Screening for gestational diabetes mellitus
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Citation for published version (APA):

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Costs and effects of screening for gestational diabetes mellitus with a prediction model based on patient characteristics

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Submitted
Abstract

OBJECTIVE To evaluate which screening strategy for gestational diabetes (GDM) is most cost-effective in reducing the risk of serious complications related to GDM.

METHODS We performed a model-based analysis to evaluate costs and effects of 8 screening strategies for GDM including three blood glucose tests and a prediction model for GDM based on patient characteristics. We estimated costs of screening and treatment to prevent one serious complication of pregnancy or delivery (neonatal death, shoulder dystocia, and birth trauma). Since no uniform screening strategy exists, costs and effects of the screening strategies were compared to no screening. Data on costs, accuracy measures and probabilities were extracted from the literature.

RESULTS Screening all women with an oral glucose tolerance test (OGTT) was the most effective strategy as it reduced the rate of serious perinatal complications from 132 to 42 per 100 000 women (compared to no screening), at incremental cost of €43 171 per prevented serious perinatal complication. A strategy in which a prediction model was combined with fasting glucose measurement in high-risk women was the most inexpensive screening strategy (incremental costs €27 661 per prevented serious perinatal complication compared to no screening), however with this strategy there was a smaller reduction in serious perinatal complications (from 132 to 81). The strategy starting with fasting glucose measurement reduced complications from 132 to 64 for €32 464 per prevented perinatal complication.

CONCLUSION Incorporation of patient characteristics in a screening strategy for GDM does reduce cost, but at the expense of a relative high rate of GDM related perinatal complications. Bases on our analysis, we recommend either a FGT or an OGTT for all pregnant women. More complications can be prevented, albeit at higher costs.
Introduction

Gestational diabetes mellitus (GDM) is a common complication of pregnancy and its prevalence is increasing. For many years the value of screening for GDM has been debated, as there was uncertainty about the risk of complications associated with GDM as well as lack of evidence on the beneficial effect of treatment. Recently it has been demonstrated that hyperglycemia in pregnancy is associated with important perinatal and maternal outcomes (HAPO-trial). Further studies showed that treatment of GDM with a diet, lifestyle advices and insulin, reduced the risk of complications significantly. Since GDM often is an asymptomatic condition, screening is compulsory in order to detect women with GDM before treatment can be started. The HAPO trial as well as the trials on the beneficial effect of treatment of GDM represent important advances in the field. Translating the results of these studies into clinical practice though, is difficult. The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) has recommended universal screening with a 75-g oral glucose tolerance test (OGTT), and has proposed new (more liberal) criteria for diagnosis of GDM. Their recommendations are based on the results of the HAPO trial. Opponents argue that adopting these new criteria and screening strategy will have an enormous financial impact on our health care system because of the substantial increase in women who will be diagnosed with GDM. The debate on the optimal screening strategy for GDM seems therefore not to be finished.

Inevitably, screening for a disease is initially associated with additional costs. However, a screening strategy that reduces risk of complications also reduces costs associated with these complications. A number of authors and institutions have evaluated costs and effects of screening strategies for GDM. The majority of these studies evaluated cost-effectiveness of blood glucose testing (e.g. random or fasting glucose measurement), or screening based on risk factors, or a combination of these. Risk factors are often evaluated dichotomous and at population level, thereby neglecting interaction between risk factors and the individual risk differences across women within a population. Screening based on individual risk estimation is potentially more accurate and effective. Round et al. assessed the cost-effectiveness of screening for GDM using a woman’s individual risk for GDM. The authors evaluated eight strategies over a range of hypothetical individual risk of GDM from 0 to 15%. The results of this study showed that the preferred screening strategy is dependent on a woman’s risk of GDM, effect of treatment and acceptability of the test strategy. A limitation of this analysis was that the pre-test risk was hypothetical and not based on women’s actual personal risk profile. Potentially, use of such personalised risk based on known risk factors for GDM could increase the cost-effectiveness of screening. For example a strategy in which a blood test...
is only applied in high-risk women might be more cost-effective than either intense or superficial screening in the general population of pregnant women.

Such an individual risk of GDM can be estimated with a prediction model, as previously published by our group. The aim of the present study was to evaluate cost-effectiveness of various screening strategies based on blood glucose tests, with or without a prediction model based on patient characteristics. We wanted to evaluate if risk indicator based screening with a prediction model is cost-effective in reducing the risk of serious perinatal complications associated with GDM.

