Prediction of preterm delivery
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Administration of antenatal corticosteroids (ACS) is probably the most effective intervention that obstetricians have for women with threatened preterm labor (PTL). However, the prediction of preterm delivery (PTD) within a short period of time and therewith the accurate timing of the first antenatal corticosteroid (ACS) course remains a challenge. This thesis addressed some of the dilemmas in risk assessment of PTD and timing and dosing of ACS.

Risk assessment of preterm delivery

In the Netherlands from 2000 until 2007, 7.7% of all deliveries were preterm and 1.3% very preterm. Of these preterm deliveries 56% occurred spontaneously without antecedent rupture of the membranes. Six percent of the singletons were delivered preterm and 0.9% very preterm. The pathophysiology behind PTL and PTD is multifactorial and complicated, and therefore not completely understood. PTL is thought of as a syndrome: the preterm parturition syndrome. Pathological processes implicated in this syndrome are:

1. intrauterine infection/inflammation;
2. uterine ischaemia;
3. uterine overdistension;
4. abnormal allograft reaction;
5. allergy;
6. cervical insufficiency;
7. hormonal disorders.

While collecting the background information about PTL and PTD one other potential risk factor for PTD caught our attention: fetal gender. Limited research suggests that being pregnant of a male fetus increases the risk of PTD, either spontaneously, by induction, or by caesarean section. In chapter 5 we have explored if we could confirm these reports. This is the first study addressing the influence of fetal gender on the onset of PTL and the risk of PTD in a population of women with symptoms of PTL. We found that the majority of women presenting with PTL is pregnant with a male fetus, which might implicate that being pregnant with a male fetus increases the susceptibility to develop symptoms. Delivery of male fetuses occurred at a slightly earlier gestational age and a male-excess at PTD was present, but the risk of actual PTD was not significantly increased in the total population. However in Caucasian women carrying a male fetus we did find an increased risk of PTD. While previously conducted studies reported an excess of spontaneous delivery in males before 32 weeks of gestation, we found such an excess in the period...
from 28 to 38 weeks’ gestation. Although several theories have been proposed to explain gender related differences in PTD, as sex-linked biochemical processes, either hormonal due to promotion of labor by estrogen production from androgen precursors or pro-inflammatory due to a different response of trophoblast cells to pro-inflammatory stimuli, no clear explanation has been found yet and further fundamental research is necessary.

In the diagnostic work up of women who present themselves with symptoms of PTL a digital examination of the cervix is often performed to detect cervical changes preceding PTD. In the Dutch setting this examination is often performed by midwives in a primary setting. The use of the digital examination on its own in the prediction of PTD seems to be of limited use.\(^8\) Repeatedly performing digital examination for early detection of women at risk for PTD is not useful.\(^9\)

Measurement of the cervical length (CL) by transvaginal ultrasound can improve the detection of cervical changes. A short cervix can be detected weeks before symptoms arise and implicates the existence of a preclinical phase.\(^10\) Screening and prevention of PTD in asymptomatic women, however, falls outside the scope of this thesis.

In symptomatic women measurement of the CL helps distinguish between those women at high risk of a preceding PTD within the following seven days and those who most probably will not deliver within a short period of time.\(^11\)\(^-\)\(^14\)

