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Vaginal Progesterone For Maintenance Of Tocolysis In A Sample Of Iraqi Women

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ABSTRACT: OBJECTIVE: Assess the effectiveness of vaginal progesterone for maintenance tocolysis and preterm labor prevention in singleton gestations and preterm uterine contraction in a sample of Iraqi women.
STUDY DESIGN: This is a prospective randomized study included 143 singleton gestation (gestational ages range from 30(0/7) to 34(6/7) weeks at enrollment, intact membrane, and without any contraindication for expectant management. Consenting women wererandomized to receive vaginal progesterone (400mg) daily.The data was collected from women who attend the outpatient clinics in different areas of Baghdad including Hay Aljameaa and AL Noaman teaching hospital from the beginning of 2017 to the end of 2018.
RESULTS: Data were collected from143 women (75 assigned to vaginal progesterone, 68 designated to control) with a single gestation,Vaginal progesterone has been correlated with a substantial decrease in preterm birth <35 weeks of gestation (95% confidence interval (0.7552% to 24.8754%);(P = 0.0359); high-quality evidence). In fact, vaginal progesterone reduce the incidence of preterm birth (35- 37 weeks) substantially (95% confidence interval (4.6025% to 35.1764%); (P = 0.0117)and the percentage of Live born delivered before 34 weeks (95% confidence interval (3.4821% to 24.6707%); (P = 0.0081), there is a statistical difference in the birth weight (≤ 1500 gm) (P = 0.0388). There were 1(1.33%) fetal deaths in the vaginal progesterone group and 3 (4.41%) in the control group (confidence interval, -3.4383% to 10.9315%, P = 0.2661 low-quality evidence).
CONCLUSION: Maintenance tocolysis with vaginal progesterone suppositories is associated with reduced frequency of uterine contractions and the percentage of preterm birthand improve outcome in perinatalperiodfor singleton pregnancy.

KEYWORDS: Vaginal progesterone suppositories; preterm birth; progestogens; Neonatal morbidity or death and live born.

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1. INTRODUCTION

About 15 million babies are born prematurely. It was found that, the main death causes among under 5 years of age children are complications of Preterm birth, and in 2015, it caused about 1 million deaths.(1) 3/4 of these deaths were preventable with simple available interventions.(2)

The drugs that demonstrate significant decrease in the proportion of preterm birth were Progestogens. The safety and efficacy of progestogens are mainly associated with pharmacologic criteria within this type of drug and also personal variation of the treatedCommunity.(3)

Fonseca was the first who investigate the role of Progesteroneadministrated via vaginal root in inhibition of preterm birth in highly risk group.(4)

The progesterone hormone should administered vaginallyevery day for all women in the study group(5) although some large studies showed that progesterone and placebo had equal effect in prevention of preterm labor.(6)

In 2011, a meta-analysis of five major clinical trials was conducted and 42% of premature labor risk in women with ultrasound of short cervix was found to be decreased by using vaginal progesterone.(7,8)

In 1954, Robert Greenblatt in was the first who study the use of progesterone as vaginal suppositories, (8) In 1955 vaginal progesterone suppositories under the brand name Colprosterone were launched for medicinal usage,(8) while in 1976, Cyclogest was used as a brand name for vaginal and rectal progesterone suppositories(10)

Pharmacology:

Pharmacodynamics of progesterone

Progesterone binds and activate the nuclear type receptors progesterone (PRs), there are 3 types: PR-A, PR-B and PR-C receptors.(11), It acts as agonist for membrane type receptors progesterone (mPRs), which are mPRα, mPRβ, mPRÿ, mPRÿ, and mPRπ.(12,13)

The PRs are commonly distributed in the body, they are found in the breast, fat, vagina, cervix, uterus,pitutary, skin,and in different areas of the brain including hypothalamus.(11,14) it is a powerfulantagonist of the mineralocorticoid receptor (anti-mineralocorticoids), aldosterone is the biological target.(15,16) it is considered a neurosteroid,(17,18)

Progesterone considers as powerful anti-estrogenic agent through its effects on the vagina, cervix, and uterus.(13) The progesterone hormone may have both harmful and beneficial effects on health.(11) also progesterone has anti-gonadotropic effects as it can prevent ovulation and inhibit gonadal sex hormone production.(11)

As this agent hasanti-mineralocorticoid activity, it can reduce blood pressure and decease water and salt retention.(11,19) Furthermore, progesterone can induce anticonvulsant, memory and motor-impaired, hypnotic, sedative, euphoric, emotional,anxiolytic, and anesthetic effects (20,21)

Pharmacokinetics of progesterone

The route of administration is known to be the key factor deciding the pharmacokinetics of the drug. It is approved as (OMP)(oral micronized progesterone) which is capsules filled with oil containing micronized progesterone used orally.[22,23] Other route of administration is, topical creams and gels,suppositories or pessaries that can use vaginally or rectally,[24] intramuscular injection in form of oil solution, and subcutaneous injection in form of aqueous solutions.[22] Vaginal preparations includes tablets,suppositories, capsules, gels and vaginal rings filled with progesterone.[22]

In this study we focusour work on the efficacy of suppositories or pessaries on prevention of preterm labor.

