Long-term follow-up of obstetric studies
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Summary and general discussion
Summary

This thesis focuses on long-term child follow-up after obstetric studies. Obstetric randomized controlled clinical trials (RCTs) are performed to evaluate the effectiveness of perinatal interventions. However, most often only short-term outcomes are reported, while long-term outcomes are just as important because serious sequelae from perinatal complications frequently manifest themselves only after several years.

In this thesis we aimed (1) to assess the current state of affairs concerning follow-up after obstetric RCTs, (2) to explore the possibilities for development of prediction models for different long-term child outcomes using existing cohort data and (3) to discuss the possibilities to formulate a brief guideline for long-term follow-up to facilitate future clinical trialists in their decisions on the need for long-term follow-up.

In chapter 2 we presented an outline of the thesis in our study protocol. We announced a systematic review of neonatal follow-up after obstetric studies, in order to provide insight in the extent and methods used for follow-up assessments after obstetric RCTs in the past. Furthermore, we planned to develop multivariable prediction models for different long-term health outcomes. We also encouraged other researchers participating in follow-up studies after large obstetric trials (> 350 women) to inform us about their studies so that we could include their follow-up study in our systematic review and we invited these researchers to join our effort and to collaborate with us on the external validation of our prediction models.

Chapter 3 presents a systematic review on long-term follow-up after large obstetric RCTs (> 350 women). In total, 212 reviews including 1,837 RCTs on perinatal interventions were studied, of which 249 (14%) included > 350 participants. Only 40/249 RCTs (16%) followed the children after discharge from the hospital to evaluate the effect of a specific perinatal intervention. The number of RCTs with long-term follow-up remained stable with 10 out of 67 RCTs (15%) that reported follow-up before 1990, 17 out of 115 (15%) between 1990-2000 and 13 out of 67 (19%) after 2000 (p=0.68). This review shows also that methods used for children’s follow-up are inconsistent. Choices need to be made, especially when there is limiting funding, concerning whether to use questionnaires and/or assessments as follow-up tool and also the optimal age has to be determined. It would be a step forward if RCTs around the world would use a similar follow-up protocol.

In chapter 4 a systematic review is presented that summarizes the short and/or long-term morbidity of late preterm infants (34 weeks and 0/7 days through 36 weeks and 6/7 days). Late preterm infants account for about 74% of all preterm births and about 8% of all births and are the fastest increasing and largest proportion of singleton preterm births. We identified 22 studies studying 29,375,675 infants. Compared with infants born at term,
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infants born late preterm were more likely to suffer poorer short-term outcomes such as respiratory distress syndrome (RR 17.3, 95% CI 9.8 to 30.6), intraventricular haemorrhage (RR 4.9, 95% 2.1 to 11.7) and death before 28 days (RR 5.9, 95% CI 5.2 to 6.8). Beyond the neonatal period, late preterm infants were more likely to die in the first year (RR 3.7, 95% CI 2.9 to 4.6) and to suffer from cerebral palsy (RR 3.1, 95% CI 2.3 to 4.2). Although the absolute incidence of neonatal mortality and morbidity in infants born late preterm is low, this review shows that its incidence is significantly increased as compared with infants born at term. We hope that the findings of this study will contribute toward determining the optimal obstetrical management as obstetricians and other clinicians weigh the risks and benefits to mother and child.

In chapter 5 we identified risk-indicators for neurological morbidity and we used these risk-indicators to develop prediction models for long-term neurological morbidity at 2 and 5 year of age. Neonates born in The Netherlands in 1983 with a gestational age < 34 weeks and without congenital abnormalities were included (n=753). Infants were divided in three groups; no handicap, minor handicap and major handicap. Common significant risk-indicators for major handicaps at 2 and 5 year of age were male gender (OR 2.7, 95% CI 1.2 to 5.8; OR 3.0, 95% 1.1 to 8.0), seizures after ≥ 2 days of life (OR 5.8, 95% CI 1.9 to 17.8; OR 5.8, 95% 1.9 to 17.9) and intracranial haemorrhage (OR 3.8, 95% CI 1.6 to 9.1; OR 2.6, 95% 1.02 to 6.8). The prediction models for major handicaps discriminated modestly well between diseased and non-diseased with an area under the curve (AUC) of 0.76 (95% CI 0.69 to 0.83) at 2 years of age and an AUC of 0.74 (95% CI 0.67 to 0.81). Overall, the prediction models showed good calibration. Before our prediction models can be used in future obstetric studies to extrapolate the short-term neonatal outcomes to a longer study horizon they should be validated in more recent cohorts to investigate if the same risk-indicators for neurological morbidity are found.

