MASTER THESIS

THE HEALTH ECONOMIC IMPACT OF (MIS)CLASSIFYING PREGNANT WOMEN WITH GESTATIONAL DIABETES MELLITUS

The incremental cost-effectiveness of the use of an alternative testing strategy in pregnant women with (suspected) Gestational Diabetes Mellitus compared to the routine laboratory strategy.

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Abstract

Introduction - Gestational Diabetes Mellitus (GDM) is defined as Diabetes Mellitus (DM) diagnosed in the second or third trimester of pregnancy that is not clearly either type I or type II DM, while pregnant women in the first trimester are classified as type II DM due to the ongoing epidemic of obesity. GDM is the most common form of metabolic disorders during pregnancy and its prevalence is around 5%, which is increasing due to advanced maternal age and obesity. GDM can cause serious complications for both mother and child, including pre-eclampsia and shoulder dystocia. Therefore an appropriate diagnostic process, including timely screening, correct diagnosis and adequate management is important to avoid or minimize the complications for both mother and child during pregnancy, at delivery and in the long-term. The Oral Glucose Tolerance Test (OGTT) is used in the diagnostic process to correctly diagnose GDM, but currently the laboratory strategy to perform the OGTT is not optimal due to the degradation of glucose by the glycolysis *in vitro.* Consequently, alternative testing strategies were examined. In this study, the Cost-Effectiveness (CE) of the optimal laboratory strategy, the use of a NaF-EDTA-Citrate tube and Point Of Care (POC) testing, as compared to the routine laboratory strategy was estimated for pregnant women with (suspected) GDM using a health economic model.

Methods – A cost-utility analysis was performed to determine the added value of the use of the optimal laboratory strategy, NaF-EDTA-Citrate tube and POC testing for diagnosing GDM by the OGTT, compared to the routine laboratory strategy. Decision trees for both mother and child were built from the hospital perspective, both when cut-off values used in the Netherlands (NL) and in the Hyperglycaemia And Pregnancy Outcomes (HAPO) study were applied. Study population was based on real patient data from the Amphia hospital in Breda and the main outcome was the Incremental Cost-Effectiveness Ratio (ICER), whereby costs were displayed in euros (€) and effects in Quality Adjusted Life Years (QALYs). ICERs were visualized by a CE plane. Furthermore, a one-way sensitivity analysis was carried out to predict the impact of changing one input parameter on the model outcome, visualized by a tornado diagram.

Results – The optimal laboratory strategy, the use of a NaF-EDTA-Citrate tube and POC testing all fell in the South-East (SE) quadrant of the CE plane, both when HAPO and NL cut-off values were applied, which means that they all dominate the routine laboratory strategy. Sensitivity analysis shows that variation in costs, QALYs and the probability of False Negative (FN) of type II DM later in life of the mother influences the ICER the most.

Discussion – This study suggests that both the optimal laboratory strategy, the use of a NaF-EDTA-Citrate tube and POC testing are cost-effective, which means that the routine laboratory strategy might be replaced. Furthermore, this study shows that the optimal laboratory strategy is the most favourite, but the differences in total costs and effects between the optimal laboratory strategy, the use of a NaF-EDTA-Citrate tube and POC testing are small. More research is needed to make the model stronger and more certain, to confirm the CE of the optimal laboratory strategy, the use of a NaF-EDTA-Citrate tube and POC testing, in comparison to the routine laboratory strategy.

Key words: Gestational Diabetes Mellitus; complication(s); Oral Glucose Tolerance Test; laboratory strategy; Cost-Effectiveness; Quality Adjusted Life Years

Content

List of tables and figures

Abbreviations

Abbreviation	Meaning
CE	Cost-Effectiveness
DBC	Diagnose Behandel Combinatie
DM	Diabetes Mellitus
FN	False Negative
FP	False Positive
GCT	Glucose Challenge Test
GDM	Gestational Diabetes Mellitus
GP	General practitioner
HAPO	Hyperglycemia and Adverse Pregnancy Outcomes
ICER	Incremental Cost-Effectiveness Ratio
LGA	Large for Gestational Age
NICU	Neonatal Intensive Care Unit
NL	The Netherlands
NZA	Dutch Health Authority ('Nederlandse ZorgAutoriteit')
OGTT	Oral Glucose Tolerance Test
POC	Point Of Care
PSA	Probabilistic Sensitivity Analysis
QALY	Quality Adjusted Life Years
SE quadrant	South East Quadrant
TAT	Turn Around Time
TN	True Negative
TP	True Positive

1. Introduction

1.1. Problem statement

Gestational Diabetes Mellitus (GDM) is defined as Diabetes Mellitus (DM) diagnosed in the second or third trimester of pregnancy that is not clearly either type I or type II DM, while pregnant women in the first trimester are classified as type II DM due to the ongoing epidemic of obesity [1]**.** GDM is the most common form of metabolic disorders during pregnancy and its prevalence is around 5%, which varies widely because of ethnic variation [2, 3]. This can partially be explained by imperfect screening due to differences in the diagnostic process, but for a large part remains unclear [4]**.** The prevalence of GDM is increasing by advanced maternal age and obesity [5, 6].

It is unknown how GDM arises exactly, but one main aspect of the underlying pathology is insulin resistance [7-9]. The β-cells of the Islets of Langerhans in the pancreas produces insulin which has to bind to the insulin receptor, where after it is responsible for the transport of glucose from the bloodstream into the cell. Insulin cannot bind to the insulin receptor in pregnant women, probably due to the fact that the placenta segregates hormones which bind to the insulin receptor, including progesterone, oestrogens and prolactin [10]. A healthy pregnant woman compensates this binding of hormones to the insulin receptor by producing more insulin, so that the transport of glucose can still continue. However, the pancreas of a pregnant woman who develops GDM does not have functional reserves of insulin in the β-cells to prevent insulin resistance [8]. As a result, the glucose cannot enter the cell and accumulates in the blood, resulting in hyperglycaemia.

GDM can cause serious complications for both mother and child [8]. Poolsup, N., Suksomboon, N. and Amin, M. (2014) performed a systematic review including ten studies that describe the outcomes of pregnant women with GDM with and without treatment, in which was found that treatment reduces the risks of complications associated with GDM for both mother and child [11]. Therefore an appropriate diagnostic process, including timely screening, correct diagnosis, and adequate management is important to avoid or minimize the complications for both mother and child during pregnancy, at delivery and in the long-term [12]. Consequently, care for pregnant women with GDM might be more cost-effective when the diagnostic process is done timely and correct.

1.2. Theoretical framework

Screening

GDM is mostly diagnosed by screening. Currently, there is a lot of discussion ongoing whether either universal or selective screening is more appropriate [9]. In the Netherlands (NL), all pregnant women with one or more risk factors for GDM undergo screening. Risk factors are macrosomia during previous pregnancies (defined as a big size of the fetus independent from gestational age), polycystic ovary syndrome, history of any type of DM, glucose intolerance and glycosuria [12, 13]. In addition, pregnant women should be screened when there is clinical evidence suggestive for GDM (e.g. symptoms such as a dry mouth and polyuria [13]).

Diagnosis

The Oral Glucose Tolerance Test (OGTT) is the only appropriate test currently available to diagnose GDM, which can be performed by an one-step or a two-step approach. The one-step approach exists of an OGTT, which consists of an overnight fast of mostly 12 hours, which will be followed by measuring the blood glucose concentration. Secondly, the pregnant woman ingests a glucose solution of 75 or 100 gram, where after two hours fasting the concentration of glucose in the blood is measured again at defined time points [14].

The two-step approach is based on an OGTT which is preceded by an initial Glucose Challenge Test (GCT), performed one hour after the women ingests a 50 gram oral glucose load, followed by an OGTT in case the pregnant women exceeds the glucose threshold value of 7.8 mmol/l [14-16]. The GCT is an easy, user friendly and cheap way to perform initial screening [17]. The GCT cannot replace the OGTT because the GCT is with a detection rate of 74% less sensitive than the OGTT, resulting in more False Negative (FN) and False Positive (FP) test results. The GCT is only to indicate the possible presence of GDM**.** Although worldwide both approaches are used, Van Leeuwen, M., et al. (2011) suggested that an one-step approach might be more cost-effective than a two-step approach in a population of pregnant women with one or more risk factor(s) [18].

Different cut-off values for blood glucose levels are handled worldwide. According to the Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study, cut-off values of the plasma glucose level are ≥5.1 mmol/l after fasting and ≥8.5 mmol/l after 2 hours [19]. In NL, cut-off values after fasting are defined as ≥6.1 mmol/l in capillary whole blood or ≥7.0 mmol/l in venous plasma. Cut-off values after two hours are ≥7.8 mmol/l for both capillary whole blood and venous plasma [3]. The diagnosis of GDM is made if there is at least one value of the OGTT above the cut-off value.

Management

Adequate management is necessary to reduce complications associated with GDM. Management exists of physical activity and diet modification, whereby the blood glucose levels will be monitored frequently [20]. If adequate blood glucose levels are not achieved, active treatment is required, which means that the woman injects herself with insulin to directly reduce blood glucose levels [21].

Complications

Sometimes even insulin injections are not enough, or pregnant women incorrectly classified as not having GDM may not receive treatment at all. In that case, serious complications might occur. GDM is associated with an increased risk of macrosomia, even as Large for Gestational Age (LGA) (defined as size of the fetus that lies above the 90th percentile for gestational age), because insulin stimulates growth through the insulin like growth factors, which leads to a storage of huge amounts of glucose in the form of glycogen and fat, resulting in a larger baby [22, 23]. Those complications can contribute to shoulder dystocia, caesarean section and operative vaginal delivery. Hypoglycaemia in the fetus may also occur, caused by the fetus' response to produce more insulin to handle the high blood glucose levels received from the mother, resulting in quickly developing low blood glucose levels after birth [7]. Other complications at time of delivery that can affect the child include preterm birth, hypocalcaemia, jaundice, polycythaemia, stillbirth and respiratory distress syndrome, which may cause admission to the Neonatal Intensive Care Unit (NICU) [10, 13, 24]. Increased risk of pre-eclampsia and hypertension are also associated with GDM [25]. Later complications for the mother include a risk of approximately 60% for developing type II DM, which is a risk factor for cardiovascular disease [26, 27]. Later complications for the child involve a risk of approximately 20% for developing impaired glucose tolerance, which might be a precursor for DM, as well as an increased risk of obesity [28]. Furthermore, GDM may lead to neurological, cardiac and digestive disorders for the child [24]. Figure 1 shows an overview.