Materials and Methods

We constructed a decision tree model to compare expected costs and effects of 8 screening strategies for GDM. A decision tree model is a schematic representation of decisions, probabilities of possible outcomes, and clinical and economic consequences. By considering probabilities and consequences of each decision, costs and effects of various screening strategies can be estimated and compared, resulting in a cost-effectiveness analysis. We wanted to calculate costs per prevented complication, where the cost per prevented complication should not exceed an acceptable level, i.e. the willingness-to-pay threshold. Although this level is not exactly specified, and depends on the nature, duration and reversibility of these complications, it reflects the economic value society attaches to achieving one additional unit for health gain (i.e. preventing complications in one patient).

We analysed a hypothetical cohort of 100 000 pregnant women at any risk level of GDM. The screening strategies consisted of one of the available blood glucose tests (random glucose test (RGT), glucose challenge test (GCT), fasting glucose test (FGT)), risk assessment using a prediction model, or a combination of these (Table 1). Women are considered at risk if the screening test exceeds the pre-defined threshold value, or if the predicted probability of GDM from the prediction model exceeds 2% (Table 1). In women classified as at risk for GDM an OGTT is performed. Women diagnosed with GDM (in case of a positive OGTT) receive dietary advice, intensive monitoring and insulin treatment if necessary.

The hypothetical cohort of 100 000 women was simulated through the model encompassing eight different screening strategies. Costs and effects of these strategies were compared to a reference strategy of no testing and no treatment. Outcome measure of effectiveness in our model was the incidence of a composite outcome of serious perinatal complications comprising neonatal death, shoulder dystocia, and birth
trauma or a combination of these. Costs associated with each screening strategy were associated with the test (RGT, GCT, FGT and/or OGTT), as well as with health care use associated with the clinical outcome, i.e. complications during delivery and in the admission period right after delivery (downstream costs). The time horizon ran from the 24th week of pregnancy until mother and child were discharged from the hospital after birth. Treatment costs were included only for women with a positive diagnosis of GDM in that strategy. In the model, all women were expected to undergo screening (acceptance rate 100%), except in the strategy in which no testing was performed. In case of an abnormal screening test result a 75 g-OGTT was performed (acceptance rate 100%). In the strategy in which no testing was performed, no OGTT was performed. Analyses were performed from the perspective of the healthcare system. Indirect medical costs (health care utilisation by mother or surviving infants not related to GDM) and non-medical costs (as for example travel expenses and time off from work) were not accounted for. All costs are expressed in 2011 Euro’s. The decision analytic model was constructed in Microsoft Excel®.

Model parameters
Model parameters (probabilities, accuracy measures of screening tests, treatment effects and cost estimates) were derived from data in the published literature. All model parameters are summarised in Table 2. The reference standard for all tests was the 75-g OGTT, which was assumed to be 100% sensitive and specific for diagnosis of GDM. Little evidence exists on costs associated with using a prediction model in clinical practice, and these costs will likely vary with how such a model is being implemented (e.g. paper based, computer or internet application, integrated in medical device). For the base-case analysis, we assumed the costs of screening with a prediction model

<table>
<thead>
<tr>
<th>Strategy no.</th>
<th>Screening test 1</th>
<th>Screening test 2</th>
<th>Diagnostic test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RGT</td>
<td>-</td>
<td>75-g OGTT</td>
</tr>
<tr>
<td>2</td>
<td>FGT</td>
<td>-</td>
<td>75-g OGTT</td>
</tr>
<tr>
<td>3</td>
<td>GCT</td>
<td>-</td>
<td>75-g OGTT</td>
</tr>
<tr>
<td>4</td>
<td>Prediction model</td>
<td>-</td>
<td>75-g OGTT</td>
</tr>
<tr>
<td>5</td>
<td>Prediction model</td>
<td>RGT in high-risk women</td>
<td>75-g OGTT</td>
</tr>
<tr>
<td>6</td>
<td>Prediction model</td>
<td>FGT in high-risk women</td>
<td>75-g OGTT</td>
</tr>
<tr>
<td>7</td>
<td>Prediction model</td>
<td>GCT in high-risk women</td>
<td>75-g OGTT</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
<td>75-g OGTT</td>
</tr>
</tbody>
</table>

