Original Article

Efficacy of Vaginal and Oral Progesterone After Tocolytic Therapy in Threatened Preterm Labor: A 3-Arm Parallel-Group Randomized Controlled Trial

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Background: Progesterone has established roles in preventing preterm labor in women with history of spontaneous preterm labor and short cervix, but there is little evidence to support its use to prevent preterm delivery in women with threatened preterm labor.

Objective: To evaluate clinical efficacy of oral and vaginal progesterone on prevention of preterm delivery before 34 and 37 weeks in threatened preterm labor.

Materials and Methods: The present study was a 3-arm randomized control trial, 231 singleton pregnancies of 28- to 33-weeks-6-days who had threatened preterm labor were recruited and randomized to three groups,1) 200 mg/day vaginal micronized progesterone, 2) 30 mg/day oral dydrogesterone and 3) control group with no progesterone. All groups received identical standard treatment for threatened preterm labor. Comparison of primary outcomes, which is the preterm delivery before 34 and 37 weeks, across groups were performed using chi-square test. Secondary outcomes, which are latency period, cervical change, maternal morbidity, neonatal morbidity, and mortality, were also compared.

Results: Proportion of preterm delivery before 34 weeks was not significantly different across the three treatment groups at 16.0%, 12.0%, and 5.2% in control, oral progesterone, and vaginal progesterone groups, respectively (p=0.098). Concerning pairwise comparison, vaginal progesterone was more efficacious in preventing preterm delivery before 34 weeks than the control group (p=0.030), while oral progesterone was similarly effective to the control group (p=0.638). Proportion of preterm delivery before 37 weeks was not significantly different across the three treatment groups at 41.3%, 45.3%, and 31.2% in control, oral, and vaginal progesterone groups, respectively (p=0.182). Latency period differed across three treatment groups with a median latency of 36.5, 42.0, and 43.0 days in control, oral, and vaginal progesterone groups, respectively (p=0.041). Changes in cervical length and Bishop scores were not different across treatment groups.

Conclusion: Vaginal progesterone could prevent preterm delivery before 34 weeks and prolong latency period in women with threatened preterm labor.

Keywords: Preterm labor, Progesterone efficacy, Threatened preterm labor, After tocolysis

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Premature infant is among the leading causes of neonatal morbidity and perinatal mortality. It results in acute complications such as respiratory distress, intraventricular hemorrhage, necrotizing enterocolitis, and neonatal jaundice as well as long-term consequences, such as bronchopulmonary dysplasia, asthma, deafness, cerebral palsy, and retinopathy. Care of these premature infant consumes a great deal of resources, increases workload of health care personnel, and causes great burden on family members. According to current diagnostic criteria for preterm delivery in Thailand, the rate of preterm delivery was 12 per 100 live births[1].

Results from the meta-analysis suggest clear benefits of progesterone in prevention of preterm labor in women with a history of spontaneous preterm labor and women with short cervix[2] and it has now become a standard treatment in this group of patients. In recent years, there has been an increasing interest in extending the use of progesterone to the treatment of threatened preterm labor. However, the evidence to support this so far is inconsistent. Only a relatively small number of high-quality trials have examined the effect of progesterone on prevention of preterm

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delivery in threatened preterm labor and these studies are heterogeneous in terms of types, doses, and routes of administration of progesterone[3]. Overall results have been conflicting, with some studies reporting beneficial effect of progesterone[4-12] and others suggesting no benefit[13,14]. The objective of the present study was to evaluate clinical efficacy and safety of oral and vaginal progesterone in prevention of preterm delivery before 34 and 37 weeks in pregnant women presenting with threatened or established preterm labor.

Material and Methods

The present study was a three-arm parallel-group randomized placebo-controlled trial conducted between August 2015 and January 2017 in the Department of Obstetrics and Gynecology of Sanpasitthiprasong Hospital, a regional referral hospital in the northeastern Thailand. Pregnant women with singleton pregnancies of 28- to 33-weeks-6-days who had threatened preterm labor or preterm labor were invited to participate in the study. The gestational age of all participants was confirmed by ultrasonographic parameters and antenatal record reviews. Threatened preterm labor was defined as the presence of regular uterine contractions without significant cervical changes as determined by digital pelvic examination. Established preterm labor was defined as the simultaneous presence of regular uterine contractions and cervical changes such as softening, effacement, or dilatation, as determined by digital pelvic examination. All participants received standard tocolysis, which is intravenous terbutaline 75.3%, oral nifedipine 16.0%, and both 8.2%, that was administered for at least 48 hours, alongside corticosteroids to enhance fetal lung maturation. The participants who had proven evidence of ruptured membranes, and those whose ultrasonographic findings suggested placenta previa, multiple pregnancy, fetal anomaly, or aneuploidy were excluded. The participants who had emergency conditions, such as fetal distress and chorioamnionitis, were also excluded.

