Prediction of preterm delivery
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Introduction
Chapter 1

Introduction

Preterm delivery (PTD) is in quantity and severity an important issue in the obstetric care in the Western world. It is defined as a delivery before a gestational age less than 37 completed weeks or 259 days. Worldwide, 5-13% of all deliveries are preterm. It therefore is a major cause of perinatal mortality and severe neonatal morbidity.1,2

Spontaneous PTD can either be preceded by preterm prelabor rupture of membranes (PPROM) or by preterm labor (PTL), defined as regular uterine contractions leading to cervical changes at a preterm gestation.

The exact pathogenesis of preterm labor, leading to preterm delivery, is unknown. PTL is thought of as a syndrome, which underlying mechanisms include infection or inflammation, uteroplacental ischemia or hemorrhage, overdistention of the uterus, stress and other immunologically mediated processes.3,4 There is considerable knowledge on maternal and obstetric risk factors for preterm labor contributing to these mechanisms.

Race is one of the maternal risk factors. Disparity between preterm delivery rates exists especially between the non-Hispanic black and non-Hispanic white women with PTD rates of 16-18% and 5-9% respectively. This disparity in preterm birth rates is poorly understood.5,6 The association between a higher risk of PTD and other demographic characteristics as low socio-economic and educational status, low and high maternal age and single marital status remains also unexplained.4 Thin women (Body Mass Index (BMI) < 19 kg/m²) have increased spontaneous PTD rates, probably related to their nutritional status. The association between BMI and spontaneous PTD seems to be inverse.7 In women who smoke, vasoconstriction and a systemic inflammatory response might be of influence of the increased risk of spontaneous PTD.4

Women with previous spontaneous PTD have a 2.5-fold increased risk of PTD in their next pregnancy. This risk is inversely related to the gestational age of the previous PTD and a prior spontaneous PTD is more closely associated with subsequent early spontaneous PTD at <28 weeks’ gestation than with spontaneous PTD overall.8 The interval between two pregnancies is more often shorter in women who delivered prematurely previously, and a short interval between two gestations even further increases the risk of spontaneous PTD. Other pregnancy characteristics known to be associated with a high risk of spontaneous preterm delivery are
multiple pregnancy, intra-uterine infection and high levels of psychological and/or social stress.4

Accurate identification of those women with symptoms of PTL who actually will deliver prematurely is difficult. Of the women with symptoms of PTL, only a small portion (3.6%) delivers within seven days after admission to the hospital, whereas about 50-70% of these women deliver after 37 weeks’ gestation.9-12

Shortening of the cervix precedes spontaneous PTD. Measurement of the cervical length (CL) by transvaginal ultrasound to detect this shorting is a useful diagnostic test in the prediction of preterm delivery in women with symptoms of preterm labor. The likelihood ratio (LR) of PTD within seven days after presentation in women with symptoms of PTL and a CL below 15 is 5.7 (95% confidence interval (CI) 3.8 to 8.65), compared to the likelihood ratio of 0.5 (0.3 to 0.8) for women with a CL above 15 mm. These LR’s are 3.74 (95% CI 2.77 to 8.65) and 0.51 (95% CI 0.33 to 0.80) in women with PTL and a CL below or above 20 mm, and 2.77 (95% CI 2.15 to 3.59) and 0.33 (95% CI 0.22 to 0.50) when the CL is below or above 25 mm respectively.13-15 Women with a CL above 30 mm are at low risk of PTD within seven days (LR of a negative test of 0.2 (95% CI 0.005 to 0.53), with a negative predictive value of 97% (95% CI 93 to 99).10

Of the many biomarkers related to inflammation associated with spontaneous PTD, like cytokines and chemokines, fetal fibronectin (fFN) has shown to be the most powerful biomarker to predict PTL and of most clinical use in symptomatic women. Fetal fibronectin (fFN) is an extracellular glycoprotein produced in the decidua and chorion, and acts as a marker of choriodecidual disruption which can be detected with a swab taken from the posterior fornix. In an uncomplicated pregnancy fFN is only detectable in cervicovaginal secretions before 21 weeks of gestation. If it is detectable between a gestational age of 24 and 34 weeks it is associated with an increased risk of PTD.

