Preterm birth

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Summary

SUMMARY

Chapter 1 gives an outline and describes the aim of this thesis.

Part I: Idiopathic spontaneous (recurrent) preterm birth

Chapter 2 *describes a nationwide retrospective cohort study of 52,978 women in which we compared the incidence of spontaneous and iatrogenic preterm birth in three sequential singleton pregnancies and the impact of the outcome of the first and second pregnancy on the (recurrent) preterm birth risk in the third pregnancy.*
We found that the incidence of PTB decreased with 50% from the 1st (7.0%) to the 2nd pregnancy (3.7%), to then stay relative stable in the 3rd (vs the second) pregnancy (3.4%). The outcome of the 2nd pregnancy is more predictive for PTB in the 3rd pregnancy then the outcome of the 1st pregnancy (sPTB aOR7.3 (95% CI 6.3-8.4) and iPTB aOR 5.9 (95% CI 4.5-7.9) in 2nd pregnancy vs. sPTB aOR 3.0 (95% CI 2.6-3.4) and iPTB aOR 2.7 (95% CI 2.1-3.4) in the 1st pregnancy). In the prediction of subtype of preterm birth, i.e. spontaneous PTB or iatrogenic PTB in the 3rd pregnancy, spontaneous PTB in the 2nd pregnancy is most predictive for spontaneous PTB in the 3rd pregnancy and iatrogenic PTB in the 2nd for iatrogenic PTB in the 3rd.

Chapter 3 *describes a nationwide retrospective cohort study of 2,361 women with three sequential singleton pregnancies with a spontaneous preterm birth <37 weeks in the first pregnancy. We evaluated the impact of interpregnancy interval on the recurrent preterm birth risk in the second and third pregnancy, using both conventional and conditional logistic regression analysis.*
Previous studies showed either a short or a long interpregnancy interval to be a risk factor for preterm birth. Whether this association is confounded by other risk factors, including various aspects of socioeconomic status, ethnicity, demographics, and lifestyle, is unclear. In this thesis we examined the association more in depth and tried to rule out any unknown confounders in between mother-comparison by using both conventional and conditional logistic regression analyses in a cohort of women who have had three births. We used a matched model to analyse the impact of the interpregnancy interval, in which each mother was used as her own control for risk factors, to adjust completely for persistent maternal factors.
We found that a short interpregnancy interval (0-5 months) is associated with an increased risk of recurrent PTB <37 weeks (OR2.2, 95% CI 1.6-3.1) and PTB <32 weeks (OR 2.9, 95% CI 1.4-5.9). A long interval (≥60 months) is also associated

with an increased risk of preterm birth <37 weeks (OR2.2, 95% CI 1.3-3.7). Conditional logistic regression analysis confirmed the effect of a short interval on the recurrence of preterm birth rate <37 weeks.

Chapter 4 *describes a nationwide retrospective cohort study with 15,351 women with two sequential singleton pregnancies with a spontaneous preterm birth <37 weeks in the first pregnancy in which the association between fetal gender in the first pregnancy and the risk of recurrent spontaneous preterm birth was assessed.*
Previous studies showed that fetal gender is a factor impacting the likelihood of spontaneous preterm birth, with male fetal gender being associated with an increased risk of preterm birth. This could suggest that women who deliver a preterm female fetus, are more likely to have an underlying maternal factor contributing to the preterm birth than women who deliver prematurely a male fetus at the same gestational age. Since this maternal factor will remain present in the second pregnancy, women who delivered a female fetus preterm, would have a higher risk of recurrent preterm birth in the second pregnancy. In this thesis we tested this hypothesis by studying the effect of fetal gender in the first pregnancy on the risk of recurrent spontaneous preterm birth in the subsequent pregnancy. We studied 15,351 women with a spontaneous PTB of a singleton pregnancy between 1999 and 2009. We found that the risk of recurrent spontaneous PTB <37 weeks was increased when the first fetus was female compared when that fetus was male (aOR 1.2, 95% CI 1.05-1.3). We found a similar effect for spontaneous PTB <32weeks (aOR4.5, 95% CI 1.5-13).

