Preterm birth

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General discussion

GENERAL DISCUSSION

Preterm birth

Preterm birth remains one of the main problems in perinatal medicine, being responsible for the majority of the neonatal morbidity and mortality with an estimated 15 million babies being born preterm worldwide annually. [1] Preterm birth can be subdivided in spontaneous and iatrogenic preterm birth. Spontaneous preterm birth is defined as spontaneous onset of labour or following prelabour premature rupture of membranes (PPROM). Spontaneous preterm birth can also occur with an underlying iatrogenic intervention, i.e. a gynaecological interventions including conisation or spontaneous preterm birth of a twin after double embryo transfer. Iatrogenic preterm birth, also known as provider initiated or indicated preterm birth, is defined as induction of labor or elective caesarean birth before 37 completed weeks of gestation for maternal or fetal indications mostly indicated for hypertensive disorder or fetal growth restriction.

Although many maternal and fetal risk factors for preterm birth have been identified, still a large proportion of spontaneous preterm birth occurs in women without any of these risk factors. Better understanding of the complex etiologies of preterm birth would increase our ability to select women at risk of preterm birth and –possibly- to prevent preterm birth.

In this thesis we focused on risk factors of -recurrent- preterm birth (part I) and preterm birth after iatrogenic, gynaecological interventions including invasive treatment for cervical intraepithelial neoplasia and assisted reproductive technology (part II).

Spontaneous - recurrent - preterm birth

Maternal risk factors

Many maternal parameters influence the risk of preterm birth during pregnancy, including a history of preterm birth, short or long inter-pregnancy intervals, low maternal body mass index, smoking, young or advanced maternal age, low socio-economic-status and non-White ethnicity.

The first and most predictive risk factor for recurrent spontaneous preterm birth - a history of spontaneous preterm birth-, has a RR 6.0 for sPTB <32 weeks and RR 4.8 for sPTB between 32-36 weeks. [2] Therefore, women with a history of spontaneous preterm birth are counseled for preventative treatment in the subsequent pregnancy, e.g. progesterone which reduces the risk of recurrent preterm birth by 36%. [3]

A second risk factor is a short or a long interpregnancy interval, but previous studies suggested this association is confounded by or completely due to other risk factors, including socioeconomic status, ethnicity, demographics, and lifestyle. [4-6] In this thesis we therefore examined the association more in depth and determined to rule out any unknown confounders by both conventional and conditional logistic regression analyses in a cohort of women who had three consecutive 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 either a short or a long interpregnancy interval, defined as 0-6 months or >60 months respectively, increases the risk of recurrent preterm birth (OR 2.2, 95% CI 1.6-3.1 and OR2.2, 95% CI 1.3-3.7 respectively) (chapter 3). This knowledge could be used to counsel women about birth spacing, particularly in those women with a previous preterm birth.

A third risk factor -maternal life style- is amenable for interventions, in which the woman herself may potentially improve the outcome of her pregnancy. Good counselling and support could help women to quit smoking or to make life style changes to reduce obesity. The same applies for counselling young women about the risks of teenage pregnancies and options for contraceptives. In the Netherlands recently the program “een kansrijke start” has been introduced since the health of a child before, during and after birth is a predictor for both physical and mental problems later in life. [7,8] The aim of this program is providing a “ promising start” to all children in which the government invests 41 million euro’s from 2018-2021 to roll out three pathways of care in vulnerable families. First a preconception pathway to reduce the amount of unplanned pregnancies and to prepare the expectant parents well before getting pregnant. The second pathway is during pregnancy in which the focus is on early recognition of medical and social problems and subsequently putting the right supportive care in place early. Finally a post pregnancy pathway to prepare expecting parents on the actual parenthood and to reduce the amount of children that need to be put in foster care.

A fourth risk factor is socio economic class and especially living in a deprived neighbourhood. With the support of the Ministry of Health and Welfare a nationwide study called ‘Healthy Pregnancy 4 All’ (HP4All), was initiated in the Netherlands. The main objective of HP4All is to evaluate the effectiveness of a multitide of interventions and their associated preventive strategies in either the preconception period or the antenatal period to reduce adverse pregnancy outcome for these women. Accordingly, two sub-studies were designed: a population-based prospective cohort study focusing on the effectiveness of customized preconception care and a systematic antenatal risk assessment score-

card including both medical and non-medical risk factors followed by patient-tailored multidisciplinary care pathways.
During preconceptional or first antenatal visits all maternal risk factors should be assessed and the modifiable risk factors should be addressed accordingly, acknowledging that still a large proportion of spontaneous preterm birth occurs in women without any of the known maternal risk factors.

