Journal of Kerman University of Medical Sciences

JKMU

Journal of Kerman University of Medical Sciences, 2018; 25 (2): 128-136

A Comparison between the Effects of Vaginal Suppository Progesterone vs. the Injection of 17-Alpha Hydroxyprogesterone Caproate on the Duration of Latent Phase After Controlled Threatened Preterm Labor

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Received: 24 January, 2018 Accepted: 26 May, 2018

ARTICLE INFO

Article type:
Original article

Keywords:
Preterm delivery
Vaginal progesterone suppository
17-alpha hydroxyprogesterone caproate

Abstract

Background: Women with preterm labor put in an arrest phase by tocolytic therapy, are at increased risk of recurrent preterm labor. The aim of this study is to evaluate vaginal progesterone suppositories as compared to intramuscular type in order to prevent preterm labor in women with episodes of threatened preterm labor.

Methods: This prospective longitudinal study was conducted on 108 pregnant women who were presented with symptoms of threatened preterm labor and went on tocolytic therapy in order to prevent uterine activity. Their gestational age (GA) ranged between 24-34 complete weeks and mothers were at risk of preterm delivery. After acute phase control and delivery supression, 400mg of prophylactic vaginal suppository was prescribed each day in the first intervention group and 250 mg of intra-muscular 17-alpha hydroxyprogesterone caproate was injected once a week in the second intervention group. Treatment continued in both groups up to 36 weeks of gestational age or until delivery.

Results: The prevalence of preterm delivery was significantly higher in patients receiving intra-muscular progesterone (55.6% vs. 37%) (P = 0.05). Moreover, the birth weight in the intramuscular progesterone group was significantly lower than the other group (2685.18 g vs. 2999.25 g) (P = 0/02). First and fifth minute Apgar score were also significantly lower in this group than the vaginal progesterone suppository group (P<0.05).). There was no statistical significance observed comparing the latent phase duration in the two groups. (46.9 days vs. 41.44 days) (P= 0.16).

Conclusion: The results of this study suggest that vaginal progesterone suppository decreases the rate of preterm delivery while it also improves the newborn outcome at a higher rate compared to intra-muscular 17-alpha-hydroxyprogesterone caproate. developed in the left eye. Two patients had no family history suspicious for keratoconus.

Citation: Mirzaei F, Azimi S, Mansouri GH. A Comparison between the Effects of Vaginal Suppository Progesterone vs. the Injection of 17-Alpha Hydroxyprogesterone Caproate on the Duration of Latent Phase After Controlled Threatened Preterm Labor. Journal of Kerman University of Medical Sciences, 2018; 25 (2): 128-136.

Introduction

Preterm delivery happens when the fetus is delivered before 37 complete weeks of gestation (259 days) from the LMP (GA). The preterm delivery rates have increased in many countries (range from 3.8% to 17.5% of live births) (1) and it has been a major health problem worldwide. Different risk factors have been introduced to cause preterm delivery like low socioeconomic and educational status, maternal short stature, young or old maternal age (<20 years or >35 years respectively), and maternal diseases like preeclampsia, eclampsia and gestational diabetes (2-4).

In women with preterm labor symptoms and intact amniotic membranes, the treatment is to prevent delivery before 34 weeks of GA. (5). If the process of preterm labor can be suppressed, the patients are at high risk of therapy failure. Tocolytic therapy may reduce the chance of delivery in some cases (6). Several drugs have been introduced for this purpose through multiple clinical trials, including beta adrenergic agonist drugs, magnesium sulfate, NSAIDs, and calcium channel blockers (7). In other words, these drugs increase the latent phase duration after controlled threatened preterm labor (8).

An initial systematic review demonstrated that progesterone administration may prevent preterm birth and increase latent phase (9). Recently, different studies demonstrated the benefits of vaginal progesterone administration instead of intramuscular type to prevent preterm birth and increase latent phase duration through promoting anti-inflammatory (by inhibiting nitric oxide, prostaglandin, and cytokine production) and pro-relaxant pathways in the uterus and consequent reduction in uterine contractility (10-13). While describing different metabolic pathways for vaginal progesterone (avoiding first pass metabolism), some authors suggest that using vaginal progesterone does not reduce the risk of preterm delivery or increase latent phase (14), while some other studies have suggested vaginal progesterone effectiveness on preterm delivery reduction and increase in latent phase duration (15). The dichotomy has led to considerable debate and differences in clinical practice recommendations (16-19). As to best of our knowledge, due studies have been conducted regarding this issue and their results have arose much dichotomy. Therefore, this study was designed to evaluate the effect of vaginal progesterone suppositories, as compared to intramuscular type, on the duration of latent phase after controlled threatened preterm labor.

