Prediction of preterm delivery
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What is the risk of preterm delivery in discharged pregnant women after an episode of threatened preterm labor?

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Abstract

Objective: To assess if women who did not deliver after an episode of threatened preterm labor, are at increased risk of preterm delivery as compared to healthy pregnant women, and to assess if digital examination, fetal fibronectin and cervical length are prognostic markers for preterm delivery in these women.

Study design: We performed a prospective matched cohort study among women with a singleton pregnancy, who were discharged after arrested preterm labor and healthy pregnant women (controls). Dilatation of the cervix, fibronectin and cervical length were assessed in the index cases.

Results: We included 74 index cases and 74 controls. Preterm delivery occurred in 20 (27%) index cases and in 5 (7%) controls (Hazard Ratio 4.5 (95% confidence interval (CI) 1.7 to 12)). A dilatation of the cervix ≥ 1 cm (HR 9.1 (95% CI 3.3 to 25), a fibronectin positive status (HR 13 (95% CI 4.3 to 40)) and a cervical length below 15 mm (HR 11 (95% CI 3.1 to 38)) increased this risk in cases compared to controls. In a multivariable analysis, the knowledge of the fibronectin result had additional value over the cervical dilatation or cervical length in the prediction of persistent preterm delivery after arrested preterm labor, with an increased risk in case of a positive fibronectin test.

Conclusion: Women stay at increased risk for preterm delivery after arrested preterm labor. This risk is further increased in case of ≥ 1 cm cervical dilatation, a positive fibronectin status or cervical length below 15 mm. The knowledge of the fibronectin result improved the prediction of persistent preterm delivery after arrested preterm labor over the cervical dilatation or cervical length measurement alone.
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Introduction

Preterm delivery (PTD) is one of the most important problems in modern obstetric care in the Western world. Of all deliveries, 5-13% occur preterm and it is the major cause of perinatal mortality and neonatal morbidity. PTD can either be preceded by premature rupture of the membranes or by regular uterine contractions leading to cervical changes. Women with symptoms of preterm labor (PTL) are treated with tocolysis to prolong pregnancy and antenatal corticosteroids to prepare the fetal lungs for a life independent of the mother. Accurate prediction of those women with symptoms of PTL who will deliver prematurely is difficult. Only a small portion (less than 5%) of these symptomatic women delivers within seven days after admission to the hospital, whereas about 50-70% delivers after 37 weeks' gestation.

Digital examination of the cervix is often the first test performed in the assessment of the risk of PTD in women with symptoms of PTL. Little research has been performed to assess the predictive value for PTD in women with symptoms of PTL. Digital examination on its own seems to be of limited use in the prediction of preterm delivery in symptomatic women. With a cut-off value of 2 cm cervical dilatation the likelihood ratio for the prediction of PTD before a gestational age of 37 weeks for a positive test was 2.4 (95% CI 1.4 to 3.8) with a corresponding LR for a negative test of 0.48 (95% CI 0.27 to 0.78). The positive LR for the effacement of the cervix with a cut-off of 40% was of 2.0 (95% CI 1.1 to 3.2) and the negative LR was 0.54 (95% CI 0.3 to 0.9).

Cervical length (CL) measurement and the fetal fibronectin test (fFN) and can support the risk assessment of preterm delivery within seven days after admission. The likelihood of PTD within seven days after presentation in women with symptoms of PTL for a cervical length below 15 is 5.7 (95% CI 3.8 to 8.65), compared to the likelihood ratio of 0.5 (0.3 to 0.8) for a CL above 15 mm. 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 than that period of time. The corresponding likelihood ratio for the negative test is 0.29 (95% CI 0.22 to 0.38). Making the test particularly of clinical interest if its result is negative, virtually ruling out a PTD within the following seven days. Combining the two tests improves the prediction of PTD within seven
days after presentation, with an additional value of fFN in women with a cervical length between 16 and 30 mm. No additional value was found for fFN testing if the CL was below 15 mm or above 30 mm. Thus, even after performing these additional tests, we treat substantially more women than actually deliver within seven days.

