

Chapter 12

General discussion



In this thesis studies on preterm birth are presented. The subjects include identification of women at risk for preterm birth, measurement of cervical length, prevention of preterm birth and women's preferences. The objective of the Triple P *screen* study (chapter 4) was to identify women at risk for preterm birth in a low-risk population. The study was designed to identify these women by cervical length measurement between 18 to 22 weeks of gestation. Although we confirmed that the risk of preterm birth is inversely related to mid-trimester cervical length, we found that cervical length measurement in women at low risk for preterm birth seems of limited clinical use to identify women subsequently giving birth prematurely. In the Triple P *trial* (chapter 10) the effect of progesterone for prevention of preterm birth in women with a short cervical length was analysed. Women identified in the Triple P *screen* study through a short cervical length (defined as ≤ 30 mm) were randomized for progesterone or placebo. Unfortunately, the trial did not reach the calculated sample size and we therefore did not find a reduction in composite adverse neonatal outcome nor a decline in numbers of preterm birth below 32, 34 and 37 weeks of gestation.

In this chapter we discuss questions remaining after previous described findings and we focus on implications for further research and clinical care.

Outline of the problem: detection and treatment of preterm birth in a low-risk population

Preterm birth is a major cause of death and a significant cause of long-term loss of human potential amongst survivors all around the world¹. Identification of women at risk for preterm delivery in an unselected low-risk population is crucial in the development of screening strategies. An important problem in identifying women at risk for preterm birth is that the majority of spontaneous preterm births occur in otherwise low-risk women². A breakthrough in the management of women at increased risk is the use of progesterone. Consequently, prevention of the onset and identification of women at risk for preterm birth is essential firstly because of its consequences and secondly because treatment might be available.

Screening for preterm birth in a low-risk population.

Wilson and Jungner already described criteria for population based screening in 1968. These criteria are globally accepted as requirements that need to be fulfilled before a program can be introduced³. The disorder to screen for, needs to be a

major health problem, needs the presence of an asymptomatic precursor, and treatment at an early stage needs to have a significantly better prognosis than at later discovery. The screening test should not cause significant illness or side effects, should be affordable, with high specificity and sensitivity and low rate of false positives and a low percentage false negatives.

In screening for preterm birth, all the described criteria are fulfilled, except for a high sensitivity of the screening test. The sensitivity of mid-pregnancy cervical length measurement to identify a subsequent preterm birth is low, both in nulliparous and low-risk multiparous women. Most cases of preterm birth (94% in this dataset) were observed in women who did not have a mid-pregnancy short cervix. Furthermore the prevalence of a short cervical length was low, as only 1.8% had a cervical length ≤ 30 mm. In this cohort, 3.9% pregnancies ended in a spontaneous preterm birth. We conclude that because of its low sensitivity, cervical length measurement is not an optimal screening tool for preterm birth in this low risk cohort.

Several questions emerged or remained after studying several major issues of preterm birth in the Netherlands. Why was the prevalence of short cervical length lower than described in earlier studies? Why was the sensitivity low? Most importantly, should we screen for short cervical length? Or should we screen for short cervical length in a defined population?

Firstly, the encountered low prevalence of short cervical length can be explained by the fact that the measurements were performed in a true low-risk population. As far as we know, there is no large cohort of women without a history of preterm birth that was screened for cervical length during the second trimester. Other factors which might explain the low prevalence of short cervical length include anthropometric characteristics e.g. a high proportion of women of European ethnicity, higher maternal age compared to previous studies, an unknown influence of time of the day. One may expect that at the end of the day or after several hours of standing or working cervical length might be shorter compared to bedrest. Other explanations for the low prevalence of cervical length ≤ 30 mm are discussed in chapter 7. The cut-off value for participation in the trial might have influenced the prevalence of cervical length measurements below 30 mm, resulting in a lower prevalence of short cervixes.

Secondly, we found a low sensitivity, which is different from previous studies. Spontaneous preterm labour is often treated as a single condition. Accumulating evidence suggests that multiple pathologic processes attribute to premature labour⁴.



