Randomized Comparison of Nifedipine and Placebo in Fibronectin-Negative Women with Symptoms of Preterm Labor and a Short Cervix (APOSTEL-I Trial)

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Abstract

Objective To evaluate whether tocolysis with nifedipine can be omitted in women with symptoms of preterm labor, a shortened cervix, and negative fetal fibronectin test.

Study Design A randomized noninferiority trial was performed in all Dutch perinatal centers. Women with symptoms of preterm labor between 24 and 34 weeks, intact membranes, cervical length between 10 and 30 mm, and negative fibronectin test were randomly allocated to nifedipine (80 mg/day) or placebo. The primary outcome was delivery within 7 days. Secondary outcomes were severe neonatal morbidity and mortality. We also followed all eligible nonrandomized women.

Results We allocated 37 women to nifedipine and 36 women to placebo. In the nifedipine group, three women (8.1%) delivered within 7 days, compared with one woman (2.8%) in the placebo group (difference −5.3%; one-sided 95% confidence limit 4.5%). Median gestational age at delivery were respectively 37 + 0 (interquartile range [IQR] 34 + 6 to 38 + 5) and 38 + 2 (IQR 37 + 0 to 39 + 6) weeks ($p = 0.008$). In the nifedipine group, three pregnancies (8.1%) had a poor outcome; there were no poor outcomes in the placebo group. We observed similar trends in eligible nonrandomized women.

Conclusion In symptomatic women with preterm labor, a shortened cervix, and negative fibronectin test, placebo treatment is not inferior to tocolysis with nifedipine.

Keywords
- preterm labor
- fetal fibronectin
- cervical length
- tocolysis
- nifedipine

Preterm delivery is a common and severe complication of pregnancy. It occurs worldwide approximately 13 million times per year, and is associated with morbidity and mortality.[1,2] In the developed world, most women with symptoms of preterm delivery before 34 weeks of gestation are hospitalized and treated with tocolytics and corticosteroids, but less than half of these women progress into imminent preterm delivery.[3] If we were able to identify women who do not benefit from treatment, we would be able to reduce maternal stress, side effects from treatment, and health care costs.

There are several tests to support the clinical evaluation of women with symptoms of preterm labor. Cervical length measurement can help in detecting women who will not progress into preterm delivery. If the cervix is 30 mm or longer, the risk of subsequent preterm delivery is estimated at less than 5%, a sound argument to withhold treatment.[4–8] On the other hand, a short cervix is not very specific for preterm birth, and treating all symptomatic women with a short cervix may lead to overtreatment.

Another method for evaluating women with suspected preterm labor is fetal fibronectin testing, based on a vaginal swab in which the concentration of the fetal fibronectin protein is measured. Cohort studies have shown that a negative fibronectin test is associated with a risk of subsequent preterm delivery of less than 5% in women with symptoms of preterm labor.[9,10] Unfortunately, it is unclear whether this is due to the fibronectin test result itself, or to the fact that tested women were treated with tocolytics. A randomized comparison showed that the use of the fibronectin test in clinical practice did not automatically reduce health-care costs, possibly because physicians were not yet convinced that treatment could be omitted in case of a negative result.[11]

To resolve this apparent contradiction between the results of cohort studies and findings from randomized trials, we conducted a new randomized trial to evaluate whether tocolysis can be omitted in women with symptoms of preterm labor and a negative fibronectin test, without a considerable increase in premature births.

Materials and Methods

We conducted a randomized controlled trial embedded in a prospective cohort study, designed to document the predictive performance of fibronectin testing and cervical length measurement.[12] The study had been approved by the ethical committee of the Amsterdam Medical Center before its initiation (trial number: NTR 1857) and ran within the Dutch Obstetric Consortium for perinatal research.

We recruited participants between December 2009 and August 2012 in all 10 Dutch perinatal centers with a tertiary referral function for high-risk obstetrics. In the Netherlands, symptomatic women with a high risk of preterm delivery before 32 weeks are usually referred to 1 of these 10 perinatal centers.

