Preventing Preterm Birth with Progesterone in Women with a Short Cervical Length from a Low-Risk Population: A Multicenter Double-Blind Placebo-Controlled Randomized Trial

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Am J Perinatol 2015;32:993–1000.

Abstract

Objective The objective of this study was to evaluate the effectiveness of vaginal progesterone in reducing adverse neonatal outcome due to preterm birth (PTB) in low-risk pregnant women with a short cervical length (CL).

Study Design Women with a singleton pregnancy without a history of PTB underwent CL measurement at 18 to 22 weeks. Women with a CL $\leq$ 30 mm received vaginal progesterone or placebo. Primary outcome was adverse neonatal outcome, defined as a composite of respiratory distress syndrome, bronchopulmonary dysplasia, intracerebral hemorrhage $>$ grade II, necrotizing enterocolitis $>$ stage 1, proven sepsis, or death before discharge. Secondary outcomes included time to delivery, PTB before 32, 34, and 37 weeks of gestation. Analysis was by intention to treat.

Keywords
- cervical length
- preterm birth
- progesterone
- neonatal outcome

received
November 19, 2014
accepted after revision
January 23, 2015
published online
March 4, 2015

DOI http://dx.doi.org/10.1055/s-0035-1547327.
ISSN 0735-1631.

Results Between 2009 and 2013, 20,234 women were screened. A CL of 30 mm or less was seen in 375 women (1.8%). In 151 women, a CL $\leq$ 30 mm was confirmed with a second measurement and 80 of these women agreed to participate in the trial. We randomly allocated 41 women to progesterone and 39 to placebo. Adverse neonatal outcomes occurred in two (5.0%) women in the progesterone and in four (11%) women in the control group (relative risk [RR], 0.47; 95% confidence interval [CI], 0.09–2.4). The use of progesterone resulted in a nonsignificant reduction of PTB $<$ 32 weeks (2.0 vs. 8.0%; RR, 0.33; 95% CI, 0.04–3.0) and $<$ 34 weeks (7.0 vs. 10%; RR, 0.73; 95% CI, 0.18–3.1) but not on PTB $<$ 37 weeks (15 vs. 13%; RR, 1.2; 95% CI, 0.39–3.5).

Conclusion In women with a short cervix, who are otherwise low risk, we could not show a significant benefit of progesterone in reducing adverse neonatal outcome and PTB.

Spontaneous preterm delivery is the most important cause of perinatal mortality in the Western world.[1] Although women with a previous preterm birth (PTB) and women with a multiple gestation are at the highest risk of PTB,[2–4] the majority of spontaneous PTBs occur in low-risk women.[5] Interventions for threatened PTB, such as tocolysis, bed rest, or placement of a cervical cerclage, have shown limited effectiveness.[6–8] Only antenatal administration of corticosteroids improved neonatal outcome.[9] Consequently, prevention of (the onset of) PTB is essential.

Identification of low-risk women who will deliver prematurely is crucial in the development of preventive strategies. One of the best predictors in this group is cervical length (CL), measured by transvaginal ultrasound at 20 to 22 weeks of gestation.[10–12] Recently, published studies showed promising results for progesterone in the prevention of PTB.[13,14] As these studies evaluated the effect of progesterone in an unselected population with a combination of high-risk and low-risk women, the effectiveness of vaginal progesterone in a population with strictly low-risk women remains unknown. Previous studies did not show maternal or fetal side effects of progesterone.[15–17] We designed a multicenter study in low-risk women to evaluate the ability of CL measurement to detect those at increased risk for PTB. Women with a short CL were asked to participate in a randomized clinical trial to evaluate whether subsequent progesterone treatment is effective.[18] We defined low risk for PTB as women who did not have a history of PTB before 34 weeks of gestation. Here, we report the results of the trial, and results of the cohort will be published separately.

