Summary

Women with a multiple pregnancy have an increased risk of preterm birth (PTB) as compared to women with a singleton pregnancy. Risks of PTB are 5-9% in singletons, 60% in twins and over 90% in triplets. Preterm birth is associated with an increased risk of neonatal mortality and neonatal morbidity which can lead to life-long disability. Prevention of PTB in women with a multiple pregnancy is urgently necessary to improve neonatal outcome of children that are part of a multiple pregnancy. Preventive methods for PTB in women with a multiple pregnancy such as pessary placement and vaginal progesterone are only available for women with a short cervical length (CL). Multifetal pregnancy reduction is a technique that has been performed since the eighties to reduce complications associated with preterm birth in women with a triplet or higher order multiple pregnancy. It has been shown to prolong gestation but to the risk of miscarriage <24 weeks.

In this thesis the predictive value of mid-term CL measurement and the pregnancy outcomes of MFPR are studied.

Chapter 1 contains a general introduction of multiple pregnancy, preterm birth, risk factors and possible preventive methods for preterm birth in women with a multiple pregnancy. The aim and outline of the thesis are described.

In chapter 2 the predictive value of CL measurement at 16-20 weeks’ gestation was studied. It was already known that CL measured at 20-24 weeks of gestation is a good predictor of PTB in women with a multiple pregnancy. As possible preventive methods such as pessary placement and administration of Progesterone can be applied at 16-20 weeks’ gestation, it was necessary to know if CL at this gestation is a good predictor as well. A multivariable prediction model was developed using data collected for the AMHIA trial that evaluated the effectiveness of 17 Alpha Hydroxy Progesterone (17P) for the prevention of PTB in women with a multiple pregnancy. In a multivariable prediction model CL <30 mm, monochorionicity,
previous PTB, smoking during pregnancy, low educational level, triplet pregnancy and randomization to 17P were predictive for time to delivery.

**Chapter 3** contains a systematic review and meta-analysis of the diagnostic accuracy of CL measurement in women with a multiple pregnancy and threatened preterm labor. Five studies reporting on 226 women were included for the meta-analysis. There was a wide variety in cut-off points for CL and definitions of PTB. Only one study reported on the most important outcome measurement, which is delivery within seven days. CL ≥25 mm had a sensitivity of 1.0 (95% CI 0.83-1.0) and a specificity of 0.31 (95% CI 0.20-0.43) for delivery within seven days. Three studies reported on predicting PTB <37 weeks at a CL cut-off 30 mm, with sROC point estimates of 0.76 (95% CI 0.66 to 0.84) and 0.37 (95% CI 0.21 to 0.56)) for sensitivity and specificity, respectively.

In **chapter 4** the predictive value of mid-term CL measurement for emergency cesarean delivery in women with a twin pregnancy was evaluated. In a vaginal twin delivery there is an increased risk on neonatal morbidity compared to singletons especially for the second twin and an increased risk on (emergency) cesarean delivery. It has been shown that there is no benefit of delivering all twins by cesarean section. As in singletons mid-term CL has been shown to be predictive for emergency cesarean delivery, the aim of this study was to know if mid-term CL is also predictive for emergency cesarean delivery in women with a twin pregnancy. A multivariable model including mid-term CL was developed based on nulliparous women included in the AMPHIA and ProTwin trial. Mid-term CL was not predictive for emergency CL (adjusted Odds Ratio (aOR) 0.97 for CL p26-50, aOR 0.71 for CL p51-75 and aOR 0.93 for CL >p75 with CL ≤p25 as reference). The only variables associated with emergency caesarean delivery were maternal age (aOR 1.07; 95% CI 1-1.13) BMI (aOR 3.99 (95% CI 1.07-14.9 for BMI 19-23, aOR 5.04 (95% CI 1.34-19.03) for BMI 23-28 and aOR 3.1 (95% CI 0.65-14.78) for BMI >28) and induction of labour (aOR 1.9; 95% CI 1.05-3.5).
In chapter 5 the natural course of 494 consecutive triplet pregnancies was studied to evaluate if there is one specific timeframe with such a high risk of delivery to warrant prophylactic administration of corticosteroids. Median gestational age at delivery was 235 days (33 4/7 week) with an interquartile range (IQR) of 217-246 days, 146 women (29.6%) delivered before 32 weeks. At a gestational age of 24 weeks, the chance to deliver within the next week was 0.6%. For 26, 28, 30 and 32 weeks these risks were 2.4%, 2.5%, 8.1% and 16.7%, respectively. Nulliparity and monochorionicity were associated with a shorter time to delivery and a higher risk of PTB <32 weeks. We concluded that prophylactic administration is not applicable in women with a triplet pregnancy.