After the participants gave written informed consent, baseline data were collected. These included socio-demographic and clinical data that included antenatal care, risk factors, pelvic examination, and ultrasonographic results. All patients received digital pelvic examination to assess Bishop score[15] and had cervical length assessed by transvaginal ultrasonography at enrollment. Cervical length was measured by Wuttikonsammakit P and Srisutham K, using a standard technique with a covered probe inserted into the vagina after each woman had emptied her bladder[16]. Excessive pressure on cervix was avoided. The mean value of three consecutive measurements of the cervical length was used for analysis.

Randomization and study interventions

After baseline data collection, the participants were then randomly assigned to three groups, (i) receiving oral progesterone (dydrogesterone 10 mg; Duphaston® three times a day), (ii) receiving vaginal progesterone (micronized progesterone 200 mg; Utrogestan® at bedtime) or (iii) no progesterone as the control group. Random numbers were prepared using computer-generated technique and were kept in opaque sealed envelopes. Information on treatment groups was blinded to the two investigators who assessed Bishop score and cervical length at follow-up study visit.

Study endpoints and safety assessments

The primary outcomes were preterm delivery before 34 and 37 weeks. The secondary outcomes included time from treatment to delivery as latency period in days, change in cervical length from initial evaluation to 2 week-follow up in millimeters, change in Bishop score, maternal outcomes as gestational age at delivery, route of delivery, postpartum hemorrhage, puerperal infection, and placenta adherens, and neonatal outcomes as respiratory distress, intraventricular hemorrhage, necrotizing enterocolitis, sepsis, perinatal asphyxia, and neonatal intensive care unit admission. Both primary and secondary outcomes were obtained from labor records and neonatal care records in case of delivery in Sanpasitthiprasong Hospital and by telephone call in case of delivery in other hospitals. Side effects of progesterone were monitored and recorded for every follow-up visit. Treatment group assignment was blinded to outcomes assessors.

Ethical approval for the study was obtained from the Ethical Review Board of Sanpasitthiprasong Hospital (No. 044/2558), Clinical trial registry at ClinicalTrials.gov Identifier: NCT02989519. The funding source had no involvement in study design, collection, analysis, and interpretation of data, writing of the manuscript, and decision to submit the article for publication. Wuttikonsammakit P and Srisutham K. had full access to all the data and Wuttikonsammakit P had final responsibility for the decision to submit for publication.

Sample size determination

The sample size was calculated based on the results of studies by Bomba-Opon et al[8] and Choudhary et al[12], which showed significant reduction in preterm delivery before 34 weeks (9.8% versus 35.3%; p=0.002) in vaginal progesterone group, and significant decreased preterm birth (33% versus 58%; p=0.034) in oral progesterone group compared to placebo. With an expected loss of follow-up of 10%, the sample size of 231 was needed to evaluate the primary outcome of both drugs, with 80% power and a 2-sided type I error at 5%.

Statistical analysis

The statistical analyses of results were performed on an intention-to-treat basis using SPSS Statistics, version 17.0 (SPSS Inc., Chicago, IL, USA). Participant characteristics were described using number (percentage), mean (standard deviation [SD]) and median (interquartile range [IQR]) for categorical, normally distributed, and non-normally distributed continuous variables, respectively. Comparisons in baseline characteristics and study outcomes across the three treatment groups were performed using chi-square test, Fisher's exact test, ANOVA and Kruskal-Wallis test for categorical, normally distributed, and non-normally distributed continuous variables, respectively. Independent t test and Mann-Whitney U test were used for pairwise comparisons. A p-value of less than 0.05 was considered statistically significant.

Results

Flow diagram of participant enrollment, randomization and follow-up is shown in Figure 1. Between August 2015 and January 2017, 760 pregnant women presented with threatened preterm labor and established preterm labor and received tocolytics. After careful history taking and physical examination, 249 cases were excluded due to multiple pregnancy (n=60), premature ruptured of membranes (n=146), placenta previa (n=35), fetal abnormality (n=4), a history of cervical cerclage (n=2), and emergency delivery due to fetal distress (n=1) and prolapsed cord (n=1). The remaining 511 patients were eligible and invited to participate in the present study. Two hundred thirty-one patients were enrolled and randomly divided into three groups, the oral progesterone, vaginal progesterone, and no progesterone or control group, with 77 participants in each group. The main outcomes such as gestational age of delivery, birth weight, and maternal and neonatal outcomes were obtained for 227 participants (98.3%). One hundred eight participants were lost follow-up at two weeks after successful inhibition for repeat measurement of cervical length. The final study participants were 51, 25, and 32 patients in control, oral progesterone, and vaginal progesterone groups. Therefore, changes in cervical length were analyzed in only 123 participants.