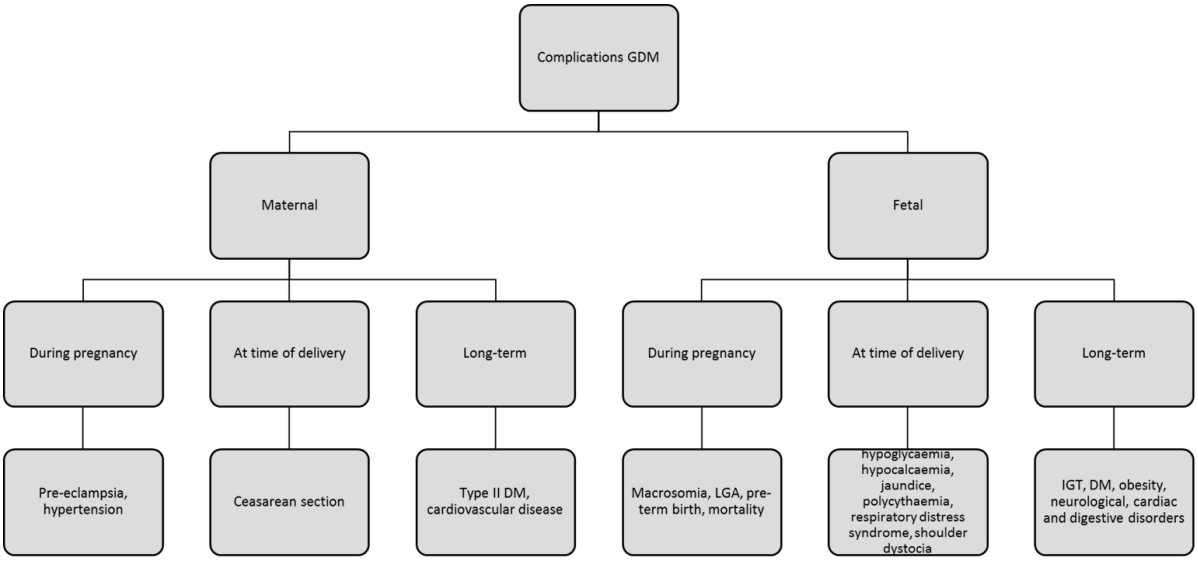


Figure 1 Complications of GDM.

1.3. Previous research

Recently, researchers from the Amphia hospital in Breda investigated the optimal laboratory conditions for the measurement of blood glucose levels, to update the clinical guidelines for the testing strategy for diagnosing GDM [29-32]. Previous results showed that glucose levels drop after phlebotomy, caused by degradation of glucose *in vitro* due to the glycolysis [31]. The glycolysis is a metabolic pathway and may affect the result of the OGTT, because the glucose concentration can fall with a rate up to 0.6 mmol/l per hour [29]. Consequently, alternative testing strategies were examined to prevent this degradation of glucose.

The current strategy (i.e. the routine laboratory strategy), is defined as the use of a tube containing Lithium Heparin as anticoagulant. This strategy may have a prolonged time between blood sampling and analysis, because the Turn-Around-Time (TAT) is not considered. TAT is defined as the time between the moment the test is ordered until the results are available [29]. As a result, the pregnant woman might have a FN test result.

The first alternative strategy is defined as the optimal laboratory strategy, which is based on a shorter TAT. This Lithium-Heparin tube must be placed on ice and centrifuged as soon as possible, but at least within 30 minutes, in order to separate the plasma from the cells [32]. The second alternative strategy is defined as Point Of Care (POC) testing, which has the shortest TAT. POC is based on a finger prick blood sample and gives the results immediately. POC might have a positive bias, caused by differences between atrial and venous blood, due to the dilution with plasma [33]. The third alternative strategy is the NaF-EDTA-Citrate tube and is based on a tube containing a glycolysis inhibitor existing of fluoride and citrate, which can keep blood glucose levels stable. Fluoride inhibits the enolase activity, which contributes to the inhibition of the glycolysis in the long term [34]. Citrate buffer causes a pH shock which inhibits the glycolysis immediately [35]. Table 1 shows an overview of all test strategies.

Table 1 The four laboratory strategies to conduct an OGTT (lab means laboratory).

Testing strategy	Laboratory condition
Routine lab strategy	
Optimal lab strategy	
Point of care testing	
NaF-EDTA-Citrate tube	

1.4. Objective

Based on previous research of clinical chemists of the Amphia hospital in Breda, a CE study will be carried out. CE of the optimal laboratory strategy, the use of a NaF-EDTA-Citrate tube and POC testing, as compared to the routine lab strategy will be estimated using a health economic model. With these insights, it may be easier for policy makers to decide which strategy to use for performing the OGTT test in pregnant women with suspected GDM. Therefore, the research question is defined as: *'What is the Incremental Cost-Effectiveness of the use of the optimal laboratory strategy (1), Point Of Care testing, (2) and a NaF-EDTA-citrate tube (3) as an alternative testing strategy in pregnant women with (suspected) Gestational Diabetes Mellitus instead of the use of the routine laboratory strategy'?*

The following sub-questions have been defined to answer the research question:

1. What is the rate of (mis)classification of GDM in the three alternative strategies and current strategy when using the OGTT?
2. What are the probabilities for the included complications?
3. What are the relevant costs, according to the hospital perspective, for three alternative strategies and current strategy?
4. Is it recommended to replace the current testing strategy by the optimal laboratory strategy, POC testing or NaF-EDTA-Citrate tube to reduce or avoid FN and TP values?

2. Methods

2.1. Study population

Based on the real patient data of the Amphia hospital in Breda, the study population was defined as pregnant women with (suspected) GDM which are qualify for an OGTT. Yet, there is no consensus worldwide about the cut-off values. Therefore this study was performed for both the NL and HAPO cut-off values. The study population includes:

1. Pregnant women who are considered at risk for GDM (according to the national guidelines)
2. Pregnant women who are not considered at risk for GDM, but present with clinical evidence suggesting GDM (e.g. symptoms like a dry mouth).

However, pregnant women who are known with type I or type II DM were excluded. 86 patients were included for the optimal laboratory strategy, the use of a NaF-EDTA-Citrate tube and for POC testing. Besides, 45 patients were included for the routine laboratory strategy.

2.2. Study design

Cost-utility analysis

This study involved a cost-utility analysis and determined the added value of the use of the optimal laboratory strategy, NaF-EDTA-Citrate tube and POC testing for diagnosing GDM by an OGTT, compared to the routine laboratory strategy [36]. Semi-structured interviews with an internist and clinical chemists were carried out to get more insight into the study objective, and a literature review was performed to determine which complications related to GDM need to be incorporated into the decision tree, based on occurrence and importance [9, 26]. It was chosen to incorporate the complications mentioned by the clinical chemists and internist, as well as complications that were included in the HAPO study [37]. Complications were also included when they are considered to have high impact on costs and/or quality of life. Hypertension, pre-eclampsia, caesarean section and type II DM were included in the decision tree for the mother. Mortality (which exists of stillbirth and neonatal death), preterm birth (delivery before 37 weeks), shoulder dystocia (which is nearly the same as brachial plexus injury), hypoglycaemia, hyperbilirubinemia, admission to the NICU and type II DM were included in the decision tree for the child.

Input parameters were collected to combine all relevant effects and costs in the health economic model. Consequently, costs were expressed in monetary units, displayed in euros (€) and determined for the year 2017. Effects were expressed as Quality Adjusted Life Years (QALYs), which will be determined as the utility of a health state multiplied by the time spent in that health state [38]. Finally, the outcome compared the incremental costs associated with one unit of effect (QALY), resulting in the Incremental Cost-Effectiveness Ratio (ICER). Results of this research will enable decision makers to make a more informed decision regarding whether or not to implement an alternative strategy for performing the OGTT. Figure 2 shows an overview of the study design.

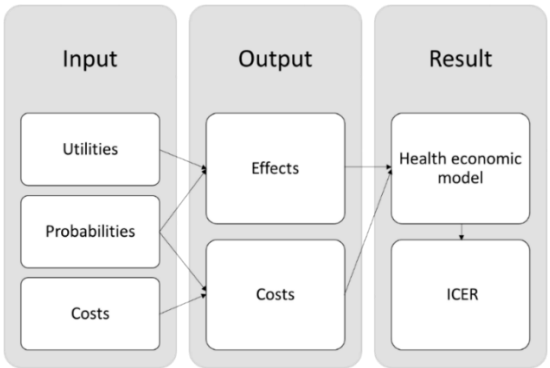


Figure 2 An overview of the study design.

Structure

The model used in this study is in the form of a decision tree, which can help to determine the most cost-effective option. Two decision trees were built, namely one with complications affecting the mother and one with complications affecting the child. This study was performed from the hospital perspective, whereby all relevant costs and effects were taken into account. The time horizon for the mother was set from the end of pregnancy (approximately 16 weeks) plus the whole time after delivery till death, while the time horizon for the child was set at the whole time after delivery. This is approximately 52 years for the mother and approximately 83 years for the child [39, 40]**.** This model focused on the three alternative strategies and the current strategy, where after each pregnant woman will be classified as either FN, True Negative (TN), FP or True Positive (TP). For each of those classifications, the risk of the included complications were modelled, and accompanying costs were quantified. The blue square at the beginning of the decision tree represents a decision node, the green circle a chance node and the red triangle a termination node. Figure 5 and 6 on the next pages are representing both decision trees.

Outcome measures

As mentioned previously, the ICER was the main outcome of this study. The ICER is defined in this study as the difference in cost between the routine laboratory strategy and each of the alternative testing strategies (i.e. interventions), divided by the difference in their effects [41]. Figure 3 illustrates the ICER.

$$\text{Incremental Cost-Effectiveness Ratio (ICER)} = \frac{\text{Costs}_{\text{intervention}} - \text{Costs}_{\text{comparator}}}{\text{QALYs}_{\text{intervention}} - \text{QALYs}_{\text{comparator}}}$$

Figure 3 Incremental Cost-Effectiveness Ratio, effects are expressed as Quality Adjusted Life Years [38].

The CE plane visualizes the ICER. When a new intervention is clinically more effective and less costly, than it is called a dominant strategy, which will be displayed in the South-East (SE) quadrant. In case the current strategy is cheaper and more effective, the new intervention is dominated by the current strategy and will fall in the North-West quadrant. The North-East quadrant is not so obvious, because the intervention is more effective but also more costly. Interventions in the South-West quadrant are also not so obvious, because they are less costly but also less effective than the current strategy [42]. Figure 4 shows an example of a CE plane.

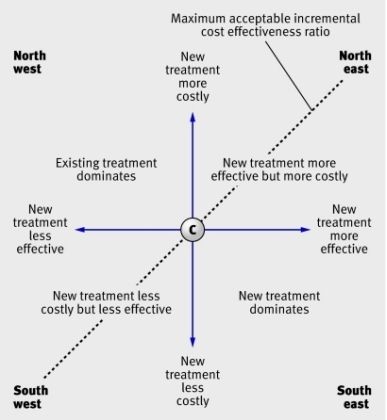


Figure 4 The Cost-Effectiveness plane. The x axis shows the difference in effects and the y axis shows the difference in costs. The slope of the line is the cost-effectiveness ratio [43].