Figure 1. Proposed mechanisms of disease implicated in spontaneous preterm labour. From Romero R, Dey S.K, Susan J. Fisher S.J. Preterm labor: One syndrome, many causes. *Science*. 2014 Aug 15;345(6198):760-5, Reprinted with permission by AAAS.

The most important symptom of premature birth is pathological ripening of the cervix. This pathological process is characterized by shortening and dilatation of the cervix and is usually accompanied by increased uterine activity⁵. Processes such as infection or bleeding, in concurrence with genetic predisposition and local or systemic hormonal influences might play a role⁶. There have been several hypotheses about infection leading to preterm birth. These hypotheses include ascending infection from the vagina to the uterus leading to intra-amniotic infection, retrograde spread of infection through the fallopian tubes, haematogenous infection through the placenta, or iatrogenic introduction of infections at the time of invasive procedures. All these routes cause intra-uterine infection leading to preterm birth⁷.

Another hypothesis is that a systemic increase of inflammatory mediators caused by infections such as periodontitis, result in an enhanced intrinsic inflammatory or immunological response, and increased production of inflammatory cytokines such as prostaglandin E₂, interleukin (IL) -6, tumor necrosis factor (TNF) and IL-1 β causing periodontal disease and preterm birth⁸⁻¹⁰.

Besides infection, other known risk factors for preterm birth include multiple gestation, uterine anomalies and a history of cervical surgery. These factors point in the direction of a mechanical cause for preterm birth. In case of preterm labour,

this specific pathway results in decrease of the tensile strength of the cervix, key for cervical ripening and dilatation.

In other words, cervical shortening can be a symptom of a process in motion, which might not have started at the time of screening, explaining the low sensitivity of mid-pregnancy screening. The various pathophysiologic pathways leading to preterm labour can also explain why other studies found different results regarding the sensitivity of cervical length measurement. When each subgroup of women follows a different pathophysiologic pathway leading to preterm labour, women from different subgroups present with a shortening of the cervix at a different stage. In the subgroup we studied, women without a history of preterm birth, short cervical length was found in a small percentage of women and may have been a symptom of a process in motion, presenting at a later stage. Based on our results, using a cervical length cut-off of 30 mm, with the assumption of a 40% reduction of preterm birth rate from treatment, the number of low risk multiparous women needed to screen to prevent one spontaneous preterm birth is almost 1500. In nulliparous women the number needed to screen is 618 using the same cut-off, and 122 at a cut-off of 35 mm. Based on our results screening for short cervical length in mid-trimester pregnancy might not be useful in a low-risk population because of the low prevalence of short cervical length and the low sensitivity of the cervical length measurement as a screening tool, combined with the lack of evidence for effectiveness of progesterone treatment in this relative small, subgroup of pregnant women. However, it is possible that this cohort does not give a rational insight in the number of short cervixes. In line with previously described studies, we found the cervical length to be inversely related to preterm birth. Nulliparous women with a cervical length between 31 and 35 mm measured in the second trimester, have a more than two fold higher risk of preterm birth compared to the risk of preterm birth in nulliparous women with a cervical length above 35 mm. Another reason not to abandon the idea of mid-trimester screening in a low-risk population is the recent published data about the effectiveness of the cervical pessary to prevent preterm birth¹¹. In 2012 Goya et al. published a study in which pregnant women with a cervical length of 25 mm or less were randomly assigned to the use of a cervical pessary or expectant management. Spontaneous delivery before 34 weeks of gestation was significantly less frequent in the pessary group than in the expectant management group (12 [6%] vs 51 [27%])¹¹. These data point out the possibility of another preventative treatment besides progesterone.

Cervical length measurement and ultrasonographic examination of the cervix.