Demographic and clinical characteristics of study participants

The three treatment groups were comparable with regard to maternal age, education, gestational age at enrollment, gravidity, parity, places of antenatal care, and number of antenatal visits. Only occupation significantly differed across the three groups, as shown in Table 1. Obstetric factors such as a presence of any risk factors for preterm labor, interval of uterine contraction, cervical dilatation, Bishop score, and cervical length at enrollment were not different across the treatment groups.

Efficacy and safety

Comparison in obstetric outcomes across the three treatment groups are shown in Table 2. Proportion of preterm birth before 34 weeks was not significantly different between the three treatment groups with 16.0%, 12.0%, and 5.2% in control, oral progesterone, and vaginal progesterone groups, respectively (p=0.098). Concerning pairwise comparison, vaginal progesterone was more efficacious in preventing preterm delivery before 34 weeks than in control group (p=0.030), while oral progesterone was similarly effective to control group (p=0.638). Proportion of preterm birth before 37 weeks was not significantly different between the three treatment groups with 41.3%, 45.3%, and 31.2% in control, oral progesterone, and vaginal progesterone groups (p=0.182). Pairwise comparisons showed no significant difference between any two groups.

Gestational age at delivery was different across groups with mean gestational age ±SD of 254.09±18.74, 256.01±16.78, 260.69±14.92 days in control, oral progesterone, and vaginal progesterone group, respectively (p=0.048). Pairwise comparison showed a significant difference in mean gestational age at delivery between vaginal progesterone and control group (p=0.018), while no difference was observed between oral progesterone and control group (p=0.742). Latency period was significantly different among groups with a median latency of 36.5, 42, and 43 days in control, oral progesterone, and vaginal progesterone group, respectively (p=0.041). Pairwise comparison showed a significant difference in latency

