Pessaries for the prevention of preterm birth in multiple pregnancies
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CHAPTER 9
General discussion
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Preterm birth is in quantity and severity the most important issue in obstetric care in the developed world. As the effectiveness of treatment of threatened preterm labour is limited, the research effort in this field is focussing on prevention. Prevention of preterm delivery is not a goal in itself, but a way of improving perinatal outcome. This thesis shows that the pessary is effective in women with a multiple pregnancy and a short cervix both in terms of prolonged gestational age at birth as well as in the prevention of adverse perinatal outcome, bringing a glimmer of hope for this major obstetric problem.

The fact that we found the pessary to be effective in women with a short cervix, but not in the overall population of women with a multiple pregnancy, gives direction to further research. Recent studies found progesterone to be potentially effective in women with a short cervix and a singleton pregnancy. This was confirmed in two recent meta-analyses with individual patient data of women, one with singletons and twins and one with twins only. They showed a clinically relevant, though statistically non-significant, benefit of treatment with progesterone in multiple pregnancies. Future studies should compare pessary and progesterone in women with a short cervix.

Plans for a new Dutch study (Quadruple P), comparing the effectiveness of vaginal progesterone and cervical pessary in the prevention of preterm birth in women with singleton and twin pregnancies and a short cervix, are already advanced. Women with a singleton or twin pregnancy undergoing fetal assessment at 16-20 weeks of gestation will be offered cervical length measurement. Women with a twin pregnancy and a short cervix, 38 mm or less (25th percentile), will be randomly allocated to daily vaginal progesterone or a cervical pessary. The same accounts for women with singletons, with the difference that the cut-off of the cervical length will be 30 mm or less (2nd percentile). As both treatments have already been found to be effective as compared to no intervention, the question is whether there could potentially be an additive effect of these two treatments. This could be the research question in a subsequent trial comparing the winner of the progesterone to pessary comparison with the combined use of progesterone and pessary.

A recent study done by the fetal medicine network led by Kypros Nicolaides showed no effect of the pessary in women with a multiple pregnancy (personal communication). Interestingly, the pessary was also not effective in the subgroup of women with a short cervical length. This differing result might be caused by the fact that the fetal medicine network study randomised women at a relatively late gestational age of approximately 24 weeks. In our ProTWIN trial, however, results demonstrated that a large part of the treatment effect had already occurred before 24 weeks gestation.

In our study, a large number of pessaries were removed before 36 weeks of gestation, probably due to the lack of equipoise of clinicians or even disbelief in the pessary as a method to prevent preterm birth. This lack of equipoise is likely to have resulted in discontinuation of the pessary at the time of the study. In chapter 6, we demonstrated in a per protocol analysis that in women with a cervical length below <38 mm the pessary could potentially cause even larger reduction in very preterm delivery rates and subsequent poor perinatal outcome, than already seen in our intention to treat analysis. This indicates that there is a potential benefit of the pessary in the prolongation of pregnancy.
when consequently applied in women with a multiple pregnancy. The treatment effect in women with a CL<38 mm was already statistical significant without censoring in both poor perinatal outcome and preterm delivery before 34 weeks and the effect became even larger after censoring. In view of our positive effects, it will be easier to convince clinicians and patients to continue the use of the pessary, as it should not be removed until labour is evident.

**Short cervix**

The pathological processes for the preterm parturition syndrome include intrauterine infection, uterine ischaemia, uterine overdistension, cervical disease, abnormal allogenic recognition, allergic-like reaction, and endocrine disorders. We believe preterm labour has a very long latent phase and that asymptomatic cervical shortening is an early symptom. This cervical shortening indicates the start of the preterm parturition syndrome, rather than being a risk factor itself. In asymptomatic women with a multiple pregnancy, second trimester cervical length is, just as in women with a singleton pregnancy, a strong predictor of preterm birth. While in Chapter 3 we identified only a few studies about the predictive capacity of cervical length measurement for preterm birth in symptomatic women with a twin pregnancy. It is remarkable that a test used in daily obstetric care is evaluated so poorly, especially since it is important to distinguish between symptomatic women who will deliver within short time and women who can be safely sent home without additional treatment. Furthermore, it is not known what the cervical length cut-off is at which intervention will lead to a better outcome. It might be that the most commonly used cut-off of 25 mm at midtrimester is an underestimation for the women at risk for preterm birth. Treatment of women with multiples and a relatively short cervical length (< 38 mm) with a pessary seems to prevent or delay the process of further asymptomatic cervical shortening. Obviously, as the baseline risk of preterm delivery in women with a twin pregnancy is much higher, and since such pregnancies involve two children for each delivery, the impact of the pessary is much stronger in multiples.

