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Summary

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

Chapter 2 reports the results of progestogen treatment for the prevention of recurrent preterm birth in the Netherlands during the first three years following the publication of two positive trials. The objective was to compare the results with those of a group of historical control subjects. Due to the limited information on obstetric history in the database of the Dutch Perinatal Registration, we were able to find matching control subjects for only 56 registered patients. Baseline characteristics were similar for both groups. The recurrence risk of preterm birth before 37 weeks was 43% after treatment with 17OHPC and 34% without such treatment (p=0.44). No clinically or statistically significant differences between women treated with 17OHPC and control subjects were found with regard to gestational age at delivery, number of preterm births before 32 and 35 weeks, perinatal mortality and neonatal admission. The beneficial effect of progestogens in the prevention of recurrent preterm birth that was found in previous studies could not be confirmed.

Chapter 3 describes the findings of a study on the application of new and established treatment strategies for the prevention of recurrent preterm birth in the year 2006. In the six obstetric clinics that were studied, 91 records were identified. In academic centres, screening for bacterial vaginosis and progesterone treatment were applied more often than in other centres (49 vs. 14%, p-value 0.001 and 63 vs. 22%, p-value <0.001, respectively). Cervical length measurement was applied more often in non-academic hospitals (58 vs. 39%, p-value 0.07), but with fewer measurements per patient (average of 3.3 vs. 5.8). There is large practice variation in the management of women with a history of preterm birth. Relatively new treatments are applied more frequently in academic centres. The differences in application of treatment between types of clinics are probably a reflection of the dissemination rate of new evidence.

Chapter 4 shows the results of a questionnaire study on reasons for not offering or not administering progesterone treatment. We interviewed obstetricians, midwives and women with a previous preterm birth and a current pregnancy or a desire to become pregnant in the future. Twenty-five percent of gynaecologists were prescribing progesterone, 21% of midwives would recommend progesterone, and 54% of patients were willing to undergo treatment in future pregnancies. Specific factors hampering implementation for gynaecologists were working in nonteaching hospitals and absence of progesterone treatment in local protocols. For midwives and patients, unfamiliarity with progesterone was the most notable finding. The major reason for failure of implementation of progesterone treatment to prevent recurrent preterm birth is absence of this treatment in protocols and lack of familiarity with this treatment in midwives and patients.

Chapter 5 presents the results of a randomized, placebo-controlled trial on 17P for the reduction of adverse neonatal outcome in children born from multiple pregnancies (the AMPHIA trial). We randomized 671 women. A composite measure of adverse neonatal outcome was present in 110 children (16%) born to mothers in the 17P group, and in 80 children (12%) of mothers in the placebo group (RR 1.34; 95% CI 0.95-1.89). The mean gestational age at delivery was 35.4 weeks for the 17P group and 35.7 weeks for the placebo group (P=.32). Treatment with 17P did not reduce the delivery rate before 28 weeks (6% in the 17P group compared with 5% in the placebo group, RR 1.04; 95% CI 0.56-1.94), 32 weeks (14% compared with 10%, RR 1.37; 95% CI 0.91–2.05), or 37 weeks of gestation (55% compared with 50%, RR 1.11; 95% CI 0.97–1.28). In conclusion, 17P does not prevent neonatal morbidity or preterm birth in multiple pregnancies. A mid-trimester cervical length measurement in participating women yielded an insufficient number of women with a cervix below 25 mm to draw any conclusions on the effect of 17P in this group.

Chapter 6 gives the findings of a secondary analysis on patients who had participated in the AMPHIA-trial. A total of 282 trial participants carried a twin pregnancy and underwent two or more cervical length measurements. Of these women, 140 were monitored in centres where repeated measurements were standard protocol. We observed an overall reduction of cervical length from 41.6 mm at randomization to 26.9 mm at 32 weeks. In the 17OHPC group, cervical length decreased by 1.04 mm each gestational week, while this was 1.11 mm per week for the placebo group (p=0.6). For the overall group, each 10% decrease in cervical length lead to an increase in the risk for preterm birth (HR 1.14; 95% CI 1.08-1.21). We found that there is progressive shortening of the cervix during twin pregnancy regardless of 17OHPC use.

Chapter 7 shows the results of a systematic review and bivariate meta-analysis on the accuracy of cervical length for predicting preterm birth in asymptomatic women with a multiple pregnancy. We found 21 studies reporting on 2757 women. There was a large variation in gestational age at measurement, cut-off point for cervical length and definition of preterm birth. The summary ROC curve indicated a good predictive capacity of short cervical length for preterm birth. Summary estimates of sensitivity and specificity for preterm birth before 34 weeks' gestation were 78% and 66%, respectively, for 35 mm, 41% and 87% for 30 mm, 36% and 94% for 25 mm and 30% and 94% for 20 mm. We concluded that in women with a multiple pregnancy, second-trimester cervical length is a strong predictor of preterm birth. In the absence of effective preventive strategies, there is currently no place in clinical practice for cervical length measurement in this population.

Chapter 8 gives an overview of the available literature on progestogens for the prevention of preterm birth. Two trials published in 2003 showed a positive effect of progesterone in the prevention of recurrent preterm birth. However, more recent data cannot support these findings. In multiple pregnancies the use of progesterone does not seem to reduce the number of preterm births. The results in pregnant women with asymptomatic shortening of the cervix are promising, although more research is needed in this group.

Chapter 9 discusses the findings in this thesis.