Pessaries for the prevention of preterm birth in multiple pregnancies
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CHAPTER 1
General introduction
Introduction

Preterm birth

Preterm birth is a major problem in obstetrical care. 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, mostly due to neonatal lung immaturity, intracranial haemorrhages and infections.\(^1\) Preterm birth is defined as delivery before 37 weeks of gestation and further categorized into: moderate preterm birth (between 32 and 37 weeks) and very preterm birth (before 32 weeks). In 2010 a total of 15 million babies were born preterm worldwide, more than one million of these neonates died from complications of preterm birth.\(^4,5\) Preterm birth is worldwide the second most common cause of death in children under 5 years of age.\(^6\) In The Netherlands the mortality rate for moderate preterm born children is about 4% and for very preterm born children 21%.\(^7\)

Preterm birth appears to be a multifactorial and heterogeneous adverse outcome of pregnancy and therefore many studies have focussed on unravelling the pathogenesis.\(^8\) Romero et al. described a conceptual framework for the understanding of preterm labor. Since preterm parturition meets all the criteria for a major obstetrical syndrome the term preterm parturition syndrome is more appropriate. The pathological processes implicated in the preterm birth syndrome include intrauterine infection, uterine ischaemia, uterine overdistension, cervical disease, abnormal allogenic recognition, allergic-like reaction, and endocrine disorders (Figure 1). Since preterm birth is a heterogeneous condition it is unlikely that a single treatment will reduce all cases of preterm birth in patients at risk and prevention of preterm birth is therefore so difficult to achieve.\(^9\)

Figure 1 Pathological processes implicated in the preterm parturition syndrome (Reproduced with permission from reference 9)
Women with a multiple pregnancy are even more at risk for preterm delivery. The exact mechanism of preterm birth in women with a twin pregnancy is unclear and is likely to differ from women with a singleton pregnancy. It has been hypothesized that relative overdistension of the uterus or increased pressure on the internal os are the most common aetiologies causing preterm birth in twin pregnancies.

In The Netherlands approximately 50% of women with a multiple pregnancy deliver prior to 37 weeks of gestation, of these 9% deliver before 32 weeks. In the United States, these rates are 60% and 12%, respectively. In comparison, 6%-10% of women with singleton pregnancy deliver before 37 weeks and only 1% before 32 weeks. Consequently, reduction of preterm birth is a major goal in obstetric care in general, and specifically in women with a multiple pregnancy.

Substantial shortening of the cervical length (CL) in the second trimester in twin pregnancies is one of the best predictors of preterm delivery. Several studies show that transvaginal cervical sonography identifies women who have an increased risk of spontaneous preterm birth. However it is difficult to apply these findings due to the wide variation in gestational age at testing and the variation in the definition of threshold of abnormality that have been used in studies. Furthermore, most of these results apply to asymptomatic women. In symptomatic women it is of clinical relevance to distinguish between women who will truly deliver and those who will not. Correct identification of these women might be effective in reducing perinatal morbidity and mortality by providing necessary interventions such as tocolysis, antenatal corticosteroid administration, and timely transfer to a tertiary care centre.

**Prevention of preterm birth**

Mechanical prevention of preterm birth was proposed six decades ago by the surgical application of a cervical cerclage. The Shirodkar and McDonald cerclage are the two most commonly used techniques. In women with a singleton pregnancy at high risk of preterm birth based on their history (e.g., previous preterm birth, cervical surgery, short CL on ultrasound, or detected cervical changes) a cervical cerclage showed a significant reduction in preterm birth before 37 weeks of gestation and before 34 weeks of gestation. Cervical cerclage in women with a multiple pregnancy was associated with an increased risk of preterm birth before 35 weeks and a trend towards higher perinatal mortality, indicating that a cerclage should not be used in twin pregnancies.