At the time the study started, cervical length measurement was the standard of care in the Netherlands for risk stratification of women with complaints of preterm labor. To standardize the methods for cervical length measurement, all physicians were given a set of instructions (see ►**Fig. 1)** and a pocket card with illustrated examples of accurate cervical length measurements.

Fetal fibronectin was not part of standard care in the Netherlands during the trial. Before the study started, physicians and midwives were trained on how to collect a specimen. A specimen had to be collected prior to vaginal examination or cervical length measurement. In the participating hospitals, the fetal fibronectin test (cutoff 50 ng/mL, "Rapid fFN for the TLiIQ System" (Hologic, Inc.) was done either at the central laboratory (four centers) or as a point-of-care

Instructions cervical length measurement

1. All cervical lengths must be measured vaginally.
2. Make sure the bladder is empty.
3. Place the ultrasound probe in the anterior fornix.
4. Visualize the endocervical mucosa, make sure both cervical lips are visualized the same size.
5. Observe the cervix for 2-3 minutes and measure the distance between the internal and external os at least three times with pauses in between.
6. A curved cervix must be measured in two steps.
7. The shortest cervical length counts.

Fig. 1 Instructions to measure the cervical length.

test at the obstetrical departments (six centers). Training on how to analyze the fibronectin test was given; participation in training sessions was registered. All centers guaranteed the results of the fibronectin tests to be available within 1 hour. During the entire study period, a researcher was available by telephone 24 hours per day to answer questions regarding inclusion criteria, how to use the fetal fibronectin test, and administration of study medication.

Participants

Pregnant women between 24 and 34 weeks with symptoms of preterm labor and intact membranes were eligible for inclusion in the cohort. They either presented as new cases of symptomatic preterm labor at one of the participating perinatal centers or had been referred to these centers from secondary hospitals, by general practitioners or by midwives. Women who had been treated with tocolytics within the previous 7 days were excluded, with the exception of women who had received a single dose of tocolytic treatment for transport from a secondary hospital. Women with placenta praevia, contraindications for tocolysis such as a lethal congenital abnormality, suspected intrauterine infection, ruptured membranes, or suspected fetal distress were also excluded.

Eligible women were informed about the study by research nurses and midwives of our nationwide clinical trials network, by the gynecologist, or resident on call. A fetal fibronectin test and a cervical length measurement were performed in all consenting women. Women within our cohort were eligible for the randomized trial if they had a negative fetal fibronectin test result and a cervical length between 10 and 30 mm. Exclusion criteria for randomization were contraindications for nifedipine, such as maternal cardiovascular disease or hypertension.

Randomization

Eligible and consenting women were randomly allocated to oral nifedipine retard (20 mg four times per day, slow release) or placebo immediately after the test results had become available. We used a blocked randomization scheme, stratified for center, which was available by a secure Web site 24 hours per day. Each block consisted of four allocation codes. Study medication was given for 48 hours. Corticosteroids, antibiotics, and maintenance tocolysis were given at the discretion of the attending physician. Progression of labor was monitored every 12 hours by clinical evaluation, and if needed by digital vaginal examination and/or cervical length measurement. In case of persistent symptoms of preterm labor, study medication could be increased up to a total dose of 120 mg nifedipine or placebo per day. In case of progression of labor under study medication to cervical dilation of 2 cm or beyond, study medication could be stopped and replaced by tocolytics according to the local protocol. Unblinding of study medication was allowed in case of suspected maternal or fetal side-effects of nifedipine. For this purpose, a 24-hour telephone service was provided.

If preterm delivery did not occur in the first 48 hours, further medical interventions and hospitalization were at discretion of the attending physician. Second courses of corticosteroids, tocolytics, and antibiotics could be given if deemed necessary.