Although cervical length measurement does not seem difficult at first glance, it has several pitfalls including correct placement of calipers on the internal and external os, pressure on the anterior and posterior cervical lip. These pitfalls are important in measuring the cervical length. We therefore studied the effect of an e-learning module on cervical length measurements by experienced ultrasonographers. We found improvement of quality of cervical length measurement by ultrasonographers who performed the e-learning module and were granted a satisfactory grade, compared to those who did not perform the e-learning module. Quality was defined as a score given by two experts using a scoring system: the cervical length measurement image score (CIS). Remarkably, the e-learning items that were most different between the trained and non-trained ultrasonographers were the visualisation of the internal os and the positioning of the calipers on internal and external os. Both items are very crucial for accuracy of cervical length measurement. Although all ultrasonographers were offered training, in chapter 7 we describe the influence of the presence of a pre-defined cut-off value (≤ 30 mm) for the distribution of cervical length measurement and its effect. In the presence of a cut-off value, the number of measurements between 20-30 mm were reported 38% less frequent than expected, compared to a simulated normal distribution of cervical length. In our cohort we found a mean cervical length of 42 mm (SD 7.8mm). Compared to previous studies^{12,13} the measured cervical length is relatively long. Several factors might explain this difference including measurement techniques and women's characteristics.

Several studies are published on technical factors^{2,12,14,15} of cervical length measurement in which the calipers are placed at the notches made by the internal os and external os, using the sonolucent endocervical mucosa as a guide to the true position of the internal os. Arisoy *et al.* defined the internal os as the junction between amniotic membrane and cervical canal¹⁶, while Iams *et al.* used the V-shaped notch made by the internal os². As a result, definitions of the internal os and external os seem to differ and uniformity is lacking. In addition, To *et al.* described the influence of cervical curvature on cervical length measurements¹⁵. A cervix with a short length (less than 16 mm) always appears straight¹⁵. It is therefore unlikely that the influence of how to approach the cervical curvature will have any clinical implications. Positioning the caliper at the internal os or at the mucosa may have an effect on the mean cervical length. However, since shortening of the cervix

starts at the internal os, it is unlikely that positioning of the calipers will have an effect on short cervical length rate. Thus, it is unlikely that a different measurement technique has an impact on the prevalence of short cervixes. Nevertheless we advise to invest in the education of sonographers and continuous quality monitoring in future research, as the visualisation and positioning of the calipers are important for the measurement of the cervix.

Cervical length in relation to other characteristics

As described cervical length might not only be influenced by technical factors, also women's characteristics may play an important role. We found that in nulliparous women, second trimester cervical length is associated with gestational age at onset of labour. Women with longer cervical length (defined as 4th quartile, with a median cervical length of 51 mm and interquartile range of 49-55mm) have a 1.5 greater risk of a pregnancy complicated by post-term delivery and a 1.7 greater risk of a caesarean section for failure to progress compared with women with a shorter cervical length (1st quartile median cervical length 35 mm and interquartile range 33-36 mm). Mid -trimester short cervical length is associated with low BMI, lower maternal age, maternal ethnicity and nulliparity, but not with maternal height (chapter 8). However, the influence of maternal characteristics on cervical length is limited and maternal characteristics cannot explain the higher mean cervical length we found in our study compared to other studies^{2,13}.

Treatment to prevent preterm birth

Progesterone has been suggested to prevent preterm birth. In 2007 the study of Fonseca *et al.* showed remarkable results regarding use of progesterone in asymptomatic women with a short cervical length. They described that spontaneous delivery before 34 weeks of gestation was less frequent in women treated with progesterone compared to women using placebo (19.2% vs. 34.4%; relative risk, 0.56; 95% confidence interval [CI], 0.36 to 0.86). The group that used progesterone had a reduction in neonatal morbidity (8.1% vs. 13.8%), but statistical significance was not reached. This study of Fonseca included a mixed group of women with high and low risks for premature birth. Thus this study was performed in women with and without a history of preterm birth, nulli and multiparous women and multiple gestations¹⁷.

The obstetrical health care system in the Netherlands with a division in the care for high-risk pregnancies and low-risk pregnancies provides us the opportunity

to analyse whether progesterone had a similar effect to the study of Fonseca in a low-risk population per se.

