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CHAPTER 12

Summary and general discussion

SUMMARY

The work presented in this thesis focused on:

- study screening options for spontaneous preterm birth in order to identify risk factors and gain insight in pathophysiologic mechanisms
- investigate the association between asymptomatic bacteriuria and poor perinatal and maternal outcome to investigate the necessity of a screen and treat program in the Netherlands
- explore differences in perinatal mortality near term in certain subgroups in order to individualize management of these pregnancies.

Below we summarize the main findings of each chapter.

Prediction of preterm delivery

It was already known that women with a previous preterm birth are at increased risk of a second preterm birth. However evidence about the risk of recurrence if one of the pregnancies is a twin was scattered. **Chapter two** is a systematic review and meta-analysis of the recurrence of spontaneous preterm birth in singleton and multiple pregnancies. We found that the risk of recurrence of spontaneous preterm birth is significantly increased in all previous preterm births regardless of pregnancy subtypes, compared to previous term births. Women pregnant with a twin after a previous preterm singleton birth, have the highest absolute risk of recurrence (57%), but even after a previous term singleton birth, the absolute risk of preterm birth in a second twin pregnancy is still high (25%). Women pregnant with a singleton after a previous preterm twin birth have the lowest risk of recurrence (10%), and a singleton pregnancy after a previous term twin birth yields the lowest absolute risk of preterm birth, at only 1.3%. Women pregnant with a singleton after a previous preterm singleton birth have an absolute risk of recurrence of 20%.

Pregnancy can be dated using the last menstrual period or by measuring the foetal crown-rump length (CRL) using ultrasound. A previous study showed an association between a relatively short CRL measurement (compared to the expected length based on the last menstrual period) and preterm birth in general (both spontaneous and iatrogenic)[16]. In **chapter three** we investigated whether a relatively short CRL in the first trimester was associated with spontaneous preterm birth before 32 weeks' gestation. We found that there was no association between relatively short CRL and early spontaneous preterm birth, thus relatively short CRL cannot be used to identify women at increased risk of spontaneous preterm birth.

Prior studies showed an increased risk of preterm birth in male foetuses compared to female foetuses but it was unclear whether this holds true for all subtypes of preterm birth. Our goal in **chapter four** was to investigate per week of gestation the risk of preterm birth between male and female foetuses subdivided by type of preterm birth. Male foetal gender is an important risk factor for spontaneous preterm birth, both with intact membranes and for premature prelabour rupture of membranes (PPROM).

The risk of preterm birth differs between countries and populations. Cervical length can be used as a predictor for preterm birth. In **chapter five** we have demonstrated that the distribution of cervical length and its predictive value for preterm birth is similar in two geographically distinct populations. Nevertheless, despite these similarities, we found nulliparous women from the Netherlands to have a 3-fold increased risk of spontaneous preterm birth between 28 and 31 weeks and a 5-fold increased risk of spontaneous preterm birth before 28 weeks of gestation compared to women from Chicago. Assuming that cervical shortening is a reflection of one type of pathophysiology leading to spontaneous preterm birth, our data suggest that the increased risk of early preterm birth among women in the Netherlands is indicative of an excess of other pathophysiologic mechanisms.

Asymptomatic bacteriuria in pregnancy

Asymptomatic bacteriuria is harmless in most healthy man and women; however several groups are at increased risk of complications. In **chapter six,** epidemiology, risk factors, complications and treatment of asymptomatic bacteriuria and urinary tract infections (UTI) in pregnant women and women with diabetes are reviewed. We found SGLT2 inhibitors to be associated with a small increased risk for UTI. In addition, UTI in diabetic women may lead to acute kidney injury. Several recent studies published on the long term effects of antibiotic treatment of ASB and UTI during pregnancy on the neonate. Up-to-date research on the effectiveness and long-term effects of ASB screening and treatment policies, is warranted to inform clinical practice.

Evidence about screening and treating ASB in pregnancy is outdated (most were conducted over 30 years ago) and of relatively bad quality. Despite the lack of appropriate evidence, many countries routinely screen and treat for asymptomatic bacteriuria in pregnancy. In view of the lack of good clinical evidence on the subject and the resulting practice variation, we designed a clinical trial evaluating the effects of a screen and treat program in the Netherlands described in **Chapter seven.**

Chapter eight describes the prevalence and risk factors of ASB in a modern Dutch cohort. Our data show that in a modern cohort, 5% of pregnant women between 16 and 22 weeks of gestation have asymptomatic bacteriuria. *Escherichia coli* was found to be the most prevalent microorganism. Risk factors associated with ASB were a higher BMI, three or more previous UTI and conception through IVF or ICSI. Despite these associations, the prediction of ASB with these risk factors was poor.