Outcomes

The primary outcome was delivery within 7 days. Secondary outcomes were preterm delivery before 34 and 37 weeks of gestation, gestational age at delivery, side effects of nifedipine, and a composite adverse neonatal outcome. The composite adverse neonatal outcome consisted of neonatal death, chronic lung disease (in need of oxygen at 28 days after birth), intraventricular hemorrhage more than grade 2, periventricular leukomalacia more than grade 1, proven sepsis, or necrotizing enterocolitis. Sepsis had to be proven by a positive blood culture. We separately assessed birth weight, Apgar score below 7 after 5 minutes, academia (cord arterial $pH \leq 7.05$), infant respiratory distress syndrome, and admission to a neonatal intensive care unit. In case of a twin pregnancy, an adverse neonatal outcome was considered to be present if at least one neonate met the definition of an adverse outcome.

Statistical Analysis

Analyses were according to the intention to treat principle. In the primary analysis, we calculated the difference in the proportion of women with delivery within 7 days between the group of women allocated to nifedipine and the group allocated to placebo. The associated one-sided 95% confidence limit for the absolute risk difference was calculated. Differences in secondary outcome were assessed similarly. For continuous outcomes, two-sided Mann–Whitney U-tests were performed. A Kaplan–Meier analysis with a log-rank test was used to compare time to delivery between groups.

We also evaluated the characteristics and outcomes of eligible nonrandomized women. These women were treated according to the discretion of the responsible gynecologist. Within this group, we compared outcomes between women who were treated with tocolytics and those monitored expectantly, without tocolytics. All analyses were performed using SPSS software (version 19; IBM Chicago IL).

Sample Size

The study was designed as a noninferiority effectiveness trial. We anticipated that in our population of women with

a cervical length of 10–30 mm, a negative fibronectin test, and nifedipine treatment, 5% would deliver within 7 days. We calculated we would need 220 women (110 per arm) to achieve 80% power with a one-side test to exclude an absolute increase in the proportion of deliveries within 7 days of 7.5% or more in the placebo group, at a 5% significance level. Expecting 33% of evaluated women to be eligible for randomization, we had to test fetal fibronectin in at least 660 consenting women.

Results

We studied 714 women with symptoms of preterm labor. Of these, 172 had both a negative fibronectin test and a cervical length between 10 and 30 mm. Thirty-three of them (19%) declined study medication after having been informed about the results of the cervical length and fibronectin testing, another 22 (13%) women had a medical contraindication, 17 (9.9%) women could not be randomized because the study medication had passed the expiration date, and 27 (16%) were not randomized for unknown reasons during busy shifts. In those cases, treatment was given at the discretion of the attending physician. The remaining 73 women were randomly allocated to nifedipine ($n = 37$) or placebo ($n = 36$) (►**Fig. 2**). Due to the expiration date of the study medication in December 2011 and limited financial support, we were not able to extend recruitment to our targeted number of randomized women.

Of the randomized women, 44 (60%) were nulliparous and 12 (16%) had a twin pregnancy. Before inclusion, 15 women (21%) had been transferred from a secondary hospital to a perinatal center, while 16 (22%) had been referred directly from a midwifery practice. There were 12 women (16%) who had been given a first dose of tocolytics before transport to a neonatal center, in most cases nifedipine capsules 2 × 10 mg ($n = 6$, half-life 1–4 hours[13]) or atosiban ($n = 4$, half-life 12–24 minutes[14]). At inclusion, median gestational age was 29 + 6 (IQR 26 + 5 to 31 + 6) weeks. The median cervical length was 22 mm (interquartile range [IQR] 18 to 26) and 24 women (33%) had cervical dilatation. Most maternal basis characteristics were comparable between the nifedipine and placebo groups, though there were twice as many twin pregnancies and women with a previous preterm delivery in the nifedipine group, and three times as many women referred from a peripheral hospital (►**Table 1**).

Four randomized women (5.5%) did not complete the full 48 hours of study medication. One woman allocated to nifedipine stopped medication after one tablet because of palpitations with diarrhea and abdominal cramps in combination with lactose intolerance. Another woman in the nifedipine group decided to withdraw from the study after three tablets because of severe headaches. Two women stopped using medication because of progression of labor after two and four tablets, respectively: one woman had been allocated to placebo and the other to nifedipine. Both women were treated with atosiban and nifedipine; one of them subsequently delivered. There was no unblinding. Corticosteroids were given to 55 women (75%), antibiotics to 16 (22%) (►**Table 2**).