Our results are in line with the results of a recently published randomised trial evaluating the effectiveness of the pessary in women with a singleton pregnancy and a short cervical length (≤25 mm). That trial demonstrated a strong reduction in preterm birth rate before 34 weeks from 27% to 6% (OR 0.18, 95% CI 0.08-0.37), resulting in a reduction of poor neonatal outcome from 16% to 3% (OR 0.14, 95% CI 0.04-0.39).

Anatomical and structural changes are accompanied by biochemical changes that can be the cause or consequence of activation of the pathway(s) leading to early cervical ripening. Theoretically progesterone inhibits early cervical ripening. Several studies demonstrated that both 17-hydroxyprogesterone caproate (17P) as well as vaginal progesterone reduces preterm birth in singleton pregnancies with a history of spontaneous preterm birth or short cervix. However, neither vaginal progesterone nor 17P was effective in the prevention of preterm birth in multiple pregnancies. As indicated, a meta-analysis with individual patient data of women with a multiple
pregnancy and a cervical length ≤25 mm also showed a reduction of poor neonatal outcome in women treated with vaginal progesterone.\textsuperscript{11}

**Safety**

The mechanical working mechanism of the pessary virtually guarantees the absence of side effects on the offspring. Neither in our study nor in the PECEP trial were major adverse events reported in women using a pessary. There was one maternal death in the pessary group in whom a McDonald cerclage was performed rather than placement of the allocated cervical pessary. This severe adverse outcome was therefore not related to pessary treatment. However, women in the pessary group had more complaints of increased discharge. Nevertheless, the results of a maternal satisfaction questionnaire in a study by Arabin et al. demonstrate that 95% of women would use the pessary again or even recommend it to others.

In the past, one case report has been published of a necrotic cervix, which was probably due to the increased pressure, and edema of the cervix caused by the pessary. Six weeks after delivery the cervix had recovered in shape but was shortened to 25 mm of length.\textsuperscript{15}

**Costs**

An important advantage of the pessary is its low cost of 38 euro per pessary. This low cost may also open the way to using pessaries in developing countries, conditional on the availability of devices to assess cervical length. In Chapter 7 we demonstrated that in unselected women with a multiple pregnancy treatment with a cervical pessary generates comparable costs as in women without treatment. However, using a pessary in women with a CL <38 mm results in better outcomes and lower costs.

In the prespecified subgroup of women with a CL <38 mm treatment with a pessary was associated with lower costs (-€5,436; 95% CI (€-11,001 to €1,456)). Cost differences were predominantly originating from the postpartum phase. Treatment with a pessary in women with a CL 38 mm also resulted in a lower risk of poor perinatal outcome. Cost-effectiveness analyses showed that treatment with a pessary in women with a CL <38 mm is most likely to be cost-effective.

**Recommendation for clinical practice**

The work presented in this thesis provides some direction for clinical practice. In view of the large benefit that we observed in a group of women where the prognosis without intervention is so poor, and in view of relative safety and low cost of the pessary the question on how to counsel the next woman with a multiple pregnancy and a short cervical length (<38 mm) outside the context of a study is an interesting one. In The Netherlands, for example, there are annually 3200 women with a twin pregnancy.\textsuperscript{16} Based on the rates observed in our study we estimate that 685 women will have a cervical length <38 mm. Among the 1370 children born from these pregnancies, we expect, based on the results of the ProTWIN trial, a reduction of 329 (24%) to 137 (10%) children with a poor
perinatal outcome per year. In terms of perinatal mortality, this compares to a reduction of perinatal deaths from 233 (17%) to 55 (4%) through the introduction of the pessary in women with a multiple pregnancy and a short cervical length.

Results of studies in the United States and The Netherlands suggest that about 30% to 40% of the patients do not receive care according to current scientific evidence and that about 20% to 25% of care provided is not needed or is potentially harmful.\textsuperscript{17,18} The uptake of new evidence into routine health care and guidelines is a long lasting complex process. In anticipation of an adjusted guideline for multiple pregnancies, implementation of our trial in The Netherlands has started by offering women with a multiple pregnancy a CL < 38 mm treatment with a pessary. To evaluate whether the results are similar to the results found in the trial, the outcome will be compared to a previous cohort managed expectantly (PIMPP study: http://www.studies-obsgyn.nl/pimpp). So far there are 35 hospitals participating in this nationwide multicenter prospective cohort study.

In view of this strong treatment effect we believe that a pessary should be offered to all women with a multiple pregnancy and a short cervical length. In future trials the cervical pessary should be randomised against other interventions in the prevention of preterm birth, of which vaginal progesterone is the most important one.
Reference List