If pregnancy continues after arrested PTL, some women might remain at higher risk for PTD, and some may be reassured. Yet, no large studies have focused on risk prediction of PTD after arrested PTL, which leaves room for improvement to individualize and optimize prenatal care in these women. We therefore studied women with arrested PTL after treatment with tocolysis and antenatal corticosteroids, to evaluate their persistent risk of PTD and evaluate the prognostic value of the digital examination of the cervix, the fFN test and the cervical length.

**Methods**

We performed a prospective matched cohort study among women with a singleton pregnancy, who were discharged after receiving treatment for threatened PTL in 2006. In the Netherlands, first assessment of initially healthy pregnant women with symptoms of PTL is most often performed by midwives by digital examination before referral to a hospital. If women are at high risk of PTD, they will be referred to one of the ten perinatal centers with a tertiary referral function to receive further treatment.

**Participants and interventions**

The women were a subset of a prospective observational cohort study performed in 2006 in three Dutch hospitals to evaluate the predictive value of fFN in 101 women presenting with symptoms of PTL at a gestational age between 24 and 34 weeks. This cohort study was approved by the institutional review board (IRB) of Leiden University Medical Centre (LUMC) (number P0-050). PTL was defined as uterine contractions leading to cervical changes. At the time of the study the use of CL measurement was not structurally implemented. Therefore, women with any cervical changes due to uterine contractions at initial assessment or at reassessment after a couple of hours of observation, either by digital examination or by measurement of the CL by vaginal ultrasound, were enrolled. Exclusion criteria...
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were preterm ruptured membranes, cerclage of the cervix, cervical dilation of more
than three centimeters at admission, and previous treatment for PTL in the current
pregnancy. Vaginal blood loss in the past 24 hours was not a reason for exclusion.
At admission, a fFN test (QuikCheck fFN, Adeza; Sunnyvale, California, USA, cut-off
0.050 μg/mL) was taken.

Providers were blinded to the results of the fFN tests until all included women had
delivered.
Treatment consisted of hospital admission, tocolysis and administration of antenatal
corticosteroids. The tocolytic drug of first choice in our hospital at the time of this
study was nifedipine, administered in a five-day reducing regime. Of the included
women in the original observational cohort study, 13% delivered within seven days
after admission. The women with arrested PTL who were discharged home were
the subset of women eligible for the present study. These women are referred to
as the index cases. The original cohort study included multiple pregnancies, but
these were excluded for these analysis.

Index cases were matched to a control group of healthy pregnant women without
an episode of PTL. Women in the control group were recruited from midwifery
practices in the same region and from our own perinatal center. The controls were
matched for age, parity, and previous PTD. Controls were randomly matched to the
cases during their pregnancy at the same gestational age (GA) as the gestational
age at admission of their matched cases. They received care as usual and their charts
were only reviewed retrospectively after delivery. Therefore, this part of the study was
not subjected to the Dutch Medical Research Involving Human Subjects Act (WMO),
since the WMO states that IRB approval is only needed if the study participants have
to be physically present during the study, and no IRB approval is necessary in The
Netherlands in retrospective studies or status studies looking at patient records.23

Outcomes, subgroups and sample size
Primary outcome was PTD, which was defined as delivery at a GA before 37 weeks.
Secondary we assessed the effect of the gestational age of PTL, digital examination,
CL and fFN status on the risk of PTD before 37 weeks gestation after arrested PTL.

The power analysis was based on the hypothesis that 28% of the women in the
index group would deliver preterm after a treated episode of PTL in comparison to
8% of the women in a healthy population. Based on this assumption, at least 57 cases in each group were needed ($\alpha = 0.05$ and $\beta = 0.80$).

**Statistical analysis**

The proportion of PTD between the index and control groups was compared with Chi Square test. Cox proportional hazards regression analysis was performed, providing a risk for PTD, calculated from the time from admission for PTL until delivery, censored at 37 weeks of gestation. Time from follow-up until preterm delivery before a gestational age of 37 weeks was expressed with a Kaplan-Meier curve. To assess the relationship between the gestational age at the first assessment of PTL and the risk of PTD, gestational ages at delivery were compared for three different groups of GA at admission for PTL (24 to 27 6/7 weeks, 28 to 31 6/7 weeks and 32 to 34 6/7 weeks).