Primary Outcome

Three women in the nifedipine group (8.1%), including one twin pregnancy, and one woman with a singleton pregnancy in the placebo group (2.8%) delivered within 7 days. The absolute risk reduction by nifedipine compared with placebo was −5.3% in favor of placebo. The one-sided 95% confidence limit of the absolute risk reduction extended to 4.7% in favor of nifedipine. Given the prespecified, noninferiority boundary of 7.5%, we can reject the null hypothesis that placebo is inferior to nifedipine ($p = 0.021$) (►**Fig. 3**).

Secondary Outcomes

In the nifedipine group, six (16%) women delivered before 34 weeks of gestation versus one in the placebo group (2.8%)

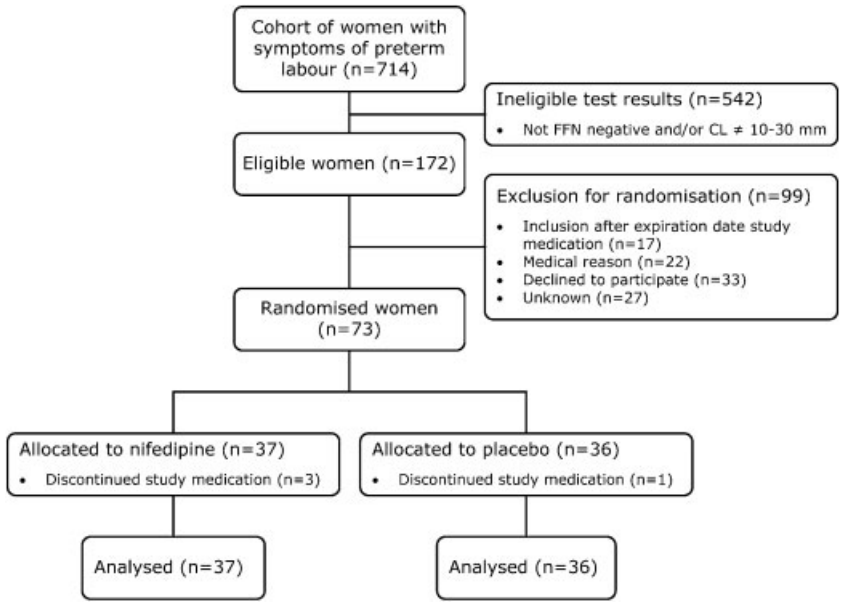

Fig. 2 Flow diagram. CL, cervical length; FFN, fetal fibronectin test.

Table 1 Maternal characteristics of randomized women and of nonrandomized eligible women