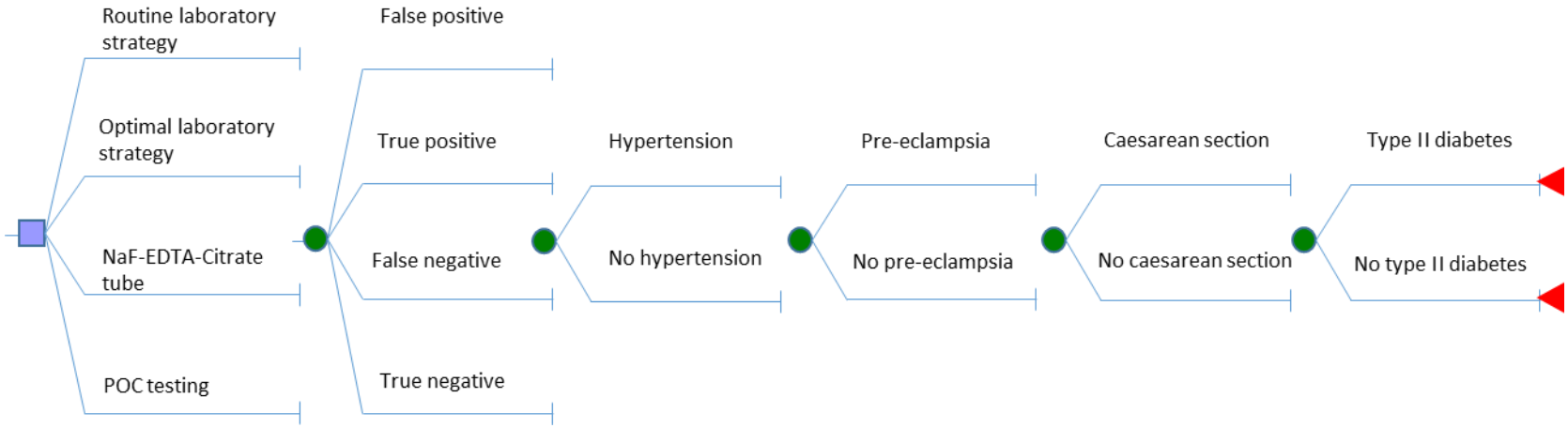


Figure 5 Decision tree mother. Not all branches are shown to facilitate display. Lines of a branch that do no terminate in a triangle indicate that each line of that branch is followed by the whole branch thereafter.

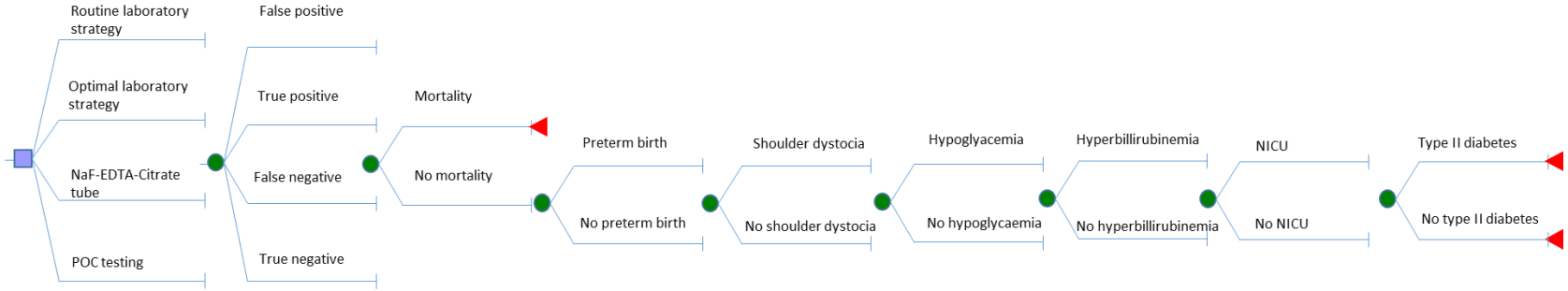


Figure 6 Decision tree child. Not all branches are shown to facilitate display. Lines of a branch that do no terminate in a triangle indicate that each line of that branch is followed by the whole branch thereafter.

2.3. Clinical pathway

The clinical pathway in the Netherlands was defined through a literature analysis and semi-structured interviews with the internist and clinical chemists. In case an OGTT is performed, pregnant women can be misclassified as FN due to the occurrence of glycolysis *in vitro,* after phlebotomy**.** Pregnant women can be classified as TN whereby the risk of complications are equal to the risk of complications for all (healthy) pregnant women without GDM. Finally, pregnant women can be classified as FP and TP. In both cases, pregnant women will receive treatment, but treatment is, logically, only necessary when the pregnant woman is classified as TP. The occurrence of FP test results depends on the diagnostic process. Figure 7 visualizes how the (in)correct classification of pregnant women with and without GDM might change this clinical pathway.

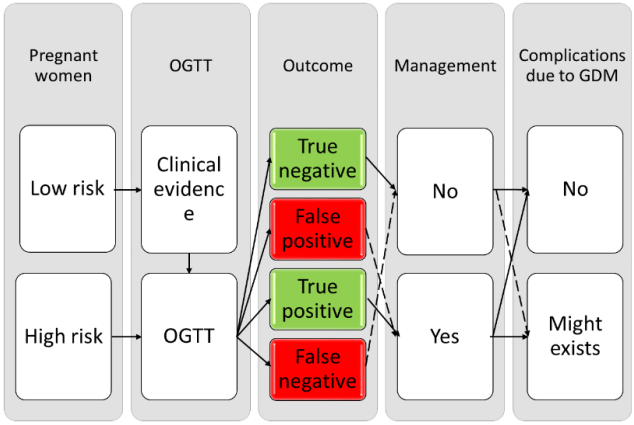


Figure 7 Clinical pathway. At this moment, pregnant women are classified as TN, FP, TP and FP. Preferred situation is to classify pregnant women as good as possible as TN and TP (green boxes), and to classify pregnant women less as possible as FP and FN (red boxes). In the preferred situation, management is only given to pregnant women classified as TP, but the dotted lines represented the current situation, in which also pregnant women who are classified as FP receives treatment, while pregnant women who are classified as FN receives no treatment, with the risk of getting complications due to GDM (last dotted line).

2.4. Data sources

Clinical inputs

Classification data was obtained by clinical chemists of the Amphia hospital in Breda. Utilities as well as the estimated duration of complications was obtained from literature. All utilities were discounted with a discount rate of 1.5%.

Probabilities of complications displayed in one of the decision trees were collected by means of a literature analysis. Articles obtained from two literature searches were combined to obtain the probabilities, according to (in)correct diagnosis of GDM in pregnant women (i.e. TP, FN, TN, TP). The search was performed through keywords in Pubmed, which are displayed in table 2. Articles were included when they were published in the last ten years. Articles were excluded when they were written in another language than English or Dutch, and when they were not accessible at the UT library or have not free access. Articles were screened by means of the title and abstract to obtain articles which comply with the inclusion criteria. Following this, relevant articles were selected and those full texts were reviewed for eligibility. Secondly, reference lists of selected articles were examined for articles who met the inclusion criteria. Besides, articles who were not found in the literature search were selected when they met the inclusion criteria and contain missing probabilities. The selected articles were included in November and December 2016.

Table 2 Keywords and search terms for search strategy 1 and 2. Search term 6: decided after the literature study to leave induction of labour out.*

Search terms	Keywords
1	Gestational diabetes OR GDM OR pregnancy diabetes OR (hyperglycemia/hyperglyc* AND maternal) OR (hyperglycemia AND pregnancy)
2	Outcome* OR complication*
3	Effect* OR improve* OR reduc*
4	Treatment OR therapy OR intervention
5	Pre-eclampsia OR preeclampsia OR hypertensive disorder*
6*	labour OR labor) AND induc*
7	Caesarean section
8	Diabetes OR DM AND (type II OR type 2)
9	Stillbirth OR death OR mortality
10	Preterm OR premature AND delivery OR birth
11	Shoulder dystocia
12	Hypoglycemia
13	Hyperbillirubinemia OR jaundice
14	NICU OR neonatal intensive care OR newborn intensive care
Search strategy 1	1 AND 2 AND 3 AND 4 AND (5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14)
Search strategy 2	1 AND 2

Costs

Costs included in this study are divided in costs of obstetric care, laboratory costs, costs of treatment, costs of delivery care and costs related to complications for both mother and child. Costs were obtained from www.medicijnkosten.nl [44] and the Dutch Health Authority ('Nederlandse ZorgAutoriteit', NZA) [45], which presents the 'Diagnose Behandel Combinatie' (DBC). A DBC is a price package for a certain treatment, and exists of A or B segment. A segment means that standard prices have been determined for every care provider, B segment means that the price of the DBC can differ between care providers. For that reason, an average of the prices for the B segment was calculated, by an weighted average of 1 academic hospital and 10 general hospitals (because academic hospitals offer treatments for higher prices than general hospitals). Besides, multiple sources were consulted to obtain the resource use, like literature and experts. Costs were measured by multiplying costs and resource use. Total costs of each strategy were determined by summing all costs of each pathway, multiplied by the corresponding probability. Costs were discounted with a discount rate of 4%.

2.5. Analysis

The health economic model of this quantitative study was built with the simple decision tree toolbar 1.4 software by Thomas Seyller (version 2008), a demo which is an add-in of Microsoft Office Excel. Sensitivity analysis was carried out in Microsoft Office Excel (version 2010).

A one-way sensitivity analysis was carried out to predict the impact of changing one input parameter on the model outcome (ICER) [38]. All parameters were examined, for each variable an upper and lower limit was determined. When the upper and lower limits of 95% confidence Intervals were present (which mostly was the case with the input parameters that were obtained from the literature review), they were used to determine the upper and lower limit. When the upper and lower limits could not be obtained from literature, an assumed variation of 25% below and above the base case value was applied (e.g. costs and utilities). The one-way sensitivity analysis was displayed in a tornado diagram.

3. Results

3.1. Input parameters

Classification

Real patient data was obtained by the Amphia hospital in Breda. Patients were classified against the optimal laboratory strategy, which is assumed to be the gold standard according to the protocol of the International Association of Diabetes and Pregnancy Study Groups, and consists of using a Heparine or NaF-Oxalate tube, putting on ice immediately after phlebotomy or centrifuged within 30 minutes [46]. Table 3 and 4 are representing the classification according to the HAPO and the NL cut-off values.

Table 3 Classification data according to the HAPO cut-off values (3 decimals).

Strategy	TN	TP	FN	FP
Routine laboratory strategy	57,778%	24,444%	15,556%	2,222%
Optimal laboratory strategy	73,256%	26,744%	0,000%	0,000%
NaF-EDTA-Citrate tube	72,093%	24,419%	2,326%	1,163%
POC testing	66,279%	23,256%	3,488%	6,977%

Tabel 4 Classification data according to the NL cut-off values (3 decimals).

Strategy	TN	TP	FN	FP
Routine laboratory strategy	80,000%	13,333%	6,667%	0,000%
Optimal laboratory strategy	88,372%	11,628%	0,000%	0,000%
NaF-EDTA-Citrate tube	87,209%	9,302%	2,326%	1,163%
POC testing	81,395%	11,628%	0,000%	6,977%

Literature search

The probabilities of each complication for a pregnant woman who is either classified as TP, FP, TN or FN were obtained from the literature review. All of the included studies provided at least one probability for the included complications. Figure 8 shows an overview of the selection process. Table 5 on the following page shows some additional information about the included studies.

