Economic evaluation studies of obstetric interventions in high risk pregnancies
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Summary

This thesis is composed of two main parts. Part I describes the results of four trial-based economic evaluations of interventions in high-risk pregnancies. Part II addresses two model-based economic evaluations. The thesis preludes with a review of the methodological quality of economic evaluations in obstetrics and gynaecology as published in the last decade.

Chapter 2 evaluates the methodological quality of economic evaluation studies in the field of obstetrics and gynaecology published in the last decade. A MEDLINE search was performed to find economic evaluation studies in obstetrics and gynaecology from the years 1997 through 2009. Full economic evaluation studies concerning tests or interventions in the field of obstetrics or gynaecology were included. Each included study was evaluated by two reviewers using a quality checklist that was based on international guidelines for medical economic evaluation studies, and a checklist used in a previous review. This resulted in a mean number of adhered quality criteria of 23 out of 30 items, whereas 5 articles (3%) met all 30 criteria. A comparison of study quality to that reported previously showed improvement in the presentation of perspective (19% to 40%), the statement of primary outcome measure (72% to 81%), completeness of costs (14% to 48%), the presentation of discount rates (10% to 54%), details of sensitivity analyses (21% to 61%), reporting of incremental results (17% to 70%), and reporting of a summary measure (57% to 74%). The conclusion could be drawn that quality of economic studies in obstetrics and gynaecology has considerably improved in the last decade, but room for further improvement is present.

Chapter 3 assessed the economic consequences of labour induction compared to expectant monitoring in women with gestational hypertension (GH) or preeclampsia (PE) at term. An economic analysis alongside the Hypertension and Preeclampsia Intervention Trial At Term (HYPITAT) was performed. Women diagnosed with GH or PE between 36+0 and 41+6 weeks gestation, were randomly allocated to either induction of labour or expectant monitoring. The analysis resulted in average per patient costs of induction of labour (n = 377) of €7077 versus €7908 for expectant monitoring (n = 379), with an average difference of -€831 (95% confidence interval: - €1561 to - €144). This 11% difference predominantly originated from the ante partum period. In conclusion in women with GH or mild PE at term, induction of labour is less costly than expectant monitoring, due to differences in resource utilization in the ante partum period. As the trial already demonstrated that induction of labour results in less progression to severe disease without resulting in a higher caesarean section rate, both clinical and economic consequences are in favour of induction of labour in these women.

Chapter 4 describes the results of the cost analysis that was done alongside the Dutch nationwide disproportionate intrauterine growth intervention trial at term (DIGITAT trial). The DIGITAT trial was a randomized controlled trial in which 650 women with a singleton pregnancy with suspected IUGR beyond 36 weeks of pregnancy were allocated to induction of labour or expectant management of which the results showed that induction of labour and expectant monitoring were comparable with respect to composite adverse neonatal outcome and operative delivery. The costs analysis resulted in
more antepartum costs in the expectant monitoring group, mainly due to longer antepartum maternal stays in hospital. Delivery and the postpartum stage, induction of labour generated more direct medical costs, due to longer stay in the labour room and longer duration of neonatal high care/medium care admissions. From a health care perspective, both strategies generated comparable costs: on average € 7106 per patient for the induction group (N=321) and € 6995 for the expectant management group (N=329) with a cost difference of € 111 (95% CI: - € 1296 to € 1641). However, costs are lower in the expectant monitoring group before 38 weeks of gestation and costs are lower in the induction of labour group after 38 weeks of gestation. So if induction of labour is considered to pre-empt possible stillbirth in suspected IUGR, it is reasonable to delay until 38 weeks, provided watchful monitoring.

In Chapter 5 the costs of induction of labour and expectant management in women with preterm prelabour rupture of membranes (PPROM) were compared. The costs were estimated alongside the PPROMEXIL trial performed in women with PPROM near term who were not in labour 24 hours after PPROM. From the trial it could be concluded that induction of labour did not significantly reduce the probability of neonatal sepsis (2.6% versus 4.1%, relative risk 0.64 (95% confidence interval [CI] 0.25 to 1.6)). The economic analysis resulted in mean costs per woman of €8094 for induction and € 7340 for expectant management (difference € 754; 95% CI - 335 to 1,802). This difference predominantly originated in the postpartum period, where the mean costs were €3669 for induction versus €4801 for expectant management. So, in women with pregnancies complicated by PPROM near term, induction of labour does not reduce neonatal sepsis, but increases medical costs.

