Pessaries for the prevention of preterm birth in multiple pregnancies
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Citation for published version (APA):
Liem, S. M. S. (2013). Pessaries for the prevention of preterm birth in multiple pregnancies

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Download date: 12 Dec 2018
CHAPTER 10
Summary
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In the Western world, preterm birth is the contributing factor to perinatal morbidity and mortality. Prematurity not only requires intensive medical care for the neonate during the first period after birth but is also associated with a higher risk of mortality, as well as handicaps and developmental disorders later in life. Women with a multiple pregnancy are at increased risk for preterm birth. Interventions to reduce preterm birth in these women have been unsuccessful. Consequently, reduction of preterm birth remains a major challenge in modern obstetric healthcare.

Part 1 Preterm birth

In Chapter 2 we present a systematic review and meta-analysis of ethnic disparities in the risk of preterm birth. We found 45 studies on the association between maternal ethnicity and the risk of preterm birth, of which 41 reported a significant positive association between at least one ethnic group and preterm birth risk. Blacks appear to have a significantly increased (range of adjusted ORs 0.6 to 2.8, pooled OR 2.0; 95% CI 1.8-2.2) risk of preterm birth when compared to whites (30 included studies). For Asian women there was no significant association, with ORs ranging from 0.6 to 2.3 (17 included studies). For women of Hispanic ethnicity there was no significant difference in the risk of preterm birth when compared to whites. Currently recognized risk factors do not appear to explain the increased risk of preterm birth among black women. Despite the heterogeneity of the included studies in defining ethnicity and adjustment for possible confounding, ethnic disparities clearly exist. This merits research on the causal pathways of these differences, and on preventative measures to reduce the incidence of preterm birth. As ethnic compositions of societies differ greatly, future prospective research should also focus on ethnic groups living outside the United States.

In Chapter 3 the results of a systematic review and bivariate meta-analysis on the accuracy of cervical length measurement for the prediction of preterm birth in symptomatic women with multiple pregnancies are presented. We identified five studies reporting on 226 women. Variation in definition of PTB and cut-off points for CL was large. One study investigated delivery within seven days, demonstrating a sensitivity of 1.0 (95% CI 0.83-1.0) and specificity of 0.31 (95% CI 0.2-0.43) for a CL cut-off at 25 mm. Three studies reported on predicting PTB <37 weeks at a CL cut-off 30 mm, with sROC point estimates of 0.76 (95% CI 0.66-0.84) and 0.37 (95% CI 0.21-0.56) for sensitivity and specificity, respectively. For preterm birth <34 weeks no pooled estimated could be estimated since only 2 studies with large heterogeneity were identified. We concluded that there is limited evidence on the accuracy of cervical length measurement testing the prediction of preterm birth in symptomatic women with a twin pregnancy, especially on the most important outcome, i.e. delivery within 7 days.
Part 2 Pessary for the prevention of preterm birth

In Chapter 4 the results of a systematic review of randomized controlled trials and cohort studies on the effectiveness of the cervical pessary to prevent preterm birth are presented. Our search revealed 125 potentially eligible abstracts of which six cohort studies and four randomized controlled trial (RCT) investigated the effectiveness of the pessary. One RCT in 380 women demonstrated a lower delivery rate prior to 34 weeks (RR 0.24; CI 95% 0.13-0.43) in the pessary group, while another RCT in 108 women showed no positive effect of the pessary for delivery before 34 weeks (RR 1.73; 95% CI 0.43-6.88). Two older quasi randomized studies and cohort studies indicated potential effect of the pessary.

Available randomized and non-randomized studies indicate potential effectiveness of a cervical pessary in the prevention of preterm birth. More randomized clinical trials are needed before this device can be used in clinical practice.