For a screen and treat strategy to be effective, knowledge about the consequences of untreated ASB are essential. In **chapter nine** we investigated maternal and neonatal consequences of untreated ASB in pregnancy. We found that women with untreated ASB were at increased risk of pyelonephritis and symptomatic UTI during pregnancy. The absolute risk of pyelonephritis with untreated ASB was small (2.5%) and much lower than currently reported in literature (21%)[15]. Pregnant women with untreated ASB were not at increased risk for preterm birth or SGA.

Optimal timing of delivery
If a woman does not deliver prematurely, it is not known what the optimal timing of delivery is in the term period. In **chapter ten** we compared expectant management with delivery in three groups of SGA foetuses, non-SGA, SGA p5-10 and SGA<p5 foetuses. Delivery of SGA < p5 foetuses at 38 and 39 weeks is associated with the best perinatal outcome whereas for non-SGA foetuses this is at 39 to 40 weeks. For the SGA p5–10 group, there is a less clear defined interval. Obviously, maternal preferences and maternal and foetal condition should be taken into account in the ultimate decision, but our data suggest that in pregnancies with suspected SGA, induction of labour should be considered from 38 weeks onwards.

In **chapter eleven** we investigated whether women from different ethnic origin have different optimal timings of delivery. Our data show that Mediterranean and African-Caribbean women at term were at increased risk of antepartum and intrapartum/neonatal mortality, and neonatal morbidity, compared with white European women. Although there are ethnic disparities in the probabilities of mortality and morbidity, the optimal timing of delivery for white European women is 39 weeks of gestation, and for women of Mediterranean descent it is 38 and 39 weeks of gestation. For African-Caribbean women no statistically significant differences were found between expectant management and delivery, but there was a trend towards better neonatal outcome with delivery from 38 weeks of gestation onwards.

GENERAL DISCUSSION

Individualized risk assessment
It is already known that certain maternal characteristics (such as maternal obstetric history) are associated with an increased risk of preterm birth. Besides maternal characteristics, also certain foetal characteristics or even environmental or pregnancy specific characteristics can increase the risk of preterm birth. In women with a history of preterm birth, we tend to focus mainly on the women and her previous performance. Foetal characteristics and pregnancy specific/environmental factors are often not incorporated in the risk assessment.

Other specialties such as cardiology are further ahead in their risk assessments, for instance by using the Euroscore method (European System for Cardiac Operative Risk Evaluation). This is a method of calculating predicted operative mortality for patients undergoing cardiac surgery[17;18], using three different levels: patient related factors, cardiac-related factors and operation-related factors.

Translating this concept into obstetric care, for instance for the potential of a women-foetus-combination to successfully carry a pregnancy till term, could lead to the following three levels: maternal potential, foetal characteristics and pregnancy-specific/environmental factors. The studies performed in this thesis help to highlight the importance of personalized medicine in both risk assessment and treatment strategies.

Maternal potential

Already during the preconceptional visit or the first antenatal visit, several maternal parameters can be collected in order to get an idea about a woman's intrinsic ability to carry a pregnancy up till term (maternal potential). Several parameters influence the maternal potential such as general health, genetic predisposition and her past obstetric performances.

General health

The general health and physical condition of a woman at the time of the pregnancy influences her risk of complications during pregnancy or delivery. Pregnancy is sometimes referred to as the ultimate stress test of a woman's body. For example, the likelihood of pre-existing comorbidities is known to increase with advancing maternal age, and women of advanced maternal age are significantly more likely to have a preterm birth [19].

Women with a pre-existing medical condition are at increased risk of pregnancy complications, and spontaneous and iatrogenic preterm birth due to these complications. Almost one-third of women with chronic hypertension deliver preterm [20] and women with pre-existing diabetes mellitus are also at increased risk of preterm birth (OR 2.2, 95% CI 1.4 to 3.7)[21].

Also a woman's current physical condition influences the course of pregnancy; both maternal underweight as obesity are significantly associated with preterm delivery[22;23].