In chapter 6 we identified risk-indicators for respiratory morbidity at 2, 5 and 19 years of age and this time we used these risk-indicators to develop prediction models for long-term respiratory morbidity. A common risk-indicator for respiratory morbidity at 2 and 5 years of age was bronchopulmonary dysplasia (OR 1.9, 95% CI 1.1 to 3.2; OR 1.8, 95% CI 1.1 to 3.0). Surprisingly, respiratory distress syndrome (RDS) seems not to be a risk-indicator for respiratory morbidity at all three ages in this cohort (OR 1.2, 95% 0.88 to 1.7; 1.3, 95% 0.88 to 2.0; OR 0.91, 95% 0.56 to 1.5 respectively). The areas under the curves (AUC) were 0.65 (95% CI 0.61 to 0.68), 0.71 (95% CI 0.66 to 0.75) and 0.61 (95% CI 0.56 to 0.66) respectively. The prediction models for respiratory morbidity at 2 and 5 years of age showed a good calibration, while the calibration plot for respiratory morbidity at 19 year was less optimal. Future obstetric studies interested in the effect of a specific perinatal intervention on long-term respiratory morbidity, should consider taking bronchopulmonary dysplasia (BPD) as primary outcome instead of RDS.
Chapter 7 discussed three follow-up strategies derived from three large obstetric studies with long-term follow-up performed in the past. To facilitate future trialist we summarized pros and cons of different strategies and provided a brief guideline to be of help in their decision making on long-term follow-up.
General discussion and implications for clinical practice and future research

The work presented in this thesis focuses on long-term child follow-up after obstetric studies. In recent years, there has been an increasing awareness in the importance of long-term child follow-up after obstetric studies. While in the past the majority of large obstetric studies did not perform long-term child follow-up, there is nowadays a tendency to plan long-term follow-up of all children in each study, sometimes even leading to designs where short-term outcomes are only reported together with long-term outcomes, as the allocation remain undisclosed until the primary endpoint is known, sometimes taking two year follow-up or even longer \(^1,2\).

The difficulty of long-term follow-up is that it is expensive, logistically difficult and time-consuming, which makes it important to pose the question if long-term follow-up of all children in each study is feasible and always necessary and therefore alternative strategies, in addition to follow-up of all children, must be considered. It is clear that at present there is no consensus worldwide on how long-term child follow-up should be performed. This thesis aims to make a step towards such a consensus. The decision whether follow-up is necessary and what strategy is most appropriate, seems to come down to four considerations:

I. Whether there is a relation between short-term and long-term outcomes.

II. Whether questionnaire based information is sufficient or whether physical assessments are required in all or part of the follow-up sample.

III. What health information is required and at which age the relevant outcomes can be appropriately measured.

IV. Whether the decision based on short-term results would change current practice.

When knowledge on the association between short-term and long-term outcomes is lacking, extrapolation of short-term findings to the long-term will not suffice. At present, this is the case for most short-term perinatal outcomes, so for the time being empirical long-term follow-up measurements should be seriously considered for trials on perinatal interventions.

When more information about long-term child outcomes becomes available, one can explore the association between short-term and long-term child outcomes and prediction models for long-term child outcomes based on these short-term outcomes can be developed. With exception of the prediction models for long-term child outcomes we recently have published, as far as we know, no other prediction models for long-term child outcomes exists \(^3,4\). We think however that such models have the potential to be a good alternative strategy for follow-up, provided that they are developed with accurate data.
As a consequence, 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. More long-term data is even required for the external validation of these models because prediction models are known to be optimised for the specific dataset in which they have been derived and external validation is required to correct for this bias due to overfitting. At present, many large randomized controlled trials with long-term child follow-up are underway in The Netherlands and these data can be used for the developing of new prediction models, but also for the external validation of our recently published models.

An alternative solution for acquiring data of long-term child outcomes would be to register long-term outcomes of all children in a national registry. For short-term outcomes there already exists such a registry. The Netherlands Perinatal Registry (PRN) consists of population-based data containing information on pregnancies, deliveries and (re) admissions until 28 days after birth. The PRN database is obtained by a validated linkage of three different registries: the midwifery registry (LVR1), the obstetrics registry (LVR2) and the neonatology registry (LNR) of hospital admissions of newborns. The coverage of the PRN registry is about 96% of all deliveries in the Netherlands.

Ideally, also long-term outcomes would be added to this registry, as is the case in Scandinavian countries. For example, every baby born in Denmark is included in the Danish Medical Birth Registry, a comprehensive electronic record of birth details. As babies grow older, more than 200 linked electronic registries keep track of every encounter with the nationalized medical establishment, recording every condition diagnosed and every drug prescribed.

In The Netherlands each child visits the Well Child Centers regularly till the age of four. During these visits, the growth of the child is checked, visual and hearing tests are performed, but also the development of the child is monitored. A limitation is however that these Well Child Centers perform only screening tests and have a limited time schedule to children, in which children may not want to perform. Additional funds will thus be needed to develop a test that obtains more valid information and for data base management, but then more data about long-term child outcomes could be easily obtained. Furthermore, in The Netherlands a CITO test is administered in every child from 5 years onwards and at the end of primary school. The result of at least the final CITO test provides valid information on school performance.

If all of this information could be linked to the PRN database, it would be a major step forwards to acquire more information about long-term child outcomes. A first step forward is recently made, because they started to register long-term outcomes of very preterm infants at 2 years of age in the PRN database in The Netherlands. With gaining more...
knowledge about the association between short and long-term child outcomes, we will be able to evaluate perinatal interventions more correctly and this will benefit the health of mother and child.
Reference list


5. Steyerberg EW. Clinical prediction models. Springer; 2009.


