Economic evaluation studies of obstetric interventions in high risk pregnancies

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General introduction

Although pregnancy itself is generally not considered as a medical condition, pregnancy and delivery inevitably bear the risk of complications. In term pregnancy, hypertension, growth restriction, gestational diabetes mellitus and preterm prelabour rupture of membranes, can occur. These complications put both the mother and/or her child at risk for both neonatal and maternal complications, including fetal and neonatal death. During labour, complications can arise due to breech presentation during birth or metabolic acidosis. Obstetricians face difficult decisions in clinical practice whether and how to intervene in these high risk pregnancies as there has been limited evidence to guide such decisions, thus limiting the value and persuasiveness of guidelines. Both for clinicians and for policy makers it is important to have evidence on clinical effectiveness as well as cost-efficiency of available diagnostic and treatment strategies for such conditions. Due to rising health care costs and scarce resources in recent decades, economic evaluations have become increasingly important to support decision-making concerning medical technologies. Economic evaluations study the incremental costs and effects related to interventions and often also future benefits or costs as a consequence of those interventions. The relevance and importance of economic evaluations in the field of obstetrics can be emphasized by the number of publications concerning economic evaluations during the past 15 years (see chapter 2 of this thesis). This thesis includes several studies investigating costs and cost-effectiveness of treatment options for high-risk pregnancies or deliveries to contribute to clinical guidelines and evidence-based policy making. This introductory chapter provides background information on major types of high risk pregnancies and their treatment options. Furthermore, a general introduction to economic evaluation strategies and the general objectives and outline of the thesis are given.

High risk pregnancies and its treatment or prevention options

This thesis focuses on four pregnancy related and two delivery related complications. The pregnancy related complications are (1) gestational hypertension and mild pre-eclampsia at term, (2) intrauterine growth restriction at term, (3) preterm rupture of the membranes and (4) gestational diabetes mellitus. The delivery related complications are (1) the risk of metabolic acidosis and (2) breech presentation during labour. For each complication, a brief outline of the health problem and current treatment options are provided.

Gestational hypertension and mild pre-eclampsia at term

Six to eight percent of all pregnancies are complicated by gestational hypertension (GH) or preeclampsia (PE). Although outcome in most cases is good, hypertensive diseases remain a major cause of morbidity and mortality for both mother and child. Moreover, the care for women with hypertensive disease in pregnancy imposes a substantial economic burden. Most hypertensive diseases occur at or near term. Evidence to support the decision between induction of labour and expectant monitoring for women with GH or mild PE at term is lacking.
Intrauterine growth restriction at term

Intrauterine growth restriction (IUGR) at term is a major problem for obstetricians in clinical practice, as it is associated with increased neonatal mortality and short and long term neonatal morbidity.\(^{12,13}\) At present there is no consensus among obstetricians on what policy to follow in pregnancies with suspected fetal growth restriction at term. Induction of labour might increase the risk of instrumental deliveries and caesarean sections, and therefore increases maternal and neonatal morbidity as well as costs. Expectant management on the other hand might increase the risk of perinatal complications, including stillbirth.

Preterm rupture of the membranes

The estimated incidence of preterm prelabour rupture of the membranes (PPROM) between 34 and 37 weeks of gestation is 1.5%, which corresponds to about 3000 pregnancies per year in the Netherlands. PPROM is an important clinical problem, and a dilemma for both patient and gynaecologist: while awaiting spontaneous labour may lead to an increase in infectious disease and stillbirth for both mother and child, induction of labour may lead to preterm birth with an increase in neonatal morbidity (e.g., respiratory distress syndrome (RDS)) and a possible rise in the number of instrumental deliveries.\(^{11}\)

Gestational diabetes mellitus

Gestational diabetes mellitus (GDM) is a common complication of pregnancy and its prevalence is increasing.\(^{12}\) Recently it has been demonstrated that hyperglycaemia in pregnancy is associated with important perinatal and maternal outcomes.\(^{13,14}\) Further studies showed that treatment of GDM with diet, life style advices and insulin reduced the risk of complications significantly.\(^{15-17}\) Since GDM often is an asymptomatic condition, screening is required in order to detect women with GDM before treatment can be started.

The delivery related complications as studied in this thesis are (1) the risk of metabolic acidosis and (2) breech presentation during labour.