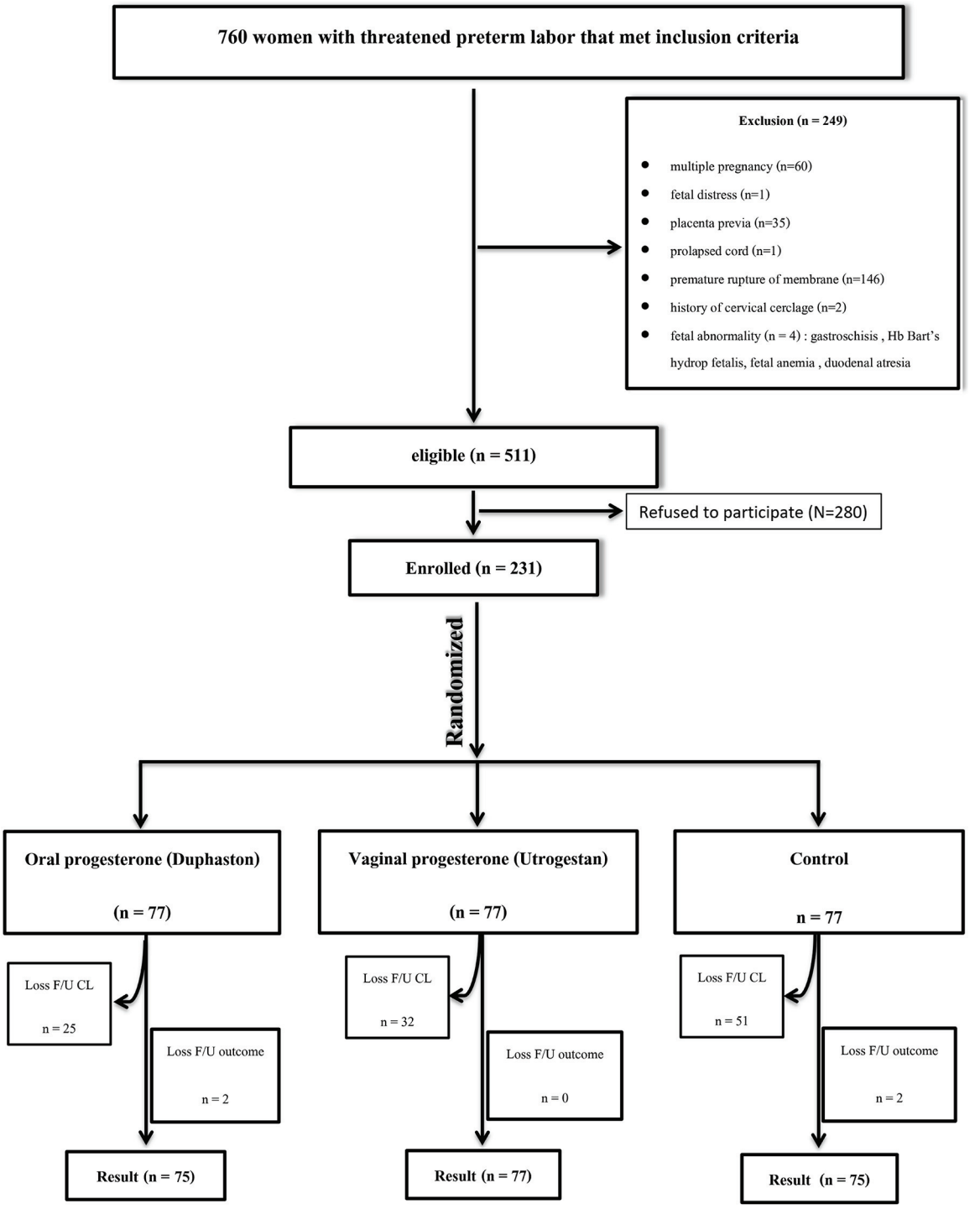

Figure 1. Enrollment, randomization, and follow-up of the study participants.

period between vaginal progesterone and control group (p=0.012), while oral progesterone group had similar latency period to the control group (p=0.210), as demonstrated in Figure 2. However, the association between progesterone treatment and latency period disappeared after adjusting for tocolytic duration in multi-factor ANOVA. Changes in cervical length and Bishop scores were not significantly different

Table 1. Baseline characteristics of the women at randomization (n=231)

	Total (n=231); median (IQR)	No progesterone (n=77); median (IQR)	Oral progesterone (n=77); median (IQR)	Vaginal progesterone (n=77); median (IQR)	p-value[b]
Age (year)	26.0 (19 to 31)	24.0 (19 to 29)	27.0 (21.5 to 33)	25.0 (19 to 32)	0.051
Gestational age at enrollment (days)	224.0 (210 to 234)	226.0 (217.0 to 235.0)	223.0 (208.0 to 232.0)	224.0 (209.5 to 233.0)	0.454
Gravidity	2 (1 to 3)	2 (1 to 3)	2 (1 to 3)	2 (1 to 2)	0.978
Parity	1 (0 to 1)	1 (0 to 1)	1 (0 to 1)	1 (0 to 1)	0.999
Abortion	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0.942
Occupation; n (%)					0.001
Farmer	34 (14.7)	15 (19.5)	9 (11.6)	10 (13.0)	
Government officials	33 (14.3)	1 (1.3)	16 (20.8)	16 (20.8)	
Self-employ	26 (11.3)	6 (7.8)	6 (7.8)	14 (18.2)	
Housewives	84 (36.4)	39 (50.6)	23 (29.9)	22 (28.6)	
Employee	35 (15.1)	12 (15.6)	15 (19.5)	8 (10.4)	
Other	19 (8.2)	4 (5.2)	8 (10.4)	7 (9.0)	
Education; n (%)					0.231
Primary school or lower	33 (14.3)	13 (19.1)	6 (8.3)	14 (19.2)	
Secondary school	123 (53.2)	44 (64.7)	43 (59.7)	36 (49.3)	
Diploma or vocational	8 (3.5)	4 (5.9)	2 (2.8)	2 (2.7)	
Bachelor degree or higher	67 (29.0)	7 (10.3)	21 (29.2)	21 (28.8)	
Place of antenatal care; n (%)					0.206
Primary care unit	43 (18.6)	16 (20.8)	10 (13.0)	17 (22.1)	
Primary and secondary hospital	82 (35.5)	34 (44.1)	24 (31.2)	24 (31.2)	
Tertiary hospital	77 (33.3)	16 (20.8)	33 (42.9)	28 (36.4)	
Private clinic	26 (11.3)	10 (13.0)	9 (11.6)	7 (9.0)	
Other	3 (1.3)	1 (1.3)	1 (1.3)	1 (1.3)	
Number of antenatal attendances (n=202)	6 (5 to 7)	5 (4 to 7)	6 (4.5 to 7)	6 (5 to 8)	0.315
Presence of any risk[a]; n (%)	170 (73.6)	56 (72.7)	61 (79.2)	53 (68.8)	0.336
Initial Bishop score	4 (3 to 6)	4 (3 to 7)	4 (3 to 6)	4 (3 to 6)	0.275
Initial cervical dilatation (cm)	1 (0 to 1)	1 (0 to 1)	1 (0 to 1)	0 (0 to 1)	0.379
Initial cervical effacement (%)	0 (0 to 50)	0 (0 to 50)	0 (0 to 50)	0 (0 to 25)	0.712
Initial contraction interval (seconds) (n=230)	300 (180 to 600)	300 (180 to 420)	360 (210 to 600)	300 (180 to 600)	0.079
Initial contraction duration (seconds) (n=230)	30 (25 to 40)	30 (20 to 40)	30 (25 to 40)	30 (25 to 35)	0.532
Initial cervical length (mm) (n=229)	31.0 (23.0 to 35.7)	31.5 (26.3 to 35.1)	30.6 (21.0 to 36.4)	29.1 (22.0 to 35.0)	0.299