Methods

Study design and target group

This prospective longitudinal study was conducted in Obstetrics and Gynecology department of Afzalipour Hospital, Kerman, Iran from February 2016 to October 2017. All the pregnant women in this study had a gestational age (GA) between 24-34 complete weeks and at risk of preterm delivery. The inclusion criteria were as follows: pregnant woman with GA ranged between 24-34 complete weeks (based on their last menstrual period - LMP) who were at risk of preterm delivery, singleton fetus, their labor pain was due to regular contractions along with cervical changes, subjects had to be between 18 to 35 years old, could recall their exact date of the LMP, have regular menstrual cycles, their body mass index (BMI) had to be between 18 to 30 kg/m^2, and willing to participate in the study. Exclusion criteria were: having multiple pregnancies, existence of cerclage, premature rupture of membranes, cervical dilatation more than 4 centimeters, fetal distress or death, intrauterine growth restriction (IUGR), and previous consumption of tocolytics in recent pregnancies. We also excluded patients with incomplete data.

Participants

During one year, 118 pregnant women at risk of preterm labor (who had been diagnosed by an obstetrician) were studied; a total of 10 cases were excluded (5 of them based on inclusion and exclusion criterion & the other 5 during the study).Vaginal progesterone suppositories was administrated for 54 patients (as the first intervention group) while 54 patients received intramuscular progesterone (as second intervention group). The study received ethics approval from the Ethics Committee of Kerman University of Medical Sciences (IR.KMU.REC.1396.1293), and all participants signed an informed consent.

Before the trial, the methods of intervention were fully explained to the parents. A standard history questionnaire including the time of arrival to the clinic, gravidity, gestational age based on LMP, labor pain onset time & the medical history of the patients were recorded. Clinical findings of the patients including the number & duration of uterine contractions and the amount of dilatation were examined by tachometer and vaginal exam respectively at the time of arrival.

In order to control the acute phase of preterm delivery, 500cc of isotonic saline was administrated along with 4g of IM magnesium sulfate as loading dose, continued by a rate of 125 cc/h of isotonic saline and 2-3g/h of IM magnesium sulfate for up to 24 hours as maintenance dose. 24 mg of betamethasone was prescribed (1 dose daily for 2 days in an attempt to stimulate fetal lung maturation. Suppressed delivery was considered as a 12-hour contraction-free period following discontinuation of intravenous therapy. After acute phase control and preterm delivery suppression patients were monitored for up to 48 hours.

Mothers were randomized into two intervention groups (vaginal suppository progesterone group and injection of 17-alpha hydroxyprogesterone caproate group). It should be noted that all injections and measurements in this study were carried out by a resident of obstetrics and gynecology with sufficient skills.

After acute phase control and preterm delivery suppression, 400 mg of vaginal suppository progesterone was prescribed to one group in a daily manner and 250 mg of intramuscular 17-alpha hydroxyprogesterone caproate was prescribed to the other group in a weekly manner. Treatment continued in both groups up to 36 weeks of gestation or until delivery.

During the study, patients were asked not to use any other drugs or tocolytics without consulting their physician. Afterwards, all patients were followed up weekly at the obstetrics and gynecology department. In cases of preterm delivery signs, vaginal examination was performed by an obstetrics and gynecology specialist. If preterm delivery was confirmed, the mother was asked to be hospitalized for further supportive measures. After the delivery, data including the delivery time, delivery method, and the cause of cesarean section (in case of cesarean section) were recorded. Also, the wellbeing of the neonate was evaluated by birth weight assessment, APGAR score, necessity of admission to NICU and the duration of hospitalization.

Data analysis

Only patients with complete data had their information analyzed and reported. Statistical analysis of data was performed using SPSS software version 18. Chi-square test was used to compare qualitative variables between groups. Kolmogorov-Smirnov test was used in order to evaluate the normal distribution of all quantitative parameters. Student t-test was used for variables with normal distribution, while Mann-Whitney and Wilcoxon tests were used for variables

without normal distribution. The two tailed p-value less than 0.05 were considered significant.

The flowchart is shown in figure 1.