Fetal risk factors

Besides maternal risk factors, some fetal risk factors have been identified as well. Male gender of the fetus, multiple gestation and congenital abnormalities are such factors.
In this thesis we studied the effect of fetal gender in the first pregnancy on the risk of recurrent spontaneous preterm birth in the subsequent pregnancy. Our hypothesis was that women who deliver a preterm female fetus, who is less likely to be born preterm than a male fetus, are themselves 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. If this were true, we would expect an increased risk of recurrent preterm birth after a preterm birth of a female fetus and indeed we found an increased risk of recurrent spontaneous PTB <37 weeks and PTB <32 weeks when the first fetus was female compared when that fetus was male (chapter 4).
A second risk factor is multiple gestation. Approximately 50% of twin pregnancies deliver preterm at less than 37 weeks, and 14% deliver at less than 33 weeks. [9] In 2015 in the Netherlands 52.7% of twin pregnancies resulted in PTB <37weeks and 9.7% in PTB <32 weeks. [10] Although women with a multiple pregnancy represent only 1-3% of all pregnancies in Europe and the USA, they account for 15-20% of all preterm births. [11, 12]
Unlike in singleton gestations, where meta-analyses have shown some benefit of progesterone, pessary, or cerclage, meta-analyses of these interventions in twin pregnancies have not found a reduction in rates of preterm birth. [13-18] The only positive finding is that vaginal progesterone improved some important secondary outcomes that are sequelae of preterm birth, including very low birthweights of <1500 g in women overall and in women with short cervices. [18] In line with these data, a recent addendum to the NVOG guideline, does not recommend routine use of preventative treatment like progesterone, cerclage or pessarium in women carrying twins. However, in women carrying twins and a short cervix, vaginal progesterone might reduce the risk of preterm birth and its sequelae, which is part of the study protocol of the Quadruple P study (Progesterone, Pessary,

Prevention Preterm birth). This study aims to compare the effectiveness of vaginal progesterone and cervical pessary in the prevention of preterm birth in women with singleton and multiple pregnancies with a short cervix.
Since there is currently limited preventative treatment for preterm birth in twin pregnancies, which do account for about 20% of all preterm birth, it is of major importance to reduce the number of twin pregnancies after gynaecological interventions, like ovulation induction or double embryo transfer.

Preterm birth after gynaecological interventions

Since preterm birth continues to be the leading cause of perinatal morbidity and mortality in developed countries, it is important to critically evaluate our routine gynaecological interventions that could induce preterm birth, since these cases of preterm birth could potentially be prevented. In this thesis we focused on the risk of preterm birth after cervical cancer screening and treatment and artificial reproductive technology. Another important routine gynaecological interventions which impacts the risk of preterm birth is curettage as treatment for first trimester miscarriage.

Screening for cervical cancer

Cervical screening is the process of detecting and removing abnormal tissue or cells in the cervix before cervical cancer develops. The incidence of cervical cancer is highest between 35-45 years, so most women undergoing local treatment for cervical preinvasive cervical disease are of reproductive age (<45 years of age), while local cervical treatment has been associated with an increased risk of preterm birth. [19] The clinical problem is thus the trade off between prevention of cervical cancer and increased risk of preterm birth. However, since the first systematic review on the risk of preterm birth associated with treatment for cervical pre-invasive laesions a decade ago, later systematic reviews and meta-analyses reached contradictory conclusions. This could potentially be due to differences in the explored comparisons or to confounding of the dysplasia itself, i.e. not the lisexcision but the underlying dysplasia increasing the risk of preterm birth. [20-23] To explore the latter, we assessed in this thesis the risk of preterm birth of *treated* versus *untreated* cervical intraepithelial neoplasia (CIN) with a systematic review and meta analysis (chapter 6). 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) than women with untreated CIN. When performed before pregnancy the risk of PTB was increased, although not statistically significant.

After our study another a systematic review and meta-analysis with several comparison groups was published. This study confirmed our findings and found an increased risk of preterm birth after LLETZ compared to women with HSIL and no treatment (RR1.48, 95%CI 1.35-4.55), thereby also ruling out the impact of the lesions itself. [25] These data warrant caution in the use of excisional procedures in women with a (future) childwish, especially since up to 40% of CIN 2 lesions regress spontaneously.

