การเปรียบเทียบประสิทธิภาพของโปรเจสเตอโรนแบบรับประทานและแบบเหน็บทางช่องคลอดในการป้องกันการคลอดก่อนกำหนดในสตรีตั้งครรภ์ที่ตรวจพบความยาวของปากมดลูกสั้น : การศึกษาแบบสุ่มและมีกลุ่มเปรียบเทียบ

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บทคัดย่อ

หลักการและเหตุผล : มีหลักฐานสนับสนุนว่าการใช้โปรเจสเตอโรนเหน็บช่องคลอดในสตรีตั้งครรภ์ที่มีความยาวปากมดลูกสั้นสามารถป้องกันการคลอดก่อนกำหนดได้ แต่ยังไม่มีข้อมูลเกี่ยวกับการให้โปรเจสเตอโรนด้วยวิธีการอื่น

วัตถุประสงค์ : เพื่อศึกษาผลของการรับประทานโปรเจสเตอโรนในสตรีตั้งครรภ์ที่มีความยาวปากมดลูกสั้นกว่าหรือเท่ากับ 25 มิลลิเมตรต่อการป้องกันการคลอดก่อนกำหนด เปรียบเทียบกับการเหน็บโปรเจสเตอโรนทางช่องคลอด

วัสดุและวิธีการ : การศึกษาแบบสุ่มและมีกลุ่มเปรียบเทียบในสตรีตั้งครรภ์ในช่วงอายุครรภ์ตั้งแต่ 20-25 สัปดาห์ที่มาฝากครรภ์ที่โรงพยาบาลสรรพสิทธิประสงค์และถูกตรวจวัดความยาวปากมดลูกโดยสตรีตั้งครรภ์ที่วัดความยาวปากมดลูกได้สั้นกว่าหรือเท่ากับ 25 มิลลิเมตรจำนวน 76 คนจะถูกแบ่งออกเป็น 2 กลุ่มเท่าๆกันโดยสุ่มกลุ่มแรกได้รับโปรเจสเตอโรน 200 มิลลิกรัม รับประทานวันละ 1 ครั้ง และกลุ่มที่สองจะได้รับโปรเจสเตอโรน 200 มิลลิกรัมไปเหน็บช่องคลอดวันละครั้ง ตั้งแต่เริ่มวิจัยไปจนกระทั่งอายุครรภ์ 34 สัปดาห์ ประเมินผลลัพธ์หลักคือการคลอดก่อนกำหนดอายุครรภ์น้อยกว่า 34 สัปดาห์ และผลลัพธ์รองคือความยาวปากมดลูกที่วัดซ้ำที่ 4 สัปดาห์หลังได้รับยา

ผลลัพธ์ : ข้อมูลพื้นฐานของประชากรทั้งสองกลุ่มไม่มีความแตกต่างกัน ในจำนวนประชากรตัวอย่าง 38 ราย พบการคลอดก่อนอายุครรภ์ 34 สัปดาห์ 1 คน และ 3 คน ในกลุ่มที่ได้รับโปรเจสเตอโรนแบบรับประทาน และ แบบสอดช่องคลอดตามลำดับ ซึ่งไม่พบความแตกต่างกันอย่างมีนัยสำคัญทางสถิติระหว่างสองกลุ่ม (ร้อยละ 2.6 ในกลุ่มรับประทาน เทียบกับร้อยละ 10.5 ในกลุ่มสอดช่องคลอด, P=0.168)

สรุป : การใช้โปรเจสเตอโรนในสตรีตั้งครรภ์ที่มีความยาวปากมดลูกสั้นเพื่อป้องกันการคลอดก่อนอายุครรภ์ 34 สัปดาห์ในแบบรับประทานและเหน็บช่องคลอด ไม่มีความแตกต่างกัน

คำสำคัญ : คลอดก่อนกำหนด, ความยาวปากมดลูกสั้น, โปรเจสเตอโรน

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Introduction

Preterm delivery is the major cause of neonatal morbidity and mortality. In Thailand, premature neonates are one of important healthcare problems due to low birth weight and immature of important organs. Premature delivery causes many serious complications such as respiratory distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis.[1, 2]