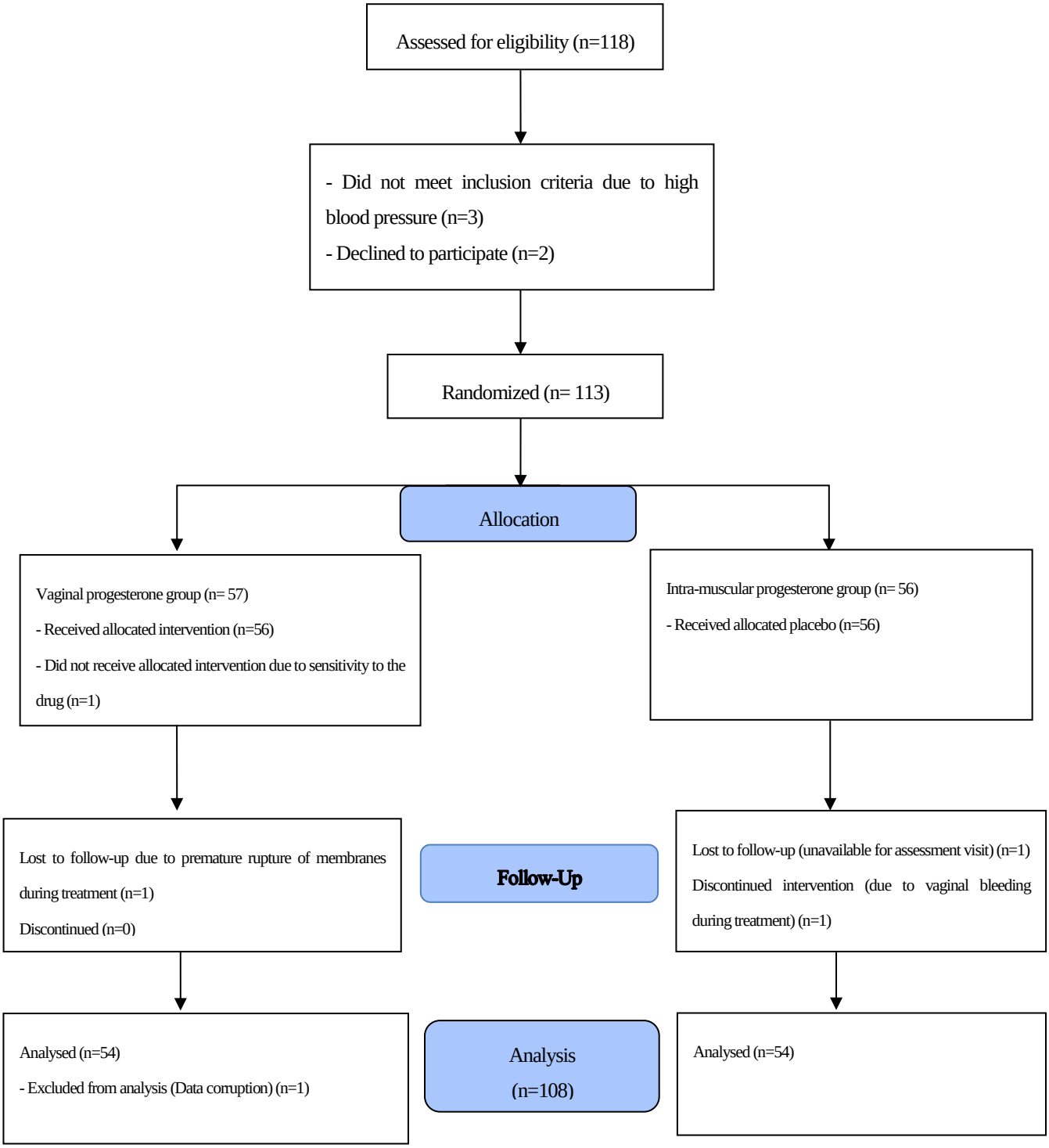

Figure 1. Study flowchart (CONSORT format)

Results

The quantitative variables of the 108 pregnant women whom completed the study, including maternal age (P= 0.261), gestational age (based on LMP) (P= 0.38), the duration between the onset of pain until arrival to OB/Gyn emergency department (P= 0.167), latent phase (P= 0.16), gestational age at delivery (P= 0.082) were not statistically different between the two groups. Moreover, type of delivery was not statistically significant between the two groups (P= 0.165). (Table 1)

Clinical examinations including cervical dilatation (P= 0.717), cervical effacement (P= 0.401) and number of contractions (P= 0.261) were not statistically significant between the two groups. (Table 1)