IQR=interquartile range

[a] Presence of one or more of the following risk factors: history of threatened miscarriage, smoking, maternal age below 19 years or above 35 years, familial history of preterm labor, interval between pregnancies less than 18 months or more than 59 months, history of prior preterm delivery, previous cesarean section, preeclampsia, gestational diabetes mellitus, urinary tract infection

[b] Comparisons across the three treatment groups were performed using chi-square test and Kruskal-Wallis test for categorical and non-normally distributed continuous variables, respectively.

across the three treatment groups or between any pairs. Comparisons in other obstetric outcomes across the three treatment groups are shown in Table 2. No difference across the three treatment groups in birth weight, routes of delivery, or doses of dexamethasone was observed. With comparable progesterone duration between the two progesterone groups, tocolytic duration was significantly longer in vaginal and oral progesterone groups than in the control group with a median duration of 15, 9, and 2 days, respectively ($p<0.001$). Further, the maintenance tocolytic therapy for more than 48 hours was significantly associated with a decreased risk of preterm birth at 37 weeks (45.5% versus 54.5%, $p=0.030$), but not at 34 weeks. Due to an imbalance in participants' characteristic in occupation, an additional analysis was performed and adjustment for occupation did not impact the main outcomes, either preterm delivery at 34 or 37 weeks.

Table 2. Comparisons of obstetric outcomes across the three treatment groups: no progesterone, oral progesterone, and vaginal progesterone (n=227)

	Total (n=227); median (IQR)	No progesterone (n=75); median (IQR)	Oral progesterone (n=75); median (IQR)	Vaginal progesterone (n=77); median (IQR)	p-value[b]
Gestational age at delivery (days)	256.96±17.02	254.09±18.74	256.01±16.78 (vs. no, p=0.510)	260.69±14.92 (vs. no, p=0.018) (vs. oral, p=0.072)	0.048
Birth weight (g)	2,726.07±569.87	2,689.19±615.47	2,686.12±543.44	2,800.91±598.40	0.368
Route of delivery					0.751
Normal labor	116 (51.1)	40 (53.3)	37 (49.3)	39 (50.6)	
Cesarean section	104 (45.8)	32 (42.7)	37 (49.3)	35 (45.5)	
Vacuum extraction	6 (2.6)	3 (4.0)	1 (1.3)	2 (2.6)	
Forceps extraction	1 (0.4)	0 (0.0)	0 (0.0)	1 (1.3)	
Dexamethasone (n=230)					0.079
None	40 (17.4)	8 (10.4)	15 (19.5)	17 (22.1)	
1 to 3 doses	8 (3.5)	5 (6.5)	3 (3.9)	0 (0.0)	
4 doses	182 (79.1)	64 (83.1)	59 (76.6)	59 (77.6)	
Tocolytic duration (days)	4.5 (2 to 30)	2 (2 to 13.75)	9 (2 to 30) (vs. no, p=0.003)	15 (3 to 36) (vs. no, p<0.001) (vs. oral, p=0.141)	<0.001
Progesterone duration (days)	16 (0 to 30)	NA	30 (15 to 30)	30 (15 to 32.5)	0.941
Preterm delivery <34 weeks	25 (11.0)	12 (16.0)	9 (12.0) (vs. no, p=0.638)	4 (5.2) (vs. no, p=0.030) (vs. oral, p=0.226)	0.098
Preterm delivery <37 weeks	89 (39.2)	31 (41.3)	34 (45.3) (vs. no, p=0.742)	24 (31.2) (vs. no, p=0.256) (vs. oral, p=0.103)	0.182
Latency period (days)	40.0 (30.5 to 57.0)	36.5 (31 to 52)	42.0 (27.0 to 57.0) (vs. no, p=0.210)	43.0 (32.0 to 61.0) (vs. no, p=0.012) (vs. oral, p=0.198)	0.041
Change in cervical length (mm) (n=120)	−3.1 (−9.28 to 1.98)	−5.7 (−13.4 to 1.8)	−3.2 (−9.2 to 2.5) (vs. no, p=0.148)	−1.4 (−7.6 to 1.7) (vs. no, p=0.140) (vs. oral, p=0.615)	0.251
Change in Bishop score (n=120)	−1 (−2 to 0)	−0.5 (−2 to 0)	0 (−2 to 0)	−1 (−2 to 0)	0.601
Any maternal complication[a]	9 (4.0)	2 (2.7)	5 (6.7)	2 (2.6)	0.342
PPH	4 (1.8)	0 (0.0)	3 (4.1)	1 (1.3)	0.160
PIH	1 (0.4)	1 (1.3)	0 (0.0)	0 (0.0)	0.361
Endometritis	3 (1.3)	0 (0.0)	2 (2.7)	1 (1.3)	0.360
Wound infection	1 (0.4)	1 (1.3)	0 (0.0)	0 (0.0)	0.361
Placental adherens	1 (0.4)	0 (0.0)	0 (0.0)	1 (1.3)	0.415