Preterm delivery means the delivery that occur before 37 complete weeks of gestation. Preterm delivery rate is increased with women who had infection, premature rupture of membrane, overdistended uterus, hypertension, smoking, and depression. However, majority of preterm birth developed in women who had no risk mentioned above, screening for shortened cervical length is the useful tool to predict preterm birth.[2, 3]

The previous studies[4, 5] showed the risk of spontaneous preterm birth was increased in women who had short cervix measuring by transvaginal ultrasonography during pregnancy. A systemic review[6] estimated the 36% sensitivity and 94% specificity of cervical length of 25 mm or shorter for prediction of preterm birth before 34 weeks of gestation. The mean cervical length from published data in Thailand range from 42.41 mm,[7] 41.00mm,[8] to 35.66 mm.[9] The preterm birth rate was 83.3% when the pregnant women had a shortened cervix.[9]

A systemic review[10] showed that the progesterone has an important role in preterm prevention, and another meta-analysis[11] reported effective route of progesterone intramuscular injection and vaginal suppository. In the pregnant women with short cervix, micronized progesterone 200 mg vaginal suppository was effective to reduce preterm birth.[12]

A previous study investigated the pharmacokinetics of progesterone and showed that serum progesterone level was significantly lower (3-4 ng/ml) in women who received micronized progesterone orally compared with vaginally which depend on serum estrogen level at the time blood sample was taken.[13] Even vaginal progesterone was used for a long period with proven efficacy,[14] some pregnant women who had antepartum hemorrhage or not willing to apply vaginally, may prefer oral administration.

To date, there were limited studies that compare head-to head efficacy to prevent preterm delivery between oral and vaginal progesterone in pregnant women with short cervix. The objective of this study was to evaluate the efficacy of oral micronized progesterone on prevention of preterm delivery before 34 complete weeks in pregnant women with short cervical length compare with vaginal micronized progesterone. The secondary objective was to investigate how the cervix changed after progesterone treatment.

Material and method

A randomized controlled trial (RCT) was conducted at, after institutional ethical committee approval. This study was registered (TCTR20190324001) at http:// www.Clinical Trials. in.th (Thai Clinical Trials Registry).

During August 2017 through July 2018, all singleton pregnant women, visited antenatal clinic at 20-25 weeks of gestation, were encouraged to measure cervical length by transvaginal sonography. The pregnant women who had cervical length of 25 mm or less were included into this study. The cervical length was measured by standard technique[14] with a covered probe inserted into the vagina after each woman had emptied her bladder. The examination was performed with 4-9 MHz transvaginal real-time ultrasound transducer (GE, Voluson E6), by PP and JW (inter-observer variation = 0.803, intra-observer variation of PP. = 0.885 and JW. = 0.811). The excessive pressure on cervix was avoided. The mean values of 3 consecutive measurements were used for analysis.

All participants were randomly allocated into 2 groups by computer program (Random UX application) to receive 1) micronized progesterone 200 mg (Utrogestan®) orally at the bedtime or 2) micronized progesterone 200 mg (Utrogestan®) vaginal suppository at the bedtime. Participants in both groups administered progesterone since the date of enrollment until 34-completed weeks of gestation. The cervical length was assessed again after 4 weeks of treatment. After allocation by opening the sealed randomization number envelopes, the participants would know the route of administration, and the care-giver including outcome assessor would know the route of administration.

The delivery outcomes, maternal cations and neonatal outcomes were collected from hospital-medical record after delivery. In case that the participants were delivered in other hospitals, the outcomes would be collected from the participants by phone call. The primary outcome was preterm delivery before 34 and 37 weeks of gestation. The secondary outcomes were change of cervical length, route of delivery, maternal obstetric complications, birthweight of the newborn, APGAR score, neonatal complications, and neonatal intensive care unit (NICU) admission.

The funding source had no such involvement in research preparation, study design; in collection, analysis, interpretation of data;writing of the report; and in the decision to submit the article for publication. PP. and JW. Had full access to all the data and PP had final responsibility for the decision to submit for publication.