	Randomized women		Nonrandomized eligible women	
	Nifedipine ($n = 37$)	Placebo ($n = 36$)	Tocolysis ($n = 59$)	Expectant monitoring ($n = 40$)
Nulliparous	19 (51)	25 (69)	38 (64)	22 (55)
Maternal age (y)	31 (26–34)	28 (25–32)	29 (24–34)	30 (26–34)
Gestational age (wk)	28 + 6 (26 + 5 to 31 + 3)	30 + 2 (26 + 5 to 32 + 0)	30 + 0 (27 + 0 to 31 + 2)	30 + 2 (27 + 1 to 32 + 3)
Multiple gestation	8 (22)	4 (11)	9 (15)	10 (25)
Caucasian race	25 (68)	23 (64)	35 (59)	23 (58)
Education[ab]				
Primary school	1 (2.7)	1 (2.8)	1 (1.7)	0
Secondary school	1 (2.7)	2 (5.6)	6 (10)	3 (7.5)
Lower professional school	5 (14)	1 (2.8)	1 (1.7)	0
Medium professional school	11 (30)	13 (36)	15 (25)	7 (18)
Higher professional school	6 (16)	6 (17)	9 (15)	7 (18)
University	5 (14)	4 (11)	6 (10)	6 (15)
Unknown	8 (22)	9 (25)	21 (36)	17 (43)
Maternal smoking[b]	9 (26)	5 (14)	4 (7.4)	4 (11)
Body mass index[b] (first antenatal visit, kg/m^2)	22.3 (20.2–25.1)	21.3 (19.3–24.7)	22.9 (20.1–24.6)	22.6 (20.7–26.2)
Previous preterm delivery (<34 wk)	8 (22)	4 (11)	13 (22)	8 (20)
Previous term delivery (>37 wk)	10 (27)	5 (14)	9 (15)	12 (30)
Previous vaginal delivery[b]	14 (39)	7 (21)	16 (28)	10 (26)
Last prenatal visit in perinatal center	18 (49)	13 (36)	15 (25)	20 (50)
Referral from peripheral hospital	11 (30)	4 (11)	34 (58)	6 (16)
Referral from midwifery practice	4 (11)	12 (33)	6 (10)	12 (30)
Other	3 (8.1)	7 (19)	2 (3.4)	2 (5.0)
Unknown	1 (2.7)	0	2 (3.4)	0
Tocolytics prior to inclusion	7 (19)	5 (14)	35 (59)[b]	0
Nifedipine capsules 2 × 10 mg	3 (8.1)	2 (5.6)	22 (37)[b]	0
Cervical length (mm)	22 (19–25)	22 (18–27)	20 (16–24)	25 (21–28)
Digital examination[b]				
Cervical dilation	12 (36)	12 (34)	21 (53)	10 (30)
Effacement (%)	25 (0–50)	50 (5–50)	50 (20–50)	25 (0–50)

Note: Data are number of patients (%) or median (IQR). Data are at baseline unless otherwise indicated.
[a]Lower, medium, and higher professional schools denote preparatory, intermediate, and higher vocational education, respectively.
[b]Data are missing for some participants.

(►**Table 3**). The median gestational age at delivery was 37 + 0 weeks (IQR 34 + 6 to 38 + 5) in the nifedipine group compared with 38 + 2 weeks (IQR 37 + 0 to 39 + 6) in the placebo group ($p = 0.008$) (►**Fig. 4**).

In the nifedipine group, three pregnancies (8.1%), including two twin pregnancies, had poor neonatal outcomes, and none in the placebo group. One intrauterine death of a twin occurred 35 days after randomization; the fetus had developed subcutaneous edema. One neonatal death of a singleton pregnancy occurred 28 days after birth due to multisystem organ failure after necrotizing enterocolitis. Both neonates of a twin pregnancy developed bronchopulmonary dysplasia, of whom one was also diagnosed with necrotizing enterocolitis and sepsis (►**Table 3**).

Of the women treated with nifedipine, 15 (41%) reported side effects, compared with 17 (47%) in the placebo group. The most frequently reported side effects in both groups were headaches and warm flushes.

Nonrandomized Eligible Women

Follow-up was available for all 99 women with a negative fibronectin test and a cervical length between 10 and 30 mm

Table 2 Medical interventions after study participation in randomized women and in nonrandomized eligible women

	Randomized women		Nonrandomized eligible women[a]	
	Nifedipine ($n = 37$)	Placebo ($n = 36$)	Tocolysis ($n = 59$)	Expectant monitoring ($n = 40$)
Antenatal corticosteroids	29 (78)	26 (72)	58 (98)	10 (25)
Second course[a]	4 (13)	0	7 (12)	2 (5.0)
Antibiotics	8 (22)	8 (22)	8 (14)[a]	10 (25)
Progesterone	4 (11)	1 (2.8)	4 (6.8)	0
Cerclage	1 (2.7)	0	0	0
Vaginal pessary	1 (2.7)	1 (2.8)	0	0

Note: Data are number of patients (%).
[a]Data are missing for some participants.

who had not been randomized. Maternal characteristics of these eligible nonrandomized women are summarized in ►**Table 1**. Of these women, 59 (60%) were treated with tocolytics and 47 (80%) with nifedipine. The 40 others did not receive treatment. The median cervical length of the women treated with tocolytics was 20 mm (IQR 16 to 24) versus 25 mm (IQR 21 to 28) in the expectant monitoring group. The medical interventions in both groups can be found in ►**Table 2**.