PPH=postpartum hemorrhage; PIH=pregnancy induced hypertension; IQR=interquartile range

[a] Presence of any following complications: postpartum hemorrhage, pregnancy induced hypertension, endometritis, wound infection, placental adherens

[b] Comparisons across the three treatment groups were performed using chi-square test, ANOVA and Kruskal-Wallis test for categorical, normally distributed and non-normally distributed continuous variables, respectively. Independent t-test and Mann-Whitney U test were used for pairwise comparisons as indicated in the bracket alongside each comparison.

Nine participants developed at least one of maternal complications, including postpartum hemorrhage, pregnancy induced hypertension, placental adherens, postpartum endometritis, and wound infection. There was no difference in any or each of these complications across the three treatment groups. No participant reported adverse effect of progesterone treatments.

Regarding neonatal outcomes, there was no difference across the three groups in the occurrence of respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, sepsis, jaundice, lung atelectasis, retinopathy of prematurity, apnea of prematurity, polycythemia, hypoglycemia, and neonatal intensive care unit admission (Table 3). However, there was significant neonatal asphyxia across the three groups. Only one infant died in control group, with a perinatal mortality 1.3%,

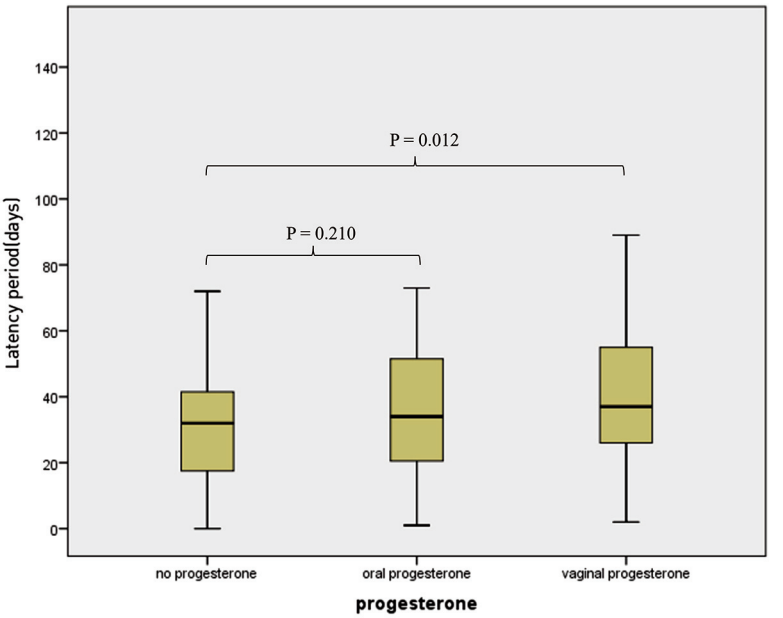

Figure 2. Box plot change of latency period among the three treatment groups (n=227).