Statistical analysis

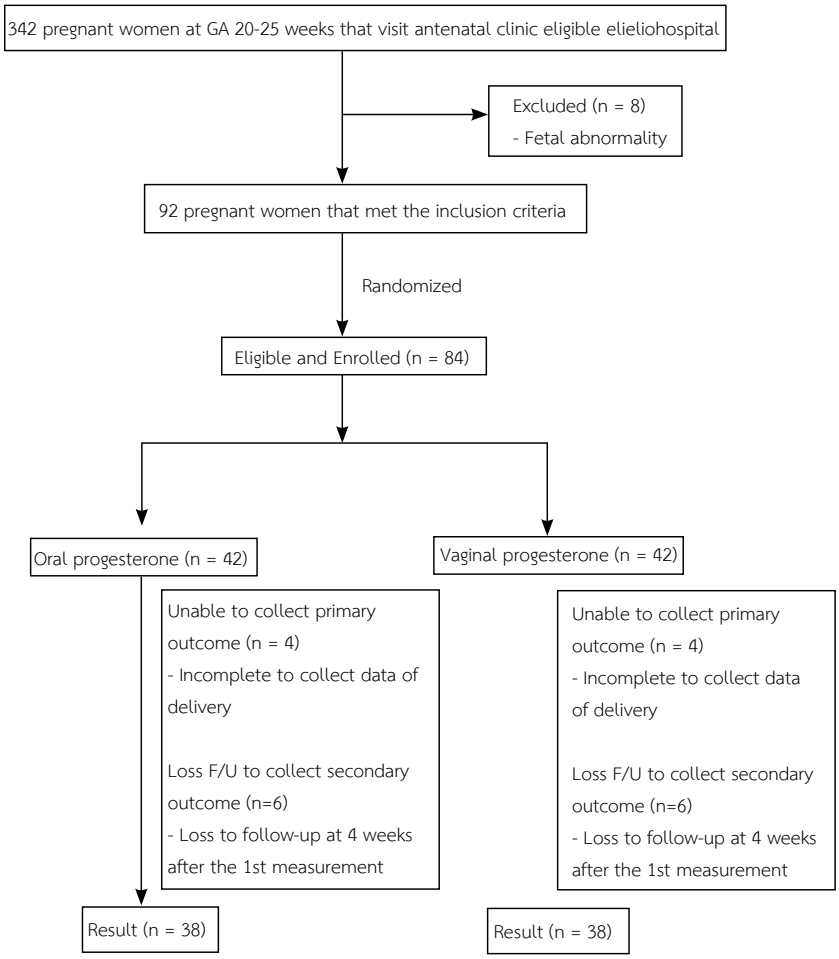
Sample size was calculated according to the previous studies by Fonseca[12] and Erny.[15] The study of Fonseca[12] showed that vaginal progesterone can prevent preterm delivery in pregnant women with short cervix for 40% compared with 74% in placebo group (P = 0.17). And the study of Erny[15] showed that oral progesterone can be reduced uterine contraction in pregnant women who had risk factor for preterm delivery 75-88% compared with 42% in placebo group. The sample size was calculated by n4studies, using formula of randomized controlled trial for binary data. The sample size 84 was required with an expected loss follow-up of 10%, 80% power and 2-sided type I error at 5%. The statistical analyses of results were performed using SPSS version 22.

Descriptive statistics were carried out using mean, median, standard deviation, and interquartile range. Continuous data were tested for normal distribution with Kolmogorov - Smirnov Test. Independent t test and Mann-Whitney U test were used for normally-distributed and non-normally distributed continuous data, respectively.Chi-square test was used for categorical data. Statistical significance was defined as P <0.05.

Result

In this study, there were 342 pregnant women at GA 20-25 weeks of gestation who visited antenatal clinic during August 2017 through July 2018 were screened cervical length by transvaginal sonography. After exclusion of 8 pregnant women who had fetal abnormalities, left 92 participants who had short cervix eligible. Eight pregnant women denied to participate this study, left 84 participants included. After given written informed consents, all participants were randomly allocated into 2 groups, 42 received oral micronized progesterone and 42 received vaginal micronized progesterone. There are 12 participants (6 in oral group and 6 in vaginal group) had loss to follow up and did not visit to measure cervical length after 4 weeks of treatment Finally, there are 8 participants who delivered at other hospitals and did not response the phone call were not able to collect delivery and neonatal outcomes, left 76 participants for analysis. (Figure 1).