Asphyxia during labour

Intrapartum fetal monitoring aims to identify foetuses at risk for neonatal and long-term injury due to asphyxia. Fetal surveillance with cardiotocography (CTG) only significantly increases the operative delivery rate, but addition of fetal blood sampling (FBS) may prevent this. In recent years, ST analysis of the fetal electrocardiogram (ECG, STAN) has been introduced. This technique detects changes in the ST-segment of the fetal ECG, which are related to metabolic acidosis. These are interpreted together with the CTG.\(^{18-20}\)

Breech delivery

About 3 to 4% of all term pregnancies are breech presentations and there is still discussion on whether women with a breech presentation should attempt to deliver vaginally or by planned caesarean section (CS). The debate on whether women with a breech presentation should deliver vaginally or by caesarean section (CS) was much influenced by the Term Breech Trial (TBT).\(^{21}\) This randomized controlled trial showed that six weeks after delivery neonatal mortality and morbidity were significantly lower in the planned CS group compared to the planned vaginal birth (VB) group. Maternal mortality and morbidity was not significantly different.\(^{22}\) As a planned CS has also implications for subsequent pregnancies and deliveries, long term consequences should be included as well. To determine the optimal delivery strategy for term breech presentation, the evaluation should not be limited to outcomes from the index pregnancy but also incorporate those from subsequent pregnancies.

**Dutch randomized clinical trials concerning high risk pregnancies**

From 2003 onwards several randomized clinical trials have been initiated in the Netherlands to address some of the above mentioned clinical dilemmas. Within the collaborative framework of the Dutch Obstetric Research Consortium, we recently performed a randomized clinical trial on the choice between induction of labour and expectant monitoring for women with GH or mild PE at term, the Hypertension and Preeclampsia Intervention Trial At Term or HYPTAT study (see appendix 1). Induction of labour resulted in a significant reduction of women with progression to severe disease, and the caesarean section rate was also lower albeit not significant. Apart from these clinical outcomes, knowledge on the costs associated with these interventions is also of importance, in order to decide whether induction should be the recommended strategy. At present, evidence on costs and cost-effectiveness of management of women with GH or PE at term is limited.

In women with a pregnancy with suspected intrauterine growth restriction, we performed a randomized clinical trial comparing induction of labour and expectant monitoring. The trial was named the Disproportionate Intrauterine Growth Intervention Trial at Term or DIGITAT study (see appendix 2). In this study, the composite adverse neonatal outcomes and caesarean sections were comparable in both groups. In the expected group babies were delivered on average 10 days later and weighted 130 grams more as compared to the induction group. Significantly more neonates from the induction group were admitted to high or medium levels of care. It is unclear whether these strategies differ in terms of costs generated by health care utilization. At present, evidence on costs and cost-effectiveness of management of women with suspected IUGR at term is limited.

We recently performed a randomised clinical trial comparing expectant management and induction of labour in women with PPROM between 34 and 37 weeks of gestation, named the Preterm Prelabour Rupture Of the Membranes Expectant management or Induction of Labour study or PPROMEXIL study (see appendix 3). In this study, we found that in pregnancies complicated by PPROM between 34 and 37 weeks of gestation, induction of labour did not reduce the incidence of neonatal sepsis (RR 0.64, [95%CI 0.25 to 1.6]), but increased the risk of hypoglycaemia (RR 2.2 [95%CI 1.4 to 3.5]) and hyperbilirubinemia (RR 1.5 [95%CI 1.1 to 1.9]).

A large multicenter randomized clinical trial was performed to evaluate the effectiveness of monitoring by CTG plus ST-analysis compared to CTG only, using a strict protocol for the performance of FBS.\(^{22}\)
The results of this Dutch trial demonstrated that addition of ST-analysis of the fetal ECG to surveillance with CTG during labour did not significantly reduce the number of newborns with (metabolic) acidosis. Also for Apgar scores, neonatal admissions or operative deliveries no differences were found. These results were achieved with a significantly lower incidence of FBS in the group monitored by CTG plus ST-analysis. As the use of ST-analysis thus did not significantly reduce the incidence of acidosis calculated in the extracellular fluid compartment, it is important to assess the economic consequences, e.g. increase in monitoring costs, to justify or discourage further introduction of ST-analysis in the Netherlands.

Economic evaluations in health care

Besides the investigation of clinical effectiveness of treatment options in health care, due to rising health care costs and budget restraints, the economic burden and impact of health care interventions have become more important. Economic evaluations evaluate the economic consequences of interventions in health care, often as a comparative analysis of alternative courses of action in terms of both their costs and health outcomes. Therefore, the basic task of any economic evaluation is to identify, measure, value, and compare the costs and consequences of the alternatives being considered. Full economic evaluations (evaluations that concern a comparison of both costs and effects) can be divided into four types of analysis depending on how the difference in effectiveness is presented: cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis and cost-minimization analysis. Cost-effectiveness analyses (CEA’s) are analyses in which costs are related to a single, common effect that may differ between analyses (CEA’s) are analyses in which costs are related to a single, common effect that may differ between the alternative programmes. The results of such CEA’s are presented as costs per unit improvement on the clinical outcome measure or per life year gained.1 In cost-utility analyses (CUA’s) health outcomes are measured as time spent in certain health states, valued by utilities reflecting the quality of life in that health state. With a combination of time (life-years) and quality (utilities) so-called QALY’s (quality-adjusted life years) can be estimated. Costs per QALY gained is a generic outcome to express the relative efficiency of a health care programme, that allows for comparison with results from alternative programmes in other medical areas.1 In cost-benefit analyses (CBA) both costs and effects are expressed in monetary values. The results of such analyses might be stated either in the form of a ratio of costs to benefits, or as a sum (possibly negative) representing the net monetary benefit (loss) of one programme over another.1 A cost-minimization analysis (CMA) is used when both interventions are equivalent in terms of health outcomes, and only costs have to be considered. However, Drummond et al. argue that it is not appropriate to view CMA as a full economic evaluation (but as a partial economic evaluation) because there is always uncertainty around the estimates of costs and effects and CMA is not a unique study design that can be determined in advance.1 It is likely only justifiable in situations where the two therapies embody a near-identical technology. Nevertheless the use of CMA as a tool for full economic evaluations is still debated.