Cox proportional hazards regression analyses were performed to assess the influence of dilatation of the cervix, the CL and fFN status on the persistent risk of PTD in the time from admission until delivery, censored at 37 weeks gestation. For the digital examination a Receiver Operator Characteristics (ROC) curve was computed to determine the best cut-off value. For the cervical length a cut-off of 15 mm was used based on literature. To evaluate whether fFN influences the predictive value of cervical dilatation or CL measurement on the outcome preterm delivery within 7 days, interaction terms were used. If the P-value for interaction was below 0.05, hazard ratios were reported for the index cases and controls. All statistical analyses were performed using SPSS software, version 21.0 (SPSS Inc. Chicago, Illinois, USA).
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Results

The initial cohort consisted of 101 women with PTL, of whom 13 women (13%) delivered within seven days after admission. Of the remaining 88 women who did not deliver after this episode of PTL and were discharged from the hospital, nine were pregnant with twins and therefore excluded for this study. Matched controls were found for 74 index cases out of the 79 eligible women, which would be sufficient based on our power calculation (Figure 1).

Figure 1 Flow diagram

<table>
<thead>
<tr>
<th>Women with symptoms of PTL from prospective observational study (n=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible: Women with arrested PTL (n=88)</td>
</tr>
<tr>
<td>Eligible women (n=79)</td>
</tr>
<tr>
<td>No appropriate match found (n=5)</td>
</tr>
<tr>
<td>Index cases (n=74)</td>
</tr>
<tr>
<td>Controls (n=74)</td>
</tr>
<tr>
<td>Healthy pregnant women with comparable GA, age, parity and previous PTD in same region.</td>
</tr>
<tr>
<td>Exclusion: Twin pregnancy (n=9)</td>
</tr>
</tbody>
</table>

GA: gestational age, PTD: preterm delivery, PTL: preterm labor

The median gestational age (GA) at inclusion was 29 3/7 (inter quartile range (IQR) 27 5/7 to 31 3/7) weeks in both groups. The median age of the cases was 30 years (IQR 26 to 33 years) versus 31 years IQR 27 to 34 years) in the controls. As a result of matching, parity in both groups was comparable, with 41 women (55%) in each group being multiparous, of whom 13 (18%) had had a previous PTD (Table 1).

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The median GA at delivery was 38 2/7 (IQR 36 3/7 to 39 3/7) weeks in the index cases, compared to 39 6/7 (IQR 39 1/7 to 40 4/7) weeks in the controls. Delivery before 37 weeks occurred in 20 (27%) index cases, and in five (7%) controls (p=0.001) (Table 2). Of the index cases, nine women (12%) delivered before 34 weeks, compared to none of the women in the control group (p=0.002). The index cases were at higher risk for PTD compared to the controls (HR 4.5 (95% confidence interval (CI) 1.7 to 12.1)) (Table 2). Time from admission to preterm delivery of index and control women is expressed in a Kaplan Meier plot (Figure 2).

**Gestational age at admission**

Of the index cases, 20 women (27 %) were admitted with symptoms of PTL at a gestational age between 24 and 27 6/7 weeks, 37 (50 %) between 28 and 31 6/7 weeks and 17 (23%) between 32 and 34 6/7 weeks. The median GA at delivery in the group of women admitted between 24-27 6/7 weeks was 38 3/7 (IQR 36 0/7 to 39 3/7) weeks, in the group of women admitted between 28-31 6/7 weeks 38 5/7 (IQR 36 3/7 to 39 6/7) weeks and in the group of women admitted between 32-34 6/7 weeks 38 0/7 (IQR 36 3/7 to 39 1/7) weeks.