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



The participants in this study were included at average age of 27.4 years old, and average gestational age of 161 days. Most of participants (70.2%) had one or more of the following risk factors: history of threatened miscarriage, smoking, obesity, maternal age below 19 years or above 35 years, short stature (height less than 140 cm), depressive disorder, 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. The demographic data and baseline characteristics were not significantly different between groups as shown in the Table 1.

Table 1 Baseline characteristics of the women at randomization[a]

	Total (n=84)	Oral progesterone (n=42)	Vaginal progesterone (n=42)	P-value
Age (years)	27.4 ±7.5	26.9 ±7.9	27.9 ±7.2	0.571
Gestational age at enrollment (days)	161 (140,175)	161 (146,175)	161 (143,175)	0.307
Cervical length at enrollment (mm)	24.2 (20.1,24.9)	24.1 (20.1,24.9)	24.3 (20.7,24.9)	0.996
Gravidity	2 (1,5)	2 (1,5)	2 (1,5)	0.897
Term parity	0.5 (0,2)	0.5 (0,2)	0.5 (0,3)	0.751
Preterm parity	0 (0,1)	0 (0,1)	0 (0,1)	1.000
Abortion	0 (0,4)	0 (0,4)	0 (0,2)	0.377
Education				0.769
- Primary school or lower	9 (10.0)	3 (7.1)	6 (14.3)	
- Lower secondary school	28 (33.3)	16 (38.1)	12 (28.6)	
- Upper secondary school or Vocational	28 (33.3)	13 (31.0)	15 (35.7)	
- Diploma	5 (6.0)	2 (4.8)	3 (7.1)	
- Bachelor degree or higher	14 (16.0)	8 (19.00)	6 (14.3)	
Occupation				0.661
- Farmer	8 (9.5)	4 (9.5)	4 (9.5)	
- Government official	16 (19.0)	7 (16.7)	9 (21.4)	
- Self-employed	16 (19.0)	8 (19.0)	8 (19.0)	
- Employee	7 (8.3)	4 (9.5)	3 (7.1)	
- Private official	6 (7.1)	3 (7.1)	3 (7.1)	
- Housewives	30 (35.7)	15 (35.7)	15 (35.7)	
- Other	1 (1.2)	1 (2.4)	0 (0%)	
Risk for preterm[b]	59 (70.2)	30 (71.4)	29 (69.0)	0.812

[a]Values are given as mean ±standard deviation, median (interquartile range), or number (percentage)

[b]Presence of one or more of the following risk factors: history of threatened miscarriage, smoking, obesity, maternal age below 19 years or above 35 years, short stature (height less than 140 cm), depressive disorder, 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

Table 2 Obstetric outcomes[a]