Basically two approaches to economic evaluation can be distinguished: trial-based economic evaluations and model-based economic evaluations. In trial-based economic evaluations patient-level data is used for both costs and effects collected alongside a randomized clinical trial (often called a piggy-back economic evaluation). For model-based economic evaluations mostly decision-analytical models are used (e.g. decision trees or Markov models) because they help to structure decisions and outcomes. Decision analytical modelling provides a framework for decision-making under conditions of uncertainty.2 A decision analytic model uses mathematical relationships to define a series of possible outcomes that would flow from a set of alternative options being evaluated.2 Also combinations of trial based and model based evaluations are possible, as the horizon of a trial may not suffice to incorporate all relevant health and economic outcomes, and modelling is required to evaluate results on the long term.

Another trend in evaluation research is the development and use of prediction models. These models optimally combine predictor variables (covariates) to estimate the absolute probability or risk that a certain outcome is present (diagnostic prediction model) or will occur within a specific time period (prognostic prediction model) in an individual patient with a particular prognostic profile.24 By statistically combining all available information in relation to the outcome of interest in a statistically optimised way, this may result in better as well as more efficient health care (improved health and/or less costs).

Economic evaluation in obstetrics

In recent decades, economic evaluations in general have become increasingly important as a means to rationalise medical decision-making. That is also the case in the field of obstetrics as can be seen from review published by Smith and Blackmore.25 This review presents among others the number of economic evaluation studies as published between 1990 to 1997 in obstetrics and gynaecology (98 economic evaluation studies). The question then arises if an increase in published studies can be seen over the last 10 to 15 years (see chapter 2 of this thesis). In this thesis we present economic evaluation studies addressing dilemmas between treatment options for several high risk pregnancies or deliveries to prevent complications. Thereby we used primary data from randomized clinical trials, as well as decision modelling when patient level data were not available or extrapolation to a long time horizon was necessary.

Objective and outline of the thesis

In this thesis we assess the quality of more recently published cost-effectiveness studies in the field of obstetrics and gynaecology, and we perform several economic evaluation studies alongside clinical trials as well as model-based cost-effectiveness analyses evaluating obstetric interventions, thereby identifying practical and methodological issues in economic evaluations in this area.
This thesis starts with a review that examines the methodological quality of economic evaluation studies in obstetrics and gynaecology from the years 1997 until 2009. These results are compared with the results of an earlier review as published by Smith and Blackmore concerning the years 1990 until 1996 (Chapter 2).

In the next four chapters the results of several trial-based economic evaluations are reported. Chapter 3 focuses on the cost-effectiveness of induction of labour versus expectant management in women diagnosed with gestational hypertension or mild pre-eclampsia between 36 and 41 weeks gestation. In the following chapter a cost analysis of induction of labour versus expectant management in women with a singleton pregnancy with suspected intrauterine growth restriction beyond 36 weeks of gestation is presented (Chapter 4). Costs of induction of labour and expectant management in women with preterm prelabour rupture of the membranes were compared in chapter 5. Finally chapter 6 focuses on the cost-effectiveness of addition of ST analysis of the fetal electrocardiogram to cardiotocography for fetal surveillance during labour compared with cardiotocography only.

Chapter 7 presents the cost-effectiveness of planned caesarean section versus planned vaginal delivery in pregnancies with breech presentation. A model-based cost-utility analysis was performed because the evaluation should not be limited to outcomes from the index pregnancy but also incorporate those from subsequent pregnancies.

Cost-effectiveness of several screening strategies for gestational diabetes mellitus is evaluated in chapter 8. A model-based analysis was performed to evaluate costs and effects of eight screening strategies for gestational diabetes mellitus including various blood glucose tests and a prediction model for GDM based on patient characteristics.

In chapter 9 and 10 we summarize and discuss the results of this thesis and evaluate their implications for clinical practice and for future research, respectively in English and in Dutch.

Reference list