In the nonrandomized tocolytics group, two women (3.4%) delivered within 7 days, compared with none in the expectant monitoring group (►**Table 4**). Ten women (17%) in the tocolytics group delivered before 34 weeks of gestation versus 6 (15%) in the monitoring group. Median gestational age at delivery was 37 + 2 weeks (IQR 35 + 3 to 38 + 5) in the tocolytics group and 37 + 3 weeks (IQR 36 + 1 to 39 + 2) in the expectant monitoring group.

Discussion

Main Findings

In this randomized study we found that placebo treatment is not inferior to tocolysis with nifedipine in women with symptoms of preterm labor, a shortened cervical length, and negative fibronectin test result. The rate of preterm deliveries within 7 days was 5.3% lower in the placebo group; this difference did not exceed the prespecified noninferiority margin.

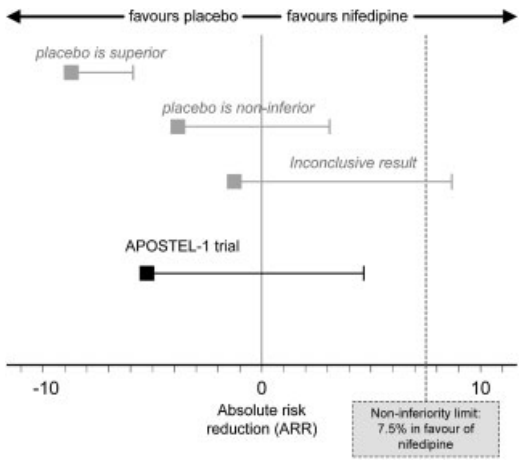

Fig. 3 Interpretation of the absolute risk reduction within a one-sided inferiority effectiveness design.

Secondary outcomes also favor refraining from treatment in these women. Women treated with nifedipine had a significant lower gestational age at delivery. All poor neonatal outcomes, low Apgar scores, and low fetal pH happened in the nifedipine group. Outcomes observed in nonrandomized women treated with tocolytics were similar to those in the placebo group. We did not see more maternal side-effects in the nifedipine group.

Strengths and Limitations

Although our outcomes favor placebo over nifedipine, strong conclusions about the general effectiveness of nifedipine testing cannot yet be drawn. We have to bear in mind that this study is small and did not reach its targeted sample size, as we included fewer women than anticipated due to limited financial resources, the expiration date of the study medication, and a high ratio of nonrandomizations among the eligible women. There were also at least twice at many twin pregnancies, women with a previous preterm delivery, and women referred from a peripheral hospital in the nifedipine group as compared with the placebo group. In addition, the women in this study population are at low risk for imminent preterm delivery, as shown by the negative fibronectin tests. To assess the effectiveness of nifedipine, a larger high-risk population might be more informative.

Interpretation

As nifedipine has not been compared with placebo before, we cannot easily compare our results with those of other studies.[15] Yet the surprising but significant disadvantages of nifedipine in this small study group show that evaluation of established therapies is necessary and worthwhile. We recommend that future studies evaluate the effectiveness of nifedipine in a higher-risk population, preferably a placebo-controlled setting.

Of all eligible fibronectin negative women, only six (3.5%) delivered within 7 days. This confirms the potential of fibronectin testing for risk stratification in women with