Chapter 6 assessed the cost-effectiveness of addition of ST-analysis of the fetal electrocardiogram (ECG) (STAN®) to cardiotocography (CTG) for fetal surveillance during labour compared to CTG only. This cost-effectiveness analysis was based on a randomized clinical trial on ST-analysis of the fetal ECG performed in labouring women with a singleton high-risk pregnancy, a fetus in cephalic presentation, a gestational age above 36 weeks and an indication for internal electronic fetal monitoring. The incidence of metabolic acidosis was 0.7% in the ST-analysis group and 1.0% in the CTG only group (relative risk 0.70; 95% CI 0.38-1.28). Per delivery, the mean costs per patient of CTG plus ST-analysis (n = 2827) was €1345 versus €1316 for CTG only (n = 2840), with a mean difference of € 29 (95% CI - € 9 to € 77) until childbirth. The incremental costs of ST-analysis to prevent one case of metabolic acidosis were €9667. The additional costs of monitoring by ST-analysis of the fetal ECG appeared to be very limited when compared to monitoring by CTG only and very low compared to the total costs of delivery.

Chapter 7 examined long term maternal and neonatal outcomes and costs of planned caesarean section (CS) versus planned vaginal birth (VB) in women with a breech pregnancy at term. A model-based cost-utility analysis was performed comparing planned VB with planned CS including outcomes of subsequent pregnancies. The planned CS strategy reduced the neonatal complications by 0.9% and the neonatal mortality by 0.4% at the expense of 28% more CS, 2.6% more maternal complications, and € 300,000 more costs. Combining the results of the maternal and neonatal model, incremental cost-effectiveness ratio of the planned CS strategy was estimated as € 561 per QALY gained. When both short and long term reproductive prospects are considered, planned CS is a cost-effective strategy in breech presentation at term.

Chapter 8 evaluated which screening strategy for gestational diabetes (GDM) is most cost-effective in reducing the risk of serious complications related to GDM. A model-based analysis was performed to evaluate costs and effects of 8 screening strategies for GDM including various blood glucose tests and a prediction model for GDM based on patient characteristics. Costs of screening and treatment to prevent one serious complication of pregnancy or delivery (neonatal death, shoulder dystocia, and birth trauma) were estimated. Since no uniform screening strategy exists, costs and effects of the screening strategies were compared to no screening. A screening strategy based on a prediction model using patient characteristics combined with fasting glucose measurement appeared to be the most inexpensive strategy to prevent serious perinatal complications at acceptable costs. More complications can be prevented using more costly test strategies depending on the willingness to pay per prevented complication.

General discussion and concluding remarks

The main goal of this thesis was to assess the quality of more recently published cost-effectiveness studies in the field of obstetrics and gynaecology, and to 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.

Transparent reporting of economic evaluations in obstetrics and gynaecology

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. Standards have been set on how to perform a good economic evaluation and a series of basic guidelines for economic evaluation research in health care have been developed with the aim to improve performance and report of economic analysis. Many of these guidelines were initiated or improved in the mid and late nineties. The question thus arises if this indeed improved the quality and increased the number of papers reporting economic evaluation studies in obstetrics and gynaecology published over the last decades. Several publications concluded that improvement was needed in the performance of cost-effectiveness analyses in the specialty of obstetrics and gynaecology. These studies showed improvement during the nineties but quality could be considerably improved on several methodological areas as can be concluded from our review as well. Improvement appeared to be still needed especially concerning the reporting of pertinent methodological features. Assumptions and methodological choices made in economic evaluation studies are mostly very site-specific and study results are often difficult to generalize to other settings. Therefore it is important to use and report methods in a transparent and unequivocal manner in order to allow judgment of the quality of such economic evaluation and the relevance of results for other settings. The use of methodological guidelines and standards also facilitates the comparison between different settings.
view of these results, both journal reviewers and researchers who are planning to perform and publish a
cost-effectiveness analysis in an obstetrics or gynaecology journal, should still be encouraged to better
use the available guidelines.16