Materials and Methods

A multicenter double-blind placebo-controlled randomized clinical trial was performed within the Dutch Obstetric Research Consortium, which is a collaborative research effort of obstetric practices in the Netherlands. The present study was conducted in 7 university hospitals, 23 general hospitals, 29 ultrasound centers, and 160 midwifery practices. The trial was approved by the Medical Ethical Committee of the Academic Medical Center, Amsterdam, the Netherlands (MEC AMC 08–328).

Women with a low-risk singleton pregnancy and a CL $\leq$ 30 mm were included in our study. Low-risk pregnancy was defined as nulliparous, or multiparous women without a history of spontaneous PTB $<$ 34 weeks of gestation. Exclusion criteria were age $<$ 18 years, cervical cerclage, previous PTB $<$ 34 weeks, preterm labor, or known congenital malformations.

CL was measured during the standard anomaly scan at 18 to 22 weeks of gestation using transvaginal ultrasound. The image had to display an empty bladder, full length of the endocervical mucosa in an exact mid-sagittal plane of the cervix, and an equal thickness of anterior and posterior cervical wall. The calipers were placed at the distance between the triangular area of echo density at the external os and the v-shaped notch at the internal os. When there was a curved aspect of the endocervical mucosa, sonographers were allowed to place the calipers on the external and internal os as described before and make a straight or a curved line between the calipers.[19,20] In the case of funneling, the funnel itself was not included in the measurement. The ultrasonographers were instructed to measure the CL approximately 3 minutes after the insertion of the vaginal probe and to document the shortest measurement. All participating sonographers were experienced, capable to perform standard anomaly scans, and completed an e-learning module on CL measurement before participation in this study.

Short CL was defined as a CL $\leq$ 30 mm. To ensure the quality of the measurement, women with a CL $\leq$ 30 mm at the initial scan were scheduled for a second assessment within 2 weeks after the first measurement. Subsequently, only women with two measurements $\leq$ 30 mm were eligible for the trial.

Eligible women were informed by a gynecologist, a midwife, or one of the trial's research nurses and had 5 days to consider participation in the trial. After obtaining written informed consent, a web-based randomization was performed.

Eligible women who declined participation in the trial received routine obstetric care, without the prescription of progesterone.

Intervention

Each study participant received a blister pack, which contained capsules with 200 mg micronized progesterone (Utrogestan, Besins International Belgium) or identical-appearing capsules of placebo (Medicaps).

The capsules were self-administered vaginally on a daily basis between 22 and 34 weeks of gestational age. Label codes indicating progesterone or placebo were only known in the central pharmacy. Disclosure of the codes was done after data on primary outcome were collected, 10 weeks after the last participant had delivered. Baseline characteristics were recorded after randomization. All participants kept a medication diary, which was collected after the delivery.

Outcome Measures

The primary outcome measure was a composite of adverse neonatal outcome until 10 weeks after the expected date of delivery, containing the following components: respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), intracerebral hemorrhage > grade II, necrotizing enterocolitis (NEC) > stage 1, proven sepsis, and death before discharge. Intracerebral hemorrhage > grade II and NEC > stage 1 were defined according to previously described classifications.[21,22] RDS was defined as need for artificial ventilation and an X-ray, meeting RDS criteria.[23] BPD was defined as need for supplemental oxygen during at least 28 days after birth.

Secondary outcome measures were time to delivery; birth before 32, 34, and 37 weeks; days of admission in neonatal intensive care unit; and days of maternal hospitalization for threatened preterm labor.

Sample Size Calculation

We anticipated an adverse neonatal outcome in 14% of the pregnancies in which CL was < 15 mm, and in 3% of the pregnancies with a CL between 15 and 30 mm.[13] We assumed 1.7% of the women would have a CL < 15 mm, and 8.3% of the women would have a CL between 15 and 30 mm based on the study by Fonseca et al.[13] The probability of adverse neonatal outcome in women with a cervix shorter or equal to 30 mm was assumed to be 5.0% in the control group. A reduction to 2.5% was expected after the use of progesterone. With the use of a two-sided test with an α of 0.05 and a β of 0.2, 1,920 women (960 per arm) were needed in this study.