As it is not yet possible to differentiate between CIN lesions that will regress naturally and those that will progress to cancer, many CIN II+ lesions are treated. Thus, the detection of precancerous lesions and subsequent treatment based upon national screening programs has – amongst others- resulted in unintended adverse effects due to preterm birth in women who became pregnant after treatment. This increased risk of preterm birth is not limited to the first birth after treatment. [24]

A second issue is that the screening programs vary widely around the world with respect to start age and screening interval. [25] This could impact the trade off between cervical cancer prevention and risk of preterm birth. In this thesis we compared the impact of eight different screening programs for cervical cancer on the risk of preterm birth in a decision and cost-effectiveness analysis. 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 (chapter 5). Consequently, women who plan to have children may benefit from well informed decision making, taking into account their risk for both cancer and preterm birth.

Since we started our studies described in his thesis, the cervical cancer screening in the Netherlands changed in 2017 from primary cytological screening to primary HPV testing. Women who are HR-HPV positive and have a cytology of Pap2 or more are now referred for colposcopy. Because of the high incidence of HR-HPV, this has lead to an increased number of women undergoing colposcopy. In the first year of primary HPV screening 6.0% of all women were referred to a gynaecologist, compared to 2.9% in the period 2012-2016 when cytology was the primary screening method. [26] Although the current HPV tests are more sensitive in detecting CIN 2 or worse and CIN 3 or worse than cytology, this higher sensitivity comes with reduced specificity. Therefore, one should be cautious with a direct "see and treat" policy at colposcopy - especially in younger women with a high chance of clearance of their HPV virus - since the majority of HPV-positive women does not have clinically relevant disease. Since the start of the primary HPV screening policy, the new guideline therefore recommends tailor made treatment

for CIN2 in women of reproductive age, balancing the risk of progression of disease versus risks and complications of the treatment, which is an important change.

Next to secundary prevention of cervical cancer by screening programs, primary prevention is currently also available. Preventive vaccination, by intramuscular injection of HPV virus-like particles, triggers the production of antibodies, which protect against future HPV infections. In young women aged 15 to 26, who are high-risk human papillomavirus (hrHPV) negative or HPV16/18 negative at baseline, HPV vaccination reduces the risk of persistent HPV16/18 infection, high-grade cervical intraepithelial neoplasia or worse (CIN2+) and adenocarcinoma in situ (AIS) associated with the vaccine types. Average rates of CIN2+ reduced from 164 to 2 per 10,000 and CIN3+ from 70 per 10,000 to 0 per 10,000 due to vaccination. [27] In 2018 globally, 74 countries have implemented the HPV vaccine in the national immunization schedule, and this vaccine is listed as an essential medicine by WHO. [28] It is worrying that the uptake of the vaccination program varies widely, with among the 2003 birth cohorts in Denmark only 17% of girls receiving a full course of the vaccine, while Australia achieved high coverage across both sexes (around 70-75%).

In Australia, the Australian National HPV Vaccination Program (NHVP) was rolled out in 2007 for both girls and boys. [29] This lead to a large reduction in the prevalence of vaccine HPV types, decreasing from 22.7% (2005–2007) to 1.5% (2015) among women aged 18–24, and from 11.8% (2005–2007) to 1.1% (2015) among those aged 25–35. [30] The early adoption of both HPV vaccination and HPV-based cervical screening, high uptake of the vaccine, and high participation in screening program in Australia could lead to less than 6 cases of cervical cancer per 100.000 women by 2020, assuming ongoing high coverage of existing vaccination and screening. [29] Since 2008 vaccination for hr-HPV 16 and 18 is offered to girls at age 13 in the Netherlands since HPV16 and 18 cause about 70% of cervical cancers worldwide. It is disconcerting that the uptake of HPV vaccination in the Netherlands is poor and decreased from 2016 to 2017 from 53.4 to 45.5%. Encouraging women to participate in the HPV vaccination program could be an important preventative strategy and we should consider offering a vaccination program to men as well.

Artificial reproductive technology

Artificial reproductive technology increases the risk of preterm birth, not only due to higher multiple pregnancy rates, but also due to singletons conceived after IVF who have an increased risk of preterm birth. [31-34] Meanwhile, the total number of ART cycles worldwide have gradually increased over the years. [35] In 2006 a total of >1,050,300 cycles resulted in an estimated 256,000 children, of which about

116,000 were born in Europe. [36] Similar figures for the most recent ICMART data in 2011show an increase to estimated nearly 400,000 children born worldwide of which 166,000 born in Europe. [37]

Partly this rise can be explained by the wider range of indications for IVF, for example unexplained subfertility. In this thesis we discussed how the indications for IVF have expanded, what the evidence is that underpins its extended remit and how the balance is between risks (i.e. preterm birth) and benefits for certain indications (chapter 8).