During the course of this study, however, the results of other trials were published. In 2011 Hassan et al. reported a progesterone trial in an unselected combined high-low risk population, without multiple pregnancies. Similar results as the study of Fonseca were found¹⁸. The women allocated to vaginal progesterone had an almost two times lower rate of preterm birth before 28 and 33 weeks compared to those allocated to placebo (8.9% vs 16.1%). This resulted in a lower neonatal morbidity/mortality rate (7.7% vs 13.5%). The importance of this study lies in the fact that it confirmed the results from Fonseca and that statistical significance was reached for the difference in neonatal outcome in favour of the progesterone group¹⁸.

In 2012 Romero et al published a meta-analysis of five trials on the subject of progesterone in women with a short cervix¹⁹. Treatment with vaginal progesterone was associated with a significant reduction in the rate of preterm birth before 28 weeks (RR 0.50, 95% CI 0.30–0.81), 33 weeks (RR 0.58, 95% CI 0.42–0.80) and 35 weeks (RR 0.69, 95% CI 0.55–0.88). Composite neonatal morbidity and mortality were reduced in the progesterone group (RR 0.57, 95% CI 0.40–0.81).

There were no significant differences between the vaginal progesterone and placebo groups in the rate of adverse maternal events or congenital anomalies. The meta-analysis included studies which were performed in mixed populations, including women with previous preterm births. This meta-analysis showed that progesterone was most effective in women with a cervical length within a certain range (10-20mm) and in the prevention of early preterm births (birth before 28 or 32 weeks of gestation).

A third trial was published in 2013 by Grobman *et al.*, which did not confirm the above described trials while using the same method for selection. The design was similar to the Triple P study, but they only included nulliparous low-risk women with a singleton gestation. The prevalence of preterm birth did not differ significantly between the women using progesterone compared to the placebo group (25.1% vs 24.2%) and no difference was found in the composite adverse neonatal outcome (7.0% vs 9.1%)²⁰.

In line with our study, Grobman *et al.* found a similar prevalence of adverse neonatal outcome (5.0%) in women using progesterone compared to 11% in women in the control group (RR 0.47; 95% CI 0.09-2.4). Use of progesterone resulted in a not statistically significant reduction of preterm birth <32 weeks (2.0% vs. 8.0%) and <34 weeks (7.0 % vs. 10%). The rate of preterm birth before 37 weeks was not different (15% vs. 13%)²⁰.

All available evidence shows that progesterone is important in the prevention of preterm birth. Progesterone seems to be most effective in decreasing the rates of early preterm birth in women with a short cervix and a previous preterm birth. Progesterone might be, however, less effective in the prevention of preterm birth in women without a previous preterm birth. This can be explained by the fact that several pathophysiological pathways can lead to a preterm birth and that progesterone might be more effective in the pathway that leads to recurrent preterm birth. Further research should focus on the possibility to differentiate between women that would benefit from progesterone and women that need other measures to detect and prevent their future premature birth.

Other research questions that are still unanswered comprise the therapeutic range of progesterone and the exact interaction of progesterone in the cascade leading to a preterm birth.

Women's awareness and choices in preterm birth risk in the Dutch system

As we reported in chapter 5 in almost half of all women who suffered a spontaneous preterm delivery, the onset of labour started in primary care. Referral to a secondary or tertiary care centre before delivery improved perinatal outcome, even in cases of late preterm birth.

One of the biggest problems in the Triple P *screen* study was the awareness of women about the risk of premature birth of pregnant women in the primary care setting. Furthermore we experienced a lack of understanding of the impact of a premature birth. Goldenberg *et al.* reported on this subject earlier. They found that 24% of the women considered their child full term at 34–36 weeks, and 51% at 37–38 weeks of gestation²¹. More than half of the mothers selected 34 to 36 weeks of pregnancy as safe to deliver the baby and fewer than 10% chose 39–40 weeks. In a discrete choice experiment for a screening and treatment program in relation with preterm birth (described in chapter 11) we found that women at low risk for preterm birth generally expressed a preference not to have any interventions. However, women who experienced adverse neonatal outcome before, were more likely to be aware of the health consequences of preterm birth. In this context a reliable risk perception seems to be important. We recommend to inform pregnant women and primary obstetrics caregivers about the risks of premature birth and the long-term consequences, to a more realistic level. This might not only improve the acceptance of a screening and/or treatment program, but also increase referrals before delivery, with improved neonatal outcome as a consequence.