As we expected that 10% of the women would have a cervix ≤ 30mm with the assumption that 50% of the eligible women would participate, we planned to screen 40,000 women.

Statistical Analysis

The analysis was performed according to the intention-to-treat principle. The effectiveness of progesterone was expressed as the ratio of the primary outcome rates, as a relative risk (RR) with a 95% confidence interval (CI), calculated using a log–binomial mixed model. Differences in time to delivery were evaluated by Kaplan–Meier estimates and tested with a log–rank test. Differences in continuous outcomes between both strategies were assessed using a linear mixed model, or a linear quantile mixed model.

Due to an unexpected low prevalence of women with a short cervix, the study was stopped early after enrolling 80 of the 1,920 planned women, after 4 years and evaluating 20,234 women for eligibility.

Role of the Funding Source

The study was funded by the Healthcare Efficiency program from ZonMw, the Dutch Organization for Health Research and Development (project number 50–501 10–96–530). The funder had no role in study design; collection, analysis, and interpretation of data; writing of the report; or the decision to submit the article for publication. The investigators had full access to all the data in the study and had final responsibility for the decision to submit the article for publication.

Results

In the study period (from November 1, 2009, to August 1, 2013), 20,234 women were screened for a short cervix. A CL of 30 mm or less was seen in 375 women (1.8%). In 151 women, a CL ≤ 30 mm was confirmed with a second measurement (40%). Of the 224 women without a confirmed short cervix, 121 women (32%) had a CL of more than 30 mm at the second measurement, whereas 103 women (28%) refused to undergo a second CL measurement, the reason for their decline was not collected. Of the 151 women with a confirmed short cervix, 80 agreed to participate in the trial of which 41 were randomly allocated to progesterone and 39 to placebo (►**Fig. 1**). The earliest gestational age for randomization was 19 + 1 weeks of gestation and the latest was 25 + 5 weeks of gestation. Baseline maternal characteristics between the two groups were comparable (►**Table 1**).

All 80 pregnancies ended in a live birth, and the primary outcome was available in all women. Adverse neonatal outcome was observed in 2 of the 41 women (5.0%) in the progesterone group and in 4 of the 39 (11%) in the placebo group (RR, 0.47; 95% CI, 0.092–2.4).

There were two cases of RDS in both groups (2 [5.0%] vs. 2 [6.0%]; RR, 0.92; 95% CI, 0.14–6.21), while none of the neonates suffered from intracerebral hemorrhage > grade II, NEC > stage 1, and/or proven sepsis. BPD was seen once in

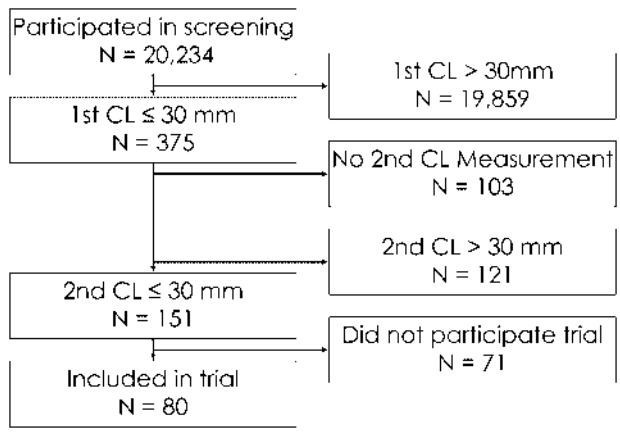

Fig. 1 Flow diagram detailing patient enrollment.

