Prediction of preterm delivery

Wilms, F.F.

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Summary
Preterm delivery (PTD) is in quantity and in severity an important issue in the obstetric care in the Western world. A delivery is considered to be preterm if it occurs at a gestational age less than 37 completed weeks or 259 days of gestation. Worldwide, 5-13% of all deliveries are preterm. It therefore is a major cause of perinatal mortality and severe neonatal morbidity. 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 PTL, leading to PTD, 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. There is considerable knowledge on maternal and obstetric risk factors for preterm labor contributing to these mechanisms. Accurate prediction of those women with symptoms of PTL who will deliver prematurely is difficult. Of all 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.

Chapter 1 gives an outline and describes the objectives of this thesis. This thesis is about diagnostic and therapeutic dilemmas in spontaneous PTD.

Part I Diagnostic dilemmas

Spontaneous PTD is preceded by shortening of the cervix. Digital examination and measurement of the cervical length (CL) by transvaginal ultrasound are diagnostic tests in the prediction of preterm delivery in women with symptoms of PTL. Testing for the presence or absence of fetal fibronectin (fFN), an extracellular glycoprotein which acts as a marker of choriodecidual disruption in the cervicovaginal secretion, further improves the risk assessment of spontaneous PTD. But even after performing these tests in symptomatic women, we treat substantially more women than actually deliver preterm. Women who remain pregnant after an episode of PTL might stay at risk of PTD. Former research suggests fetal gender to be a risk factor of PTD. The first part of the thesis focuses on the accurate identification of women at risk of spontaneous PTD.
Summary

Chapter 2 presents a prospective cohort study on the prognostic value of the fFN test in women with symptoms of PTL in the Dutch setting. Women with symptoms of PTL with intact membranes at a gestational age between 24 and 34 weeks were included. At the time of the study fFN testing and measurement of the cervical length by ultrasound were not routinely performed in the Netherlands. The first assessment of symptomatic women is often performed in primary care by digital cervical examination prior to referral to a hospital. This digital examination might deteriorate the accuracy of the fFN test. The aim of this study was to evaluate the prognostic value of the fFN test and measurement of the CL. And to determine if the fFN test is influenced by digital examination. The primary outcome was a delivery within seven days after inclusion. Thirteen of the 108 (12%) included women delivered within seven days after inclusion. The sensitivity and specificity of the fFN test were 92% and 60% respectively. The corresponding positive predictive value was 27% and the negative predictive value 98%. Thirty (30%) women had a digital examination 2 hours prior to the fFN test. The sensitivity and specificity of the fFN test in these women was 80% and 52% respectively, with a negative predictive value of 93%. Time to delivery in relation to the fFN test result was visualized in a Kaplan-Meier-Curve. The sensitivity of the CL at a cut-off value of 15 mm was 45% and the specificity 79%. A ‘receiver operating characteristics’ (ROC)-curve was produced for the performance of the CL. None of the women with CL above 35 mm delivered within a week. In our study the measurement of the CL hardly contributed in the prediction of PTD. However, the two tests combined showed that none of the women with a CL above 15 mm and a negative fFN test delivered within seven days after inclusion. In conclusion, especially a negative fFN test is of clinical value. The prior performed digital cervical examination is of limited influence. PTD within seven days can virtually be ruled out in case of a negative fFN test in women with a CL longer than 15 mm. If the CL is more than 35 mm, fFN testing could be omitted.

Chapter 3 describes and assesses the methodology of studies concerning the clinical value of fFN testing. A systematic search lead to four randomized controlled trials (RCT’s) which evaluated the influence of the knowledge of the fFN test result on treatment in symptomatic PTL. These studies had different outcome measures, but all had hypothesized that fFN testing in women with symptoms of PTL would result in a reduction of health care
resource utilization. Although the negative predictive value of the fFN test speaks to its potential to decrease unnecessary treatment of women with symptoms of PTL, none of the randomized studies evaluating its use have demonstrated a clear benefit. Our analysis of the characteristics of the studies gives a possible explanation for the absence of positive findings. Most sample sizes were too small to detect a significant difference between the groups. Moreover the prevalence of women delivering within seven days after randomization was rather low, so was the amount of positive fFN tests, reflecting that the study populations were not at very high risk. The four RCT’s did not have a fixed protocol concerning the treatment strategy based on the fFN result; consequently the physicians might not have incorporated the test into their decision making. A study design that links the test result to a fixed management protocol might elucidate whether the fFN test can reduce resource utilization.