Table 3 Pregnancy outcomes in randomized women

	Randomized women		ARR (%) (95% one-sided confidence limit)[a]
	Nifedipine ($n = 37$)	Placebo ($n = 36$)	
Delivery within 7 d	3 (8.1)	1 (2.8)	−5.3 (4.7)
Gestational age at delivery (wk)	37 + 0 (34 + 6 to 38 + 5)	38 + 2 (37 + 0 to 39 + 6)	0.008[b]
Preterm delivery before 34 wk	6 (16)	1 (2.8)	−13 (−1.8)
Preterm delivery before 37 wk	18 (49)	8 (22)	−26 (−8.0)
Birth weight (g)[c]	2750 (2395–3240)	2812 (2510–3316)	0.37[b]
Apgar score below 7 after 5 min[d]	3 (8.1)	0	−8.1 (0.54)
Acedia (arterial pH $\leq$ 7.05)[d]	2 (6.5)	1 (3.3)	−3.1 (8.0)
Infant respiratory distress syndrome[d]	2 (5.6)	0	−5.6 (2.4)
Composite adverse neonatal outcome	3 (8.1)	0	−8.1 (0.38)
Fetal deaths	2 (5.4)	0	−5.4 (2.5)
Neonatal sepsis	1 (2.7)	0	−2.7 (4.6)
Bronchopulmonary dysplasia	1 (2.7)	0	−2.7 (4.6)
Necrotizing enterocolitis	2 (5.4)	0	−5.4(2.5)
Intraventricular hemorrhage grade $\geq$ 3	0	0	0 (7.0)
Periventricular leukomalacia grade $\geq$ 2	0	0	0 (7.0)
Neonatal admission			
Medium/high care	19 (51)	11 (31)	−21 (−1.9)
Intensive care	5 (14)	1 (2.8)	−11 (0.34)
Side effects and complaints	15 (41)	17 (47)	6.7 (25)
Nausea	4 (11)	5 (14)	3.1 (16)
Vomiting	1 (2.7)	1 (2.8)	0.08 (9.1)
Abdominal pain between contractions	5 (14)	5 (14)	0.38 (14)
Headaches	9 (24)	7 (20)	−4.9 (11)
Dizziness	4 (11)	6 (17)	5.9 (20)
Trembling	3 (8.1)	4 (11)	3.0 (15)
Warm flushes	8 (22)	9 (25)	3.4 (19)
Rash	2 (5.4)	0	−5.4 (2.5)
Red, warm cheeks	8 (22)	6 (17)	−5.0 (10)

Note: Data are number of patients (%) or median (IQR) unless otherwise indicated.
[a]Absolute risk reduction (ARR) by nifedipine compared with placebo in percentages; a negative ARR indicates that more events occurred in the nifedipine group.
[b]Two-sided *p*-values are given for the Mann-Whitney U-test.
[c]Calculation based on the mean value per pregnancy in case of a multiple gestation.
[d]Data are missing for some participants.

symptoms of preterm labor and short cervical length; it suggests that tocolytic treatment can be omitted in case of a negative fibronectin test. This implies that the vast majority of these women can be reassured and sent home, which could save a lot of stress for these women and their families and potentially lead to major cost reductions. As the proportion of fibronectin-negative women who were treated with tocolytics in the nonrandomized group was as high as 60%, there is still much to gain.

The majority of our study population had been referred to a perinatal center because of preterm labor complaints. In the Netherlands, most low-risk pregnant women are under the care of a midwife. If there are any problems, such as preterm contractions, the midwife performs the first triage and decides whether a referral to a gynecologist is indicated. The gynecologist performs the second triage and decides who will be admitted. In general, only women who progress into labor before 32 weeks of gestation are transferred from a secondary hospital to a tertiary perinatal center. As this study was conducted in tertiary perinatal hospitals, many women in our population were preselected as being at very high risk for imminent preterm delivery. As the a priori risk for preterm

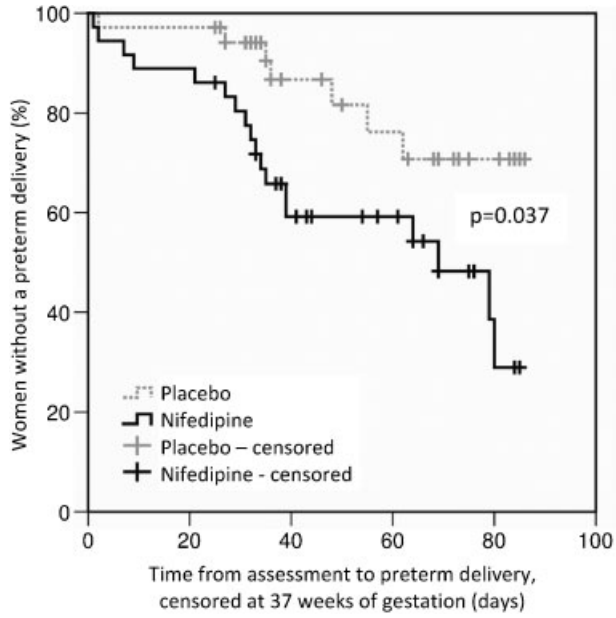

Fig. 4 Time to preterm delivery in the nifedipine and placebo group, censored at 37 weeks of gestation.