Table 1 Baseline characteristics of the participants in the progesterone and placebo group

Maternal characteristic	Progesterone ($N = 41$)	Placebo ($N = 39$)
Maternal age at randomization (y)	31 (5)	30 (5)
Gestational age at randomization (wk)	21.7 (20.7–22.6)	21.6 (20.9–22.7)
Cervical length (mm)	26 (23–29)	27 (25–28)
Body mass index (kg/m^2)	23 (21–25)	23 (22–27)
Ethnic origin		
Caucasian	27 (71%)	26 (67%)
Higher professional education	6 (29%)	7 (39%)
Nulliparous	30 (73%)	25 (64%)
Obstetric history		
Spontaneous abortion	11 (25%)	13 (33%)
Extra uterine pregnancy	0 (0%)	1 (2%)
Abortion	5 (10%)	4 (8%)
Smoking during pregnancy	8 (21%)	8 (24%)
Alcohol use during pregnancy	1 (3%)	0 (0%)
Drug use during pregnancy	1 (3%)	0 (0%)
Risk profile		
DES exposure	0 (0%)	0 (0%)
Conization or LLETZ	5 (14%)	2 (5%)
GBS colonization	2 (6%)	1 (3%)
Gingivitis/periodontitis	1 (3%)	1 (3%)
Uterine anomaly	1 (2%)	0 (0%)
Uterine surgery	1 (2%)	0 (0%)
Bacterial vaginosis	3 (8%)	2 (6%)

Abbreviations: DES, diethylstilbestrol; GBS, group B streptococcus; LLETZ, large excision of the transformation zone.
Note: Data are mean (standard deviation) number (%) or median (interquartile range).

the placebo group (3.0%). Death before discharge occurred in one child (2.0%) in the progesterone group and two (5.0%) in the placebo group (RR, 0.46; 95% CI, 0.031–6.8). Death in the progesterone group was caused by extreme prematurity in combination with RDS at 24 weeks of gestational age. The two deaths in the placebo group were caused by extreme prematurity at 24 and 25 weeks of gestational age. Congenital anomalies were observed in five children (12%) in the progesterone group and in two (5.0%) in the placebo group (RR, 2.31; 95% CI, 0.48–11.20). The anomalies consisted of polydactyly, atrial septal defect, Noonan syndrome, mild hypospadias, spherocytosis, cystic fibrosis, and pes equinovarus. All neonates were treated following standard procedures; follow-up after 24 months is planned.

After birth, eight children were admitted to a neonatal intensive care unit, three (13%) in the progesterone group, and five (7.0%) in the placebo group (RR, 0.53; 95% CI, 0.12–2.25). Days of admission ranged from 1.5 to 8 days in the progesterone group and from 4 to 31 days in the placebo group.

Progesterone led to a statistically nonsignificant prolonged time to delivery (►**Fig. 2**). The use of progesterone led to a nonsignificant reduction of spontaneous PTB < 32 weeks of gestation (2.0 vs. 8.0%; RR, 0.33; 95% CI, 0.04–3.0) and < 34 weeks of gestation (7.0 vs. 10%; RR, 0.73; 95% CI, 0.18–3.1) but not < 37 weeks of gestation (15 vs. 13%; RR, 1.2; 95% CI, 0.39–3.5).

Side effects related to study treatment were reported in four (12%) women who received vaginal progesterone compared with seven (23%) who received placebo (RR, 0.51; 95% CI, 0.16–1.6) (►**Table 2**). Eleven (27%) women in the progesterone group and 12 (31%) in the placebo group stopped treatment before completion. In the progesterone group, six women did not take any capsules, two used less than half of the prescribed capsules, and three stopped after using more than half of the prescribed capsules (►**Table 2**).

In the placebo group, five women did not use any medication, five used less than half of the prescribed capsules, and two stopped after using half of the prescribed capsules. In total, four medication diaries were lost to follow-up. Reported reasons for premature discontinuation of treatment were side effects, feelings of anxiety about the use of medication in pregnancy, and disagreement/nonapproval of the partner.