Chapter 4 evaluates the persistent risk of PTD in women who remained pregnant after an episode of PTL. Of the prospective cohort described in chapter 2, 74 women (index cases), pregnant with a singleton, were discharged from the hospital after arrested PTL. These women were prospectively matched to 74 healthy pregnant women (control cases). Controls were randomly matched in their pregnancy at the same gestational age (GA) as the gestational age at admission of their matched cases. The match was based on age, parity and prior PTD. PTD occurred in 20 (27%) index cases and in 5 (7%) controls (p 0.001) (HR 4.5 (95% confidence interval (CI) 1.7 to 12.1)). In cases compared to controls a dilatation of the cervix ≥ 1 cm (HR 9.1 (95% CI 3.3 to 25.2), a CL below 15 mm (HR 11.0 (95% CI 3.1 to 38)) or a fFN positive status (HR 13.0 (95% CI 4.3 to 39.7)) further increased the risk of PTD before a gestational age of 37 weeks. The risk of PTD in women with cervical dilatation less than 1 cm, a CL above 15 mm or a negative fFN not differ significantly from the control cases. The knowledge of the fFN result improved the prediction of persistent PTD after arrested PTL compared to digital examination of the cervix or CL measurement alone. Based on these results we can conclude that women with arrested PTL stay at increased risk of a PTD. This risk is further increased in case of a cervical dilatation of ≥ 1cm, a CL below 15 mm or a positive fFN status.
Chapter 5 reports the relation between fetal gender and the onset of PTL and occurrence of spontaneous PTD.

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 at a gestational age of 24 to 34 weeks and intact membranes. Multiple pregnancies were excluded for this secondary analysis. In this explorative research we investigated the proportion of women carrying a male or female fetus at the onset of PTL. The gestational ages at delivery and risk of PTD for both fetal genders were compared. Interaction of fetal gender with maternal ethnicity, fFN and the CL on the risk of PTD was evaluated.

Of the 594 included women with PTL 55% carried a male fetus (p < 0.001). Median gestational age at delivery was shorter in women pregnant with a male fetus (median 37 5/7 weeks (Inter quartile range (IQR) 34 4/7 to 39 1/7 weeks) compared to women pregnant with a female fetus (38 1/7 weeks (IQR 38 1/7 to 39 5/7 weeks)) (p = 0.032). No differences in the risk of PTD before 37 weeks gestation or within seven days after onset of symptoms were found between the pregnancies with different fetal genders (OR 1.29 (95% CI 0.90 to 1.83) and OR 1.40 (95% CI 0.81 to 2.30) respectively). A fetal male excess at birth is present at deliveries between 28 and 37 6/7 weeks and mainly in Caucasian women. Caucasians pregnant with a male fetus are at increased risk of PTD (OR 1.88 (95% CI 1.19 to 2.96). Knowledge about the fetal gender had no additional clinical value over fFN testing or CL measurement in the prediction of PTD.

Concluding, the majority of women with PTD are pregnant with a male fetus. Delivery of male fetuses occurs at a slightly earlier gestational age than delivery of female fetuses. Male-excess at PTD and increased risk of PTD in women pregnant with a male fetus was mainly seen in Caucasians. Fetal gender has no additional value to fFN or CL measurement.

Part II Therapeutic dilemmas

Treatment of women with symptoms of PTL consists of hospital admission, inhibition of uterine contractions by tocolytic agents and administration of antenatal corticosteroids (ACS) to the mother to enhance fetal lung maturity and preparing the fetus to a life independent of the mother. ACS reduce the incidence of respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH) and
mortality of the premature neonate. The optimum and the duration of the therapeutic effect of ACS are uncertain. And with the above mentioned inability to adequately predict PTD, a clinical dilemma is created concerning the optimal treatment strategy. The second part of this thesis targets the timing of ACS.

Chapter 6 presents a retrospective cohort study on the respiratory morbidity in relation to the interval between the administration of ACS and delivery. Data were collected of women who were treated with a complete course ACS at a gestational age between 24 and 34 weeks and of their neonates. These women were categorized in groups according to the interval between the ACS course and the delivery (ACS-to-delivery interval): 0 to 7 days, 8 to 14 days, 15 to 21 days and 22 to 28 days. Multivariable logistic regression analysis was performed, corrected for gestational age at delivery, to determine the association between this interval and the respiratory morbidity of the neonate. Respiratory morbidity was defined as the need for intubation at the neonatal intensive care unit (NICU). Secondary outcomes were: respiratory distress syndrome (RDS), continuous positive air pressure (CPAP), chronic lung disease (CLD) and a composite morbidity.