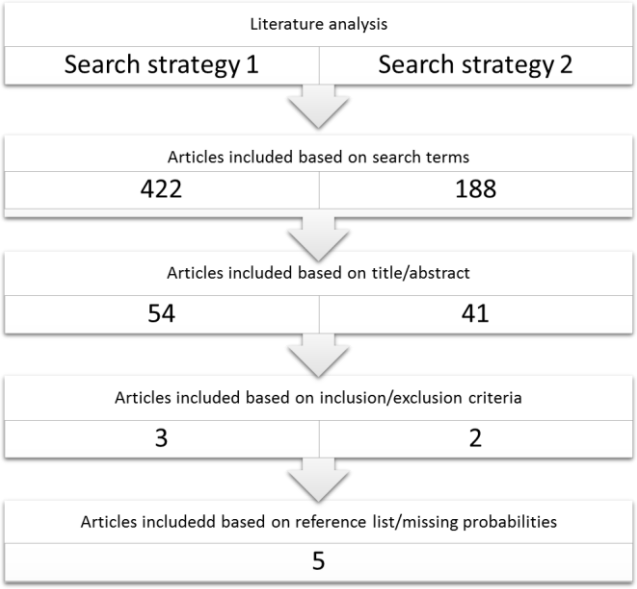


Figure 8 Selection process of the included articles.

*Table 5 Included studies. *: Article included older than 10 years, because a more recent article reporting that probability could not be obtained.*

Nr.	Title	Date	Author(s)	Journal	Design	Ref.
1	A Multicenter, Randomized Trial of Treatment for Mild Gestational Diabetes	2009	Landon, M.B., et al.	NEJM	RCT	[47]
2	Effect of Treatment of Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis	2014	Poolsup, N., Suksomboon, N. and Amin, M.	PLOS one	Systematic review	[11]
3	Treating mild gestational diabetes mellitus: a cost-effectiveness analysis	2011	Ohno, M.S., et al.	Am J Obstet Gyneco	Model	[48]
4	"[Increased risk of type II diabetes mellitus and cardiovascular disease after gestational diabetes mellitus: a systematic review]	2015	Hopmans, T.E., et al.	NtvG	Systematic review	[49]
5	Increased Risk of Cardiovascular Disease in Young Women Following Gestational Diabetes Mellitus	2008	Shah, B.R., Retnakan, R. and Booth, G.L.	Diabetes care	Literature	[50]
6	Effect of Treatment of Gestational Diabetes Mellitus on Pregnancy Outcomes	2005*	Chrowther, C.A., et al.	NEJM	RCT	[51]
7	Future risk of diabetes in mother and child after gestational diabetes mellitus.	2009	Damm, P.	Elsevier	Literature	[52]
8	Diagnostic thresholds for gestational diabetes and their impact on pregnancy outcomes: a systematic review."	2014	Hartling, L., et al.	Diabetic medicine	Systematic review	[53]
9	Gestational Diabetes Mellitus: Risks and Management during and after Pregnancy	2012	Buchanan, T.A., Xiang, A.H. and Page, K.A.	Nat Ref Endocrino.	HAPO, IADPSG criteria	[54]
10	Risk of Stillbirth and Infant Death Stratified by Gestational Age	2012	Rosenstein, M.G., et al.	Obstet Gynecol.	RCT	[55]

Probabilities of complications when a pregnant woman with (suspected) GDM is classified according to the OGTT as TP, FP, TN or FN are expressed in table 6 and 7. Evidence from multiple studies was combined. Probabilities related to TP and FN classifications were obtained from articles that described the impact of treatment on health outcomes, and the probabilities of TN and FP from articles who gives the basic risk for each pregnant woman (TN). It is assumed that the probability on type II DM later in life for both mother and child is the same for both TP and FN, and TN and FP, because a pregnant woman with GDM (or a child of a woman who had GDM during pregnancy) gets, probably despite treatment, always type II DM later in life. Crowther, C.A. et al. (2005) mentioned that the probability of mortality of the baby is 0,00% with treatment (TP) and 0,95% without treatment (FN), while Rosenstein, M.G., et al. reported that the basic risk of mortality is 0,17% [55]. Therefore, the risk of mortality of the baby with treatment (TP) is set at 0,17% [51].

Table 6 Probabilities of the maternal complications when a pregnant woman undergoes testing to diagnose GDM by the OGTT and will be classified as TP, FP, TN or FN (3 decimals).

Complication	TP	FP	TN	FN	Ref. (for TP and FN)	Ref. (for FP and TN)
Hypertension	0,061	0,060	0,060	0,081	[47]	[53]
Pre-eclampsia	0,086	0,045	0,045	0,136	[48]	[54]
Caesarean section	0,269	0,168	0,168	0,338	[47]	[54]
Type II DM	0,270	0,032	0,032	0,270	[50]	[50]

Table 7 Probabilities of the neonatal complications when the mother undergoes testing to diagnose GDM by the OGTT and the mother will be classified as TP, FP, TN or FN (3 decimals).

Complication	TP	FP	TN	FN	Ref. (for TP and FN)	Ref. (for FP and TN)
Mortality	0,002	0,002	0,002	0,010	[51]	[55]
Pre-term birth	0,094	0,064	0,064	0,116	[47]	[54]
Shoulder dystocia	0,015	0,013	0,013	0,040	[47]	[54]
Hypoglycemia	0,163	0,019	0,019	0,154	[47]	[54]
Hyperbillirubinemia	0,096	0,080	0,080	0,129	[47]	[54]
NICU	0,090	0,078	0,078	0,116	[47]	[54]
Type II DM	0,040	0,010	0,010	0,040	[52]	[52]

Effects

Utilities were obtained from literature and were multiplied with the duration of that health state. As mentioned before, complications were discounted at a rate of 1.5%. Table 8 and 9 are displaying the utilities and time in each of the health state for each complication for both mother and child.

Table 8 Utilities and duration of health states for the mother (3 decimals).

Complications mother	Utility	Time	Ref.	Comment
Hypertension	1,000	16 weeks	[56]	During pregnancy
Pre-eclampsia	1,000	16 weeks	[56]	During pregnancy
Cesarean section	0,865	1 year	[57]	Up to 1 year after delivery
Vaginal delivery	0,920	1 year	[57]	Up to 1 year after delivery
Type II DM	0,780	47 years	[58]	Within 5 years after delivery

*Table 9 Utilities and duration of health states for the child. *: Shoulder dystocia was set on a utility of 0.951 because of the fact that +/- 90% recover within 2 months (utility of 0.990) and +/- 10% do have a serious form of brachial plexus injury (utility of 0.600) (3 decimals).*

Complications child	Utility	Time	Ref.	Comment
Mortality	0,000	83	[48]	-
Pre-term birth	0,960	83	[56]	Life long
Shoulder dystocia*	0,951	83	[59]	Life long
Hypoglycemia	1,000	2 days	[48]	Short term
Hyperbillirubinemia	1,000	4 days	[48]	Short term
NICU	1,000	5 days	[48]	Short term
Type II DM	0,799	68 years	[58]	+/- 15 years after birth

Costs

The following section evaluates all incremental costs included in this study from the hospital perspective. Costs included in this study are divided in costs of obstetric care, laboratory costs, costs of treatment, costs of delivery care and costs related to complications for both mother and child.

Obstetric care

All pregnant women (TP, FP, TN, FN) who are insured receive complete obstetric care. As mentioned before, all pregnant women in NL with one or more risk factors for GDM undergo screening for GDM. Pregnant women should also be screened for GDM when there is clinical evidence suggestive for GDM

(e.g. symptoms such as a dry mouth). In the first place, a pregnant woman and the obstetrician discuss the suspicion of GDM and the usefulness of laboratory research with each other. Eventually, the obstetrician can discuss about it with the general practitioner (GP). Thereafter, the obstetrician arranged an OGTT for the pregnant woman. Table 10 shows the costs of obstetric care [60].

Table 10 Costs obstetric care (in euros).

Obstetric care	Total costs
Insured persons living in suburbs	€ 1.612,23
Insured persons not living in suburbs	€ 1.310,75
Total (average)	€ 1.461,49

Laboratory costs

Laboratory costs were obtained from the NZA and expert opinions. An OGTT exists of two glucose tests of €1,54 each. Besides, an order price of €10,94 was used for each OGTT. Clinical chemists were consulted for the (small) differences in prices between the four strategies. Table 11 shows the costs.

Table 11 Laboratory costs (in euros).

Laboratory strategy	Total costs	Comment
Routine laboratory strategy	€14,02	Standard price, exists of OGTT (fasting glucose and after 2h) and order price
Optimal laboratory strategy	€14,02	No difference with routine
NaF-EDTA-Citrate tube	€14,17	€0,15 additional costs related to the tube used
POC testing	€14,52	€0,50 additional costs, related to the reagents used

Treatment costs

Treatment costs were displayed in the decision tree which belongs to the mother, classified as TP or FP. All components were measured for a maximum of 16 weeks. Management exists of repeatedly measuring the blood glucose level by the patient herself (3-4 times a day), consultations at the internist (often 1 consultation in the beginning and 1 consultation 6 weeks after delivery) and at the gynaecologist (begins with a consultation every four weeks, but the frequency will be higher as the pregnancy progresses). For measuring the blood glucose level by herself, a blood glucose meter and accessories are necessary [61]. A blood glucose meter is approved for three years, which means that a blood glucose meter for one pregnant woman costs a small part of the whole price. When a pregnant woman is insured, she doesn't have to pay it by herself. The costs of consultations and management were obtained from the NZA [45], while the costs of the blood glucose meter and accessories were obtained from an online drugstore [62]. Approximately 25% of the pregnant women should inject themselves with insulin. In practice, only TP classified pregnant women potentially need insulin injections, because only measuring the blood glucose levels and consultations at the internist and gynaecologist, is, logically, enough for FP classified pregnant women. The cost of insulin was obtained from medicijnkosten.nl [44]. Table 12 shows the treatment costs.

Tabel 12 Treatment costs (in euros).

Treatment	Total costs TP/FP	Comment
Measuring blood glucose levels + accessories	€269,88	Type: Accu-check performa
Consultations	€2.137,19	Obstetrician, internist and gynaecologist
Insulin injections (eventually)	€11,96	25% of women with GDM
Total	€2.419,03	

Delivery costs

Delivery costs includes costs related to deliveries with and without the most common complications. There is a price difference between delivery costs of TP/FP classified women and TN/FN classified women, because women classified as TP/FP will give birth under the supervision of a gynaecologist and women classified as TN/FN might give birth without the supervision of a gynaecologist. The most common complications are bleeding (approximately 5%), bounce position (2-3%) and help with vaginal delivery (extractor or vacuum pump, approximately 10%). Delivery costs were obtained from the NZA [45]. Table 13 shows the delivery costs.

Table 13 Delivery costs (in euros).