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics</th>
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<tbody>
<tr>
<td>Maternal characteristic</td>
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<tr>
<td>----------------------------------</td>
</tr>
<tr>
<td>Gestational age at inclusion, weeks*</td>
</tr>
<tr>
<td>Age, years*</td>
</tr>
<tr>
<td>Parity</td>
</tr>
<tr>
<td>- Nulliparous (%)</td>
</tr>
<tr>
<td>- Multiparous (%)</td>
</tr>
<tr>
<td>- Previous PTD (%)</td>
</tr>
</tbody>
</table>

* Data given as median (Inter Quartile range (IQR))

PTD: preterm delivery, IQR: inter quartile range, SD: standard deviation
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Figure 2 Kaplan Meier plot: time from admission to preterm delivery: cases vs controls
PTD: preterm delivery, PTL: preterm labor

Figure 3 ROC curve of cervical dilatation for preterm delivery
Digital examination
Among the 74 index cases, 36 (49%) women had no cervical dilatation, 23 (31%) women had a cervical dilatation of 1 cm, in 6 (8%) women the dilatation was 2 cm and in 2 (3%) women it was 3 cm. The mean cervical dilatation was 0.61 cm (SD +/- 0.78 cm). The best cut-off for the cervical dilatation determined by a ROC curve was 1 cm (using cervical dilatation < 1 cm as a positive test result and a cervical dilatation ≥ 1 cm as a negative test result) (sensitivity 78% and specificity 65%, with an area under curve of 0.69) (Figure 3). Four of the 36 (11%) index cases with a cervical dilatation < 1 cm delivered prematurely, compared to 14 of the 31 (45%) index cases with a cervical dilatation of ≥ 1 cm (p=0.002) (Table 2).

A cervical dilatation of ≥ 1 cm increased the risk for delivery before 37 weeks as compared to cases with less dilatation (HR 5.4 (95% confidence interval (CI) 1.8 to 16.5)). Cases with a cervical dilatation ≥ 1 cm had an increased risk of PTD compared to controls (HR 9.1 (95% CI 3.3 to 25.2)), while cases with a dilatation < 1 cm were not at higher risk of PTD compared to controls (HR 1.6 (95% CI 0.44 to 6.1)) (Table 2).

Cervical length
Index cases had a mean CL at admission of 28 mm (SD +/- 14 mm). Ten index cases had a CL ≤ 15 mm, of whom 6 (60%) delivered preterm and 57 had a CL > 15 mm, of whom 11 (19%) delivered prematurely (p=0.006) (Table 2). A CL ≤ 15 mm increased the risk for delivery before 37 weeks as compared to cases with a CL > 15 mm (HR 4.4 (95% CI 1.6 to 11.9). In comparison to the control group, index cases with a CL ≤ 15 mm were at higher risk of PTD (HR 11 (95% CI 3.1 to 38)), whereas the risk in cases with a CL > 15 mm did not differ significantly from the control group (HR 2.5 (95% CI 0.84 to 7.5)).

Fibronectin
Among the 74 index cases, fFN tests were positive in 28 women. These 28 women had a median GA at delivery of 36 5/7 (IQR 33 2/7 to 39 0/7) weeks. The 46 index cases with a negative fFN test had a median GA at delivery of 39 0/7 (IQR 37 4/7 to 39 5/7) weeks. Fourteen (50%) of the fFN positive index cases delivered prematurely. Among the fFN negative cases, four (9%) women delivered preterm (p=0.001) (Table 2). In comparison to the women of the control group, index women with a positive fFN test were at increased risk of PTD (HR 13.0 (95% CI 4.3 to 39.7)), while no significant difference in delivery rates before 37 weeks was found between the fFN negative cases and the controls (HR 2.0 (95% CI 0.60 to 6.4). The index cases with a
positive fFN test were at higher risk for PTD weeks compared to the fFN negative cases (HR 5.7 (95% CI 2.2 to 15.2)).

**Digital examination and fetal fibronectin**

The mean cervical dilatation in the index cases with a positive fFN test was 0.85 cm (+/- SD 0.83) and differed significantly from mean cervical dilatation of 0.46 cm (SD +/- 0.7) in the index cases with a negative fFN test (p=0.037).