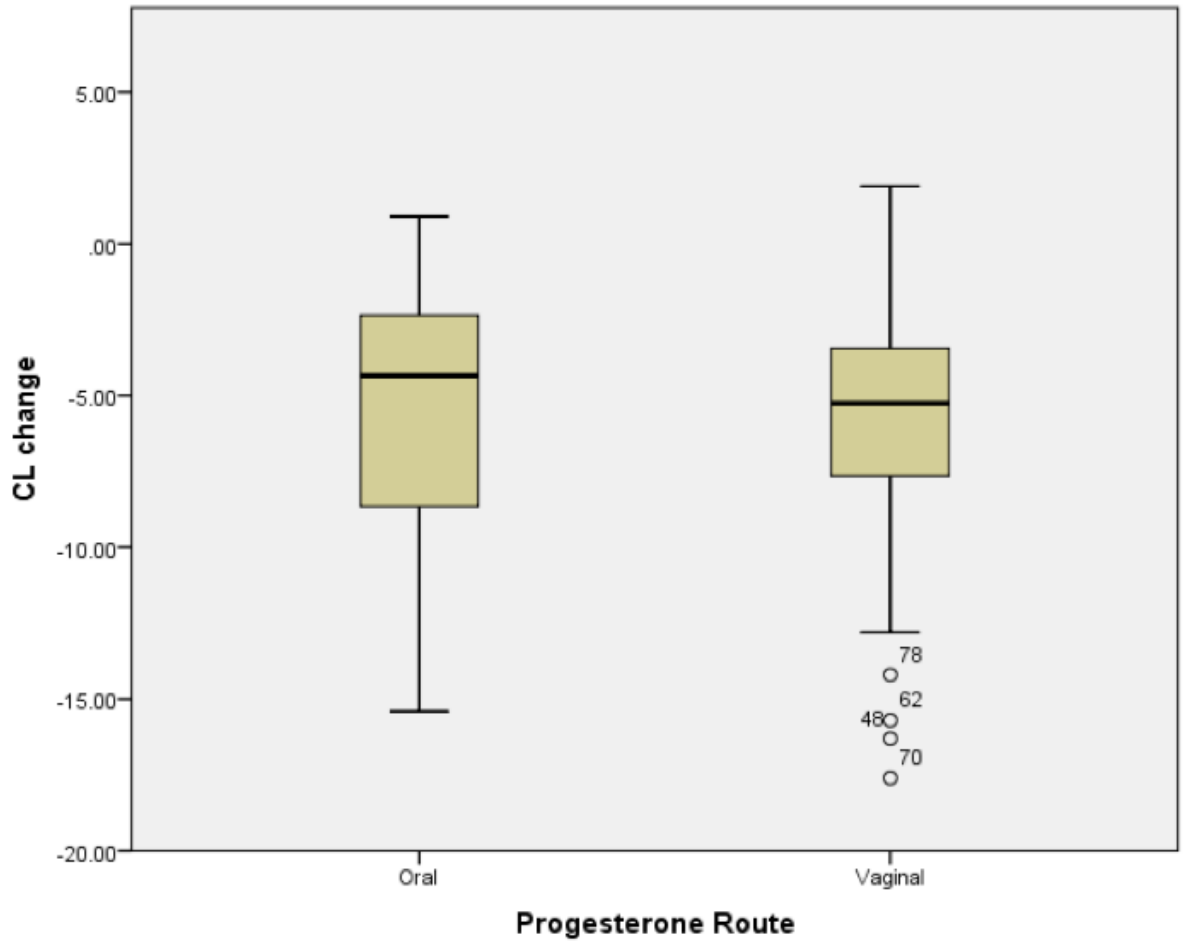
	Total	Oral progesterone	Vaginal progesterone	P-value
Cervical length after 4 weeks of progesterone (mm) (n = 72)	28.9 (15.0,54.0)	28.0 (15.0,54.0)	29.8 (18.8,40.9)	0.148
Change of cervical length (mm) (n=72)	-5.1 (-30.0, – 9.1)	-4.3 (-30.0, – 9.1)	-5.3 (-17.6, – 1.9)	0.193
Delivery before 34 weeks (n=76)	5 (6.6)	1 (2.6)	4 (10.5)	0.168
Delivery before 37 weeks (n=76)	20 (26.5)	11 (28.9)	9 (23.7)	0.605
GA at delivered (days) (n=67)	264.9 ±17.0	267.0 ±14.6	263.1 ±18.9	0.358
Route of delivery (n=67)				0.911
Normal delivery	41 (61.2)	19 (61.3)	22 (61.1)	
Vacuum extraction	2 (3.0)	1 (3.2)	1 (2.8)	
Ceasarean section	24 (35.5)	11 (35.5)	13 (36.1)	
Birthweight (n=67)	2,755.5 ±420.3	2,857.6 ±373.7	2,667.6 ±443.0	0.065

avalues are given as mean ±standard deviation, median (interquartile range), or number (percentage)

Table 2 shows obstetric outcomes. The average gestational age at delivery was term (264.9 days) with most normal delivery 61.2%. The gestational age at delivery was not significantly different between groups (38+1 weeks in oral group VS 37+4 weeks in vaginal group, P = 0.193). The average birthweight of newborn was 2,755.5 grams and was not significantly different between groups (2,857.6 grams in oral group VS 2,667.6 grams in vaginal group, P = 0.065). There is only one participant had preterm delivery before 34 weeks of gestation in oral progesterone group and there are 4 participants were delivery before 34 weeks in vaginal group. The primary outcome of preterm delivery before 34 weeks slightly lower in oral group, but not significant different between groups (2.6% in oral group VS 10.5% in vaginal group, P = 0.168). All participants received tocolytic drug and a complete course of dexamethasone except only one participant in vaginal group received only one dose of dexamethasone. There are 11 and 9 participants in oral and vaginal progesterone group were delivered before 37- completed weeks. Preterm delivery before 37- weeks were not different (28.9% in oral group VS 23.7% in vaginal group,

P = 0.605). The median change of cervical length was not significantly different (4.3 mm in oral group VS 5.3 mm in vaginal group, P = 0.193) as illustrated in Figure 2.