The fetal fibronectin test is 4.2 times (95% CI 3.5 to 5.0) more likely to be positive in symptomatic women who will deliver within seven to ten days after testing, than in symptomatic women who stay pregnant beyond that period of time. The corresponding likelihood ratio for the negative test is 0.29 (95% CI 0.22 to 0.38).11 Making the test particularly of clinical interest if its result is negative, virtually ruling spontaneous PTD within the following seven days out.16,17
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Combining measurement of the CL and fFN testing improves the prediction of spontaneous PTD within seven days after presentation, in comparison to performing only a CL measurement or fFN test. Different methods in combining the two tests have been published, performing CL and fFN in all women with PTL, or performing a two-step contingent approach in which fFN was tested in women with a midrange CL (16-30 mm). The LR for preterm delivery within seven days of a combined positive test of the used methods in literature (CL under the used cut-off and a positive fFN test) is 22.0 (95% CI 13.6 to 35.7).\textsuperscript{9} No additional value for fFN testing was found in women with a cervical length above 30 mm.\textsuperscript{10,18,19} The LR of a negative fFN test in women with a CL above 30 mm is 0.76 (95% CI 0.14 to 1.13).\textsuperscript{10} The LR of preterm delivery within seven days in women with a CL < 15 mm for a positive fFN test is 2.29 (95% CI 0.95 to 6.60) and for a negative fFN test 0.43 (95% CI 0.18 to 1.07), showing that fFN testing in women with a short cervix has virtually no additional value. Moreover, over 90% of the women with a cervical length less than 10 mm have a positive fFN test.\textsuperscript{20}

In the Dutch obstetric care system initial assessment of women with symptoms of PTL is mostly performed by midwives, who take care for low-risk women in primary care. Their risk assessment that involves digital cervical examination to determine cervical dilatation or effacement is thought to influence the accuracy of the fibronectin test.\textsuperscript{21}

**Consequences of preterm delivery**

Neonates that are born prematurely are at increased risk of acute and chronic medical complications and mortality. The complications of preterm birth arise from immature organ systems that are not yet prepared to support life in the extrauterine environment. The risk of acute neonatal illness decreases with gestational age. In general, the earlier premature delivery occurs, the more neonatal life support is required.\textsuperscript{22} Innovation in the treatment of preterm infants has improved their survival, but short term morbidity, including respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), patent ductus arteriosus (PDA) and sepsis, still complicates the premature life. Long-term morbidity includes cerebral palsy, visual and hearing impairment and behavioral issues.\textsuperscript{23}
**Antenatal corticosteroids**

To optimize neonatal health after preterm delivery, women with symptoms of preterm labor are treated with tocolysis to prolong pregnancy and antenatal corticosteroids (ACS) to prepare the fetal lungs for a life independent of the mother.\(^{23-30}\)

Graham Liggins, in the late 1960’s, incidentally discovered that preterm lambs that were exposed to corticosteroids had more mature lungs than expected, were viable at an earlier gestational age and had less severe respiratory distress at birth.\(^{31}\) Together with pediatrician Ross Howie he published a landmark article in 1972. In their randomized controlled trial (RCT) that followed their initial findings, they found a significant reduction of the incidence of RDS from 15.6 % to 10.0% in those preterm neonates whose mothers received two 12-mg injections of betamethasone administered 24 hours apart.\(^{27}\) Furthermore a reduction in mortality from 11.6% to 6.0% and a significant reduced risk of IVH in preterm neonates was found after antenatal betamethasone.\(^{28}\) It took over 20 years before the administration of antenatal corticosteroids to mothers at risk of a premature birth was implemented, due to fears of potential side effects.\(^{32}\) After a consensus conference, held in 1994 by the National Institutes of Health (NIH), administration of ACS was recommended to all women between 24 and 34 weeks’ gestation at risk of premature delivery. Endorsement of these recommendations by the American College of Obstetricians and Gynecologists (ACOG) resulted in a drastically increase of the use of ACS.\(^{33}\)