Compared to the prediction model of digital examination as a sole predictor of persistent preterm delivery, the model fit improved if fFN was added to the model (Chi Square 8.648, p=0.003). In comparison to controls, the risk of delivery before 37 weeks was increased in index cases with ≥ 1 cm dilatation and a positive fFN test (HR 16.5 (95% CI 5.7 to 47.9)). No difference was found among index cases with < 1 cm dilatation and a negative fFN test, cases with ≥ 1 cm dilatation and a negative fFN test and in cases with < 1 cm dilatation and a positive fFN test (Table 2).

**Table 2 Delivery before a gestational age of 37 weeks**

<table>
<thead>
<tr>
<th>Delivery &lt; 37 weeks GA</th>
<th>Cases (n=74) N (%)</th>
<th>HR PTD &lt; 37 wks (95% CI)</th>
<th>Controls (n=74) N (%)</th>
<th>HR PTD &lt; 37 wks (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>20/74 (23%)</td>
<td>5/74 (7%)</td>
<td>5/74 (7%)</td>
<td>4.5 (1.7 – 12.1)</td>
</tr>
<tr>
<td>Dilatation *</td>
<td></td>
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<tr>
<td>&lt; 1 cm</td>
<td>4/36 (11%)</td>
<td>5.4 (1.8-16.5)</td>
<td>16 (0.44 – 6.1)</td>
<td></td>
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<tr>
<td>≥ 1 cm</td>
<td>14/31(45%)</td>
<td>9.1 (3.3 - 25.2)</td>
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<tr>
<td>Cervical length</td>
<td></td>
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<tr>
<td>≤ 15 mm</td>
<td>6/10 (60%)</td>
<td>4.4 (1.6 – 11.9)</td>
<td>11 (3.1 – 38)</td>
<td></td>
</tr>
<tr>
<td>&gt; 15mm</td>
<td>11/57 (19%)</td>
<td>2.5 (0.84-7.5)</td>
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<tr>
<td>Fetal fibronectin</td>
<td></td>
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<tr>
<td>positive</td>
<td>14/28 (50%)</td>
<td>5.7 (2.2 – 15.2)</td>
<td>13.0 (4.3 – 39.7)</td>
<td></td>
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<tr>
<td>Dilation</td>
<td></td>
<td></td>
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<tr>
<td>&lt; 1 cm</td>
<td>2/10 (20%)</td>
<td>3.55 (0.69 – 18.3)</td>
<td></td>
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</tr>
<tr>
<td>≥ 1 cm</td>
<td>11/16 (69%)</td>
<td>16.5 (5.7 – 47.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL ≤ 15 mm</td>
<td>5/7 (71%)</td>
<td>26.8 (17.4 – 96.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 15 mm</td>
<td>6/17 (35%)</td>
<td>6.0 (1.8 – 19.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>negative</td>
<td>4/46 (9%)</td>
<td>2.0 (0.60 – 6.4)</td>
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</tbody>
</table>

CL: cervical length, GA: gestational age, HR: Hazard ratio, IQR: inter quartile range, PTD: preterm delivery, wks: weeks
Cervical length and fetal fibronectin
The mean CL in the index cases with a positive fFN test was 23 mm (SD +/- 15 mm) and differed significantly from the mean CL in the index cases with a negative fFN test (31 mm (SD +/- 13 mm) (p=0.03).
Compared to the prediction model of CL as a sole predictor of persistent preterm delivery, the model fit did improve if fFN was added (Chi Square 7.20, p=0.007). In comparison to controls, the risk of delivery before 37 weeks was increased in index cases who had a positive fFN test and a CL > 15 mm (HR 6.0 (95% CI 1.8 to 19.7)) and in cases with a positive fFN test and a CL ≤ 15 mm (HR 26.8 (95% CI 7.4 to 96.8)). No significant increase in this risk could be found in index cases with a negative fFN and either a CL >15 mm or a CL ≤ 15 mm (Table 2).