Chapter 5 presents the results of the randomised controlled trial on the cervical pessary to prevent poor perinatal outcome in women with a multiple pregnancy. We randomly allocated 813 women to the pessary (403 women) or the no-pessary group (410 women). There were 53 (13%) women with a least one child with a poor perinatal outcome in the pessary group and 55 (14%) women in the no-pessary group (RR 0.98; 95% CI 0.69 to 1.4). Delivery before 32 weeks occurred in 10% (41/401) of women in the pessary group and 12% (49/407) in the no-pessary group (RR 0.86; 95% CI 0.65 to 1.1), and before 37 weeks in 55% (222/401) and 57% (233/407) of women (RR 0.94, 95% CI 0.87 to 1.0), respectively. In the prespecified subgroup of women with a cervical length below the 25th percentile (38 mm), these rates were 12% (9/78) for the pessary and 29% (16/55) for the no-pessary group (RR 0.40; 95% CI 0.19 to 0.83), which was accompanied by a significantly reduced delivery rate before 32 weeks (14% (11/78) vs 29%, (16/55), RR 0.49; 95% CI 0.24 to 0.97). In unselected women with a multiple pregnancy prophylactic use of a cervical pessary does not reduce poor perinatal outcome. However, in women with a cervical length below 38 mm at 16-22 weeks, a pessary significantly reduces both poor perinatal outcome and very preterm birth rates.

In Chapter 6 we investigated the full potential treatment effect of the pessary by performing a per protocol analysis. We randomly allocated 403 (50%) women to a pessary and 410 (50%) women to no intervention. In 23 (6%) of the 403 women randomized to the pessary group, the pessary was never placed, while 47 (12%) women discontinued the use of the pessary before 36 weeks without delivering immediately thereafter. In the per protocol analysis of all women, poor perinatal outcome and preterm birth <32 weeks of gestation in the pessary group occurred less frequent compared to the intention-to-treat analysis (RR 0.86; 95% CI 0.59-1.3 and RR 0.75; 95% CI 0.49-1.1, respectively). For women with a cervical length (CL) <38 mm the treatment effect was statistically significant (reduction of poor perinatal outcome RR 0.32; 95% CI 0.13-0.78, preterm birth <32 weeks of gestation RR 0.41; 95% CI 0.20-0.87, respectively). The Cox regression following per protocol analysis showed time to
delivery to be longer in the pessary group than in the control group (whole group: HR 0.68; 95% CI 0.55-0.82, CL < 38 mm: HR 0.35; CI 0.22-0.57). We concluded that in women with a twin pregnancy and a cervix below the 25th percentile, the treatment potential of the pessary if applied consequently was stronger than we found in the intention-to-treat analysis.

Chapter 7 presents the results of the economic analysis of use of a cervical pessary to prevent preterm delivery in women with a multiple pregnancy. Costs were estimated between randomisation and 6 weeks postpartum. We separately analysed the prespecified subgroup of women with a cervical length (CL) below the 25th percentile (<38 mm). The mean costs in the pessary group (401 women) were €21884 versus €22030 in the no pessary group (407 women), with an average difference of -€146 (95% CI €-5648 to €4718). In the prespecified subgroup of women with a CL <38 mm the mean costs in the pessary group (78 women) were €25142 versus €30577 in the no pessary group (55 women) (difference of -€5436 (95% CI €-11001 to €1456). Analysis showed that in women with CL <38 mm, pessary treatment is the dominant strategy (more effective and less costly) with a probability of 94%. Our study shows that in unselected women with a multiple pregnancy treatment with a cervical pessary generates comparable costs as in women without treatment. However, a screen-treat program using a pessary in women with a CL <38 mm results in better outcomes and lower costs.

Part 3: Modus partus

In Chapter 8 we studied the influence of duration of twin-to-twin delivery interval on neonatal outcome of the second twin. We selected women that had delivered the first twin vaginally after 34 weeks of gestation, either in cephalic or in breech position.

We used data on 628 twin deliveries. An increasing twin-to-twin interval was correlated with a decline in arterial pH (difference -0.04 (95% CI:-0.05 to -0.03)) on the transformed natural log scale. Second twins born after 15 minutes more frequently had an arterial pH <7.10 (15-30 min: OR 5.1; 95% CI 2.4 to 11) and >30 min: OR 6.1; 95% CI 2.8 to 13)). After 30 minutes there were significantly more neonates with lower Apgar scores (OR 3.0; 95% CI 1.3 to 6.9) or were admitted to NICU (OR 3.1; 95% CI 1.4 to 6.9). From our results, we concluded that the risk of neonatal acidosis, low Apgar scores and NICU admission increases when the twin-to-twin interval exceeds 15 minutes. These data justify further evaluation of active management of delivery of the second twin in randomized controlled trials.