In chapter 6, 7 and 8 the pregnancy outcome of MFPR is described. Data were collected in all ten hospitals that perform MFPR in The Netherlands.

In chapter 6, the effectiveness of elective reduction from a trichorionic triplet (TCT) to a twin pregnancy is described. A nationwide cohort of 86 women with a TCT that was reduced to a twin pregnancy was described and the outcome was compared to the outcome of women with an ongoing TCT and women with a primary dichorionic twin pregnancy. Reduced triplets had a median gestational age at delivery of 36.1 weeks (inter quartile range (IQR) 33.3-37.5 weeks), versus 33.3 (28.1-35.2) weeks for ongoing triplets and 37.1 (35.3-38.1) weeks for primary twins (p<0.001). Rates of PTB <24 weeks and PTB <32 weeks were not significantly different in the reduction group and the ongoing triplet group as well as the proportion of women that had all or no children surviving.

In chapter 7, the pregnancy outcomes of 45 women with a dichorionic triplet (DCT) pregnancy reduced to a singleton pregnancy were described and compared to the outcome of women with an ongoing DCT pregnancy and to women with a primary low risk singleton pregnancy. Moreover a review of literature was made of this issue. In the study groups, median gestational ages at delivery were 38.7 weeks (IQR 35.2-40.3), 32.8 weeks (IQR 29.6-34.3) and 40.1 weeks (IQR 39.1-40.9) for reduced DCT, ongoing DCT and primary
singleton pregnancies respectively, p<0.001. Reduction resulted in a non-significant increased risk of delivery <24 weeks, but a decreased risk of delivery <32 weeks. The proportion of women that had all or no children surviving was not different for women with a reduced DCT and an ongoing DCT pregnancy. In the literature five studies with small sample sizes (n=7-29) reported about MFPR from DCT to a singleton pregnancy. Mean or median gestational ages varied between 36.8 and 39.1 weeks and loss rates <24 weeks varied from 0-23%.

In chapter 8 the outcomes of MFRP from a dichorionic twin to a singleton pregnancy were described and compared to the outcomes of women with an ongoing dichorionic twin and women with a primary low risk singleton pregnancy. Most reductions (105 out of 188) were performed because the fetuses were discordant for fetal anomaly. Median gestational age at delivery was 38.9 (IQR 34.7-40.3) weeks for reduced twins compared to 37.1 (35.1-38.1) weeks for ongoing twins and 40.1 (39.1-40.9) weeks for primary twins, p<0.001. Risk of delivery <24 weeks and <32 weeks were significantly increased in the reduction group as compared to the ongoing twin group. Perinatal survival was lower in the reduction group than in the ongoing twin group.

Chapter 9 contains a general discussion of the results described in this thesis and future perspectives are described. It is stated that the best way of preventing complications associated with preterm birth in multiple pregnancies is to prevent the multiple pregnancy to occur by restrictions in ART. If a multiple pregnancy develops, it is important to perform mid-term cervical length measurement as preventive methods are available for women with a short cervix. MFPR for elective indications is an option in women with a triplet pregnancy or higher order multiple pregnancy and can prolong pregnancy but to a considerable risk of miscarriage <24 weeks. In choosing the number of fetuses to be reduced, chorionicity is an important factor. Reduction of a twin pregnancy should be selected to women with a twin that is discordant for a severe non-lethal anomaly, whereas elective reduction to improve obstetric outcome is currently not applicable.
Future research should include prospective follow-up of all women counseled for MFPR and long term infant follow-up.