Discussion

Main Findings
In this prospective matched cohort study, we found that women who remain undelivered after an episode of preterm labor remain at increased risk of preterm delivery as compared to low risk pregnant women without such symptoms (HR 3.8 (95% CI 1.4 to 10)). Especially women with dilatation of the cervix of ≥ 1 cm, a positive fFN test or a CL below 15 mm remained at higher risk for PTD compared to healthy pregnant women, whereas this difference was not found in women with a dilatation < 1 cm and in women with a CL above 15 mm and/or a negative fFN test. The knowledge of the fFN status improved the prediction of persistent preterm delivery in women with arrested PTL when added to examination of the cervical dilatation of CL measurement. A fFN positive status further increases the persistent risk of PTL.

Strengths and Limitations
To our best knowledge, our study is unique in comparing the risk of preterm delivery in women after arrested preterm labor to the risk of preterm labor in a healthy population of pregnant women. Even though the mean CL and the median gestational age at delivery of the women who remained pregnant after an episode of threatened PTL might suggest we studied a low risk population, their PTD risk was higher than the overall PTD risk in the Netherlands. In the Netherlands among singleton pregnancies, the incidence of PTD before 37 weeks is 6% and 0.9% before
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32 weeks’ gestation. The incidence of PTD in our control group is comparable. We do acknowledge that even stronger evidence for persistent risk of PTD might have been found if we would have structurally incorporated the measurement of the CL, in combination with the fFN test, in the risk assessment and diagnosis of PTD. Furthermore, the digital examination, CL and the fFN status of the control group were unknown as the data from this group were extracted from charts of healthy pregnant women. The data concerning the digital examination, the CL and the fFN status were collected at admission of the index cases, but these data were not available at discharge.

Another limitation of our study was the small sample size. The absence of a significantly different instantaneous risk for PTD between the control group and women with a long cervix and a negative fFN test might be due to insufficient power. The small sample size also limits us in the number of risk factors for PTD that were evaluated.

Interpretation

A prospective cohort study performed in the United States by McPheeters et al. describes that 72% of the women admitted for threatened PTL, without immediate delivery, delivered at term. This is comparable to our results (77%). They found a PTD rate of 8% in women who had never been diagnosed with PTL, which corresponds to the PTD rate in our control group (7%). They did not provide information about the CL measurement or fFN status.

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 than infants born at later gestational age. However, providing a clear advice on the further management of pregnant women with arrested PTL who remain at higher risk for PTD is difficult. Several treatment strategies have been assessed. Prolongation of hospital admission does not change the course of the pregnancy. There is no evidence to support bed rest. When these women are sent home, they should be counseled about recurrence of symptoms of PTL. Prolongation of the pregnancy by maintenance tocolysis has been evaluated. Although a meta-analysis showed a prolongation of the mean number of days gained in patients receiving maintenance tocolysis, they found no difference in neonatal outcome. A large RCT evaluating the effectiveness of maintenance tocolysis with nifedipine in women with threatened PTL showed no statistically significant reduction in


adverse perinatal outcomes when compared with placebo.\textsuperscript{34} Systematic reviews have shown that there is insufficient evidence to support the use of maintenance tocolysis with magnesium, terbutaline or oxytocin antagonists in the prevention of PTD after threatened PTL.\textsuperscript{35,36,37} The reported effect of progesterone administration in women with arrested PTL after treatment with tocolysis is ambivalent.\textsuperscript{38,39,40}

**Conclusion**

Pregnant women who have been admitted for threatened PTL, but remain undelivered during their first admission, stay at increased risk for PTD after discharge. The risk is increased in case of $\geq 1$ cm cervical dilatation, a positive fFN status or CL below 15 mm. The knowledge of the fFN result improved the prediction of persistent PTD after arrested PTL over the cervical dilatation or CL measurement alone.

Further research is recommended on the pathophysiological pathways that precede PTL and PTD, to improve identification of the women who actually will deliver premature and on the treatment strategies in women who remain at risk of PTD after arrested PTL.
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References

Chapter 4