Delivery	Costs TP/FP	Costs TN/FN
'Normal' delivery	€2.048,75	€614,41
Bleeding	€419,51	€419,51
Bounce position	€90,65	€90,65
Help with vaginal delivery	€292,39	€292,39
Total	€2.851,30	€1.416,96

Costs complications mother

Costs for pregnant women with hypertension exist of costs for oral medication and consultations with the gynaecologist. A minimum of twice a day till a maximum of six a day oral medication (labetalol) is required, for 1 day till 112 days (a maximum of 16 weeks), where after the average medication intake was assumed [63]. The gynecologist begins with a consultation every four weeks, but the frequency will increase as the pregnancy progresses. The costs for pregnant women with pre-eclampsia exist of costs for hospitalization and costs for magnesium sulphate given by the infuse [64]. The average costs of hospitalization was measured for a maximum of 112 days. Magnesium sulphate is given for a maximum of 24 hours. Costs of caesarean section exists of a price package established by the NZA [45]. The costs for pregnant women who develop type II DM later in their life (for approximately 47 years) were calculated by means of the most common complications, namely heart and vascular diseases (approximately 50%), retinopathy (approximately 17%), neuropathy (approximately 15%) and kidney insufficiency (approximately 6%). Besides, consultations at the general practice (every three months at the 'praktijkondersteuner huisarts' and every year at the GP) and measuring the blood glucose level by herself (twice a day) are an important aspect of the costs for type II DM. A blood glucose meter and accessories are necessary for measuring the blood glucose level by herself [61]. A blood glucose meter is approved for three years, which means that a woman who had GDM during pregnancy needs approximately 16 blood glucose meters for the rest of her life. The costs of the blood glucose meter and accessories were obtained from an online drugstore [62]. Approximately 75% of the people have oral medication, in the form of metformin [65]. 25% of the people need insulin injections. Those costs were obtained from the NZA [45] and medicijnkosten.nl [44]. Table 14 shows the costs of complications for the mother.

*Table 14 Costs complications mother. *: The costs of type II DM later in life for the child are almost the same as the costs of type II DM later in life for the mother, the only difference is the duration. The mother has approximately 47 years type II DM, while the child has approximately 68 years type II DM. Therefore, type II DM later in life of the child is more costly than type II DM later in life of the mother. Besides, the total costs for the mother are higher, because the probability that a mother gets type II DM later in life is higher (in euros).*

Complication	Total costs TP/FP	Total costs TN/FN
Hypertension	€ 1.304,02	€ 1.844,58
Pre-eclampsia	€ 14.307,35	€ 14.307,35
Caesarean section	€ 2.016,18	€ 3.450,53

Type II DM*	€ 15.353,08	€ 15.353,08

Costs complication child

There are no costs from the hospital perspective associated with mortality. Costs incurred for preterm birth for a baby of a mother who had GDM during pregnancy are the costs for a maximum of 13 weeks nursing days, because the baby can be alive from 24 weeks of gestation. This information was used to determine the average costs of preterm birth. Shoulder dystocia results in several consequences for the baby. The most common consequences of shoulder dystocia are brachial plexus injury (12%), fracture (7%) and asphyxia (0,3%). It should be noted that a fracture heals itself, asphyxia occurs rarely and 15% of the babies with brachial plexus injury need surgery. The costs of hypoglycaemia exists of the costs for glucose measurement, glucose infuse and admission to the NICU. The costs of hyperbilirubinemia exist of measurement of bilirubin and photo therapy. The duration of NICU length of stay is approximately five days [66]. The costs of type II DM for the child later in life (for approximately 68 years) include the most common complications, namely heart and vascular diseases (approximately 50%), retinopathy (approximately 17%), neuropathy (approximately 15%) and kidney insufficiency (approximately 6%). Besides, consultations at the general practice (every three months at the 'praktijkondersteuner huisarts' and every year at the GP) and measuring the blood glucose level by him- or herself (twice a day) are an important aspect of the costs for type II DM. For measuring the blood glucose level by him- or herself, a blood glucose meter and accessories are necessary [61]. A blood glucose meter is approved for three years, which means that the child needs approximately 23 blood glucose meters in his or her life. The costs of the blood glucose meter and accessories were obtained from an online drugstore [62]. Approximately 75% of the people do have oral medication, in the form of metformin [65]. 25% of the people do need insulin injections. Costs were obtained from NZA [45] and medicijnkosten.nl [44]. Table 15 shows an overview of the costs for the complications affecting the child.

*Table 15 Costs complications child. *: The costs of type II DM later in life for the child are almost the same as the costs of type II DM later in life for the mother, the only difference is the duration. The mother has approximately 47 years type II DM, while the child has approximately 68 years type II DM. Therefore, type II DM later in life of the child is more costly than type II DM later in life of the mother. Besides, the total costs for the mother are higher, because the probability that a mother gets type II DM later in life is higher (in euros).*

Complication	Total costs TP/FP	Total costs TN/FN
Mortality	-	-
Preterm birth	€ 15.340,15	€ 15.340,15
Shoulder dystocia	€ 428,43	€ 428,43
Hypoglycemia	€ 5.268,50	€ 5.268,50
Hyperbillirubinemia	€ 2.545,34	€ 2.545,34
NICU	€ 2.777,98	€ 2.777,98
Type II DM*	€ 11.164,85	€ 11.164,85

3.2. Incremental cost-effectiveness

Table 16 shows the total effects and total costs of all three alternative strategies and current strategy. Incremental effects, incremental costs and the ICER of all three alternative strategies when applying either the HAPO or the NL cut-off values were also displayed. In addition, Appendix A shows the ICERs for mother and child separately, for all three alternative strategies for both HAPO and NL cut-off values.

Table 16 ICERs for all three alternative strategies, for both the HAPO and NL cut-off values (effects: 3 decimals, costs: in euros).

Strategy	Cut-off values	Total effects	Total costs	Incremental effectiveness	Incremental costs	ICER
Routine laboratory strategy	NL	83,118	€ 7.935,66	-	-	-
	HAPO	82,738	€ 9.571,36	-	-	-
Optimal laboratory strategy	NL	83,289	€ 7.287,02	0,171	€ -648,63	€ -3.791,67
	HAPO	83,029	€ 8.525,06	0,291	€ -1.046,30	€ -3.593,40
NaF-EDTA-Citrate	NL	83,280	€ 7.298,73	0,162	€ -636,92	€ -3.940,87
	HAPO	83,020	€ 8.536,77	0,282	€ -1.034,59	€ -3.672,34
POC testing	NL	83,289	€ 7.434,82	0,171	€ -500,83	€ -2.927,68
	HAPO	83,015	€ 8.653,48	0,277	€ -917,88	€ -3.313,65

Table 17 shows the total costs divided into laboratory costs, treatment costs, delivery costs, costs for complications of mother and costs for complications of child. Costs were the same for both HAPO and NL cut-off values. The cost of pre-eclampsia, type II DM later in life of the mother, preterm birth and type II DM later in life of the child are the highest.

Table 17 Breakdown of costs. Only an average of total costs was measured for the laboratory costs, the other categories include total costs (in euros).

Category	(Average) costs TP/FP	(Average) costs TN/FN
Laboratory	€14,24	€14,24
Treatment	€2.419,03	€ 1.461,49
Delivery	€2.851,30	€1.416,96
Complications mother		
Hypertension	€ 1.304,02	€ 1.844,58
Pre-eclampsia	€ 14.307,35	€ 14.307,35
Caesarean section	€ 2.016,18	€ 3.450,53
Type II DM	€ 15.353,08	€ 15.353,08
Complications child		
Mortality	-	-
Preterm birth	€ 15.340,15	€ 15.340,15
Shoulder dystocia	€ 428,43	€ 428,43
Hypoglycaemia	€ 5.268,50	€ 5.268,50
Hyperbilirubinemia	€ 2.545,34	€ 2.545,34
NICU	€ 2.777,98	€ 2.777,98
Type II DM	€ 11.164,85	€ 11.164,85

3.3. Cost-effectiveness plane

A CE plane was made to visualize the corresponding ICER, by displaying the relationship between costs and effects of the optimal laboratory strategy, the use of a NaF-EDTA-Citrate tube and POC testing compared to the routine laboratory strategy. All strategies fell in the SE quadrant for both HAPO and NL cut-off values, which means that they all dominate the routine laboratory strategy. Figure 9 shows the CE plane off all ICERs. Appendix B shows the CE planes of mother and child separately.

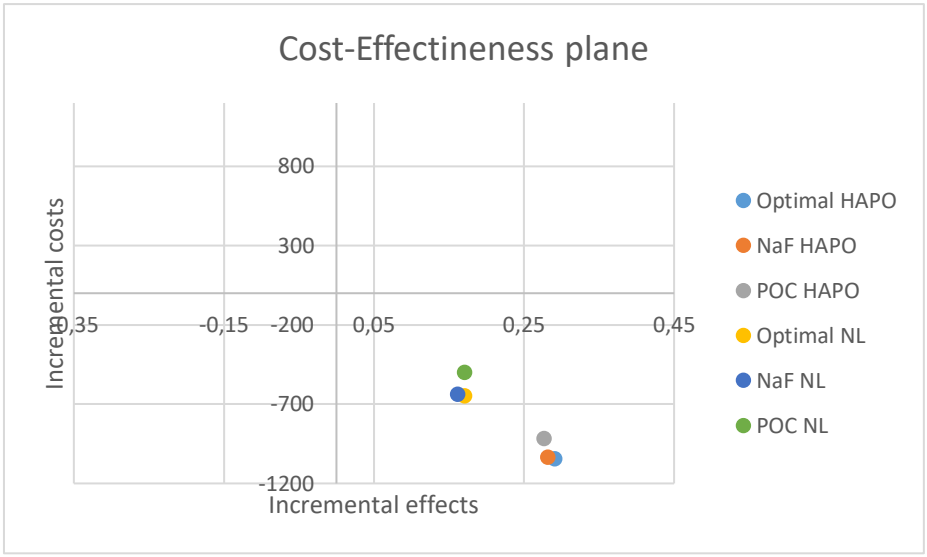
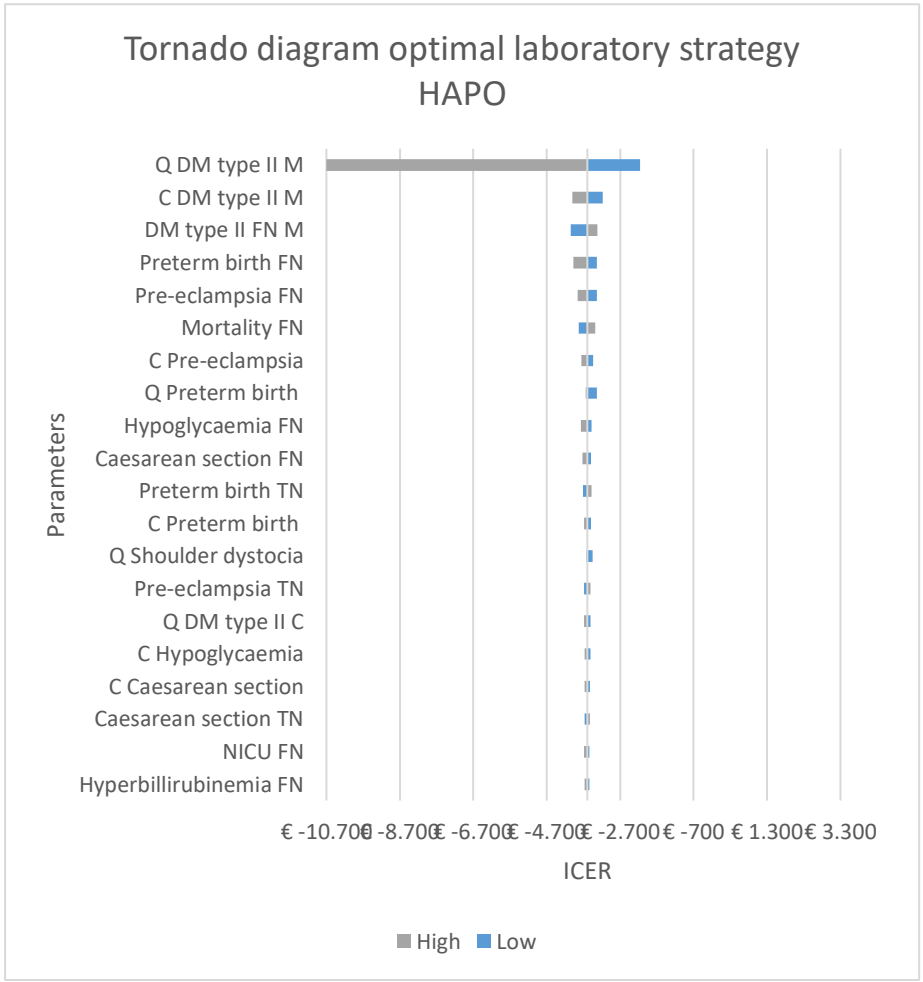


Figure 9 Cost-Effectiveness plane off al ICERs, the light blue, orange and grey spots belong to the study performed according to the HAPO cut-off values. The yellow, dark blue and green spots belong to the classification according to the NL cut-off values.