RGT: Random glucose testing; measurement of blood glucose value at a random point in time without specific preparation; FGT: Fasting glucose test; measurement of a blood glucose value after an overnight fast; GCT: 50 g glucose challenge test; measurement a of blood glucose value one hour after ingestion of 50 g glucose; OGTT: Oral glucose tolerance test; measurement of blood glucose values after an overnight fast and one and two hours after ingestion of 75 g glucose (WHO criteria). This test is performed if the screening test exceeds pre-defined threshold values. High-risk women: Women with risk of GDM > 2% based on a prediction model for GDM.
to be €1.00 per person. Treatment costs were costs generated by visits to a dietician and diabetes nurse and visits to an endocrinologist, and by insulin therapy if necessary. Downstream costs included in the analysis were costs directly related to the clinical composite outcome (perinatal complications) and were generated by induction of labour or caesarean section when indicated, postpartum admission of the neonate to the neonatal nursery, and phototherapy if indicated.
Outcome
The cost-effectiveness of each screening strategy was evaluated by comparing cost-effectiveness ratios, calculated as the ratio of expected costs per strategy and the expected proportion of deliveries with serious perinatal complications. Each screening strategy was compared to a reference strategy in which no tests for GDM were performed, resulting in incremental cost-effectiveness ratios (ICER). The ICER reflects the costs needed to avert one delivery with serious perinatal outcome for a strategy relative to the reference strategy.

Sensitivity analysis
The base case analysis was based on the best available estimate for each model parameter. To assess robustness of our model to uncertainty around these estimates, we performed univariate sensitivity analyses on several relevant model variables. In the sensitivity analyses we varied the values of these variables between their upper and lower limits. We evaluated the following variables: prevalence of GDM, costs of screening and costs of treatment. We varied the prevalence of serious perinatal complications by excluding the outcome of shoulder dystocia from the composite outcome. The composite outcome is then a combination of perinatal death and trauma. In a multivariable sensitivity analysis several probabilities were varied simultaneously, allowing us to examine the combined influence of variation in model assumptions on the results.

Results
Costs and effects from the base-case decision analytic model are summarised in Table 3. In absence of screening, 132 serious perinatal complications were expected in our hypothetical cohort of 100 000 women, generating downstream costs of €14 986 593, or €150 per woman. A universal OGTT was most effective in reducing the number of serious perinatal complications, with an expected number of complications 42. The least effective screening strategy was screening with the prediction model followed by random glucose testing in women identified as high risk by the prediction model, with an expected number of complications 69. Universal screening with the OGTT also incurred the highest incremental costs of screening and subsequent treatment (€3 885 428 in 100 000 women to prevent 90 serious complications, or €39 per woman) and lowest for the combined strategy of the prediction model followed by fasting glucose measurement in women identified as high risk by the prediction model (€1 400 311 to prevent 51 complications in 100 000 women) (Table 3).

The most cost-effective screening strategy to prevent one case of serious perinatal complication will depend on the maximum amount that one is willing to pay (WTP). At
a maximum WTP of €30 000 this will be the combined strategy of a prediction model followed by fasting glucose measurement in high-risk women and an OGTT if indicated (€27 661 per prevented complication). If it is acceptable to pay at least €43 171 to prevent one perinatal complication, universal screening of all women with OGTT would be most effective as well as cost-effective (Table 3).

### Table 3. Summary of results for screening strategies (base case) (per 100 000 women)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Complications (n)</th>
<th>Δ Complications (n)</th>
<th>Costs (€)</th>
<th>Δ Costs (€)</th>
<th>ICER (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No screening</td>
<td>132</td>
<td>14 986 593</td>
<td>17 317 226</td>
<td>2 330 632</td>
<td>36 994</td>
</tr>
<tr>
<td>RGT</td>
<td>69</td>
<td>63</td>
<td>17 177 913</td>
<td>2 191 320</td>
<td>32 464</td>
</tr>
<tr>
<td>FGT</td>
<td>64</td>
<td>68</td>
<td>17 553 115</td>
<td>2 566 521</td>
<td>38 536</td>
</tr>
<tr>
<td>GCT</td>
<td>65</td>
<td>67</td>
<td>17 220 580</td>
<td>2 233 987</td>
<td>33 096</td>
</tr>
<tr>
<td>Prediction model</td>
<td>64</td>
<td>68</td>
<td>16 420 102</td>
<td>1 433 509</td>
<td>30 338</td>
</tr>
<tr>
<td>Model + RGT</td>
<td>85</td>
<td>47</td>
<td>16 386 904</td>
<td>1 400 311</td>
<td>27 660</td>
</tr>
<tr>
<td>Model + FGT</td>
<td>81</td>
<td>51</td>
<td>16 546 843</td>
<td>1 560 250</td>
<td>31 236</td>
</tr>
<tr>
<td>Model + GCT</td>
<td>82</td>
<td>50</td>
<td>18 872 021</td>
<td>3 885 428</td>
<td>43 171</td>
</tr>
<tr>
<td>Universal OGTT</td>
<td>42</td>
<td>90</td>
<td>18 872 021</td>
<td>3 885 428</td>
<td>43 171</td>
</tr>
</tbody>
</table>