We included 254 neonates of 220 mothers. Eighty-two (32%) neonates needed intubation. In comparison to neonates born at an ACS-to-delivery interval of 0 to 7 days an increased risk of intubation was found in all other interval groups. (OR 2.3 (95% CI 1.1 to 5.4); OR 5.6 95% CI (1.8 to 18) en OR 4.8 (95% CI 0.71 to 32) (not significant), respectively). The length of the interval between ACS administration and delivery was of minimal influence in neonates born before 28 weeks of gestation, since most of these neonates needed to be intubated. Neonates born between a gestational age of 28 and 30 weeks had an increasing risk of intubation with prolongation of the interval. The risk of CLD and the composite morbidity increased significantly if the ACS-to-delivery interval was between 15 and 21 days (OR 4.0 (95% CI 1.1 to 15); OR 3.2 (95% CI 1.0 to 9.7) respectively). The risk of intubation was low in neonates born after 30 weeks of gestation. We concluded that the effect of ACS diminishes only in neonates who are born at a gestational age between 28 and 30 weeks, when the time interval between a complete ACS course and delivery become longer than seven days. The first administration of ACS should be considered carefully.
Chapter 7 evaluates the interval between the administration of ACS and delivery in different subgroups of women at risk of PTD.

The interval between the administration of the first complete course of ACS and delivery were compared in women with different medical indications anticipating a PTD: symptomatic PTL with intact membranes (PTL), preterm prelabor rupture of the membranes (PPROM), (pre)eclampsia (PE) and HELLP syndrome (Hemolysis Elevated Liver enzymes Low platelets), intra uterine growth restriction (IUGR), vaginal blood loss and suspected fetal distress. Of the 439 included women, 348 were treated with a complete course ACS. Of these women 41% delivered within 7 days after ACS administration. A Kaplan-Meier-Curve visualizes the time between the ACS course and delivery of each medical indication. The median interval in the total study population was 11 days. In women with vaginal blood loss the median time to delivery was 41 days, it was 25 days in women with symptoms of PTL, 7 days in women with PPROM, 7 days in case of IUGR, 8 days in fetal distress and 8 days in PE/HELLP (p<0.001)

The long interval between the administration of ACS and the delivery in women with PTL and VBL makes a beneficial effect of ACS less probable. Optimal timing of the administration of ACS could result in better neonatal outcomes and reduce overtreatment.

Chapter 8 addresses the impact of measurement of the CL and fFN testing on the clinicians’ decision to prescribe ACS to women with symptoms of PTL.

A secondary analysis was performed of the prospective cohort of the APOSTEL-1 study including women with symptoms of PTL and intact membranes between a gestational age of 24 and 34 weeks. Based on their CL and fFN result the included women were divided in four groups: group 1 had a CL less than 10 mm, group 2 a CL between 10 and 30 mm and a positive fFN test, group 3 a CL between 10 and 30 mm and a negative fFN test and group 4 a CL above 30 mm. For these groups we analyzed the proportion completed ACS courses at study enrollment, PTD within seven days and median intervals from ACS administration of a complete course and delivery.

ACS were prescribed to 97% of the women in group 1, to 91% of the women in group 2, to 65% of the women in group 3 and to 23% of the in group 4. Delivery within seven days occurred in 65% of the women in group 1, in 18% of the women in group 2, in 3% of the women in group 3 and in 1% of the women in group 4. Two (1%) of the women who did not receive ACS at enrollment (n=266) delivered
within seven days. The median intervals between study enrollment and delivery were 6 days (IQR 3 to 61 days), 44 days (IQR 17 to 69 days), 53 days (IQR 37 to 77 days) and 66 days (IQR 43 to 78 days) in group 1, 2, 3 and 4 respectively.

Thus, although clinicians were informed about the CL and fFN result and therefore could assess the risk of PTD within seven days, ACS were prescribed to a large portion of the women at low risk for PTD within seven days (i.e. a CL longer than 30 mm or a CL between 10-30 mm and a negative fFN test). The interval between ACS administration and delivery by far exceeded the recommended maximum of seven days. Better prescribing patterns and timing may result in better therapeutic results, avoids the question whether or not to repeat ACS and might prevent overtreatment and therewith lower health care costs. Consensus about ACS administration is needed and a fixed treatment protocol based on the CL and fFN results might help clinicians to rely on these diagnostic tests.

Part III General discussion and summary

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