3.4. Sensitivity analysis

A one-way deterministic sensitivity analysis was performed. The results of the sensitivity analysis were displayed by a tornado diagram. The tornado diagram is very large, and exists of much parameters (costs, utilities and probabilities), therefore it was chosen to display in figure 10 only the 20 parameters with the most impact on the ICER for the tornado diagrams of the optimal laboratory strategy for both HAPO and NL cut-off values. The other tornado diagrams are displayed in Appendix C.



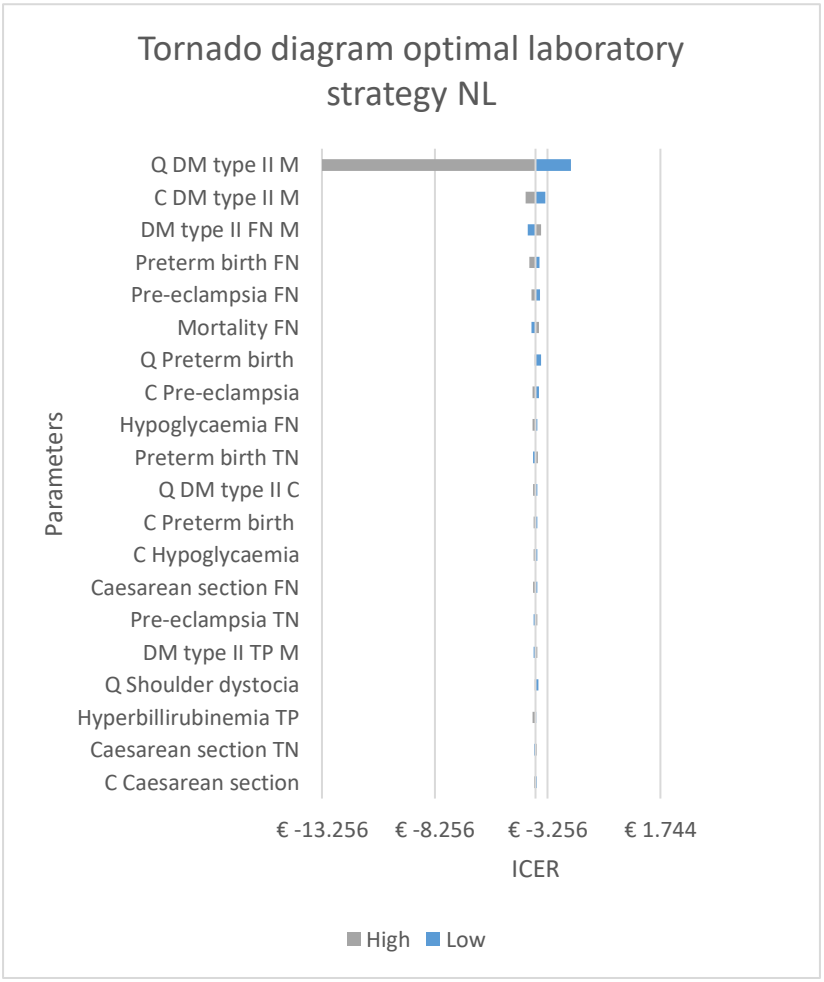


Figure 10 Tornado diagrams optimal laboratory strategy, left where the HAPO cut-off values applied, right NL. Q means QALY, C means costs, M means mother and C means child. High means that the corresponding parameter was +25%, low means that the corresponding parameter was -25%. To facilitate display, only the 20 parameters with the most impact on the ICER were included in the figure.

4. Discussion

In response to previous research of clinical chemists from the Amphia hospital in Breda, an economic analysis was performed to evaluate the incremental CE of the optimal laboratory strategy, the use of a NaF-EDTA-Citrate tube and POC testing for diagnosing pregnant women with (suspected) GDM, in comparison to the routine laboratory strategy. Recent research by clinical chemists from the Amphia hospital in Breda suggests that optimal laboratory conditions are very important for performing an OGTT (e.g. TAT, glycolysis inhibitor). Currently, the routine laboratory strategy does not meet de optimal laboratory conditions. Therefore an alternative laboratory strategy for diagnosing GDM is necessary. Three alternative strategies have been investigated for replacing the current laboratory strategy.

4.1. Interpretation

Data from the current study suggests that that for HAPO and NL cut-off values both the optimal laboratory strategy, the use of a NaF-EDTA-Citrate tube, and POC testing are cost-effective, in comparison to the routine laboratory strategy. The main difference between ICERs of the HAPO and NL cut-off values is the fact that the total costs of the current laboratory strategy and all three alternative strategies are higher when HAPO cut-off values are applied. Those differences can be caused by the lower cut-off value that is used for fasting glucose in the HAPO study, compared to fasting glucose cut-off value used in NL, which results in the fact that more pregnant women are diagnosed with GDM after fasting when the HAPO cut-off values are applied.

Results of the total CE plane for HAPO and NL cut-off values shows that both the optimal laboratory strategy, the use of a NaF-EDTA-Citrate tube and POC testing fall in the SE quadrant. These results indicate that all alternative laboratory strategies are more effective and less costly than the routine laboratory strategy. It can thus be suggested that more pregnant women will be correctly classified as having GDM (TP) or not (TN) when conducting an OGTT through an alternative laboratory strategy. This means that less pregnant women will be classified as FP, resulting in less unnecessary costs of treatment. Besides, less pregnant women will be classified as FN, resulting in the fact that the probability of a complication will not be increased.

It is interesting to note that the optimal laboratory strategy seems to be the best option in this research. Contrary to the other two alternative laboratory strategies, it is presented by a bigger difference in incremental effects and a bigger difference in incremental costs, compared to the routine laboratory strategy. The optimal laboratory strategy is defined as the gold standard. As a result, FP and FN classification will not occur. Furthermore, the use of a NaF-EDTA-Citrate tube and the optimal laboratory strategy are nearly the same in incremental effects and costs, while POC testing is a little less cost-effective. This result might be explained by the fact that the NaF-EDTA-Citrate tube contains an effective glycolysis inhibitor which keep the blood glucose levels stable. On the other hand, POC testing is a relative new test for GDM and can have a positive bias due to differences between atrial and venous blood, caused by the dilution with plasma.

Results of the CE plane for mother, both when HAPO and NL cut-off values are applied, indicate that the optimal laboratory strategy, the use of a NaF-EDTA-Citrate tube, as well as POC testing are all cost-effective. Results also suggest that the use of a NaF-EDTA-Citrate tube and the optimal laboratory strategy are nearly the same, while POC testing is a little less cost-effective.

Results of the CE plane for the child, both when HAPO and NL cut-off values are applied, indicate that the optimal laboratory strategy, the use of a NaF-EDTA-Citrate tube, as well as POC testing are cost-effective. Interesting to note is, when the NL cut-off values are applicable, the optimal laboratory

strategy and POC testing are exactly the same. This can be explained by the fact that TP and FP are classified the same for those strategies when the NL cut-off values are applied.

Results of the one-way sensitivity analysis shows, for all alternative strategies, when both HAPO and NL cut-off values are applicable, that the costs and QALYs of type II DM later in life of the mother influence the ICER the most. The high impact of type II DM is in line with previous studies, because type II DM become epidemic [67, 68]. Type II DM has an adverse outcome on health and it also involves economic burden [69]. Type II DM is a complex disease with multiple aspects, such as complications and consultations. Besides, most people do have type II DM for many years. As a result, the costs will be high. Quality of life is decreased in patients with type II DM. It was written by Schram, M.T., Baan, C.A. and Pouwer, F. (2009) that patients with type II DM have an increased risk of depressive symptoms [70]. Therefore, QALYs of type II DM do have a large impact in this study. Furthermore, most parameters do (almost) have no influence on the ICER.

4.2. Strenghts

This is the first study that evaluates the impact of laboratory strategies on the classification of pregnant women according to the OGTT. Many CE studies in the field of GDM have already been performed, but those studies concern the CE of either screening for GDM, or treatment of GDM [48, 56, 59].

Both HAPO and NL cut-off values were applied in this study, because there are no universal cut-off values handled worldwide. NL cut-off values were applied because the study population in this research is a real population existing of pregnant women living in NL. HAPO cut-off values are internationally oriented and were applied because those cut-off values come from an prominent study in the field of GDM. Furthermore, the study population was very large and pregnant women were obtained from different countries [19].

4.3. Limitations

The total ICER is determined by summing the total costs and total effects of the decision trees of mother and child. It was not found in literature that summing two decision trees was ever done before. Besides, for simplicity, the current model is based on the assumption that each women gets one child, indicating that, for example, twin births, or the birth of a second or third child have not been incorporated.

Data obtained from the Amphia hospital in Breda was delivered in two data sets, namely one dataset included 86 patients for both the optimal laboratory strategy, the use of a NaF-EDTA-Citrate tube and POC testing, while the other data set included 45 patients for each routine laboratory strategy and POC testing. Appendix D shows how this was solved by determining from a large data-set whether there is a difference in POC bias between different glucose concentrations, which was not the case. It was assumed that the optimal laboratory strategy is perfect (i.e. the gold standard). As patients in the other three strategies were classified against this gold standard, the effectiveness of those competing strategies is always inferior.

Different articles were combined to obtain TP, FP, FN and TN probabilities of the complications. It would be perfect when all parameters are from one source, but unfortunately this was not the case in this study. Therefore, evidence of multiple articles were combined.

Remarkable is the utility of pre-eclampsia, which was found to be 1. The utility of hypertension was also found to be 1. This is at least remarkable, because hypertension exists of only a high blood pressure, while pre-eclampsia exists of a high blood pressure and proteinuria [71]. Thus, expected was that pre-eclampsia would have a lower utility than hypertension, but that was not found in literature.

Several assumptions were done for measuring costs. No evidence was found for the length of hospital stay for pre-eclampsia, therefore it was measured by summing the minimum amount of days and maximum amount of days, divided by two. Besides, there was no literature found for the amount of medicines for hypertension, therefore it was calculated on the same way as the length of hospital stay for pre-eclampsia. Type II DM for both mother and child has very much costs components, and because they are all combined, the costs for type II DM is very sensitive.