Testing for the presence or absence of fetal fibronectin (fFN) in the cervicovaginal secretion can be of additional value. A negative fFN test is of particular clinical value; since it identifies symptomatic women at low risk of a PTD within one week after testing.\(^15\)\(^-\)\(^17\) The fFN test is applicable in the Dutch obstetric care system as shown in chapter 2. The prior performed digital examination of the cervix, which is thought to influence the reliability fFN test result,\(^18\) appeared to be of little influence on the predictive value of the fFN test. It has been proposed that fFN testing can be omitted in women with symptoms of PTL with a CL above 30 mm or less than 15 mm, since it is of limited additional value in these cases.\(^19\)\(^-\)\(^21\) In contrast to international literature, we found hardly any improvement of the prediction of PTD by measurement of the CL (chapter 2). However we could confirm that the fFN test could be omitted when the cervix is long, longer than 35 mm in our study. A recent systematic review showed that combining the measurement of the CL with fFN testing improved the prediction of spontaneous PTD within seven days after presentation, in comparison to performing only CL measurement or fFN testing. However, heterogeneity exists.
with respect to the variation in cutoff values for the diagnosis of a short cervix.\textsuperscript{22} Chapter 8, using combined testing according to a two-step approach, showed that women with a short CL (less than 10 mm) and women with an intermediate CL (10 to 30 mm) and a positive fFN test were at high risk of PTD within seven days after testing. At low risk were the women with a CL above 30 mm and women with an intermediate CL and a negative fFN test. Chapter 5 showed that the knowledge of the fetal gender has no additional value to CL measurement or fFN testing in the prediction of PTD, so as yet seems to have no clinical implications.

**Implementation of fetal fibronectin testing**

At the moment fFN testing is not routinely performed in women presenting with symptoms of PTD in the Netherlands. In the tertiary centers, fFN tests are mostly performed in the context of clinical studies. So far randomized controlled trials on the implementation of fFN testing failed to demonstrate a reduction in health care resource utilization, although its high potential to differentiate between high and low risk of PTD in women with symptoms of PTL.\textsuperscript{23-26} This means that clinicians have not incorporated a risk assessment based on CL and fFN testing into clinical routine. And treatment is not omitted in low-risk-women. In chapter 3 we have purposed this phenomenon might be due to methodological pitfalls and the absence of a fixed protocol.

**Persistent risk after arrested preterm labor**

Of all women presenting with symptoms of PTL only a small portion (less than 5%) delivers within seven days after the onset of symptoms and about 50 to 70% of these women will deliver after a gestational age of 37 weeks.\textsuperscript{6,10,17} Women who remain pregnant after an episode of PTL, so called arrested PTL, are thought to be of increased persistent risk of PTL. Although the risk of neonatal mortality is relatively low in neonates born after 34 weeks’ gestation, neonates born late preterm appear to be less healthy in later life than infants born at a later gestational age.\textsuperscript{28-33} No large studies have focused on the persistent risk of PTD after arrested labor and the prognostic value of the digital examination, the CL measurement
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...and fFN testing performed at admission. In comparison to a healthy population of pregnant women, in chapter 4 we conclude that women after arrested PTL stay at increased risk of PTD. This risk is even further increased in those women who had more than 1 cm cervical dilatation, a CL less than 15 mm and/or a positive fFN test at initial admission to the hospital.

With the identification of the women who stay at increased risk of PTD after arrested PTL, as is done in this thesis, the question arises on how to address them. This however is still unclear. Several treatment strategies have been assessed. There is no evidence supporting prolongation of the hospitalization, bed rest or maintenance of tocolysis. The reported effect of progesterone administration in women with arrested PTL after treatment with tocolysis is ambivalent.

The discrimination of symptomatic women at high or low short-term risk of PTD is of great importance, since this might optimize obstetric management with antenatal corticosteroids and tocolytics and might reduce health care costs.

Timing of antenatal corticosteroids

A single course of antenatal corticosteroids is known to reduce the mortality and morbidity in the neonate born between 24 and 34 weeks of gestation. ACS were recommended to all women between 24 and 34 weeks' gestation at risk of premature delivery after a consensus conference in 1994 held by the National Institutes of Health (NIH). A Cochrane review published in 2006, including 21 studies involving more than 4200 infants reported besides a reduction in respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH) and neonatal mortality, also a reduced risk of necrotizing enterocolitis (NEC) and systemic infection in the first 48 hours of life.

