Summary

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

Chapter 2 gives an overview of literature about the prediction of preterm birth. Literature was reviewed in order to determine the potential impact of individualized risk indicators on the prediction of preterm birth. Review of the literature indicates the importance of distinguishing modifiable risk indicators from non-modifiable indicators. Risk for preterm birth can be seen as a continuous transition from one state to the other. For instance shortening of the cervix and the presence of fetal fibronectin have been shown to be predictive of preterm birth. These indicators where seen as risk indicator but may in fact be the first symptoms of preterm birth

Chapter 3 describes the protocol of the Triple P *screening* study and the randomised clinical trial, Triple P *trial*. Spontaneous preterm delivery is the single most important cause of perinatal mortality in the Western world. It is known that cervical length measurement at 20 to 24 weeks gestation can identify women at increased risk for preterm delivery. The problem with the use of progesterone at present is that, based on current evidence, it can only be applied in order to reduce preterm birth for women with a history of preterm birth. However, the large majority of spontaneous preterm delivery occurs in nulliparous women. It is unknown whether progesterone has not been assessed in those women. In view of the lack of good clinical evidence and potential positive effect on reduction of preterm birth we designed a trial evaluating the effects of a screen and treat program in the Netherlands in a low risk cohort.

Chapter 4 describes the observational cohort study, the Triple P *screening* study. Cervical length was measured transvaginally between 16^{+0}-21^{+6} weeks in women without a history of spontaneous preterm birth. The predictive capacity of cervical length measurement on preterm birth (<37 weeks) of nulliparous- and multiparous women was analysed. We studied 11,943 women, of whom 666 (5.6 %) delivered preterm (3.9% spontaneous and 1.7% iatrogenic). Mean cervical length was 44.1 mm (SD 7.8 mm). In nulliparous women, the likelihood ratios for spontaneous preterm birth varied between 27 (95%CI: 7.7-95) for a cervical length ≤ 20 mm, and 2.0 (95%CI: 1.6-2.5) for a cervical length between 30 and 35 mm. For low risk multiparous women, these likelihood ratios were 37 (95%CI: 7.5-182) and 1.5 (95%CI: 0.97-2.2) respectively. When a cervical length cut-off of 30 mm was used 6.0% of all women with a spontaneous preterm birth were identified. The numbers needed

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to screen to prevent one case of preterm birth was 618 in nulliparous women and 1417 for low risk multiparous women (40% treatment effect, cut-off 30 mm). In women at low risk of preterm birth the capacity of cervical length measurement to identify those women who consequently will have spontaneous preterm birth is limited, although the risk of preterm birth was inversely related to mid-trimester cervical length.

Chapter 5 describes the results of an explanatory study. We assessed the incidence of spontaneous preterm birth in singleton pregnancies according to level of care and the association between level of care at time of labour onset and delivery and adverse perinatal outcome. The Dutch obstetric care system is different from most other developed countries, since the level of care is organised according to the presence or absence of risk factors in medical and/or obstetrical history. Although (impending) preterm delivery is an indication for referral to secondary care, preterm birth sometimes occurs in primary care. We defined three categories: (1) onset of labour and delivery in primary care, (2) onset of labour in primary care and delivery in secondary care (intrapartum referral) and (3) onset of labour and delivery in secondary care. Of all spontaneous preterm births 42.2% had labour onset in primary care and 7.9% of these births subsequently ended in primary care. Of all preterm births in primary care 85% occurred late preterm ($34^{+0} – 36^{+6}$ weeks) and almost 60% between 36^{+0} and 36^{+6} weeks. The risk on adverse perinatal outcome after spontaneous preterm birth, was lowest for women with labour onset in primary care who were referred to a secondary care setting before delivery. The risk of perinatal mortality and the risk of low Apgar score after 5 minutes were significantly increased for those women with both labour onset and delivery in primary care compared to women with labour onset and delivery in a secondary care setting.

Chapter 6 describes a study with the aim to assess the effect of an e-learning module (CLEM) on the quality of cervical length measurements comparing CLEM trained and non-CLEM trained ultrasonographers. The quality of the cervical length measurements of CLEM participants was compared to images of non-participants using a cervical length measurement image score (CIS) defined as the sum of six items which assess the quality of the image. The cervical length image score of the CLEM participants (n= 61) was significantly higher than the CIS of non-CLEM participants (n= 23, 164.9 vs. 155.6 respectively, p = 0.03). Visibility of the internal

os and positioning of the calipers on internal and external os was found to have a significantly higher CIS score in the CLEM participants compared to non-CLEM participants (p = 0.001 and p <0.001).The CLEM might improve the quality of cervical length measurements performed by trained and untrained sonographers.

Chapter 7 describes a study in which the distribution of cervical length, was analysed and the influence of a predefined cut-off value on the prevalence of short cervical length was reviewed. Mean cervical length was 44.2 mm. A typical 'dip' was observed around the cut-off of 30 mm, resulting in a lower prevalence of short cervical length. The 'dip' seemed to be present in the majority of participating centres. All levels of care and low, intermediate and high volume centres had a gap below 30 mm. A significant difference was found in the distributions over time before and after publicly addressing the low incidence of short cervix. We hypothesize that since the measurement is not blinded, possibly non-blinded assessors favoured the control intervention, inducing selection bias. This effect should be taken into account in future research, trials using similar design could benefit from this observation.

