Long-term follow-up of obstetric studies
Teune, M.J.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 1

General introduction
General introduction

Obstetric randomized controlled trials (RCTs) are performed to evaluate the effectiveness of perinatal interventions. At the start of such trials, trialists have to determine the primary outcome. As the ultimate goal of many perinatal interventions is to prevent morbidity in later life and to optimise neurodevelopmental outcome, long-term outcome is rarely used as a primary end-point in perinatal randomised controlled trials (RCTs)\textsuperscript{1,2}. There are some obstetric studies that had a long-term child outcome as primary outcome, for example, studies evaluating the effect of MgSO\textsubscript{4} given for preterm birth to protect infant brain \textsuperscript{3-5}, but the large majority of studies on perinatal interventions does not report long-term child outcomes, as it is thought to be expensive, time consuming and a logistic challenge.

Nevertheless, knowledge of long-term outcomes is important because serious sequelae from perinatal complications frequently manifest themselves only after several years \textsuperscript{6}. If known, these outcomes can change the overall conclusion regarding the optimal diagnostic or treatment strategy in a pregnant woman. The administration of diethylstilbestrol during the fifties or more recently, the administration of antenatal thyrotropin-releasing hormone for prevention of neonatal respiratory disease or antibiotics for spontaneous preterm labour are prime examples of interventions that turned out to have important negative long-term effects \textsuperscript{7-14}.

As stated, the difficulty of long-term follow-up is that it is thought to be expensive, logistically difficult and time-consuming. Long-term child follow-up increases the duration of a study, and it takes longer before the study results are known. This increases the cost of a study and it is therefore for obstetricians less attractive to perform. However, follow-up is sometimes necessary as it can demonstrate that a perinatal intervention is not effective on the long-term and should not be implemented in current clinical practice. Another factor that hampers long-term child follow-up is the fact that usually an obstetrician plans the RCT. Obstetricians often have less knowledge of child development and they are less aware of the importance of this matter. This complicates the planning of appropriate child follow-up.

From practical, ethical and economic considerations, long-term child follow-up of all children participating in the original RCT is often not feasible and in some situations also not necessary. Several alternative follow-up strategies could be explored. Firstly, the exact content of long-term follow-up could be decided on later, for example, based on the short-term results that are observed in an intervention study. One can decide to follow only children long-term with abnormal short-term outcomes. A disadvantage of this strategy is that abnormal long-term outcomes of children with normal short-term outcomes can be missed. A second alternative is to send questionnaires out to all families included, as sole
outcome measure or as step up for selection of certain groups, identified by scores on such questionnaires. Only children with abnormal outcomes, for example, can then be invited for further assessments. Questionnaires, like the Ages-and-Stages questionnaire (ASQ), have the advantage that they are relatively inexpensive and easy to organise. A disadvantage is that they are designed as developmental screening tools and therefore are less useful to detect mild problems, that tend to be common in (preterm born) children. Thirdly, representative random samples of the cohort could be assessed. Nevertheless, trialists have to consider a power calculation for the long-term outcome because enough children have to be followed long-term to be able to detect a significant difference between two groups of a study.

When more information about long-term child outcomes becomes available, one can also explore the association between short-term and long-term child outcomes and perhaps prediction models for long-term child outcomes based on these short-term outcomes can be developed. As far as we know, such prediction models for long-term child outcome do not exist. The development of such models requires large birth cohorts, in which data surrounding pregnancy, delivery and short-term outcomes are available, as well as follow-up data on various health related outcomes. Acquiring this information is expensive, but can be cost-effective on the long-term because with the help of these prediction models future trialists would be able to extrapolate short-term outcomes to a long-term horizon and less children have to be followed long-term.
Outline of the thesis

In this thesis, we will address the extent to which long-term child outcomes of perinatal interventions have been included in major obstetric randomized trials in the literature, explore possibilities for development of prediction models using existing long-term cohort data, and discuss the possibilities to formulate a brief guideline to determine whether and in which neonates follow-up needs to be performed to allow adjustment of trial conclusion based on long-term outcomes. The study protocol is published in BMC Pregnancy & Childbirth in 2010. The contents of this thesis will be discussed in more detail below.

For the development of prediction models for different long-term outcomes, we choose to use a Dutch cohort study of preterm (< 32 weeks) and/or small for gestational age infants (< 1500 g) (POPS study). These infants were born in The Netherlands in 1983 and followed until they reached the age of 19.

Chapter 2 presents our study protocol “Long-term health-related and economic consequences of short-term outcomes in evaluation of perinatal interventions”.

Chapter 3 describes the results of a systematic review on the frequency of long-term follow-up after large perinatal RCTs and whether or not this was planned before the start of the RCT. If follow-up was performed, we documented the percentage of children that was followed after discharge from the hospital and the follow-up methods that were used.

Chapter 4 describes the result of a systematic review to access the short- and/or long-term morbidity of late-preterm infants. Late preterm infants (34 0/7-36 6/7 weeks gestation) represent the largest proportion of singleton preterm births. This review summarizes all relevant studies on this subject between January 2000 to July 2010.

Chapter 5 describes the development of prediction models for neurological development at 2 and 5 years of age. Furthermore, different perinatal risk-indicators for long-term neurological morbidity were identified. We think that the development of prediction models for long-term child outcomes based on short-term neonatal outcomes might be an alternative to expensive and often underpowered follow-up studies.

Chapter 6 presents prediction models for long-term respiratory morbidity at 2, 5 and 19 years of age. Again different perinatal risk-indicators were identified, but now for long-term respiratory morbidity. Also is explored if respiratory distress syndrome really is a risk-indicator for long-term respiratory morbidity.
Chapter 7 describes three different follow-up strategies derived from three large obstetric randomized controlled trials. Systematically, pros and cons of these three different follow-up strategies will be discussed, and a brief guideline that can facilitate future perinatal trialist in their decision on follow-up is presented.

In Chapter 8 and 9 we summarize our results, and make recommendations for current research as well as for future developments.
References