delivery might differ in other populations, this could influence the negative predictive value of the fibronectin test. In addition, introducing the fibronectin test in low-risk populations could increase overtreatment in case of fibronectin positive results if women would otherwise have been discharged.

Whether fibronectin testing should become standard of care in women with symptoms of preterm labor, or be used only in addition to an (inconclusive) cervical length measurement, should be further evaluated. The APOSTEL-1 cohort study will soon provide more information about the test characteristics of the cervical length measurement and the fibronectin test alone, combined, and as a stepwise test strategy. Data from this cohort will also be used to evaluate cost-effectiveness of these strategies, providing us information about the optimal test strategy for women with symptomatic preterm labor.

In conclusion, the low risk of preterm delivery in fibronectin-negative women and the demonstrated noninferiority of placebo relative to nifedipine strongly suggest that expectant monitoring is the treatment of choice in fibronectin test negative women with symptoms of preterm labor and a shortened cervical length.

Table 4 Pregnancy outcomes in nonrandomized women

	Nonrandomized women		ARR (%) (95% one-sided confidence limit)[a]
	Tocolysis ($n = 59$)	Expectant monitoring ($n = 40$)	
Delivery within 7 d	2 (3.4)	0	−3.4 (3.3)
Gestational age at delivery (wk)[b]	37 + 2 (35 + 3 to 38 + 5)	37 + 3 (36 + 1 to 39 + 2)	0.62[b]
Preterm delivery before 34 wk	10 (17)	6 (15)	−1.9 (11)
Preterm delivery before 37 wk	21 (36)	15 (38)	1.9 (18)
Birth weight (g),[bc]	2860 (2350–3260)	2880 (2490–3420)	0.46[b]
Apgar score below 7 after 5 min[d]	3 (5.2)	0	−5.2 (1.9)
Acedia (arterial pH $\leq$ 7.05)[d]	2 (3.4)	1 (2.5)	−0.9 (8.4)
Infant respiratory distress syndrome	2 (3.4)	2 (5.0)	1.9 (12)
Composite adverse neonatal outcome	7 (12)	1 (2.5)	−9.3 (0.2)
Fetal deaths	1 (1.7)	1 (2.5)	0.8 (8.9)
Neonatal sepsis	2 (3.4)	0	−3.4 (3.3)
Bronchopulmonary dysplasia	0	0	0 (6.6)
Necrotizing enterocolitis	1 (1.7)	0	−1.7 (4.8)
Intraventricular hemorrhage grade $\geq$ 3	3 (5.2)	0	−5.1 (1.9)
Periventricular leukomalacia grade $\geq$ 2	2 (3.4)	0	−3.4 (3.3)
Neonatal admission			
Medium/high care	21 (36)	12 (30)	−5.6 (10)
Intensive care	6 (10)	7 (18)	7.3 (20)

Note: Data are number of patients (%) or median (IQR) unless otherwise indicated.
[a]Absolute risk reduction (ARR) by nifedipine compared with placebo in percentages; a negative ARR indicates that more events occurred in the nifedipine group.
[b]Two-sided *p* values are given for the Mann–Whitney U-test.
[c]Calculation based on the mean value per pregnancy in case of a multiple gestation.
[d]Data are missing for some participants.

Clinical perspective

- In women with symptoms of preterm labor, a cervical length between 15 and 30 mm, and negative fibronectin test result, placebo treatment is not inferior to tocolysis with nifedipine to postpone preterm delivery
- In these women, nifedipine might impair neonatal outcomes.
- We suggest expectant monitoring in symptomatic women with a cervix between 15 and 30 mm and a negative fibronectin test.

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