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# 1

# Introduction

# Preterm birth

Every year, throughout the world approximately 12.9 million children are born before 37 weeks of gestation, adding up to a global prevalence of preterm birth of 9.6%.[1] In the Netherlands, 7.1% of all children that are born after a gestational age of at least 22 weeks are born before 37 weeks and 1.1% even before 32 weeks.[2] The neonatal mortality in the first 28 days of life is 3.8% and 21% for these two groups respectively. A total of 22% of all children born preterm are admitted to a Neonatal Intensive Care Unit (NICU). Preterm children who survive the neonatal period are at considerable risk of developing handicaps later in life. Thus, preterm birth is one of the major causes of perinatal mortality and morbidity and therefore a major issue in obstetrics.

Several factors are known to increase the risk of spontaneous preterm birth. Among these are multiple gestation, a history of preterm birth, cervical shortening, uterine or cervical anomalies, a history of uterine or cervical surgery and bacterial vaginosis. Demographic factors such as ethnicity and socio-economic status are also associated with preterm birth risk.

In women with a singleton pregnancy and a history of preterm birth, the risk of recurrent preterm birth before 35 weeks is increased to about 15%.[3] The most notable preterm birth risk can be seen in women with a multiple pregnancy. In the Netherlands, 48% of women with a multiple pregnancy deliver before 37 weeks, and 9% even before 32 weeks.[2] Part of the preterm birth rate in multiple pregnancies can be attributed to iatrogenic preterm birth, as there is higher risk of maternal morbidity during pregnancy in this group. However, even when iatrogenic premature birth is excluded, the risk ratio of delivering preterm in multiple versus singleton pregnancies remains similar. The risk rises with an increasing number of foetuses. The cause of prematurity in these pregnancies is often hypothesized to lie in mechanical factors such as overdistension of the uterus and increased pressure on the cervix.

In pregnant women both with and without symptoms of preterm labour, transvaginal sonography of the cervix is able to identify women who are at increased risk of preterm birth. However, the exact attribution of cervical length to the risk of preterm birth is difficult to express in numbers due to a large variety in measurement techniques, cervical length cut-off values and outcome measures that have been used to study this risk factor.

# Prevention of preterm birth

Strategies to prevent preterm birth have proven to be largely unsuccessful. When preterm labour has already been initiated, a treatment strategy consisting of administration of corticosteroids in conjunction with 48 hours of tocolysis has been proven to significantly

reduce neonatal morbidity.[4] Extended tocolysis beyond 48 hours has not been shown to further improve neonatal outcome.

Systematic reviews on preventive measures such as bed rest, monitoring uterine activity and prophylactic hospital admission have all failed to show a beneficial effect on gestational age and neonatal outcome.[5, 6]

Many studies have focussed on the application of cervical cerclage, where a suture is placed around the cervix. Prophylactic cerclage before 16 weeks of gestation is sometimes applied in women with a history of multiple extremely preterm births, even though a systematic review on this intervention has shown no beneficial effect on the occurrence of preterm birth or neonatal outcome.[7] Emergency cerclage remains a controversial intervention in pregnant women with cervical shortening, with trials generating mixed results. A meta-analysis indicated that cerclage in case of cervical shortening might prevent preterm birth in women with singleton gestations, especially in those with a prior preterm birth.[8] No randomized controlled trials have been conducted to determine optimal gestational age at which to perform screening and intervention or optimal cut-off value for cervical length. In multiple gestations, cerclage has been found to increase pregnancy loss or neonatal death before discharge from the hospital.[9]