4.4. Conclusion

In conclusion, this research suggests to replace the routine laboratory strategy by the optimal laboratory strategy, the use of a NaF-EDTA-Citrate tube or POC testing, both when HAPO and NL cut-off values are applied. This research suggest to use the optimal laboratory strategy in the future, but the differences between the alternative strategies are very small. Furthermore, costs and QALYs of type II DM later in life of the mother has by far the greatest influence on the ICER. Due to the uncertainty of this model, more research is needed to confirm the CE of the optimal laboratory strategy, the use of a NaF-EDTA-Citrate tube and POC testing, in comparison to the routine laboratory strategy. Below are some recommendations that can make the model stronger and more certain. At the end, it is up to the policy makers which alternative laboratory strategy they choose.

4.5. Recommendations

There was no probabilistic sensitivity analysis (PSA) included in this study. The one-way sensitivity analysis used in this study is limited, as it does not show the likelihood of the occurrence of each possible scenario, while PSA do by modelling distributions of the input parameters. Therefore it would be recommended to perform a PSA [72].

In addition, more research is needed to assess the utilities. Previous CE studies mentioned some utilities, but for pre-eclampsia, as described before, there was an utility of 1 found. A suggestion would be to assess experts instead of the literature.

Table 17 in the results section shows the breakdown of costs. Laboratory costs will most likely remain the same in the future. Profits can be achieved by reduction of costs for treatment, delivery and complications. Costs of treatment can be reduced by for example lowering the frequency of consultations. Delivery costs will also be made, but costs will be reduced if the probabilities of complications are decreased. Most cost savings can be made in the cost of complications. Results of this study shows that the most costs-benefit can be achieved for the complication type II DM (e.g. consultations, complications).

Furthermore, it is important that the same cut-off values are applied worldwide, because in this study was seen that different cut-off values have different effects. In practice, that means that a pregnant woman in NL will not have GDM, while she has for instance in America (where the HAPO cut-off values are applied).

Current study indicates that there is more evidence needed of laboratory processes. It is always ‘a game’ between the unit costs and rapid delivery of results [73]. Price differences between the laboratory strategies are very small. It seems that it don’t have any effect, but the price will affect larger quantities of the OGTT. Hospitals do have many laboratory measurement each year, the Amphia hospital in Breda have 70.000 OGTTs each year. This results in the fact that, even if the additional laboratory costs are very small, the additional laboratory costs per year can rise. To give the hospital the opportunity to achieve the associated increased effects and lower costs mentioned in this study, the laboratory first need a budget increase.

It should be noted that the use of a NaF-EDTA-Citrate tube might also be introduced for glucose measurements in general (e.g. DM). CE has to be studied seperately for the case DM, but the NaF-EDTA-Citrate tube can relative easily replace the currently used Lithium-Heparine tube, while NaF-EDTA-Citrate tube is an effective glycolysis inhibitor and Lithium-Heparine not [31].

Acknowledgements

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Appendix

Appendix A

The following tables shows total costs and effects for all three alternative strategies and current strategy. Incremental effects, incremental costs and ICERs for mother and child were presented for all three alternative strategies.

Table 1 ICERs mother (effects: 3 decimals, costs: in euros).

Strategy	Cut-off values	Total effects	Total costs	Incremental effectiveness	Incremental costs	ICER
Routine laboratory strategy	NL	35,645	€ 5.965,25	-	-	-
	HAPO	35,315	€ 7.237,79	-	-	-
Optimal laboratory strategy	NL	35,784	€ 5.481,22	0,139	€ -484,03	-€ 3.494,49
	HAPO	35,534	€ 6.473,46	0,220	€ -764,33	-€ 3.482,09
NaF-EDTA-Citrate tube	NL	35,784	€ 5.483,00	0,138	€-482,25	-€ 3.483,86
	HAPO	35,534	€ 6.475,24	0,219	€ -762,55	-€ 3.475,38
POC testing	NL	35,784	€ 5.629,02	0,139	€ -336,23	-€ 2.427,44
	HAPO	35,534	€ 6.586,98	0,219	€ -650,81	-€ 2.966,71

Table 2 ICERs child (effects: 3 decimals, costs: in euros).

Strategy	Cut-off values	Total effects	Total costs	Incremental effectiveness	Incremental costs	ICER
Routine laboratory strategy	NL	47,473	€ 1.970,40	-	-	-
	HAPO	47,423	€ 2.333,57	-	-	-
Optimal laboratory strategy	NL	47,505	€ 1.805,80	0,033	€ -164,60	-€ 5.056,08
	HAPO	47,495	€ 2.051,60	0,072	€ -281,97	-€ 3.934,32
NaF-EDTA-Citrate tube	NL	47,496	€ 1.815,73	0,023	€ -154,67	-€ 6.668,19
	HAPO	47,486	€ 2.061,53	0,062	€ -272,04	-€ 4.365,94
POC testing	NL	47,505	€ 1.805,80	0,033	€ -164,60	-€ 5.056,08
	HAPO	47,481	€ 2.066,49	0,058	€ -267,07	-€ 4.634,32

Appendix B

The following figures shows all CE planes separately.

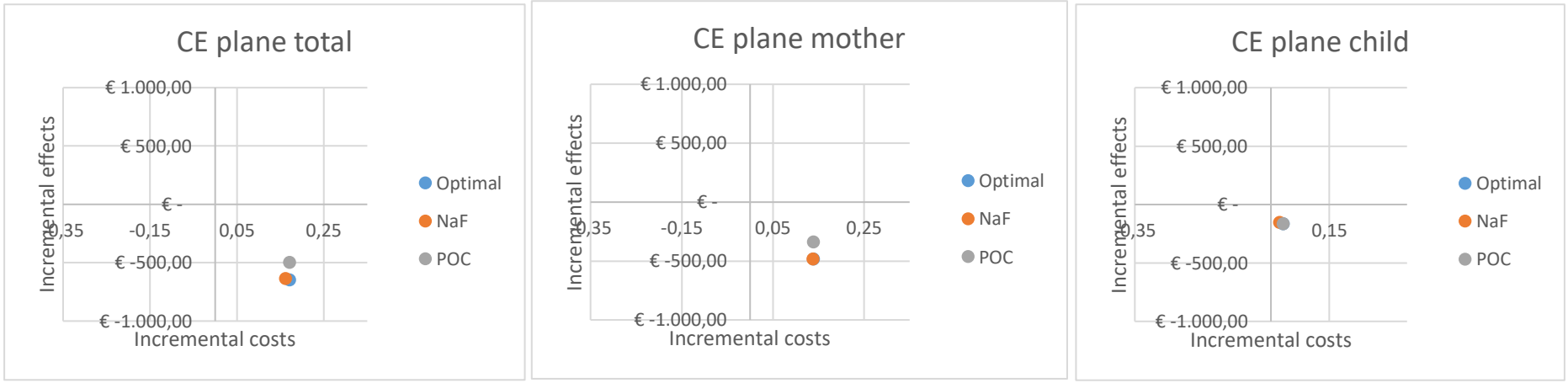


Figure 11 Cost-Effectiveness planes NL cut-off values; total, mother and child (from left to right).

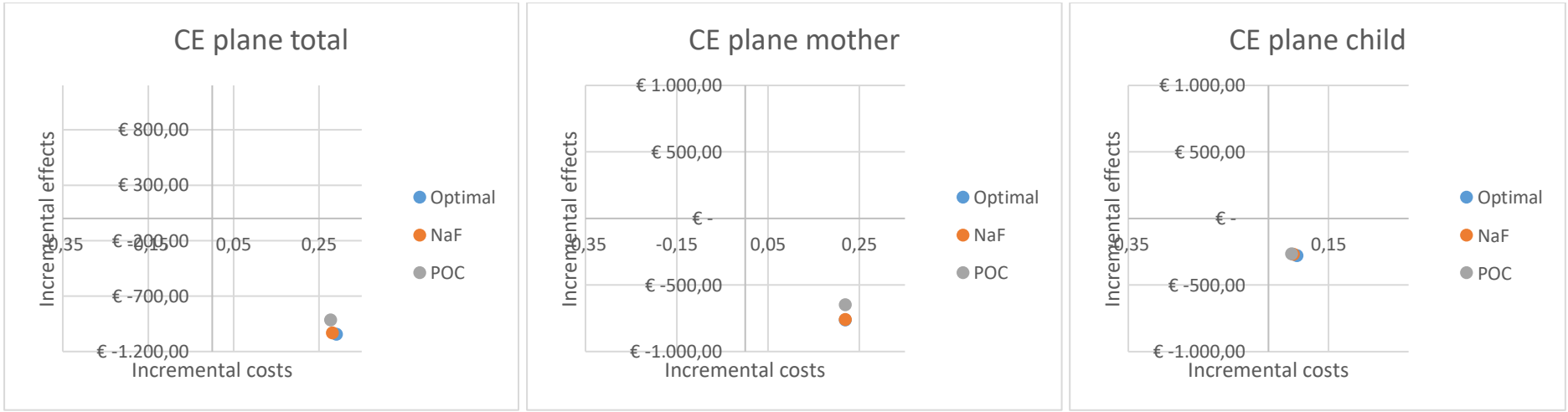
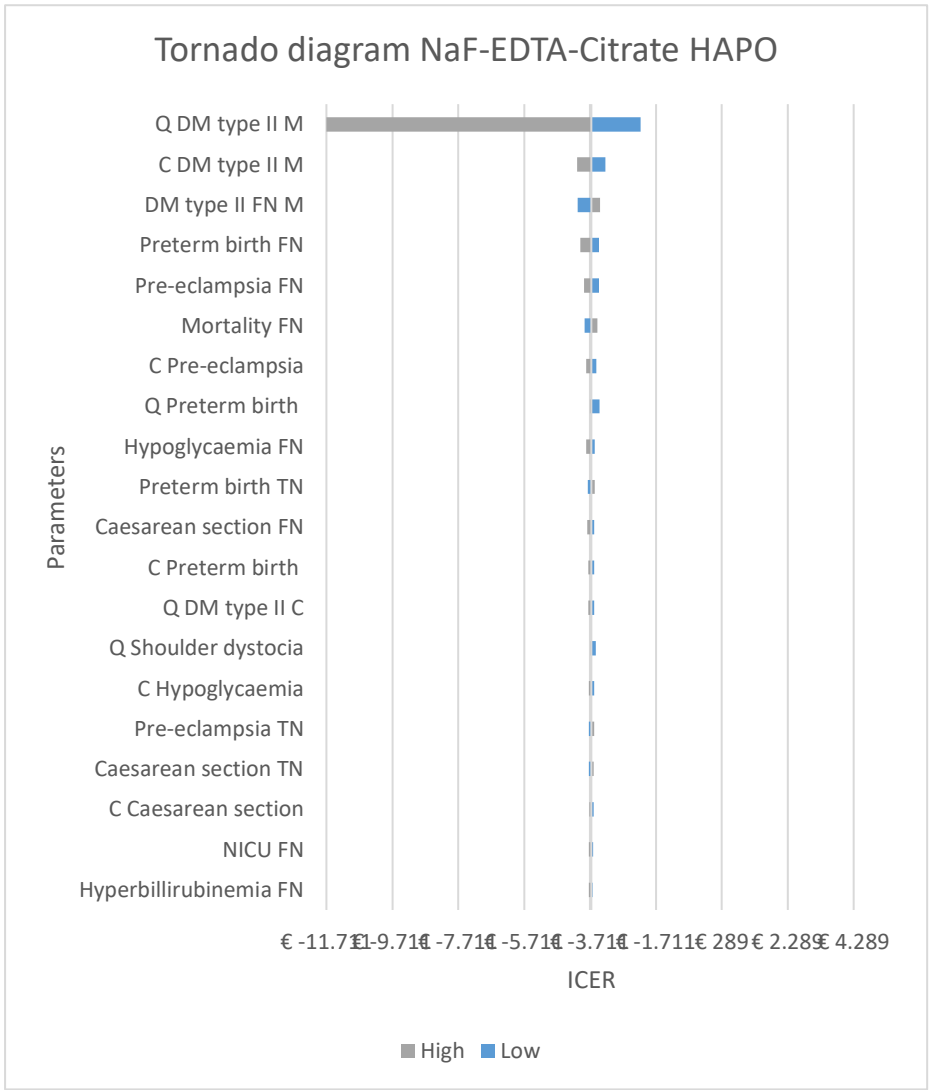


Figure 12 Cost-Effectiveness planes HAPO cut-off values; total, mother and child (from left to right).