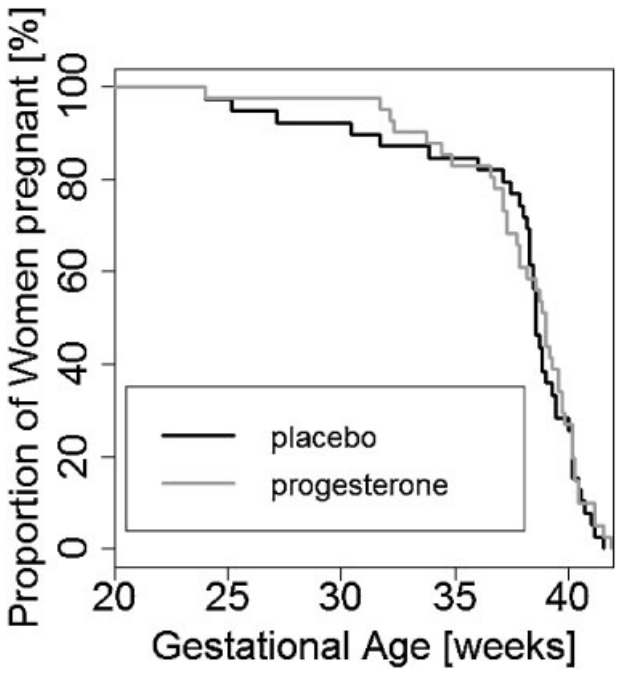

Fig. 2 Kaplan–Meier curve of the time to delivery among patients receiving vaginal progesterone compared with placebo. A nonsignificant prolongation of time to delivery in the progesterone group (log–rank test *p*-value 0.636).

None of the randomized women underwent an emergency cervical cerclage after randomization. Tocolytics were used in seven women (18%) in the progesterone group and in four women (10%) in the placebo group. Corticosteroids for fetal lung maturation were given to nine women (22%) in the progesterone group and to six women (16%) in the placebo group. No other interventions were reported.

Discussion

In this double-blind, placebo-controlled study, which was discontinued early, we evaluated the efficacy of vaginal progesterone in reducing adverse neonatal outcome through a reduction in PTB rate in women with a low-risk pregnancy and a short cervix ($\leq$ 30 mm). Less than 2% of all screened women had a CL $\leq$ 30 mm. Adverse neonatal outcome occurred less often in those treated with progesterone, but this difference was not statistically significant. Women who used progesterone had a nonsignificant longer duration until delivery with lower rates of PTB $<$ 32 weeks and $<$ 34 weeks of gestation.

The strengths of this study are that it is a multicenter, placebo-controlled, double-blind randomized trial. The placebo and vaginal progesterone capsules were identical in appearance. Furthermore, the CL measurements were performed in a true low-risk population. A strength but at the same time a limitation might have been the second CL measurement of which the aim was to ensure a high-quality measurement and true short cervix. This might have contributed to high-quality measurements, however, it resulted in less trial participants because 27% of the women who had a short cervix at the first measurement declined to have a second measurement. Moreover, one-third of the women with an initial short cervix had a longer cervix at repeat measurement. Although this might indicate a lack of test reproducibility, normal biological variation should not be excluded as a cause.

Another limitation is the compliance of the participants, in both the progesterone and the placebo group, as approximately 30% of the women did not use the prescribed medication until 34 weeks of gestation or delivery.

The results of this study, in which a combined approach of transvaginal sonographic CL measurement and subsequent administration of vaginal progesterone capsules from mid-trimester pregnancy until 34 weeks of gestation to the women with a short cervix, indicate that although there were fewer adverse neonatal outcomes in the progesterone group, this trial failed to show a statistically significant benefit from vaginal progesterone in reducing PTB and adverse neonatal outcome. Given that the study was stopped early after inclusion of only 80 of the targeted 1,920 women, a beneficial effect of progesterone cannot be excluded because the needed sample size was not reached.