A possible diminishing effect of the initial course ACS, the optimal interval of 7 to 14 days between the administration of ACS and delivery, and the difficulty to accurately predict which women with symptoms of PTL actually will deliver in the short term, created a clinical dilemma.\(^{34-37}\) Consequently, despite initial hesitation to adopt the use of a single course ACS, in the 1990’s ACS courses were routinely repeated all around the world.\(^{38-40}\) Seven years after the first consensus conference, the NIH held a second one which concluded that repeat courses should be reserved for patients enrolled in randomized controlled trials, since the implementation of repeat courses was not based on sufficient data concerning safety and efficacy.\(^{41}\) The subsequently conducted RCT’s and a Cochrane review on repeat doses ACS concluded a reduction in occurrence and severity of neonatal lung disease and serious infant morbidity.\(^{42-44}\) Although a lower birth weight and smaller head circumference were reported after repeat courses,\(^{44}\) the long-term outcomes at 2-3 years of age seemed to be reassuring. However, no evidence was found for long-term benefit of repeat doses ACS.\(^{46,47}\)
Currently, over four decades after the initial trial that showed a beneficial effect of ACS and to strike the golden mean, clinicians started to administer a “rescue” course ACS. The ACOG guideline of 2011 states that a rescue course may be considered if the antecedent treatment was given more than 2 weeks prior, the gestational age is less than 32 6/7 weeks, and the women are judged by the clinician to be likely to give birth within the next week.\textsuperscript{48} This recommendation is based upon a limited amount of RCT’s. ACOG therefore suggested further research on “rescue” courses.\textsuperscript{49,50} The Dutch society of obstetrics and gynecology (NVOG) added to this recommendation that the first course had to be given before 30 weeks’ gestation.\textsuperscript{51}

**Background and outline of the thesis**

With the discovery of the treatment effects of antenatal corticosteroids and their subsequent implementation, the outcome of premature neonates has improved significantly. So clinicians do know that treatment of a woman at risk of preterm delivery is aimed at the improvement of the outcome of the prematurely born neonate, but keep struggling with the identification of the women who actually need this treatment and the appropriate treatment strategy. This thesis aims to address some of the dilemmas we face in diagnostics in preterm labor and treatment with antenatal corticosteroids:

**Part I** - *Diagnostic dilemmas* - focuses on the identification of women at risk of spontaneous preterm delivery.

**Part II** - *Therapeutic dilemmas* - targets the timing of antenatal corticosteroids.

**Part III** - *General discussion and summary* - provides a summary of this thesis and describes the general considerations and clinical implications.

**Part I Diagnostic dilemmas**

**Chapter 2** presents the results of a prospective cohort study on the prognostic value of the fFN test and CL among women with preterm labor in a Dutch setting. The influence of the digital examination, often performed prior to fFN testing, on the predictive value of the fFN test was also assessed.

**Chapter 3** reviews the methodology of studies on the clinical utility of fFN and addresses the strengths and weaknesses of these trials.
Chapter 4 evaluates the persistent risk of preterm delivery after arrested preterm labor. Women who remained pregnant and were discharged from the hospital after an episode of preterm labor were matched with healthy pregnant women.

Chapter 5 reports the relation between fetal gender and the onset of preterm labor and preterm delivery in women with symptoms of PTL. Data were extracted from the prospective cohort of the APOSTEL 1 study, a randomized controlled trial studying the accuracy of fFN testing and CL measurement in a triage of women with symptoms of PTL and intact membranes.

Part II Therapeutic dilemmas
Chapter 6 presents the results of a retrospective cohort study of preterm neonates who received a single complete course of ACS and who were born alive before a gestational age of 34 weeks. The relationship between respiratory morbidity, defined as intubation, and the interval between ACS administration and delivery was assessed. Furthermore the need for continuous positive airway pressure (C-PAP), development of RDS, chronic lung disease (CLD) and a composite outcome was evaluated.

Chapter 7 shows the interval from the administration of the first course of ACS to delivery in women at risk for preterm delivery, due to different medical indications (PTL, Preterm prelabor rupture of membranes, Pre-eclampsia/HELLP, Intra-uterine growth restriction, vaginal blood loss and suspected fetal distress). We identified which of the above would benefit from better risk stratification to optimize ACS administration and neonatal outcome.

Chapter 8 studies the clinicians’ prescribing patterns of ACS in women with PTL, included in the cohort of the APOSTEL 1 study. We suggest a strategy for prescribing ACS according to risk stratification by CL measurement and fFN testing.

Part III Summary and general discussion
Chapter 9 summarizes the data presented in this thesis. A Dutch version is included.

Chapter 10 provides a general discussion of the results presented in this thesis and outlines their clinical implication. Suggestions for future research are given.
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References