RGT: Random glucose testing; blood glucose at a random point in time without specific preparation; FGT: Fasting glucose test; blood glucose after an overnight fast; GCT: 50-g glucose challenge test; blood glucose one hour after ingestion of 50 g glucose; OGTT: Oral glucose tolerance test; blood glucose after an overnight fast and one and two hours after ingestion of 75 g glucose (WHO criteria). Prediction model: Women with risk of GDM > 2% based on a prediction model for GDM. Δ costs: difference in costs (relative to the reference strategy of no screening); Δ complications: difference in number of deliveries with complications (relative to reference strategy of no screening); ICER: incremental cost-effectiveness ratio (Δ costs / Δ complications)

Results of the sensitivity analyses are displayed in Table 4. For all scenarios that we tested ICERs changed, but for the vast majority of the scenarios the order of the strategies concerning costs to prevent one serious perinatal outcome did not change. Only if costs of the prediction model were increased to higher than €3.00, screening with the prediction model combined with fasting glucose measurement was not the most favourable strategy anymore. Increasing the prevalence of GDM to 17% (the prevalence of GDM if the newly proposed IADPSG criteria would be introduced), ICERs of all strategies approached the favourable strategy. But the strategy in which a fasting glucose test was performed in women defined as high risk with the prediction model remained the favourable strategy in term of lowest costs per prevented complication. If shoulder dystocia was excluded from the composite outcome costs to prevent one serious perinatal complication would rise to €65 430 for the most favourable strategy.
Discussion

In this study cost-effectiveness of eight screening strategies for GDM was evaluated in a hypothetical cohort of 100,000 unselected pregnant women. A prediction model for GDM combined with fasting glucose measurement in women identified as being high risk by the prediction model had the lowest costs per prevented complication, with incremental costs to prevent one serious perinatal complication of €27,660. The two strategies with lowest costs per prevented complication were both based on the prediction model, but only at the expense of a relatively high rate of GDM related perinatal complications. An OGTT for all pregnant women reduced GDM related complications considerably for an acceptable cost-effectiveness ratio of €43,171 per prevented complication.

A strength of this study is that the outcome measure of effectiveness is clinically relevant. Previous studies assessed cost-effectiveness of screening for GDM, but the vast majority of these studies evaluated costs to identify one case of GDM, instead of more clinically relevant complications associated with GDM. As there has been discussion on the relevance of shoulder dystocia as serious perinatal complication, we assessed cost-effectiveness of all strategies with and without including this complication in the composite outcome. Without including shoulder dystocia in the composite outcome costs of the least expensive strategy to prevent one serious perinatal complication (i.e. death or trauma) would rise to €65,430. Costs of universal screening with OGTT would yield costs of €107,929 per prevented complication if the prevalence of GDM would be 3%. Health care resources are finite and have competing uses. Demonstrating a clinical benefit from a particular use of resources does not mean that an even greater benefit could not be derived if those resources were deployed elsewhere. It depends on

<table>
<thead>
<tr>
<th>Table 4. Result of the sensitivity analysis (€)</th>
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<tbody>
<tr>
<td>RGT</td>
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<tr>
<td>-----</td>
</tr>
<tr>
<td>Base case</td>
</tr>
<tr>
<td>Prevalence GDM 17%</td>
</tr>
<tr>
<td>Costs prediction model €5</td>
</tr>
<tr>
<td>SD not in outcome</td>
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<tr>
<td>Costs prediction model €5 and prevalence GDM 17%</td>
</tr>
<tr>
<td>SD not in outcome and prevalence GDM 17%</td>
</tr>
</tbody>
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RGT: Random glucose testing; blood glucose at a random point in time without specific preparation; FGT: Fasting glucose test; blood glucose after an overnight fast; GCT: 50-g glucose challenge test; blood glucose one hour after ingestion of 50 g glucose; OGTT: Oral glucose tolerance test; blood glucose after overnight fast and 1- and 2- h after ingestion of 75 g glucose (WHO criteria). Model: Prediction model for GDM; SD shoulder dystocia.
the willingness to pay, if screening for GDM is cost-effective if shoulder dystocia is not considered to be part of the composite outcome.