Initially, the main reason for the increased risk of preterm birth after ART was the high multiple pregnancy rates after ART. When pregnancy rates after assisted reproductive technology increased, single embryo transfer (SET) was introduced to diminish the risk of multiple pregnancies and subsequent preterm birth. In this thesis we assessed the impact of the individual preterm birth risk on ongoing pregnancy rates, multiplicity and neonatal outcome after SET and DET in a decision analysis. Our analysis pleads for a tailored management strategy, taking into account the personalized prognosis for (multiple) pregnancy and PTB (chapter 7).

In 2013 repeated SET, defined as either two cycles of fresh SET (one study) or one cycle of fresh SET followed by one frozen SET in a natural or hormone-stimulated cycle (two studies) was compared with DET in a systematic Cochrane review. The cumulative live birth rate after repeated SET was not significantly different from the rate after one cycle of DET (OR 0.82, 95% CI 0.62 to 1.09) with a 42% chance of live birth following a single cycle of DET and between 31% and 44% after repeated SET. The multiple pregnancy rate was significantly lower in the SET group (OR 0.03, 95% CI 0.01 to 0.13), with a 13% risk of multiple pregnancy following a single cycle of DET and 0-2% following repeated SET. [38] National data from the USA in 2013 also demonstrate that clinics that perform higher rates of elective single-embryo transfer (eSET) in women aged <38 years have decreased rates of multiple gestation, without a significant negative impact on cumulative live-birth rates. [39]

In view of these data, ESHRE published a revised guideline in 2015 for good clinical practice in IVF laboratories. [40] This guideline states that single embryo transfer is recommended to avoid multiple pregnancies. The decision on the number of embryos to transfer should be based on embryo quality and stage of development, female age, ovarian response and rank of treatment. The NICE guideline (2017) (CG156) also recommended single embryo transfer in most cases, based on maternal age and quality of embryos. [41]

Despite the evidence and guidelines, the global uptake of elective SET has been variable. For example in 2014 in the UK 48.7% of cycles were SET of which only 28.7% eSET. [42] The use of eSET was higher in the USA with 42.2% across all age

groups in 2016, with a multiple pregnancy rate of 16% after ART. [43] In Europe in 2014 the percentage of SET varied from 4.3% in Albania to 79.9% in Sweden, with an average of 34.9% and an average multiple pregnancy rate of 17%. [44] In Australia and New Zealand in 2016 87.7% of the cycles were SET cycles, leading to only 3.8% of multiple pregnancies. [45] So worldwide the implementation of SET can still be improved.

Treatment of miscarriage

A first trimester miscarriage is the most common complication in pregnancy and occurs in 10-15% of pregnant women. [46] Several treatment options are available like expectant management, curettage or medical treatment with misoprostol. A systematic review and meta-analysis in 2016, including 21 studies and 1,853,017 women, showed an increased risk of preterm birth <37 weeks (OR1.29, 95% CI 1.17-1.42), preterm birth <32 weeks (OR 1.69, 95% CI 1.20-2.38) and preterm birth <28 weeks (OR 1.69, 95% CI 1.47-1.92) after curettage. [47] Multiple curettages increased the risk of preterm birth <37 (OR1.74, 95% CI 1.10-2.76). Although not addressed in this thesis, medical management i.e. misoprostol is effective in 50-85% of the women. We also know that in cases of an initial incomplete evacuation after misoprostol treatment, 5 out of 6 women have an empty uterus after expectant management. [48] These data warrant caution in the use of curettage for a miscarriage since less invasive effective options are available, which do not increase the risk of preterm birth in a subsequent pregnancy. These data should also be considered when counselling (young) women for an unwanted pregnancy for which they request abortion.