The optimum effect of antenatal corticosteroids is thought to be between 48 hours and 7 days after the initiation of ACS treatment. An increased short term respiratory support has been reported in neonates born more than seven days after the administration of ACS. But no difference in other neonatal outcomes was found, thus challenging the concept of a diminishing effect of ACS and questioning the need for rescue courses of ACS.
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Chapter 6 of this thesis shows that virtually all neonates born at a gestational age less than 28 weeks needed intubation, and the length of the interval between ACS and delivery was of limited impact on the respiratory morbidity in these neonates. Same results were found by Ring et al. who concluded that no differences were found in the need for ventilatory support or surfactant use in neonates that were delivered before 28 weeks of gestation and received ACS less than or more than 14 days prior to delivery. We found that after a gestational age of 30 weeks the need for intubation was low in neonates whose mothers were treated with ACS, independent of the length of the interval between administration of ACS and delivery. It is the group of neonates born between 28 and 30 weeks of gestation, who benefited most of an accurate timing of ACS, i.e. less than seven days between the administration of ACS and delivery. Peaceman et al. found similar beneficial effects of ACS in neonates born before a gestational age of 30 weeks.

Unfortunately, the interval between a complete course of ACS and delivery very often exceeds the recommended 7 days. Prescription patterns of ACS for various indications with an increased risk of PTD, spontaneously or medically indicated, shows that especially in women with premature vaginal blood loss or symptoms of PTL the median time from the administration of a complete ACS course to delivery is fairly long (41 and 25 days, respectively) (chapter 7). These findings were recently supported by a retrospective cohort study in the Netherlands, finding prolonged intervals between prescription of ACS and delivery in women with vaginal blood loss and in women with symptoms of PTL. Their intervals were slightly shorter (35 days in women with vaginal blood loss and 19 days in women with PTL), as compared to the intervals we found in our study, which might be explained due to the fact that they included women who received an incomplete course and we did not. PTD rates within seven days in both studies were comparable, 41% in our cohort and 45% in their cohort. But especially among women with vaginal blood loss, minority of the women who receive ACS deliver within seven days (13% and 7% respectively). Improving the prediction of PTD in women with vaginal blood loss is difficult; the fear for placental abruption lowers the clinician's threshold to administer ACS.

After the first consensus conference ACS were routinely repeated all around the world. In 2001 a second conference 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.\textsuperscript{51} Recently, after the purposed research had been conducted, the American College of Obstetricians and Gynecologist (ACOG) could come to the following guideline concerning repeated treatment with ACS in 2011:

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{52} The Dutch society of obstetrics and gynecology (NVOG) added to this recommendation that a rescue course only could be considered in situations where the first course had been given before 30 weeks' gestation.\textsuperscript{53}

The fact that it took 20 years before treatment with ACS was implemented, and another 20 years before we found the balance between no treatment versus treating all women with at potential risk of preterm labor repeatedly, indicates the difficulty in influencing doctors prescribing patterns and behavior. First, they needed to be convinced that ACS were effective and relatively safe. When this was finally implemented, a subsequent emotion was the fear that withholding treatment would lead to insufficient preparation of the presumed preterm neonate, therefore lowering the threshold so drastically that women were severely overtreated.\textsuperscript{54} The latest guideline statements seem to strike the golden mean, but it took almost 40 years to reach this state. Moreover, as chapter 7 and 8 show, prescribing patterns of ACS can still be improved. Proper timing of the initial course can reduce the need for a rescue course. As stated above this is not an easy task.