However, the effect of progesterone on PTB and neonatal outcome has been studied in larger studies.[13,14,24–26] A reduction of PTB before 34 weeks of gestational age was found by Fonseca et al and Hassan et al who administered vaginal progesterone to women with a CL of, respectively, $<$ 15 mm and between 10 and 20 mm. Our study results point in the same direction, though there was no statistically significant difference. In our study, we found 1.8% of women with a CL $\leq$ 30 mm, which is low compared with the number of short cervices both studies found within their cutoff range, respectively. Possible explanations for this difference are that both the Fonseca and Hassan trial did not measure CL in a strictly low-risk population and used shorter CL as a cutoff. However, they did use a similar approach to identify the patients at risk by screening with transvaginal sonography to diagnose a short cervix.[13,14]

Grobman et al[27] conducted a randomized trial among nulliparous women with a singleton gestation and mid-trimester CL $<$ 30 mm. Weekly injections with 17-α-hydroxyprogesterone caproate or placebo did not alter the frequency of PTB $<$ 37 weeks of gestation or neonatal outcomes, such as in our study, there was a statistically nonsignificant reduction of early PTB $<$ 32 and $<$ 34 weeks of gestation.[27] Again these results show a strong similarity to our trial results except for the fact that this trial found 10% of the measured CLs to be 30 mm or less, which is again substantially more than the 1.8% found in our study. This study used another dosage and type of progesterone, which might also have an effect on the outcome. Results of larger studies as; PROGRESS (progesterone after previous preterm birth for prevention of neonatal respiratory distress syndrome) and OPPTIMUM (does progesterone prophylaxis for the prevention of preterm labour improve outcome?) have to be awaited, before more definite conclusions can be drawn.[28,29]

Be it as it may, the number of screen positives in our population was so low that this questions the effectiveness of a screen–treat program with short cervix measurement and progesterone, as most of the PTBs that occurred in our low-risk population cohort were not identified by CL measurement.[30] Formal cost-effectiveness analysis, also addressing the value of

Table 2 Maternal and perinatal outcomes according to treatment group

Characteristic	Progesterone ($N = 41$)	Placebo ($N = 39$)	Relative risk (95% CI)
Neonatal outcome			
Composite adverse neonatal outcome	2 (5%)	4 (11%)	0.47 (0.092–2.4)
Respiratory distress Syndrome	2 (5%)	2 (6%)	0.92 (0.14–6.21)
Bronchopulmonary dysplasia	0 (0%)	1 (3%)	NA
Intracerebral hemorrhage grade II or worse	0 (0%)	0 (0%)	NA
Necrotizing enterocolitis > stage 1	0 (0%)	0 (0%)	NA
Proven sepsis	0 (0%)	0 (0%)	NA
Death before discharge	1 (2%)	2 (5%)	0.46 (0.031–6.8)
Mean birth weight (g)	3035 (2580–3450)	3318 (2842–3606)	-247 (-642–147)[a]
Birth weight			
< 2,500 g	9 (22%)	8 (21%)	1.07 (0.46–2.48)
< 1,500 g	2 (5%)	4 (11%)	0.46 (0.081–2.62)
Congenital anomalies	5 (12%)	2 (5%)	2.31 (0.48–11.20)
5-minute Apgar score < 7	1 (2%)	3 (8%)	0.30 (0.033–2.76)
NICU admission	3 (7%)	5 (13%)	0.53 (0.12–2.25)
Days of NICU admission for those admitted	3 (1.5–5.5)	8 (7–31)	-5.0 (-27–0.15)[a]
Delivery			
Total preterm births (wk)			
< 37	9 (22%)	7 (18%)	1.25 (0.52–3.034)
< 34	5 (12%)	6 (15%)	0.81 (0.27–2.44)
< 32	3 (7%)	5 (13%)	0.58 (0.14–2.30)
Spontaneous preterm births (wk)			
< 37	6 (15%)	5 (13%)	1.17 (0.39–3.52)
< 34	3 (7%)	4 (10%)	0.73 (0.17–3.057)
< 32	1 (2%)	3 (8%)	0.33 (0.035–2.99)
Start of labor by PPROM/SROM	8 (20%)	13 (33%)	0.6 (0.28–1.29)
Labor induction			
Fetal indication	0 (0%)	3 (38%)	NA
Hypertensive disorders	4 (40%)	1 (12%)	3.2 (0.36–29)
Post term	1 (10%)	1 (12%)	0.80 (0.050–13)
Other	5 (50%)	3 (38%)	1.3 (0.32–5.6)
Mode of delivery			
Spontaneous vaginal	32 (78%)	30 (77%)	1.0 (0.61–1.7)
Caesarean before labor	5 (12%)	2 (5%)	2.4 (0.50–12)
Caesarean after labor	0 (0%)	3 (8%)	NA
Operative vaginal	4 (10%)	4 (10%)	0.98 (0.26–3.6)
All live births at any GA	41 (100%)	39 (100%)	NA
Death within 24 h after delivery	0	2 (5%)	NA
Pregnancy outcome			
Tocolytic treatment	7 (18%)	4 (10%)	1.8 (0.54–5.9)
Corticosteroids	9 (22%)	6 (16%)	1.4 (0.56–3.6)
Cerclage placement	0 (0%)	0 (0%)	NA
PPROM	3 (7%)	5 (13%)	0.59 (0.15–2.3)