Table 3. Neonatal outcomes

	Total(n=227); n (%)	No progesterone (n=75); n (%)	Oral progesterone (n=75); n (%)	Vaginal progesterone (n=77); n (%)	p-value[b]
Any neonatal complication[a]	48 (21.1)	19 (25.3)	18 (24.0)	11 (14.3)	0.189
RDS	36 (15.9)	14 (18.7)	14 (18.7)	8 (10.4)	0.271
IVH	1 (0.4)	1 (1.3)	0 (0.0)	0 (0.0)	0.661
NEC	1 (0.4)	1 (1.3)	0 (0.0)	0 (0.0)	0.661
Sepsis	9 (4.0)	4 (5.3)	2 (2.7)	3 (3.9)	0.776
Jaundice	31 (13.7)	10 (13.3)	12 (16.0)	9 (11.7)	0.738
Lung atelectasis	2 (0.9)	2 (2.7)	0 (0.0)	0 (0.0)	0.216
ROP	2 (0.9)	1 (1.3)	0 (0.0)	1 (1.3)	1.000
AOP	4 (1.8)	2 (2.7)	1 (1.3)	1 (1.3)	0.849
Asphyxia	5 (2.2)	4 (5.3)	1 (1.3)	0 (0.0)	0.049
Polycythemia	1 (0.4)	1 (1.3)	0 (0.0)	0 (0.0)	0.661
Hypoglycemia	1 (0.4)	1 (1.3)	0 (0.0)	0 (0.0)	0.661
Perinatal mortality	1 (0.4)	1 (1.3)	0 (0.0)	0 (0.0)	0.661
NICU admission	29 (12.8)	11 (14.7)	11 (14.7)	7 (9.1)	0.492
LOS; median (IQR)	3 (2 to 3)	3 (2 to 3)	3 (2 to 3)	3 (2 to 3)	0.381

RDS=respiratory distress syndrome; IVH=intraventricular hemorrhage; NEC=necrotizing enterocolitis; ROP=retinopathy of prematurity; AOP=apnea of prematurity; NICU=neonatal intensive care unit; LOS=length of stay in hospital; IQR=interquartile range

[a] Presence of any following complications: respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, sepsis, jaundice, lung atelectasis, retinopathy of prematurity, apnea of prematurity, asphyxia, polycythemia, hypoglycemia

[b] Comparisons across the three treatment groups were performed using chi-square test, Fisher's exact test, and Kruskal-Wallis test for categorical and non-normally distributed continuous variables, respectively.

due to complications related to prematurity, which are respiratory distress syndrome, intraventricular hemorrhage, neonatal jaundice, and neonatal sepsis. Lengths of hospital stay for neonate were comparable in the three treatment groups.

Discussion

In this 3-arm randomized control trial, vaginal

progesterone could prevent preterm birth before 34 weeks but not 37 weeks, in women presenting with threatened or established preterm labor. This vaginal progesterone treatment helped prolong latency period and consequently increased gestational age at birth without adverse effects or increased maternal and neonatal complications, compared to standard treatment.

Evidence on the benefits of progesterone on prevention of preterm birth in threatened or established preterm labor is inconsistent. While some previous individual-level meta-analyses[3,17-19] found no benefits of progesterone as maintenance tocolytics, other meta-analyses[20] could observe the efficacy of progesterone in preventing preterm delivery either before 34 weeks or before 37 weeks. Interestingly, the present study found the efficacy of progesterone on prevention of preterm delivery before 34 weeks, but not 37 weeks. The present study findings may be explained the beneficial effect of vaginal progesterone may be adequately strong to prevent preterm birth before 34 weeks but minimally strong before 37 weeks of gestation. This may be supported by the present study findings that vaginal progesterone had clear benefits on latency period but no change in cervical length. The discrepancy between the results of meta-analyses[3,17,18] and the present study may be due to inadequate power to detect the difference in preterm birth at 37 weeks between the treatment groups in the present study or simply reflect differences in doses and routes of progesterone and choices of tocolytic agents used in previous studies and the present.

Consistent with a few previous trials[7,8,21], the present study found that vaginal, not oral progesterone could prevent preterm birth before 34 weeks of gestation. The benefits of vaginal progesterone may essentially be through its pharmacological action on prostaglandins cascades, which could lead to reduction of the frequency of uterine contractions, prolongation of latency period, and attenuation the shortening of cervical length[3]. The superior efficacy of vaginal administration over other routes may be due to a so-called "first uterine pass effect" or local direct vagina-to uterus transport, which is known as the basis of the uterine targeting of vaginal progesterone[22]. It has been reported that vaginal administration of progesterone resulted in more than 10-times higher uterine tissue concentration than systemic administration, although with lower circulating level and side effects[23]. It may also be explained by greater binding affinity of natural progesterone to the progesterone receptors when vaginal administration of progesterone agents is used[23].