To develop the decision analytic model, we used, to our knowledge, data from the best available evidence. Costs of screening and treatment for GDM were estimated from systematic review that evaluated the effect of treatment in women with GDM.\textsuperscript{4,5} One of the trials also evaluated the policy of additional testing and treatment in women who were classified not to have GDM, which is a reliable measure for the costs in women who were classified as false negative in the present study.\textsuperscript{15} Any decision model is subject to inaccuracies in estimates of its input parameters derived from the literature. We therefore performed sensitivity analyses across all input parameters to determine which estimates and assumptions substantially affect results of our decision model. Varying costs of screening tests did not change the direction of results of our analyses. If the risk of complications in women who were not treated, i.e. false negative screening test results, was increased, the ICER of all screening strategies approached the ICER of the strategy in which fasting glucose measurement was performed in women classified as high risk, but the latter still remained the most inexpensive strategy.

One of the randomised controlled trials from which we used data for our decision analysis evaluated treatment of women with “mild” GDM.\textsuperscript{5} Costs and effects of treatment may therefore be underestimated, thereby generating too optimistic ICERs. However, if the number needed to treat declines due to treatment of more severe cases of GDM, this will in turn decrease the costs per prevented complication. A limitation of this study is that we did not take into account the uptake of screening. If uptake of screening would not be 100% as we assumed, costs of screening and treatment decreases, probably at the expense of more serious perinatal complications.

To estimate costs of treatment we accounted for costs of different delivery modalities (caesarean section, induction) and admission of the neonate to the neonatal care unit, reflecting clinical practice. For the outcome of effectiveness we only used serious perinatal complications, which was considered to be an important clinical outcome. The final costs- effectiveness ratio therefore did not account for the impact of other potential relevant outcomes on the overall maternal and neonatal health status (e.g. caesarean section versus vaginal delivery). Our choice for this explicit outcome of effectiveness simplified the decision analysis. A way to overcome this is to calculate the more generic health outcome quality adjusted life years (QALY’s) instead of considering only the intermediary clinical outcome of serious perinatal complications. The use of QALY’s on the other hand adds complexity to the decision analysis, because all possible outcomes of the analysis need to be converted to QALY’s by means of utilities. Although
we are aware that we evaluated strategies only for serious perinatal complications, we considered this intermediary outcome as being a clinical important outcome.

A potential benefit of screening for GDM that we did not take into account in the present cost effective analysis is the benefit of early identification of women who are at high risk of subsequent type 2 diabetes in the future. In these women lifestyle and pharmacological interventions might be effective in reducing the incidence of type 2 diabetes and its associated costs. International expert groups suggest that, based on the results of the HAPO study, universal screening with the OGTT should be introduced. Although this would be the most effective strategy in preventing serious perinatal complications, it also appears to be the most expensive strategy. If society is willing to pay €43 171, universal OGTT would be cost-effective. The NICE guideline advises to perform an OGTT in all women with risk factors for GDM. This advice was based on a cost-effectiveness analysis that was comparable to the analysis in the present study. The difference between the two analyses is that in the present study we used a prediction model to estimate the risk of GDM based on several risk factors, whereas the NICE guideline was based on a study evaluating screening based on the presence of a single risk factor. It is important to note that the prediction model that we used for economic modelling was not externally validated. Usually, external validation shrinks the performance of prediction models.

Conclusion

The most cost-effective screening strategy depends on the willingness to pay per prevented complication. Universal screening with the OGTT is the most effective strategy in reducing the number of serious perinatal outcomes albeit at €43 171 per prevented complication. Screening based on risk assessment with a prediction model followed by a fasting glucose test in women classified as high risk for GDM has the lowest costs per prevented complication, but for a relative low reduction in serious perinatal complications.
References