The frequency of NICU admission and duration of hospitalization in NICU was not statistically significant in both groups (P>0.05). However, the weight of newborns in the intramuscular progesterone group was significantly lower than the other group (2685.18 g vs. 2999.25 g) (P = 0/02). First and fifth minute Apgar scores were also significantly lower in this group compared to the vaginal suppository progesterone group (P<0.05). (Table 2)

The prevalence of preterm delivery was significantly higher in patients receiving intramuscular progesterone (55.6% vs. 37%) (P = 0.05). (Table 1)

Table 1. Studied variables of mothers in both vaginal progesterone suppository group and intramuscular progesterone group

Variables \ Groups		Intramuscular progesterone (n=54)	Vaginal progesterone suppository (n=54)	P-value
Mother's age (years)		24.79 ±5.4	25.72 ±5.34	0.261
Onset of pain until arrival to the obstetrics emergency department (hours)		3.29 ±.66	3.48 ±.72	0.167
Gestational age based on LMP (weeks)		30.7 ±2.75	31.16 ±2.7	0.38
Latency phase (Days ± 1 SD)		41.44 ±18.79	46.09 ±15.16	0.16
Type of delivery	**Vaginal**	30 (55.6%)	37 (68.5%)	0.165
	Cesarean section	24 (44.4%)	17 (31.5%)	
Mean gestational age at delivery (weeks)		35.92 ±3.39	36.98 ±2.83	0.082
Gestational age at delivery	**Less than 34 weeks**	5 (9.3%)	10 (18.5%)	0.116
	34 to 37 weeks	20 (37%)	25 (46.3%)	
	More than 37 weeks	29 (53.7%)	19 (35.2%)	
Number of contractions (in 10 minutes)		3.29 ±.66	3.48 ±.72	0.261
Cervical dilatation	**1 cm**	6 (11.1%)	6 (11.1%)	0.717
	2 cm	22 (40.7%)	26 (48.1%)	
	More than 2 cm	26 (48.1%)	22 (40.7%)	
Cervical effacement	**<50%**	4 (7.4%)	2 (3.7%)	0.401
	>50%	50 (92.6%)	52 (96.3%)	
Preterm delivery		30 (55.6%)	20 (37%)	0.05

Table 2. Studied variables of neonates in both vaginal progesterone suppository group and intramuscular progesterone group

Groups / Variables	Intramuscular progesterone (n=54)	Vaginal progesterone suppository (n=54)	P-value
Weight (g)	2685.18 ±700.18	2999.25 ±637.06	0.02
Apgar in first minute	8.25 ±.87	8.64 ±.61	0/009
Apgar in fifth minute	9.18 ±.99	9.61 ±.71	0/012
Admitted to the NICU	24 (44.4%)	16 (29.6%)	0/111
Duration of admission to NICU (day)	10 ±15.77	2.87 ±2.5	0/082

Discussion

According to our results, vaginal suppository progesterone decreases the rate of preterm delivery at a higher rate compared to intramuscular progesterone. Moreover, infants in vaginal suppository progesterone group had better first and fifth minute Apgar scores and had higher birth weights compared to the other group.

In a study performed by Romero R. et al. vaginal progesterone decreased the risk of preterm delivery and improved perinatal outcomes (including reduction in RDS, reduction in birth weights below 1500gr and below 2500gr, and admission to NICU) in singleton gestations, without any demonstrable deleterious effects on childhood neurodevelopment. (20) Daskalakis G et al. suggested that the combination of vaginal progesterone and cervical pessary prevents spontaneous preterm birth in women with a short cervical length and also it was associated with pregnancy prolongation, decreased prematurity rate and a low rate of perinatal complications (including lower body mass index values, RDS, and the number of second trimester miscarriages). (21) Moreover, in a systematic review and meta-analysis of randomized controlled trials performed by Saccone G et al. it was suggested that women who received vaginal progesterone had significantly lower rates of spontaneous preterm birth (below < 34 weeks), adverse drug reactions, and duration of admission to NICU compared with women who received 17α-hydroxyprogesterone caproate (22). Furcron AE et al. reported that vaginal progesterone (but not 17α-hydroxyprogesterone caproate) has local anti-inflammatory effects on the maternal-fetal interface and the cervix which protects against endotoxin-induced preterm birth (23). Our study had numerous common results when compared to the above mentioned studies.