Genetic predisposition

The ethnicity of a woman has been previously shown to influence gestational age at delivery. Black ethnicity is associated with an increased risk of preterm birth when compared with whites (pooled OR 2.0; 95% CI 1.8 to 2.2)[24]. In addition, we showed disparities in perinatal mortality risk near term between different ethnicities (**chapter eleven**).

Furthermore, there is evidence for an inherited predisposition for preterm birth. Women born spontaneously preterm or with siblings delivered in a similar manner, or with either a mother or a father born preterm, are at increased risk of spontaneous preterm delivery[25;26].

Past obstetric performance

In **chapter two** we showed that women with a previous preterm birth are at increased risk of a preterm birth in the second pregnancy compared to women with a previous term birth. Not only ongoing pregnancies should be taken into account in this evaluation but also previous miscarriages or even previous pregnancy terminations. An increased risk of spontaneous preterm birth was noted in women with previous spontaneous abortion or induced abortion, especially after multiple abortions (OR 2.6, 95% CI 1.7 to 4.0) [27;28].

Foetal characteristics

The foetus grows inside the mother and influences the course of pregnancy as well. In order to get information about the foetus and its condition, ultrasound is most often used.

In the first trimester crown-to-rump length (CRL) is measured in order to date the pregnancy. In **chapter three** we showed that there is no association between early

spontaneous preterm birth and relatively short CRL. However, a relatively short CRL may be a sign of early growth restriction[29;30]. Possibly signs of individual growth potential are already present in the first trimester.

Ultrasound can also be used to assess foetal gender as early as the first trimester[31]. Male foetal gender was shown to be associated with spontaneous preterm birth, both with intact membranes and with PPROM (**chapter four**).

Around 20 weeks gestation, a standard ultrasound scan is performed in the Netherlands to screen for congenital birth defects. Several congenital birth defects can directly lead to preterm delivery. On the other hand, certain foetal conditions may necessitate premature delivery in order to prevent perinatal mortality or to decrease morbidity[32]. Therefore, it's not only the maternal potential that should be taken into account, but also foetal characteristics.

Pregnancy specific/environmental factors
Besides the foetus, certain pregnancy specific/environmental are associated with pregnancy complications. Whether a women carries a multiple or a singleton pregnancy influences perinatal outcome. We showed that multiple pregnancies are at increased risk of preterm birth (**chapter two**).

Another important pregnancy-specific factor is the type of conception. Infertility treatments can lead to increased rates of multiple pregnancies but also the IVF/ICSI treatment in itself is associated with an increased risk of preterm birth[33].

Midtrimester cervical length can help identify women at risk of preterm birth, especially if information about previous pregnancy is not available (e.g. nulliparous women) or in women with an obstetric history of preterm birth. Although not all women ultimately destined to deliver preterm will present with a short cervix, (**chapter five**) we found that cervical length is able to identify some women at high risk

Pregnancy-specific complications can also influence pregnancy outcome. Acute maternal disease such as maternal sepsis is associated with preterm birth (OR 2.8, 95%CI 2.0 to 4.0) [34]. ASB is thought to cause maternal pyelonephritis. Although maternal pyelonephritis, which is able to cause maternal sepsis, was found to be associated with preterm birth[35;36], we found no association between asymptomatic bacteriuria and preterm birth (**chapter 9**).

Additionally, lifestyle factors and socio-economic status play a role in pregnancy outcomes. Living in a deprived neighbourhood is associated with preterm birth, small-for-gestational age and stillbirth[37]. In addition, substance abuse such as cigarette and cocaine use are negatively associated with gestational age at delivery[38].

Individualized management

The characteristics in the above-mentioned three levels are not meant to be exhaustive, they just serve as an example for the variety of factors involved. The goal of this approach is to gain insight in the individual potential of a woman, her child and their environment, in order to individualize management for this specific pregnancy and thereby improve perinatal outcome.

Same condition, different management

Preterm birth was generally considered to be one disease. Nowadays more evidence is gathered that it might be a syndrome caused by a variety of mechanisms[39]. In **chapter 5** we found that early cervical shortening is a common path for some but not all preterm births, possibly indicating different phenotypes of preterm birth. Whether these different phenotypes respond as effectively to the same treatment is questionable. It is possible that certain treatments are beneficial for some subgroups, but not for all. Gaining insight in the pathways and phenotypes is therefore an important step to go from identification of a woman at risk to preventing preterm labour.