## Progesterone

The steroid progesterone was discovered in the late 1920s and turned out to be one of the most important factors in maintaining pregnancy due to its role in endometrial proliferation. This discovery was ensued by the theory that administration of exogenous progesterone can increase the duration of pregnancy. In several species of mammals, a marked drop in the serum progesterone concentration can be observed preceding delivery.[10] In sheep and cows this drop can be attributed to a decreased placental secretion; in other mammals progesterone levels decline due to regression of the corpus luteum. In humans however, where the production of progesterone is passed on from the corpus luteum to the placenta in the 12$^{th}$ week of gestation, such a decrease in serum progesterone cannot be observed. The working mechanism of progesterone after the first trimester of pregnancy is probably based on several factors. In vitro it has been shown that progesterone has an inhibitory effect on prostaglandins and oxytocin, and that it can decrease the number of oxytocin receptors and gap junctions in the myometrium.[11, 12] Mifepristone, a progesterone antagonist, is an effective inductor of abortion.[13] How progesterone suppletion is able prevent preterm birth in pregnant women who already have very high endogenous progesterone concentrations, is unclear. Exogenous progestogens are available in forms suitable for oral, vaginal and intramuscular administration. For intramuscular injection 17-alpha hydroxyprogesterone caproate (17OHPC) is used.

In the first decade of the new millennium numerous studies have been conducted on progesterone as a preventive treatment for preterm birth. Interest in the subject was sparked by two randomised controlled trials, both indicating a substantial decrease in recurrent spontaneous preterm birth after the use of progesterone.[14, 15] These findings led to trials being performed in several groups of pregnant women with a high risk of spontaneous preterm birth. Trials have so far indicated a reduction in preterm birth rate in women with a previous preterm birth and women with asymptomatic cervical shortening in the second trimester.[16, 17]

# Study aim

The aim of this thesis was to explore the application of progesterone treatment for the prevention of recurrent preterm birth in the Netherlands and to study the effect of progesterone treatment in multiple pregnancies.

The specific research questions were:

Does progesterone treatment decrease the recurrent preterm birth rate in the Netherlands?

To what extent are new and established strategies to prevent recurrent preterm birth applied in the Netherlands?

Which factors hamper or facilitate the use of progesterone treatment for the prevention of recurrent preterm birth in clinical practice?

Can progesterone treatment reduce the incidence of neonatal morbidity in multiple pregnancies?

Is second trimester cervical length a predictor for the effect of progesterone treatment on neonatal outcome in multiple pregnancies?

Does progesterone treatment have an effect on cervical shortening in multiple pregnancies?

How accurately can cervical length predict preterm birth in asymptomatic women with a multiple pregnancy?

# Outline of the thesis

## Part 1: Prevention of recurrent preterm birth

In **chapter 2** the results are presented of a cohort of Dutch women that were treated with progesterone to prevent recurrent preterm birth. The pregnancy outcomes of this group are compared to those of matched control patients who delivered before progesterone treatment was applied in the Netherlands.

In **chapter 3** data are presented on the application of new and established strategies to prevent recurrent preterm birth in six different obstetric clinics in the Netherlands.

In **chapter 4** the results are presented of a questionnaire study that was held among obstetricians, midwives and patients to identify factors that can hamper of facilitate the use of progesterone treatment for the prevention of recurrent preterm birth in clinical practice.

## Part 2: Preterm birth in multiple pregnancies

In **chapter 5** the results are presented of the AMPHIA-trial, a randomized controlled trial that addresses the question whether progesterone treatment can reduce neonatal morbidity in multiple pregnancies by decreasing the preterm birth rate. A subgroup analysis was performed on women with a short cervix in the second trimester.

In **chapter 6** a secondary analysis of data from the AMPHIA-trial is performed that assesses the effect of progesterone treatment on cervical shortening during pregnancy in multiple gestations.

In **chapter 7** the results of a systematic review on cervical length measurement for the prediction of preterm birth in multiple pregnancies are presented. A bivariate meta-analysis was performed on the collected data.

## Part 3: Overview of the literature

In **chapter 8** an overview is given of the literature that has been published on progesterone treatment for the prevention of preterm birth.

## Part 4: General discussion, conclusion and summary

In **chapter 9** the results are discussed and clinical implications and implications for future research are given.

In **chapters 10 and 11** we summarize the results presented in this thesis in English and Dutch.

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