Appendix C

The following figures shows the tornado diagrams with the 20 most important parameters for the NaF-EDTA-Citrate tube and POC testing, both when HAPO and NL cut-off values are applicable.



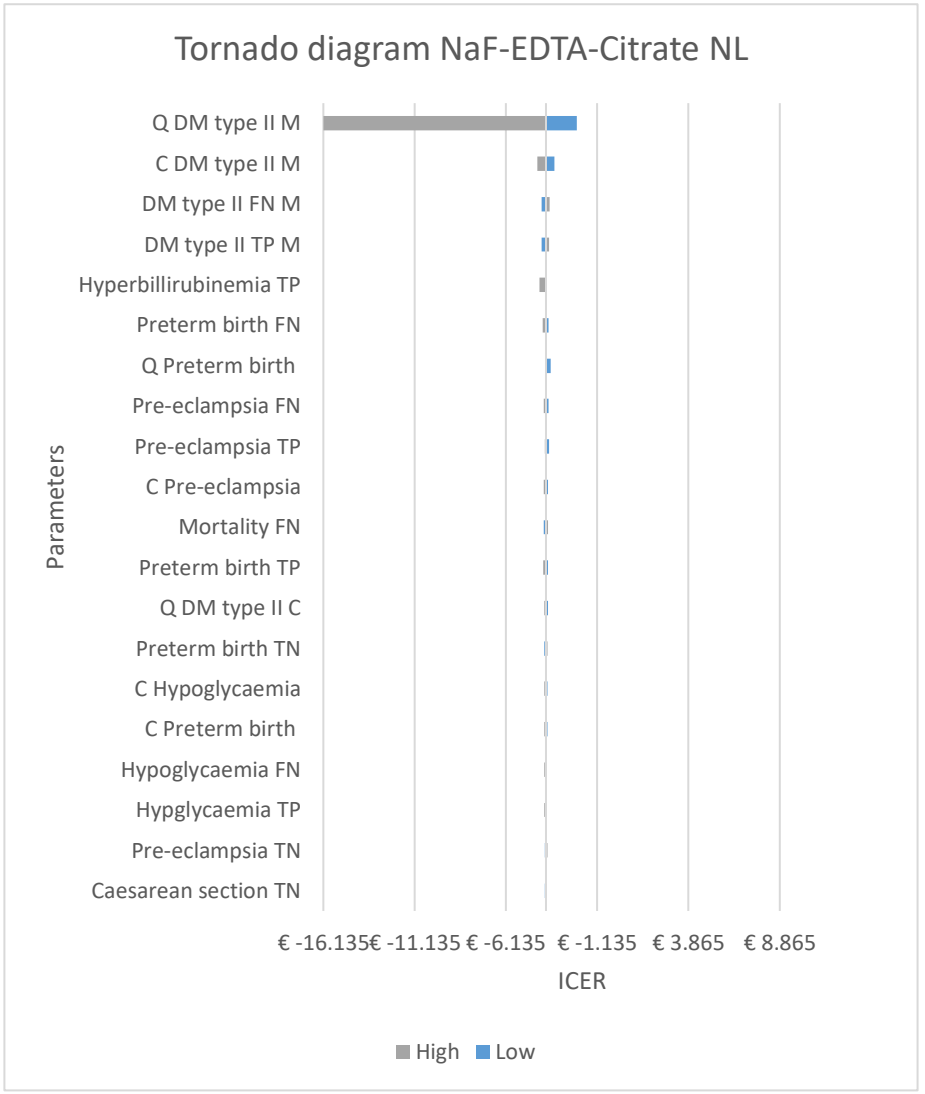


Figure 13 Tornado diagrams NaF-EDTA-Citrate, left where the HAPO cut-off values are applied, right NL.Q means QALY, C costs, M mother and C child. High means that the corresponding parameter was +25%, low means that the corresponding parameter was -25%.To facilitate display, only the 20 parameters with the most impact on the ICER were included in the figure.

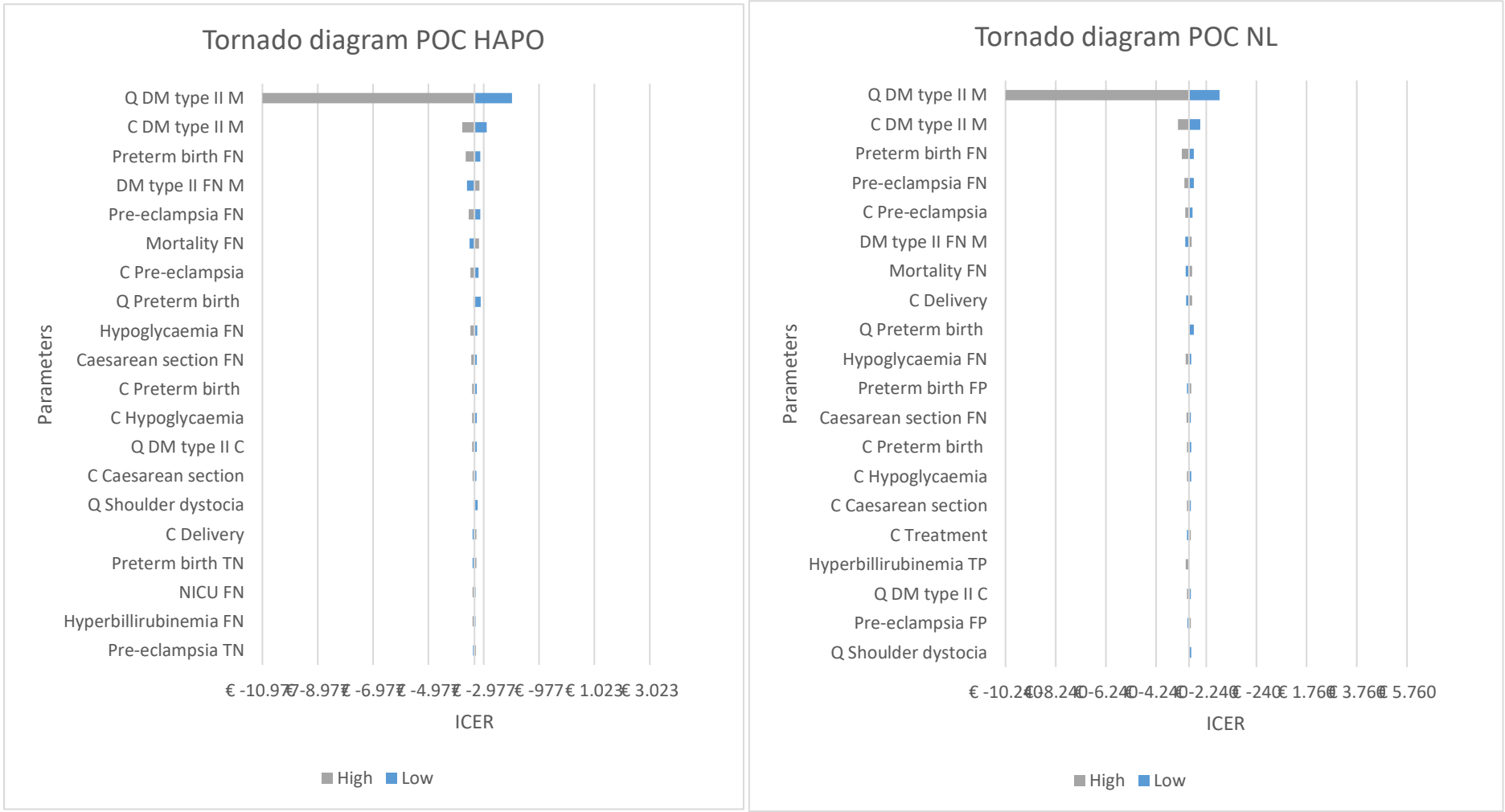


Figure 14 Tornado diagrams POC testing, left where the HAPO cut-off values are applied, right NL. Q means QALY, C costs, M mother and C child. High means that the corresponding parameter was +25%, low means that the corresponding parameter was -25%. To facilitate display, only the 20 parameters with the most impact on the ICER were included in the figure.

Appendix D

A large POC dataset was obtained by the Amphia hospital in Breda to calculate the influence of the glucose concentration on the POC bias. Following figure shows that there is no specific correlation between glucose concentration and POC bias.

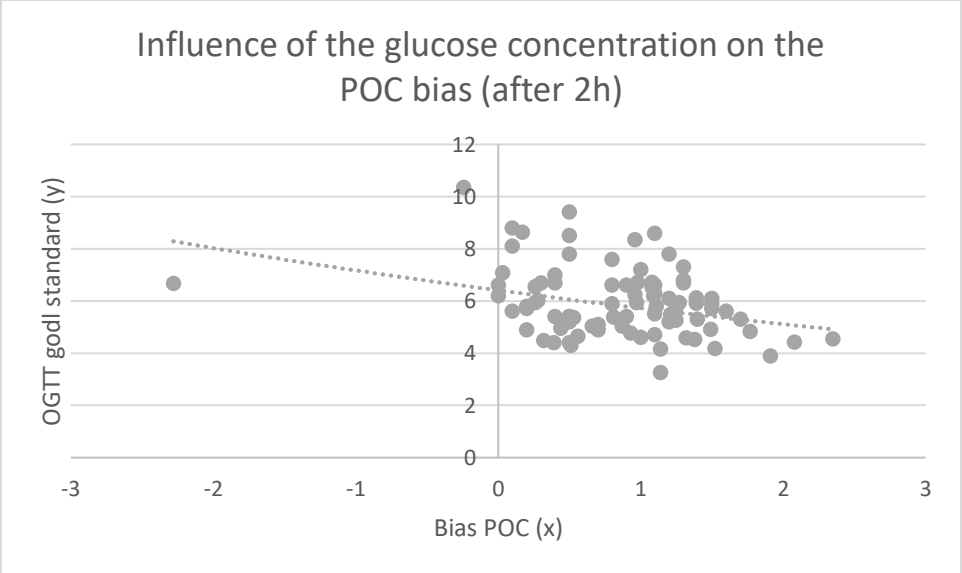


Figure 15 Influence glucose concentration on POC bias.