)</td>
<td>20 (33.3)</td>
<td>29 (30.2)</td>
</tr>
<tr>
<td>Universal OGTT</td>
<td>8 (22.2)</td>
<td>0 (0)</td>
<td>8 (8.3)</td>
</tr>
<tr>
<td>Breakfast or lunch test</td>
<td>15 (41.7)</td>
<td>19 (31.7)</td>
<td>34 (35.4)</td>
</tr>
<tr>
<td>Day curve</td>
<td>17 (47.2)</td>
<td>26 (43.3)</td>
<td>43 (44.8)</td>
</tr>
<tr>
<td>Risk factors</td>
<td>32 (88.9)</td>
<td>51 (85.0)</td>
<td>83 (86.5)</td>
</tr>
<tr>
<td>Most frequently used method in 2nd trimester</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting glucose measurement</td>
<td>1 (2.8)</td>
<td>3 (5.0)</td>
<td>4 (4.2)</td>
</tr>
<tr>
<td>Random glucose measurement</td>
<td>18 (50.0)</td>
<td>26 (43.3)</td>
<td>44 (45.8)</td>
</tr>
<tr>
<td>Challenge test with 50 g glucose</td>
<td>2 (5.6)</td>
<td>1 (1.7)</td>
<td>3 (3.1)</td>
</tr>
<tr>
<td>Universal OGTT</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Breakfast or lunch test</td>
<td>6 (16.7)</td>
<td>8 (13.3)</td>
<td>14 (14.6)</td>
</tr>
<tr>
<td>Day curve</td>
<td>3 (8.3)</td>
<td>9 (15.0)</td>
<td>12 (12.5)</td>
</tr>
<tr>
<td>Risk factors</td>
<td>6 (16.7)</td>
<td>13 (21.7)</td>
<td>19 (19.8)</td>
</tr>
</tbody>
</table>

from different practices to participate in the survey. Response rates were 73% (68/93) and 71% (92/129) for gynaecologists and midwives respectively. Results of the survey are shown in Tables 1 and 2. The majority of the gynaecologists and midwives performed screening in the first trimester (68% (46/68) and 82% (75/92) respectively). Screening in the second trimester was performed by 53% (36/68) of the gynaecologists and 65% (36/68) of the midwives, mostly screening was performed in women with risk factors for GDM. There was a large variety in screening strategies. Random glucose measurement was the most frequently used test for screening in the second trimester. Most frequently used test to diagnose GDM was a “lunch” test (measuring glucose values one and two hours after lunch) (43% (29/68)), followed by the 75-g OGTT (31% (21/68)) and a series of multiple random measurements on one day (19% (13/68)).
Discussion

GDM is associated with higher levels of maternal and neonatal morbidity and treatment of GDM reduces the rate of complications.\textsuperscript{14,16} Timely detection of GDM is important, but is also difficult since GDM often is asymptomatic. A way to identify women with GDM is screening. The results of a survey amongst Dutch gynaecologists and midwives show that before introduction of the guideline “Diabetes and Pregnancy” issued by the Dutch Society of Obstetrics and Gynaecology (NVOG) in 2010 there was large variety in the policy on screening and diagnosis of GDM. Most frequently applied screening test in the second trimester of pregnancy was random glucose testing. The random glucose test has moderate reproducibility and accuracy\textsuperscript{19} and therefore should not be used as a screening test in the second trimester of pregnancy. Nearly 2/3 of gynaecologists performed a lunch test or a series of multiple measurements on one day to diagnose GDM. Reproducibility and accuracy of these tests for GDM however are unknown. The HAPO study as well as the two intervention studies that were discussed in this article used the OGTT to diagnose GDM.\textsuperscript{14-16} Although critics consider the OGTT to be not physiologic and therefore unreliable, reproducibility is acceptable (75-79\%).\textsuperscript{20,21}

The use of inaccurate and inconsistent test strategies may lead to under-diagnosis and suboptimal treatment of GDM leading to potentially avoidable complications. The current Dutch guideline on diabetes and pregnancy recommends screening of at least all women with risk factors for GDM in the 1st trimester of pregnancy, by means of fasting or random glucose measurement. For women with risk factors 2nd trimester screening with a 75-g OGTT is recommended. For women with GDM in a previous pregnancy a 75-g OGTT at 16 weeks of gestation is recommended, followed by an OGTT between 24 and 28 weeks of pregnancy if the first OGTT is normal.\textsuperscript{18} It is unknown which part of the midwives and gynaecologists follow these recommendations from the renewed guideline.

\begin{table}
\centering
\caption{Diagnostic testing before 2010.}
\begin{tabular}{|l|l|}
\hline
Diagnostic test & Gynaecologists n (\%) \\
\hline
If screening test is abnormal & 43 (63.2) \\
If symptoms present & 37 (54.4) \\
If risk factors present & 34 (50.0) \\
Universal & 8 (11.7) \\
Most frequently used diagnostic test & \\
OGTT 75 gram & 21 (30.9) \\
OGTT 100 gram & 4 (5.9) \\
Breakfast / lunch test & 29 (42.6) \\
Day curve & 13 (19.1) \\
\hline
\end{tabular}
\end{table}
Conclusion

GDM is associated with higher levels of maternal and neonatal morbidity and treatment of GDM reduces the rate of complications. 14-16 Further studies on costs and effects of various screening strategies for GDM need to clarify the optimal strategy to identify women with GDM in order to reduce the number of perinatal and maternal adverse outcomes. Until more evidence on costs and effects of various screening strategies is generated, the pathway and treatment strategy as recommended by the guideline “Diabetes and Pregnancy” of the Dutch Society of Obstetrics and Gynaecologists (NVOG) based on the best available evidence should be followed.
Literature