In case of symptomatic PTL we do think prescribing patterns can be improved with the available diagnostic tools. Looking at the prescribing patterns of ACS in women with symptoms of PTL, in chapter 8, we noticed that the negative predictive value of a CL above 30 mm and of the negative fFN test, were not fully exploited. Treatment with tocolytics was recommended according to a protocol but the decision to prescribe ACS was left to the clinicians. Women with an intermediate CL (10 to 30 mm) and a negative fFN test or a long CL (above 30 mm) were at low risk of PTD. Although clinicians were informed about these test results, and therefore were made able to discriminate between high and low risk women, they prescribed ACS to a large portion of the low risk women and overtreated them.
A recent model-based cost-effectiveness analysis that evaluated seven test-treatment strategies in women with threatened preterm labor conducted in the Netherlands, found that additional fFN testing in the case of a CL between 10 and 30 mm, and only treating women with a CL less than 10 mm or a CL between 10 and 30 mm with a positive fFN test, is cost saving without compromising neonatal health outcomes, compared with a treat-all strategy or single CL testing. Implementing this strategy could lead to an annual cost saving between 2.8 million euros and 14.4 million euros in The Netherlands.55

Overuse of ACS might be explained by concerns of the clinician about the possibility of proceeding PTL and therewith the risk of suboptimal preparation of the neonate if treatment with ACS was omitted. Of the low risk women in our study who received no ACS at study enrollment, one (0.4%) delivered before a gestational age of 34 weeks without receiving ACS. The other women were treated further on in pregnancy. However, there is no clear strategy to identify initially low-risk women who will deliver preterm later on in pregnancy. In case of persisting symptoms of PTL or recurrent threat of PTD later on in pregnancy, reassessment by measuring the CL and testing fFN might be considered.

Suggested treatment strategy and future research

In conclusion, in women who present themselves with symptoms of preterm labor, it is of great importance to differentiate between women who will truly deliver within the following week, and women who have signs and symptoms of preterm labor without delivery. The treatment strategy should be adjusted to this risk assessment to optimize maternal and neonatal outcomes.

The studies presented in this thesis have shown that CL measurement and fFN testing are reliable diagnostic tools in this risk assessment, and that the fFN test is applicable in the Dutch obstetric care system in which a substantial number of women are initially assessed in primary care. We have shown that the interval between the administration of ACS and delivery widely exceeds the recommended seven days in women with preterm vaginal blood loss and PTL. We demonstrated that prescribing patterns of ACS can be improved in women with PTL but at low risk for PTD. Especially the neonates born between a gestational age of 28 and 30
weeks would benefit from optimal timing of the administration. If the first course is timed adequately, there is less need for a rescue course.

CL measurement and the fFN result are at the moment not implemented in the obstetric management in the Netherlands, as the guideline on this issue has not been adapted according to the latest knowledge. Consensus about the administration of ACS in women with preterm labor is needed; therefore we suggest the following treatment strategy based on these powerful diagnostic tools.

Again, consensus is needed on the definition of a “short” and “intermediate” and “long” cervix as different studies use different cut-offs. An answer to this issue might be soon provided by the APOSTEL 1 study, in which the accuracy of fFN testing and CL measurement was addressed in women with symptoms of PTL and intact membranes. A quantitative fFN result might further improve the prediction of PTD within seven days after testing. Momentarily the ongoing EuFis study assesses the capacity of quantitative fFN testing as compared to or in addition to CL measurements and vaginal digital exams to predict PTD in women with symptoms of PTL. Women after arrested PTL stay at increased risk of PTD, however no clear strategy exists on the follow up and treatment of women with arrested PTL. Future research could therefore focus on the predictive value of CL measurement and fFN testing in women after arrested PTL and with a renewed threat of PTD. At the moment the prolongation of pregnancy in women with arrested PTL is assessed in a randomized controlled trial comparing a cervical pessary to expectant management (APOSTEL VI study).
Furthermore we found that fetal gender might influence the onset of symptoms of PTL. Only in Caucasian women pregnant with a male fetus we found an increased risk of PTD. This higher risk of PTD in male pregnancies is hypothesized to be caused by a more pro-inflammatory environment. One could hypothesize that the administration of ACS could improve this pro-inflammatory environment in pregnancies with a male fetus and therewith prolongation of the pregnancy. As far as we know now no research has been reported on this topic, which might also be interesting to investigate in the future.
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