Figure 2 Box plot change of cervical length (CL) among groups (n=72)



There was no report about adverse effect from progesterone used in both oral and vaginal group. There were 3 participants had obstetric complication and immediate postpartum hemorrhage, all these 3 women were are in vaginal group. There is only one newborn had birth asphyxia. He was delivered from the participant in vaginal micronized progesterone group at GA 28+4 weeks and admitted in NICU. There is neither stillbirth nor neonatal death in this study.

Discussion

In our study, preterm birth before 34 weeks of gestation was 2.6% in oral progerone group compared with 10.5% in vaginal progesterone group. And preterm birth before 37 weeks of testation was 23.7% and 26.5% in oral and vaginal progesterone group, respectively. The efficacy of oral progesterone tend to prevent the preterm birth before 34 weeks of gestation more than vaginal progesterone, but not statistically significant. For secondary outcomes, there were a few maternal and neonatal complications reported in our study. In this study, there were only 3 participants experienced immediate postpartum hemorrhage and only one gave birth of neonatal asphyxia.

The rate of preterm birth of our study was less than the previous study by Fonseca.[12] This may result from the different criteria of cervical length used to start progesterone. The prior study used the criteria of short cervix 15 mm to start progesterone while the present study used the cut-off 25 mm for recruiting participants to administer progesterone. Besides, and the minimum cervical length of participants in our study was 20.1 mm which longer than Fonseca study for 5 mm.

The recent study by Abd Elaziz[16] reported that vaginal progesterone was more effective than oral progesterone in prevention of preterm delivery before 34 weeks in high-risk for preterm labor woman. The different results of this study and the present study may affect by the dose and kind of progesterone, the previous study used 10 mg of dydrogesterone orally twice a day and 200 mg of progesterone vaginally twice a day.

The strength of this study was randomized controlled trial by design. This study is one of a few studies comparing oral and vaginal progesterone in pregnant women with short cervical length. The demographic data and the other risk for preterm birth were equally in both groups. The sample size is appropriate to analyze primary outcome.

The limitation is that this study was not blinded by different route of administration. It may be confounded by external factors such as special care from any care givers, other medications that may be prescribed from our or other hospitals, preterm labor management policy in those individual hospitals, especially management of preterm labor at GA 34-37 weeks that varied by the individual doctors and capability of the hospitals. The other limitation of this study was the potential to collect the sufficient data when some of participants delivered at the other hospitals such as community hospital and private hospitals. In addition, some of these participants did not respond telephone call resulted in missing some secondary outcomes.

Usually, Thai people familiar with drug administration by oral route rather than vaginal route since it is easier and more acceptable. The result of this study may be the supporting information for physician to make decision whether to prescribe progesterone orally or vaginally for the pregnant women with short cervix. However, in the medical practice, universal screening of cervical length may not available in all hospital and cost-effective should be discussed.[17, 18]

Conclusion

Oral micronized progesterone can be used to prevent preterm delivery before 34 weeks of gestation in pregnant women with short cervix, the efficacy is not different from using micronized progesterone vaginal suppository.