This individualized approach is not specific for preterm birth but is also relevant for other conditions. Almost all pregnancy complications have risk factors in the three levels. For example growth restriction is also the result of interplay between maternal factors (genetic potential of mother, pre-existing disease), foetal factors (congenital abnormalities) and environment (pregnancy induced hypertension, smoking). As a consequence, recurrence of small for gestational age is different in women with and without a hypertensive disorder[40]; possibly optimal management is different as well.

Active versus passive management

It is important to stress that individualized management does not equal interference or action. Management can either be active (e.g. medication, induction of labour) or passive (e.g. watchful waiting, let nature run its course). In a healthy pregnancy, which is thankfully still the majority, the best management strategy so far is watchful waiting.

One example is asymptomatic bacteriuria; a lot of countries routinely screen pregnant women for the presence of bacteria in urine without complaints of a urinary tract infection (ASB). If bacteria are found, the woman gets treated with antibiotics because normally urine is sterile; the idea is therefore that the bacteria need to be eradicated. In **chapter 9** however, we showed that the natural course of untreated ASB is mild. Moreover, awareness of possible adverse effects of maternal antibiotics on the neonate[41;42,43;44] has grown and antibiotics use is increasingly recognized as a factor that drives antibiotic resistance[45]. Our advice is therefore not to screen or treat ASB in women with a singleton pregnancy without previous preterm birth and without diabetes mellitus.

Recommendations for future research

Although in the 1970's studies on individual risk assessment for preterm birth were first developed, none of the models are suitable for actual implementation in current practice. Honest *et.al.* found that antenatal scoring systems are poor in predicting the risk of spontaneous preterm birth later on in pregnancy[46]. The performance of almost all models

is disappointing. Possibly this could be explained by the fact that preterm birth is not one disease but a syndrome with a variety of pathogenesis. Why do some women have a recurrent preterm birth and some women deliver their next pregnancy up to term? Maybe also the recurrence risk is dependent on the specific phenotype of preterm birth. These different phenotypes make it difficult to predict spontaneous preterm birth with one model.

The three levels with all its factors and its interactions underline the complexity of preterm birth. Currently, we are only grasping at what we think are causes of preterm birth. We need more insight in the different pathways leading to preterm birth, the factors involved in the separate pathways and the interplay between factors from different levels. Integrating the levels will help us understand the biological process in which all these risk indicators play a role, taking into account that biological processes differ between ethnical groups and even between male and female foetuses.

In **chapter 5** we showed marked differences in preterm birth rate between Chicago and the Netherlands that could not be explained by differences in short cervical length. It makes us wonder what differences, besides the geographical location, can cause this disparity in preterm birth. Is it difference in lifestyle, genetics/race, access to health care, obstetrical interventions, maternal comorbidities or something completely different? Gaining insight in the pathophysiology is essential to answer this question. By comparing preterm birth rates and risk factors between countries, we can gain more insight in the pathophysiology and environmental differences of preterm birth. These collaborations will also lead to exchange in knowledge which will benefit overall preterm birth research.

The studies presented in **chapter 10 and 11** in this thesis are a very humble start of trying to define the optimal timing of delivery for different subgroups. Ideally, the optimal timing of delivery for all women should be determined using large randomized controlled trials thereby taking into account interactions between different factors involved.

Ideally, we should be able to create a large scoring system, incorporating maternal, neonatal and pregnancy specific/environmental factors, so that individual risks can be calculated. During pregnancy, we should be able to add changes, measurements and possible complications to get individualized management strategies for each patient. In that way patients get offered individualized treatment plans based on their specific needs.

Recommendations for clinical practice

Do:

- take into account both maternal, foetal and pregnancy specific/environmental factors when estimating a women's individual risk of pregnancy complications such as preterm birth
  - *Maternal*: Use obstetric history and pregnancy subtype (twin versus singleton) to estimate the risk of spontaneous preterm birth
  - *Foetal*: Assessment of foetal gender can help predict preterm birth
  - *Pregnancy specific*: Measure cervical length to identify some nulliparous women at high risk of spontaneous preterm birth
- deliver SGA foetuses without other indications for induction from 38 weeks onwards
- take ethnicity into account when making decisions about delivery or expectant management in the term period.

Don't:

- Use relatively short CRL to predict spontaneous preterm birth
- Screen for ASB in low risk singleton pregnancies

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