Ongoing research in the Netherlands

Increasing evidence suggests that utero-placental ischemia plays a role in the genesis of spontaneous preterm birth. Placental vascular and placental bed pathology or an abnormal angiogenic/anti-angiogenic profile in maternal plasma are commonly seen in women with a spontaneous preterm birth and these women are at increased risk of developing cardiovascular disease later in life. [49-55] These findings suggest a possible similar underlying mechanism with other ischemic placental diseases such as preeclampsia and therefore preventive measures for ischemic placental disease might also be effective in preventing recurrent spontaneous preterm birth. Aspirin – a thromobycte aggregation and prostaglandin inhibitor - is used in daily obstetrical practice for the prevention of severe fetal growth restriction and preeclampsia after this was proven effective in several studies. [56] Based upon the presumed similar underlying mechanism of

spontaneous preterm birth with severe fetal growth restriction and preeclampsia, the APRIL trial (Low dose Aspirin in the Prevention of Recurrent Spontaneous Preterm Labour) has been initiated in the Netherlands.
The APRIL trial is a multicentre double-blinded randomised trial, to answer the question whether aspirin reduces the risk of recurrent spontaneous preterm birth < 37 weeks. Secondary outcome measurements are spontaneous PTB < 28, 32 and 34 weeks, neonatal morbidity and SGA (<p10).
Women with a history of spontaneous preterm birth are counseled for preventative treatment in the subsequent pregnancy, like progesterone. Additionally, women with a prior preterm birth due to cervical insufficiency can be offered a primary cervical cerclage, i.e. history based cerclage. [57] Recently, several randomised trials showed that the cervical pessary may be potentially effective as a treatment for preterm birth prevention. [58-60] Based upon this preliminary evidence, the PC study (Pessary – Cerclage Study) is currently ongoing in the Netherlands, which is a multi-centre, non-inferiority, randomised controlled trial to compare a cervical pessary with a cervical cerclage in the prevention of preterm delivery in women with short cervical length and a history of preterm birth. The primary outcome is delivery before 32 weeks. Secondary outcomes will be gestational age at birth, preterm birth rate before 24, 28, 34 and 37 weeks of gestation, premature rupture of membranes, use of tocolysis and/or corticosteroids during pregnancy, mode of delivery, maternal infections, maternal side effects, neonatal and maternal hospital admissions, and a composite of adverse perinatal outcomes including both morbidity and mortality.
When a woman is presenting with threatening labour <34weeks of gestation, corticosteroids are offered to a woman to improve neonatal outcome. Whether or not tocolytics are added to the corticosteriods varies worldwide. For example, Canada and Ireland do not give tocolytics, in the Netherlands nifedipine or atosiban is given, while the USA indocid is given and in Australia nifedipine. The WHO recommendations on interventions to improve preterm birth outcomes, do not include tocolytic treatment in women at risk of imminent preterm birth for the purpose of improving newborn outcome. [61] They do state that in women with an otherwise uncomplicated pregnancy the acute use of tocolytic drug to prolong the pregnancy (up to 48 hours) can be considered to provide a window for the administration of antenatal corticosteroids, although there is currently no direct evidence that this improves neonatal outcome. There are many trials and systematic reviews that have studied tocolytic treatment, but most of them originally examined the effectiveness of a particular class of tocolytics, not the intervention itself. Therefor the APOSTEL VIII trial is ongoing in the Netherlands

and soon also in the United Kingdom, Ireland and Belgium. The APOSTEL VIII trial is a multicenter, double blinded, placebo controlled, randomised clinical trial. The aim of this study is to investigate if tocolysis with atosiban in late preterm birth (30 to 34 weeks) is (cost-) effective compared with placebo in improving neonatal morbidity and mortality. The primary outcome is a combined perinatal outcome of severe neonatal morbidity and perinatal mortality. Secondary outcomes are birth within 48 hours, time to delivery, gestational age at delivery, birth weight, number of days on invasive mechanical ventilation, length of admission in NICU, convulsions, asphyxia, meningitis, pneumothorax and mortality until 3 months corrected age, maternal infection, maternal side effects and costs.
These studies, combined with the previous mentioned Quadruple P study will provide important information on the effectiveness of -preventative- treatment in -recurrent- preterm birth.
Obviously, further research is needed to fully understand the complex etiology of preterm birth. Better understanding of the pathophysiology of this heterogenetic complication would increase our ability to select women at risk of preterm birth so we can intervene in an earlier phase. The next step is to use the NIPT test for prediction of preterm labor. A set of clinical parameters, including i.e. treatment of the cervix, fetal sex, interpregnancy interval, obstetric history and biochemical data (to develop from the NIPT) will ultimately enable us to predict preterm labor.
Finally, since preterm birth remains one of the major problems in perinatal medicine and since its complications are responsible for the majority of neonatal deaths in otherwise healthy infants with accompanying costs, it is of major importance to consider potential consequences of routine gynaecological interventions on the risk of preterm birth - cause these preterm birth could be prevented - and to add this to the national research agenda.

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