Part II: Spontaneous preterm birth after routine interventions

Chapter 5 *describes a decision and cost-effectiveness analysis to compare the impact of eight different screening programs for cervical cancer on the risk of preterm birth and subsequent neonatal outcome relative to maternal live years gained and costs of both screening and preterm birth.*
Early detection and treatment of cervical intraepithelial neoplasia (CIN) have considerably reduced the incidence of cervical cancer and lowered the mortality of the disease. However cervical surgery is associated with preterm birth. Previous studies comparing the cost-effectiveness of cervical screening programs, have not taken these unintended adverse effects, like preterm birth, into account. In this thesis we assessed the impact of 8 cytology-based screening programs on the risk of additional preterm birth and subsequent neonatal morbidity and mortality,

relative to the maternal the life years gained due to prevented cervical cancer and the costs of both screening and preterm birth.
We found that cervical cancer screening every 3 years and subsequent treatment in women aged younger than 30 years yield limited life-years but may have substantial perinatal adverse effects. Consequently, women who plan to have children may benefit from a more cautious screening approach, taking into account their risk for both cancer and preterm birth.

Chapter 6 *describes a systematic review and meta-analysis of 20 studies with a total of 12,159,293 women. We assessed the risk of preterm birth of treated versus untreated cervical intraepithelial neoplasia (CIN).*
Although cervical surgery is associated with preterm birth, recent studies question whether this is related to the surgery itself or due to the cervical intraepithelial neoplasia or maybe even to an underlying communal disorder resulting both in cervical intraepithelial neoplasia and preterm birth, thus potentially confounding the association between cervical surgery and preterm birth. To address this issue, we conducted a systematic review and meta-analysis, in which we compared pregnancy outcomes between women with CIN who have been treated before pregnancy, treated during pregnancy, or not treated as well as women without CIN. We found that women treated for CIN before or during pregnancy, had a significantly higher risk of PTB<37 weeks (OR 1.7, 95% CI 1.0-2.7) then women with untreated CIN. When comparing women treated for CIN before pregnancy to women with untreated CIN, we found an OR of 1.4 (95% CI of 0.85-2.3). Women treated during pregnancy had a clearly increased risk for PTB (OR 6.5, 95% CI 1.1-37), and (P)PROM (OR 1.8, 95% CI 1.4-2.2).
The increased risk of PTB in women who underwent cervical surgery for CIN is especially increased when performed during pregnancy. When performed before pregnancy the risk of PTB is increased, although insignificant.

Chapter 7 *describes a decision analysis to assess the impact of the individual preterm birth risk on the ongoing pregnancy rates, multiplicity and neonatal outcome after single and double embryo transfer according to the Hunault model.*
We found that In women with good fertility prospects, one IVF cycle with DET increases the ongoing pregnancy rate (OPR) from 29 to 39% compared with SET, whereas the chances of poor neonatal outcome in these extra pregnancies range from 1.4 to 11% per pregnancy depending on the individual PTB risk. However, for women with poor fertility prospects, DET increases the OPR from 8 to 11% with minimal additional poor neonatal outcome, ranging from 0.3 to 4.0% per

pregnancy for women with a low or high PTB risk, respectively. In an IVF program, the optimal embryo transfer strategy is dependent on the singleton and multiple pregnancy chances of a woman, but also on her PTB risk. Our analysis pleads for a tailored management strategy, taking into account the personalized prognosis for (multiple) pregnancy and PTB.

Chapter 8 *describes an opinion paper in which we discuss how the indications for IVF have expanded, what the evidence is that underpins its extended remit and how the balance is between risks and benefits for certain indications.*
Although IVF has allowed many infertile couples to have a family, nowadays IVF is also offered in couples with mild male subfertility, endometriosis, and unexplained subfertility. Since IVF is associated with an increased risk of preterm birth, can the risks of IVF be justified for these more liberal applications? In this thesis we gave an overview of the little existing evidence underpinning the use of IVF for different types of infertility and the change in indications over the years and the adverse pregnancy and health outcomes in IVF children.