Hernandez WR et al. suggested that because of preterm delivery, prophylactic use of 200 mg of vaginal progesterone does not have any significant effects on the latent phase in women with twin pregnancy treated with tocolytics (24). Moreover, Pirjani R et al. suggested that vaginal progesterone and 17α-hydroxyprogesterone caproate had similar effects on the risk of preterm delivery in asymptomatic women with a sonographically short cervical length. They did not detect a significant difference between the effects of 17α-hydroxyprogesterone caproate and vaginal progesterone on cervical length changes over time. (25). Furthermore, Beigi A et al. suggested that the risk of preterm labor in the vaginal progesterone group and 17-alpha-hydroxyprogesterone caproate group in pregnant women with threatened abortion is the same. (26). Elimian A et al. suggested that the administration of weekly intramuscular hydroxyprogesterone caproate or daily vaginal progesterone have similar efficacy in reducing the rate of preterm delivery. (27) In addition Martinez de Tejada B et al. reported that vaginal progesterone may be effective in reducing preterm labor. Moreover, they mentioned that a recent clinical trial study has shown that

vaginal progesterone can even be deleterious in this group of women. (28) Bafghi AS et al. suggested that vaginal progesterone and intramuscular 17-alpha-hydroxyprogesterone caproate had the same levels of effectiveness, safety and acceptance by patients in the prevention of preterm labor, however they proposed that more studies are needed (29) These results are contrary to ours, which may be due to different sample sizes with different demographic features and different inclusion and exclusion criterion.

Conclusions

The results of this study suggest that vaginal progesterone suppository decrease the rate of preterm delivery more than intramuscular 17-alpha-hydroxyprogesterone caproate. Moreover, infants in vaginal progesterone suppository group had better first and fifth minute Apgar scores and had higher birth weight. Therefore, we can suggest the administration of vaginal suppository progesterone after 24 weeks of gestational age for all high risk pregnant women in order to decrease preterm delivery and improve neonatal outcome, especially Apgar score and birth weight.

Conflicts of interest

The authors declare that there were no conflicts of interests regarding the content of this article.

Acknowledgments

We are highly indebted to Kerman University of Medical Sciences for their guidance and constant supervision as well as their support in providing the necessary information regarding the project and also for their cooperation in completing the project.

References

1. Nyarko KA, Lopez-Camelo J, Castilla EE, Wehby GL. Explaining racial disparities in infant health in Brazil. Am J Public Health 2013; 103(9):1675-84.
2. Howson CP, Kinney MV, Lawn JL. Born Too Soon: The Global Action Report on Preterm Birth. World Health Organization (WHO); 2012. (cited) Available from: http://www.who.int/pmnch/media/news/2012/201204_borntoosoon-report.pdf
3. Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller AB, et al. Born too soon: the global epidemiology of 15 million preterm births. Reprod Health 2013; 10 Suppl 1:S2.
4. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet 2008; 371(9606):75-84.
5. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. N Engl J Med 2000; 342(20):1500-7.
6. Cunningham FG, Leveno KJ, Bloom SL, Dashe JS, Hoffman BL, Casey BM, et al. Williams Obstetrics. 23 th ed. New York: McGraw-Hill; 2010.
7. Gibbs RS, Karlan BY, Haney AF, Nygaard IE. Danforth's Obstetrics and Gynecology. 9th ed. Philadelphia, USA: Lippincott Williams & Wilkins; 2003.

8. Salari Z, Mirzaei S, Ravari A, Mirzaei T. The comparison between vaginal progestrone and isoxuprine tab on duration of latent phase after controled preterm labor. J Rafsanjan Univ Med Sci 2012; 11(4): 301-12. In Persian

9. Keirse MJ. Progestogen administration in pregnancy may prevent preterm delivery. Br J Obstet Gynaecol 1990; 97(2):149-54.

10. Anderson L, Martin W, Higgins C, Nelson SM, Norman JE. The effect of progesterone on myometrial contractility, potassium channels, and tocolytic efficacy. Reprod Sci 2009; 16(11):1052-61.

11. Hardy DB, Janowski BA, Corey DR, Mendelson CR. Progesterone receptor plays a major anti-inflammatory role in human myometrial cells by antagonism of nuclear factor-kappaB activation of cyclooxygenase 2 expression. Mol Endocrinol 2006; 20(11):2724-33.

12. Loudon JA, Elliott CL, Hills F, Bennett PR. Progesterone represses interleukin-8 and cyclo-oxygenase-2 in human lower segment fibroblast cells and amnion epithelial cells. Biol Reprod 2003; 69(1):331-7.