A breakthrough in the prevention of preterm birth in women with a singleton pregnancy occurred when it was shown that both 17α-hydroxyprogesterone caproate (17P) as well as vaginal progesterone reduced preterm birth in women with a history of spontaneous preterm birth. In women with a short cervix there is no evidence that 17P is effective in reducing preterm delivery. However, vaginal progesterone is effective in reduction of preterm birth in these women. Furthermore, neither vaginal progesterone nor 17P were effective in the prevention of preterm birth in women with a multiple pregnancy. Other interventions to reduce preterm birth such as routine hospitalisation with bed rest and prophylactic use of a cervical cerclage have not been shown to be effective.
**Pessary**

The vaginal pessary to prevent preterm birth was introduced in 1959. Previous studies were relatively small and non-randomised. A glimmer of hope arose recently when the PECEP trial demonstrated that a cervical pessary could prevent preterm birth in women with a singleton pregnancy and a cervical length <25 mm. The exact mechanism for effect is not known. It has been hypothesized that the pessary encompasses the cervix and compresses the cervical canal, and may therefore prevent deterioration of the cervical mucus plug. The pessary also alternates the inclination of the cervical canal and corrects the cervix pointing forward in the axis of the vagina. It relieves direct pressure on the internal cervical os by distributing the weight of the pregnant uterus onto the vaginal floor, retrosymphyseal osteomuscular structures, and Douglas cavity and so may prevent premature dilatation of the cervix and premature rupture of the membranes. Furthermore, it blocks the fetal head from descending and reduces the pressure on the lower uterine segment and the internal cervical os. There are different types and sizes of pessaries available. The cervical pessary is a relatively non-invasive, not operator dependent intervention, which can be easily placed or removed in an outpatient clinic and does not require anesthesia (Figure 2). With a vaginal speculum examination the cervix is identified to determine an appropriate pessary size. The silicon Arbin pessary is the most popular in The Netherlands and has different sizes of diameter and height. It is flexible and fits high around the cervix, so that the smaller inner diameter encompasses the cervix. After placement the patient is briefly observed to ensure there is no discomfort, vaginal blood loss or uterine activity.

![Figure 2 Sagittal view of a cervix with cerclage pessary (Reproduced with permission from reference 34)](image)

**Aim of this thesis**

The studies presented in this thesis aim to investigate the effectiveness of a cervical pessary in preventing preterm birth in women with a multiple pregnancies. The aim of this thesis was to answer the following questions:

Is treatment with a cervical pessary effective in reducing the incidence of perinatal morbidity and mortality in women with a multiple pregnancy?
What is the full potential of a cervical pessary in preventing preterm birth in short cervix twins?
Is the use of a cervical pessary to prevent preterm delivery in women with a multiple pregnancy cost-effective?
How accurately can cervical length predict preterm birth in symptomatic women with a multiple pregnancy?

**Outline of the thesis**

**Part 1 Preterm birth**
In Chapter 2 a systematic review and meta-analysis of the literature on ethnic and racial disparities in the risk of preterm birth is presented. It summarizes all relevant studies of which the majority were performed in the United States. Chapter 3 demonstrates the results of a systematic review on cervical length measurement for the prediction of preterm birth in symptomatic women with multiple pregnancies. A bivariate meta-analysis was performed on the collected data.

**Part 2 Pessary for the prevention of preterm birth**
Chapter 4 provides a systematic review of the literature on cervical pessaries to prevent preterm birth. In Chapter 5 the results of the ProTWIN trial, a randomized, controlled trial that investigated whether the prophylactic use of a cervical pessary can reduce perinatal morbidity and mortality in multiple pregnancies by decreasing the preterm birth rate, are presented. A planned subgroup analysis was performed on women with a short cervix (cervical length below the 25th percentile (<38 mm)). Chapter 6 expands on the first ProTWIN trial report. The objective was to estimate the full potential treatment effect of the cervical pessary by performing a per protocol analysis and separately analyse the data of women in whom the pessary was removed before 36 weeks of gestation. In Chapter 7 an economic analysis of the use of a pessary to prevent preterm birth in women with a multiple pregnancy is described.

**Part 3 Modus partus**
Chapter 8 investigates the influence of duration of the twin-to-twin delivery interval on neonatal outcome of the second twin.

**Part 4 General discussion, conclusion and summary**
In Chapter 9 the results are discussed and clinical implications and suggestions for future research are given. In Chapter 10 and 11 the results of this thesis are summarized in English and Dutch.
Reference List