Limitations of the Triple P study and opportunities for future studies.

The triple P study was set in the Dutch Obstetric Consortium which is a collaboration of academic medical centres, teaching hospitals, and midwifery practices in the Netherlands. Despite our small country it was a challenge to out roll the study covering the country and all three levels of care. One of the reasons was the diversity in the organisation of local health care systems in hospitals and midwifery practices. The Triple P study was the first study within the Dutch Obstetric Consortium in which ultrasound centres and midwifery practices were involved. After one year seven university hospitals, 23 general hospitals, 29 ultrasound centres and 160 midwifery practices participated in the study. This is about one third of the total numbers of the midwifery practices in the Netherlands. Reasons mentioned for not participating were convictions about the risk of preterm birth in women with a cervical length below 30 mm and doubt about the safety of the intervention. The degree of participation varied considerably, i.e. in some regions the uptake was very low. An explanation for this could be the lack of information and time, lack of compensation for counselling or preferences of the pregnant women (chapter 11). Involvement of all echelons of the Dutch obstetric system in research especially in low risk pregnancies is of major importance. This will benefit the cooperation within all levels of care and increase both knowledge and motivation. Both are necessary to encourage participation and finally implementation.

The primary goal of the study was a reduction in adverse neonatal outcome. Assuming a decrease of the prevalence of adverse neonatal outcome from 5% to 2.5%, using a two-sided test with an alpha of 0.05 and a beta of 0.8, we calculated the need of 1,920 women (960 per arm) in this study. We assumed from previous studies that 10% of the women would have a cervix ≤ 30 mm. With the assumption that 50% of the eligible women would participate, almost 40,000 women had to be screened. We encountered, however, a lower prevalence (4%) in the first 6 months of recruitment. The feasibility of recruitment, the available budget and the start of similar international trials forced us to adjust our protocol to screen 15.000 women. We hypothesized that we would be able to randomize 100 women with that strategy. In the end after screening more than 20.000 women, the study was stopped after randomising 80 women for progesterone vs placebo. The main reason we did not meet the initial number of inclusions was the overestimation of the prevalence of short cervical length. The assumption that 10% of the women would have a cervical length below 30 mm was made on the basis of existing

Figure 2 Simulation of spread of participating centres in The Netherlands



literature. However, these studies were performed in a population different from ours, low risk cohort, including women with a history of preterm birth and multiple gestation.

The fact that our study was underpowered is a major limitation, which makes interpretation of the results of the trial difficult. A second limitation is discussed in chapter 7. We found a dip in the distribution of cervical length measurements around the cut off value of 30 mm. The origin and cause of this dip is still unclear, but it is possible that it caused by observer bias.

We advise future researchers to make use of the infrastructure between all levels of care that was founded within the Triple P study as in routine care setting. Furthermore, the possible influence of the predefined cut-off value has to be taken into account. Continuously quality monitoring seems essential and in retrospect we have to conclude that Triple P underestimated this aspect.

Further research should focus on the question whether cervical length measurement in mid pregnancy is useful in the prediction of preterm birth in women without a previous preterm birth. The question remains whether the whole population should be screened or just a subgroup of women. The role of other methods for screening like fetal fibronectin should be investigated.

More research should be performed on the pathways leading to preterm labour. Knowledge about the aetiology of preterm birth could also lead to information about which subgroup of women truly benefit from progesterone and the

development of new interventions. Besides progesterone other preventative strategies like the use of a cervical pessary or cerclage should be explored. Combination of progesterone with pessary or cerclage also deserves further research.

We are looking forward to the sequel of the Triple P study, a new randomised control trial started in the structure of the Dutch consortium. The Quadruple P study, Pessary or Progesterone to Prevent Preterm delivery in women with short cervical length. Results will improve the knowledge about preterm birth and its prevention and improve care for women at risk for preterm birth.

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