13. Tan H, Yi L, Rote NS, Hurd WW, Mesiano S. Progesterone receptor-A and -B have opposite effects on proinflammatory gene expression in human myometrial cells: implications for progesterone actions in human pregnancy and parturition. J Clin Endocrinol Metab 2012; 97(5):E719-30.

14. O'Brien JM, Adair CD, Lewis DF, Hall DR, Defranco EA, Fusey S, et al. Progesterone vaginal gel for the reduction of recurrent preterm birth: primary results from a randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol 2007; 30(5):687-96.

15. da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. Am J Obstet Gynecol 2003; 188(2):419-24.

16. Committee on Practice Bulletins—Obstetrics, The American College of Obstetricians and Gynecologists. Practice bulletin no. 130: prediction and prevention of preterm birth. Obstet Gynecol 2012; 120(4):964-73.

17. Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Progesterone: Use in the second and third trimester of pregnancy for the prevention of preterm birth RANZCOG Melbourne: Women's Health Committee, 2013.

18. The Royal College of Obstetricians and Gynaecologists (RCOG). Communication: The Use of Progesterone to Prevent Preterm Delivery; 2010. (cited)Available from: https://www.rcog.org.uk/en/news/rcog-communication-the-use-of-progesterone-to-prevent-preterm-delivery/

19. Society for Maternal-Fetal Medicine Publications Committee, with assistance of Vincenzo Berghella. Progesterone and preterm birth prevention: translating clinical trials data into clinical practice. Am J Obstet Gynecol 2012; 206(5):376-86.

20. Romero R, Conde-Agudelo A, Da Fonseca E, O'Brien JM, Cetingoz E, Creasy GW, et al. Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: a meta-analysis of individual patient data. Am J Obstet Gynecol 2018; 218(2):161-80.

21. Daskalakis G, Zacharakis D, Theodora M. Safety and efficacy of the cervical pessary combined with vaginal progesterone for the prevention of spontaneous preterm birth. J Perinat Med 2017.

22. Saccone G, Khalifeh A, Elimian A, Bahrami E, Chaman-Ara K, Bahrami MA, et al. Vaginal progesterone vs intramuscular 17alpha-hydroxyprogesterone caproate for prevention of recurrent spontaneous preterm birth in singleton gestations: systematic review and meta-analysis of randomized controlled trials. Ultrasound Obstet Gynecol 2017; 49(3):315-21.

23. Furcron AE, Romero R, Plazyo O, Unkel R, Xu Y, Hassan SS, et al. Vaginal progesterone, but not 17alpha-hydroxyprogesterone caproate, has antiinflammatory effects at the murine maternal-fetal interface. Am J Obstet Gynecol 2015; 213(6):846.e1-846.e19.

24. Hernandez WR, Francisco RP, Bittar RE, Gomez UT, Zugaib M, Brizot ML. Effect of vaginal progesterone in tocolytic therapy during preterm labor in twin pregnancies: Secondary analysis of a placebo-controlled randomized trial. J Obstet Gynaecol Res 2017; 43(10):1536-42.

25. Pirjani R, Heidari R, Rahimi-Foroushani A, Bayesh S, Esmailzadeh A. 17-alpha-hydroxyprogesterone caproate versus vaginal progesterone suppository for the prevention of preterm birth in women with a sonographically short cervix: a randomized controlled trial. J Obstet Gynaecol Res 2017; 43(1):57-64.

26. Beigi A, Esmailzadeh A, Pirjani R. Comparison of risk of preterm labor between vaginal progesterone and17-Alpha-Hydroxy-progesterone caproate in women with threatened abortion: a randomized clinical trial. Int J Fertil Steril 2016; 10(2):162-8.

27. Elimian A, Smith K, Williams M, Knudtson E, Goodman JR, Escobedo MB. A randomized controlled trial of intramuscular versus vaginal progesterone for the prevention of recurrent preterm birth. Int J Gynaecol Obstet 2016; 134(2):169-72.

28. Martinez de Tejada B, Othenin-Girard V, Irion O. Prevention of preterm birth with vaginal progesterone in women with preterm labor: which are the evidences? Rev Med Suisse 2015; 11(492):2004, 2006-8, 2010. In French

29. Bafghi AS, Bahrami E, Sekhavat L. Comparative study of vaginal versus intramuscular progesterone in the prevention of preterm delivery: a randomized clinical trial. Electron Physician 2015; 7(6):1301-9.