**Standardization of data collection in trial based economic evaluations**

A crucial component of a high quality economic evaluation study is the quality and completeness of
the gathered data. Strength of trial-based economic analyses is the use of prospective patient level data
for both the effects and the costs. It is therefore very important that cost-relevant data that are needed
to perform trial based economic evaluations are very well outlined before the start of the clinical trial.
A limitation of our trial-based economic studies is that for reasons of practical and financial feasibility
a short horizon was chosen, so that predominantly clinical data concerning the period between
randomization and hospital discharge or childbirth were available. As we only included short term
medical costs and effects in the evaluation, disregarding indirect and non-medical costs, the performed
studies were analyses from a health care perspective instead of the preferred societal perspective. One
could argue that downstream consequences of short term outcomes are more or less known, short
term outcomes are sufficient as input for decision making. In some studies, such short term results may
suffice, e.g. when costs and effects are in favour of the same strategy, and long term costs will just be
an extrapolation of this dominance. However, when short term costs and effects are contradicting (or
opposite findings in major health outcomes), the evaluation could benefit of a formal synthesis of long
term consequences. The question is whether actual empirical measurements are always required or that
in case of known associations between short term and long term outcomes, modelling will suffice (see
below). In order to efficiently allocate limited resources for evaluation research, rational decision making
regarding follow-up measurements is required.11

The Dutch trials as reported in this thesis were conducted within the Dutch Obstetrics Research
Consortium, which is a national research network in the field of obstetrics and gynaecology with
more than 50 participating centres, including teaching, non-teaching and general hospitals. With this
number and variety of recruiting hospitals, study samples are likely to be highly representative for
the population of pregnant women in the Netherlands. Another major advantage of this network is
the multicenter infrastructure that facilitates a standardized way of performing randomized clinical
trials. This standardization includes general trial management and coordination, patient recruitment,
design of research instruments, data collection and data entry, analysis and reporting of results. This
standardization also stretches to (piggy-back) economic evaluation studies alongside these trials, as they
may use (adaptations of) previous questionnaires, cost calculations and analytical procedures. To some
test, this standardization is reflected in the economic evaluations performed alongside trials reported
in this thesis. However, not all potential advantages have actually materialised, as such standardization
does not come in a single strike but gradually evolves over time. For instance, relevant information
on resource utilisation was gathered via standardized items on case record forms. Unfortunately, these
forms did not include information concerning non-medical costs and longer term costs (after hospital
discharge). In one evaluation, the cost questionnaire was only developed during the course of the
study, and we have sent additional questionnaires about non-medical costs and follow-up costs to
the remaining subsample of participants. However, subsequent studies could benefit both in terms of
efficiency and reliability by reusing and adapting this questionnaire and systematically gathering cost
data from the start of the RCT onwards. So, when starting new trials it is recommended to immediately
plan the data collection for the economic evaluation, thereby building upon existing studies, and
considering non-medical and long term economic aspects.

**Long-term time horizon**

In nearly all studies as reported in this thesis a short term time horizon was used (follow-up of less than
1 year). In the field of obstetrics there is growing awareness of the importance of long-term follow up of
the child after obstetric interventions. Decisions made during pregnancy or delivery can affect the future
health of the child enormously.

For evaluating treatment options during pregnancy or labour, long term consequences (and costs) for
both mother and child might be relevant. In economic evaluation studies long term consequences can
be integrated in two ways: 1) empirically evaluate long term effects and costs of a perinatal intervention
by following up the neonates after the trial or, 2) extrapolate short term trial data by using modelling
techniques. At present, it is not standard policy to measure long-term effects of a perinatal intervention
by following-up the neonate after an obstetric trial. Long term follow-up is time-consuming, expensive
and does not fall within the funding-period of most obstetric trials.12 Teune et al. concluded in their
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and does not fall within the funding-period of most obstetric trials.12 Teune et al. concluded in their
review that only a small proportion of large perinatal trials report the long-term follow-up of the child.
They therefore emphasize that future obstetric trials should consider performing long-term follow-up
at the start of the trial.13 As the horizon for costs should be the same as for health outcomes, the same
holds for economic consequences. It is also mentioned that empirical long-term follow-up of infants
may not always be feasible, and alternative strategies should be considered. They therefore developed
several prediction models to estimate long-term health outcomes of the new-born based on specific
perinatal outcomes and other covariates.13 Such prediction models may prove useful in future studies
to extrapolate short-term outcomes to a long-term horizon, only if there is a strong relation between
the short and long term outcomes (as reflected by good model fit, and confirmed after validation in
large external studies). For short term outcomes without clear predictive value for long-term health
economic consequences, empirical long term follow up is necessary. Thereby, sometimes it may suffice
to perform measurements in specific subgroups only, in other situations it will be indispensable to
follow-up all children. However, considerable further research is required before this approach becomes
commonplace in economic evaluation studies for obstetric interventions. Additional prediction models
have to be developed – for other short-term perinatal outcomes – and all models need external validation
in other, preferably more recent datasets. This requires large long term cohort studies, such as the POPS-
study, to be made available for this purpose, preferably from different countries.
Potential relevance for clinical practice and policy