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References

1. Cunningham FC, Leveno KJ, Bloom SL, et al. The preterm newborn. In : Williams Obstetrics. 24th ed. New York : McGraw - Hill Education, 2014:653-60.
2. Simhan HN, Berghella V, Iams JD. Preterm labor and birth. In : Creasy and Resnik's Maternal-Fetal Medicine. 7th ed. Elsevier Saunders, 2014:624-53.
3. Cunningham FC, Leveno KJ, Bloom SL, et al. Preterm labor. In: Williams Obstetrics. 24th ed. New York : McGraw - Hill Education, 2014:829-61.
4. Iams JD, Goldenberg RL, Meis PJ, et al. The length of the cervix and the risk of spontaneous premature delivery. N Engl J Med 1996;334:567-72.
5. Berghella V, Roman A, Daskalakis C, et al.Gestational age at cervical length measurement and incidence of preterm birth. Obstet Gynecol 2007;110:311-7.
6. Lim AC, Hegeman MA, Huis MA, et al. Cervical length measurement for the prediction of preterm birth in multiple pregnancies a systematic review and bivariate meta-analysis. Ultrasound Obstet Gynecol 2011; 38:10–7.
7. Tongsong T, Kamprapanth P, Pitaksakorn J. Cervical length in normal pregnancy as measured by transvaginal sonography. Int J Gynecol Obstet 1997;58:313-5.
8. Wanitpongpan P, Sutchritpongsa P, Rongluen S. Cervical length at mid-trimester in Thai women with normal singleton pregnancies. Siriraj Med J 2015;67:33-6.
9. Pattanapanyasat N, Luengratsameerung S, Charoenchainont P. Comparison of the cervical length during second trimester of pregnancy between teenageand adult primigravidae. Thai J Obstet Gynaecol 2016; 24 :14-9.
10. Rode L, Langhoff-Roos J, Andersson C, et al. Systematic review of progesterone for the prevention of preterm birth in singleton pregnancies. Acta Obstet Gynecol Scand. 2009 ;88 :1180-9.
11. Dodd JM, Jones L, Flenady V, et al. Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. Cochrane Database of Systematic Reviews 2013, Issue 7. Art. No. :CD004947

12. Fonseca EB, Celik E, Parra M, et al. Progesterone and the risk of preterm birth among woman with short cervix. N Engl J Med 2007; 357:462-9.
13. Choavaratana R, Manoch D. Efficacy of oral micronized progesterone when applied via vaginal route. J Med Assoc Thai 2004;87:455-8.
14. Romero R, Yeo L, Miranda J, et al. A blueprint for the prevention of preterm birth: vaginal progesterone in women with a short cervix. J Perinat Med 2013;41:27-44.
15. Erny R, Pigne A, Prouvost C, et al. The effects of oral administration of progesterone for premature labor. Am J Obstet Gynecol 1986;154:525-9.
16. Abd Elaziz MA. Oral versus vaginal progesterone in preterm labor. EBWHJ 2018;7:141-9.
17. Cahill AG, Odibo OA, Caughey AB, et al. Universal cervical length screening and treatment with vaginal progesterone to prevent preterm birth. Am J Obstet Gynecol 2010;202:548.e1-8.
18. Campbell S. Universal cervical-length screening and vaginal progesterone prevents early preterm births, reduces neonatal morbidity and is cost saving. Ultrasound Obstet Gynecol 2011;38: 1-9.

Comparison of efficacy of oral and vaginal progesterone to prevent preterm birth in pregnant women with short cervix : Randomized controlled trial

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ABSTRACT

Background : There is an evidence support that vaginal route of progesterone in pregnant woman with short cervix can prevent preterm delivery, but there are no data about preterm prevention for other route of progesterone

Objective : To study efficacy of oral route of progesterone in pregnant woman with cervical length 25 mm or less to prevent preterm birth, compare with vaginal route of progesterone

Materials and methods : A Randomized control trial conducted in pregnant women at gestational age of 20-25 weeks who visited antenatal clinic, Sunpasitthiprasong Hospital for measuring cervical length. Seventy-six participants who cervical length 25 mm or less were equally randomized into 2 groups : 1) received progesterone 200 mg orally once daily and 2) received progesterone 200 mg vaginal suppository once until gestational age of 34 weeks. The primary outcome was preterm birth before 34 weeks of gestation. The secondary outcome was cervical length attenuation after 4 weeks of treatment.

Results : The demographic data were not different between groups. Among 38 participants in the oral progesterone group, there is only one woman who delivered before 34 weeks. While, there are 3 women among 36 participants in vaginal progesterone group delivered before 34 weeks. The preterm birth before 34 weeks was not significantly different between the two groups of administrative routes (2.6% in oral group vs 10.5% in vaginal group, P=0.168).

Conclusion : There was no significant difference in route of progesterone administration to prevent preterm birth before 34 weeks in pregnant woman with short cervical length.

Keyword : Preterm birth, Short cervical length, Progesterone

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