Evidence on the benefits of vaginal progesterone on prolongation of latency period is inconsistent. Many trials including the present study have shown that vaginal progesterone was effective in prolonging latency period in threatened or established preterm labor, ranging from three to 17 days[4-6,8-10,17,18,24]. The present study found that vaginal progesterone could prolong latency period for approximately seven days, and this may be an explanation for the benefits on preventing preterm birth at 34 weeks, but not 37 weeks. Varying effects on latency period might be due to discrepancies between studies in progesterone doses and ethnics of study populations[25]. In the contrary, a trial in high-risk group[26], as indicated by positive fetal fibronectin in vaginal secretion, did not show the benefits of progesterone on latency period.

The benefits of progesterone on reduction of preterm birth observed in this group of patients may be mediated through its impact on attenuation in cervical changes or ripening. As demonstrated in the present study, women receiving vaginal progesterone appeared to have greater attenuation in cervical lengths on follow-up at day 14 than those receiving oral progesterone and no progesterone, although the differences were not statistically significant. The beneficial effect on cervical length was observed, although on different days, for other systemic administration such as the intramuscular route, of progesterone[27]. Of note, it appears that such impact on other indicators of cervical changes such as Bishop scores, was not observed. This might possibly be because Bishop score, which is primarily used to determine how favorable the cervix is for induction may not be adequately sensitive to detect cervical changes in this group of patients.

Benefits of progesterone as an adjunct to maintenance tocolytics for threatened preterm labor may also reflect complex interplay between the two treatments in prolongation of pregnancy. The differential benefits of progesterone on preterm birth before 34 weeks and 37 weeks, observed in the present study, may be a result of maintenance tocolytics, mostly terbutaline, which were not balanced between the treatment groups in the present study. In an exploratory analysis, some participants received the maintenance tocolytics for a period of longer than 48 hours. It is notable that receiving maintenance tocolytic of longer than 48 hours was associated with a more prolonged latency period

and reduced risk of preterm birth before 37 weeks, regardless of progesterone treatment. In the light of currently inconclusive evidence from meta-analyses of trials directly examining the effect of different maintenance tocolytics[20,28-32], larger trials or further stratified analyses within meta-analyses are needed to identify certain groups of patients with threatened and established preterm labor that could benefit from the use of tocolytics.

The present study was among the first few studies examining the efficacy and safety of progesterone on multiple outcomes including preterm birth, changes in cervical length, maternal and neonatal outcomes, in both threatened and established preterm labor in Thai pregnant women. A 3-arm parallel-group randomized control trial design allowed comparison of different routes of progesterone with no progesterone, while most confounding and biases were minimized. However, the present study had some limitations. First, a parallel group randomized controlled trial by design could not directly demonstrate the interaction effects of tocolytics and progesterone on the outcomes. An alternative design such as a 2×2 factorial design may be needed to address the above issue. Second, although randomization in the present study was performed according to the standard of trial, there remained one variable 'occupation' that was systemically different across the three treatment groups. This could be a difference by chance, a result of variable categorization, and may reflect the quality of randomization in the present study. However, an additional analysis suggested that adjusted for occupation did not impact the main outcomes. Third, because blinding to patients and treating physicians was not possible, performance biases may exist. Physicians and care team as well as patients themselves may practice differently from standard normal practice and unequally in the three treatment groups. Additionally, as a significant proportion of patients were lost to follow-up for reassessment of cervical length and Bishop score, the present study may not have adequate power to detect the benefit on such outcomes. Unequal loss to follow-up in the three treatment groups may have led to some attrition bias that could have altered the result on the above outcomes. Lastly, as the authors studied solely in low-risk singleton pregnancy with intact membrane. Therefore, the present study results may not be able to be generalized to multiple pregnancy or other high-risk pregnancy, which are more likely to present with threatened or established preterm labor in clinical practice.

Conclusion

Vaginal progesterone was efficacious and safe in prevention of preterm birth before 34 weeks, prolongation of latency period, and increasing gestational age at birth in pregnant women presenting with threatened or established preterm labor. Progesterone as an adjunct to tocolytic treatment may be considered for this group of patients in clinical practice.

What is already known on this topic?

Progesterone has an established role in preventing preterm labor in women with history of spontaneous preterm labor and short cervix. However, evidence on its benefits to prevent preterm delivery in threatened or established preterm labor is limited. Available trials were heterogeneous in term of types, doses, and routes of administration, and showed conflicting results.

What this study adds?

Vaginal progesterone as an adjunct to tocolytics was efficacious and safe in preventing preterm birth before 34 weeks in Thai pregnant women presenting with threatened or established preterm labor. This treatment helped prolong latency period for an additional seven days.

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Conflicts of interest

The authors declare no conflicts of interest.

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