Table 2 (*Continued*)

Characteristic	Progesterone ($N = 41$)	Placebo ($N = 39$)	Relative risk (95% CI)
GA at PPROM (wk)	34 (33–35)	31 (27–34)	0.46 (0.11–1.9)[b]
Chorioamnionitis	1 (12%)	1 (11%)	1.1 (0.083–15)
Funisitis	1 (12%)	0 (0%)	NA
Side effects medication	4 (12%)	7 (24%)	0.51 (0.16–1.61)
Pain	1 (3%)	0 (0%)	NA
Vaginal discharge	4 (12%)	5 (17%)	0.77 (0.22–2.7)
Itching	2 (6%)	3 (10%)	0.59 (0.11–3.29)
Local irritation	1 (3%)	0 (0%)	NA
Redness	0 (0%)	0 (0%)	NA
Maternal admission days for preterm labor	6 (25%)	7 (25%)	1.03 (0.39–2.70)
Compliance			
Used $\geq$ 80% of study medication	23 (57%)	18 (50%)	
Used $\geq$ 50% of study medication	32 (80%)	27 (75%)	

Abbreviations: GA, gestational age; NA, not applicable; NICU, neonatal intensive care unit; PPROM, preterm prelabor rupture of membranes; SROM, spontaneous rupture of membranes.
[a]Median difference, 95% CI.
[b]Hazard ratio 95% CI.
Note: Data are mean (standard deviation) number (%) or median (interquartile range).

repeated CL measurement, is needed to address this issue. Apart from progesterone, the other intervention that should be addressed here is cervical pessary. The latter intervention, known since 1959, has recently be found to be promising in women with a short cervix.[31,32]

In summary, the results of this trial show no statistically significant benefit of vaginal progesterone in reducing composite adverse neonatal outcome and PTB in women with a short cervix. Our study was underpowered due to a much lower than anticipated number of women with short cervix and was stopped early because of this. Further investigation in the form of extrapolation and data pooling through meta-analysis is needed to evaluate the use of vaginal progesterone in the prevention of PTB in a low-risk population.

Conflict of Interest

Ben W. Mol has been a paid advisor of Besins Health Care.

Acknowledgments

We thank the participants, the research nurses, and midwives of our consortium; the primary care midwives and sonographers of the participating ultrasound centers along with the sonographers, residents, and obstetricians of the participating hospitals for their help with patient recruitment and data collection.

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