The ultimate purpose of evaluating interventions used in clinical practice is to improve quality of care and to provide the most possible care for money. The key question is whether one intervention (often a new, innovative technology) is beneficial in terms of health outcomes compared to the next best alternative (mostly the standard care). For that purpose in the United Kingdom, the National Institute for Health and Care Excellence (NICE) was initiated in 1999 as an authority to register and to look after the safety and (cost-)effectiveness and publish recommendations and guidelines of new or already existing health care interventions. NICE undertakes appraisals of selected technologies and issues guidance intended to ensure quality and value for money. Its decisions are binding within the NHS and potentially also affect decisions by health technology assessment bodies and payers in other countries. In the Netherlands such external policy institute doesn’t exist yet and therefore clinicians themselves are left the initiative to undertake evidence-based evaluations and actualize their guidelines, just like the situation is in the United States.

The Dutch Association for Obstetrics and Gynaecology (NVOG) emphasizes that the introduction of new technologies should be based on evidence-based principles, indicating that the implementation of new interventions is only possible after evaluating safety and (cost-)effectiveness. The NVOG defines a guideline as the way clinicians should behave (based on consensus within the professionals group) to result in appropriate use of care. A guideline aims to support (guide) physicians and patients to make better choices in their daily practice. It is a quality instrument that contributes among others to cost-effective care (efficiency). Evidence-based guidelines are determined by performing the (cost-)effectiveness of interventions. Appropriate use of care depends on the real use of the evidence-based guidelines in clinical practice. In practice this is not always the case, a major part of the interventions used in health care in general and in obstetrics and gynaecology specifically have never been systematically evaluated. In addition, due to lack of clear regulations, many innovative technologies (e.g. diagnostic tools, surgical instruments, devices) are being introduced without adequate evaluation. In this situation, it is highly questionable whether use of these technologies contributes to the quality of care, and for acceptable costs.

In 2011 the American Board of Internal Medicine Foundation and nine American scientific committees in the United States initiated the campaign Choosing Wisely. This campaign focuses on encouraging physicians, patients and other health care stakeholders to think and talk about medical tests and procedures that may be unnecessary, and in some instances can cause harm. Each committee constructs a list of interventions concerning their specialism that can be abandoned or performed less. These advices are evidence based and contain an explanation for patients. In the Netherlands such campaign is initiated as well by the National Physicians Alliance (Orde van Artiﬁciële Medisch Specialisten) and ZonMw (Dutch research funding institute), with the goal to achieve evidence-based guidelines in obstetrics. Completed multicentre randomized trials in obstetrics (among others those mentioned in this thesis) were included, and their potential health gains and budget impact was estimated (based on realistic implementation percentages). In case of adequate implementation of the trial results (for example health gains could be achieved by implementing induction of labour for pregnant women with GH or PE at term or by abandoning induction of labour in case of PPRMI) better care can be provided at lower costs. This study estimated that potential cost savings of € 9.6 million per year could be achieved, when the results of eight trials are effectively implemented (on basis of an investment of €300,000 per year for conduction of the studies). This figure includes one-time costs associated with undertaking the RCT’s as initiated by the Dutch Obstetrics Consortium (approximately €300,000 per year), indicating that health care evaluation research is likely also economically worthwhile. The Dutch government is considering to demand cost-effectiveness as a legal requirement and the Dutch Health Care Insurance Board is examining the implementation of such a concept. Economic evaluation studies, will therefore become increasingly important in critically appraising new as well as existing technologies or treatment options in health care.

Concluding remarks

In this thesis we performed comparative costs and cost-effectiveness analyses for several clinical dilemmas in high risk pregnancies or deliveries, and explored practical and methodological issues in such research and to discuss the context of evidence-based policy making in relation to complex dilemmas in clinical practice. Three approaches were presented: trial based economic evaluations prospectively comparing two treatment options; a model based approach, allowing to evaluate health economic consequences of all subsequent pregnancies following a decision for a current mode of delivery; and a clinical prediction model to formalize clinical reasoning in screening and diagnostic interventions. In view of observed quality of current research in this area, there is still much potential for improvement. Finally, both with respect to promising methodological approaches as well as the health care policy context (research infrastructure, financial resources, legal framework), there is ample work to do in the near future by clinicians, researchers, policy makers and all other relevant parties. This is in line with the growing awareness among clinicians and policymakers that economic evaluation studies should become less one-off projects, but should be more structurally integrated in the health care system in order to counter unsustainable rising health care costs.
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