Chapter 8 describes influence of maternal characteristics such as maternal height, weight, maternal age, ethnicity and parity on mid trimester cervical length, in order to explore if patient specific charts are needed for mid-trimester cervical length to predict preterm birth. Studying cervical length we found prevalence of short cervical length considerably lower and a higher mean cervical length compared to other studies. Dutch women are on average taller than women of non-European origin and the Dutch population is one of the tallest in Europe. We questioned whether there is an association between maternal anthropometry and cervical length. We found a relationship between mid-trimester cervical length and BMI, maternal age, maternal ethnicity and parity. Cervical length increases with maternal BMI (adj R^2 0.004, p <0.001) and with lower maternal age (adj R^2 0.01, p < 0.0001). European white women had on average a longer mean cervical length (45.0 mm) than women from other ethnicities. Nulliparous women were found to have a shorter mean cervical length than multiparous women (mean cervical length 43.5 mm versus 45.3mm respectively, (adj R^2 0.012, p-value < 0.0001). However, an association between maternal height and cervical length was not found. Consequently, when screening for preterm birth by cervical length measurement, the cervical length cut-off for increased risk does not need to be adjusted for maternal height.

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Chapter 9 describes the association between mid-pregnancy cervical length in nulliparous women and its association with post-term delivery and intra partum caesarean delivery. Post-term pregnancy is defined by the World Health Organization as a pregnancy continuing beyond 42 completed weeks of gestation i.e. ≥ 294 days. Maternal and obstetrical complications increase as pregnancy progresses beyond term. Moreover, neonates born after post-term pregnancies are at increased risk of perinatal mortality and morbidity. We performed a secondary analysis of 5,321 nulliparous women who delivered ≥ 34 weeks of gestation and who did not have a planned caesarean delivery or a stillbirth before labour. We compared the risk of post-term delivery and intrapartum caesarean delivery to cervical length quartiles, using the lowest quartile as a reference. We adjusted for induction of labour, maternal age, ethnicity, cephalic position, pre-existing hypertension and gestational age at delivery. Women with cervical length in the 3rd and 4th quartile were more likely to deliver at 42^{+0} to 42^{+6} weeks (OR 2.02, 95%CI 1.07-3.79 and OR 1.97, 95%CI 1.06-3.67, respectively). The frequency of intrapartum caesarean delivery increased with cervical length quartile from 9.4% in the 1st to 14.9% in the 4th quartile (p= 0.01). This increase was only present in intrapartum caesarean delivery because of failure to progress and not because of fetal distress. The added value of our finding is in clinical counselling of women regarding the management of post-term delivery or when induction of labour has to be considered because of pregnancy complications.

Chapter 10 describes the results of the randomised controlled trial the Triple P trial. The aim of the trial was to evaluate the effectiveness of vaginal progesterone in reducing adverse neonatal outcome due to preterm birth, in low-risk pregnant women with a short cervical length. Women with a cervical length ≤ 30 mm received vaginal progesterone or placebo. A cervical length of 30 mm or less was seen in 375 women (1.8%). Adverse neonatal outcomes occurred in 2 (5.0%) women in the progesterone and in 4 (11%) women in the control group (relative risk (RR) 0.47; 95% confidence interval (CI) 0.09 to 2.4). Use of progesterone resulted in a non-significant reduction of preterm birth <32 weeks (2.0% vs. 8.0%; RR 0.33 95% CI 0.04 to 3.0) and <34 weeks (7.0 % vs. 10%; RR 0.73; 95% CI 0.18 to 3.1), but not on preterm birth < 37 weeks (15% vs. 13%; RR 1.2; 95% CI 0.39 to 3.5). In women with a short cervix, who are otherwise low-risk, there was no significant benefit of progesterone in reducing adverse neonatal outcome and preterm birth.

Chapter 11 describes the results of a discrete choice experiment. A questionnaire was used to explore pregnant women's preferences regarding sonographic cervical length measurement and treatment with progesterone in relation to preterm birth prevention. Understanding the considerations in pregnant women in expressing their preferences can contribute to improvement in patient counselling. Among pregnant women between 15-36 weeks of gestation who all received information about the Triple P *screening* (described in chapter 4), 156 questionnaires were handed out and 138 were returned (response rate 88%). Each questionnaire included management options in relation to preterm birth, i.e. cervical length measurement and progesterone administration, versus health outcome of the new born child as a consequence of preterm birth. The participating low risk women generally expressed a preference for as little as possible interventions and side effects, but were willing to make trade-offs between attributes when this resulted in better health outcomes for their child. A cervical length measurement and progesterone administration were not preferred. However a transvaginal ultrasound cervical length measurement was accepted in exchange for a 6.5% decrease in long-term neonatal complication rate. The results of this study can be used to improve the counselling for the prevention of preterm birth in pregnant women and to achieve an enhanced participation in screening and treatment programs to prevent preterm birth.

Chapter 12 in this chapter we discuss questions remaining after previous described findings.

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