Chemistry

Progesterone is a C21-steroid hormone with a pregnane skeleton[25] the C4 and C5 positions connected with double bond (4-ene), and it has two ketone groups (3,20-dione), first at the C3 position and the second at the C20 position.[26] It is abbreviated as P4, while in pregnenolone, C5(6) double bond presents so it abbreviated as P5.

Derivatives

Progesterone has produced a significant types of progestins, or organic progestogens.[11,25] they divided into different categories according to their structure: derivatives of retroprogesterone e.g. dydrogesterone,17α-hydroxyprogesterone e.g. medroxyprogesterone acetate, 17α-methylprogesterone e.g.medrogestone and 19-norprogesterone e.g. promegestone.[11] Testosterone derived progesterons e.g. norethisterone (norethindrone) and levonorgestrel.[15]

2. METHOD

Study Design:

This is a prospective randomized study included 143 high-risk singleton gestations with gestational ages from 30(0/7) to 34(6/7) weeks at time of registration, without contraindication to expectant management and intact membrane. Women who agreed to receive medication were given daily vaginal progesterone (400mg) or placebo. The data was collected from women who attend the outpatient clinics in different areas of Baghdad including Hay Aljamiaa and AL Nu'man teaching hospital from the beginning of 2017 to the end of 2018.

The research protocol was reviewed and approved by the Scientific Committee in the college of Medicine /Al-Iraqia University and the Ministry of Higher Education and Scientific Research andthe Scientific Committee in College of Pharmacy, University of Baghdad.

Study Population And Exposure Variable

All ladies with singleton with a confirmed diagnosis of preterm labor were included, (total n=143), divided in 2 groups, first group received Progesterone (n = 75) and the other one is the control (n = 68). Multiple gestation, Ultrasound finding short cervix, Cervical cerclage,

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frank rupture of membranes, uterine malformation preeclampsia, history of medical disorders was excluded from our study. A Control population was including all women who had evidence of preterm labor 30(0/7) weeks, both study groups were compared for epidemiologic criteria, uterine contraction frequency, a frequency of preterm birth, any hospital admission during time of the study, mode of labor, Apgar score and admission to neonatal care unit.

PROCEDURES

Vaginal progesterone suppositories were administered at bedtime daily, intramuscular injection of progesterone not associated with same patient satisfaction as vaginal suppositories, in addition to fast drug delivery to the target tissue [(29)]regular application of 400 mg vaginalprogesterone daily used in the study, administrated from about 30–34 weeks of gestation until 37 weeks or until delivery. Compliance assessment by using medication pack returns and patient self-reports, 100% was considered as adequate compliance. Data were collected at different occasions starting at randomization, screening, 34 weeks of gestation, at time of labor and delivery to determine clinical outcomes.

OUTCOMES

The clinical definition of Preterm birth is the delivery of a baby at less than 37 weeks' gestational age, according to National Institutes of Health [(30)] Continuation of gestation until a favorable gestational age (describedas 35 weeks of gestation) was decided to be the primary outcome, while secondary outcome was 36(6/7) weeks of gestation. All patients viewed twice a week for 60 minutes for evaluation of uterine contraction, between 24 and 34 weeks of gestation, while period from randomization to delivery was pre-specified as secondary outcome.

COVARIATES

There are many covariates considered in this research included participant socio-demographic and behavioral characteristics like maternal age, cigarette smoking during pregnancy and employment. Medical and reproductive histories like maternal height and weight (BMI), parity and prior history of preterm labor were considered in this study.

Body mass index (BMI) before pregnancy was estimated as weight measured in kilograms divided by the square of height in meters, when BMI is <20 kg/ m2 it described as underweight; while when BMI is 20–24.9 kg/m2 it considered as normal and it described as overweight when BMI is 25.0– 29.9 kg/m2 and obese with BMI 30 kg/m2. Parity was defined asnumber of pregnancies a woman had that have each resulted in the birth of an infant capable of survival'or lasting more than 24 weeks gestation.

3. STATISTICAL ANALYSIS

An intent-to-treat (ITT) approach was used to analyzeall the efficacy endpoints. The ITT population has been identified as patients randomized based on a presentation of preterm labor with uterine contraction and intact membrane.

Statistical analyses were done according to the intention-to-treat principle. Both treatment and control groups were compared for the primary and secondary outcomes utilizing linear and logistic regression models including treatment allocation. The collected sample size was 163 participants, depending on the presence of uterine contraction and intact membrane. Sensitivity analysis included repeating the first analyses in a per-protocol dataset (excluded any data from female participant who was found not compatible with the inclusion or exclusion criteria, or who had a multiple pregnancy discovered after inclusion or who had rupture membrane after inclusion, or women were inadequately compliant with treatment).

STATISTICAL METHODS

Odds ratio (OR) and 95% confidence interval (CI) were calculated. A P-value < 0.05 was considered statistically significant. Mean ± standard deviation and percentage were calculated. The T-test used for comparing the mean of one group to another.

SPSS (version 23.0 statistical software) were used to complete all analyses.

STRENGTHS AND LIMITATIONS OF THE STUDY

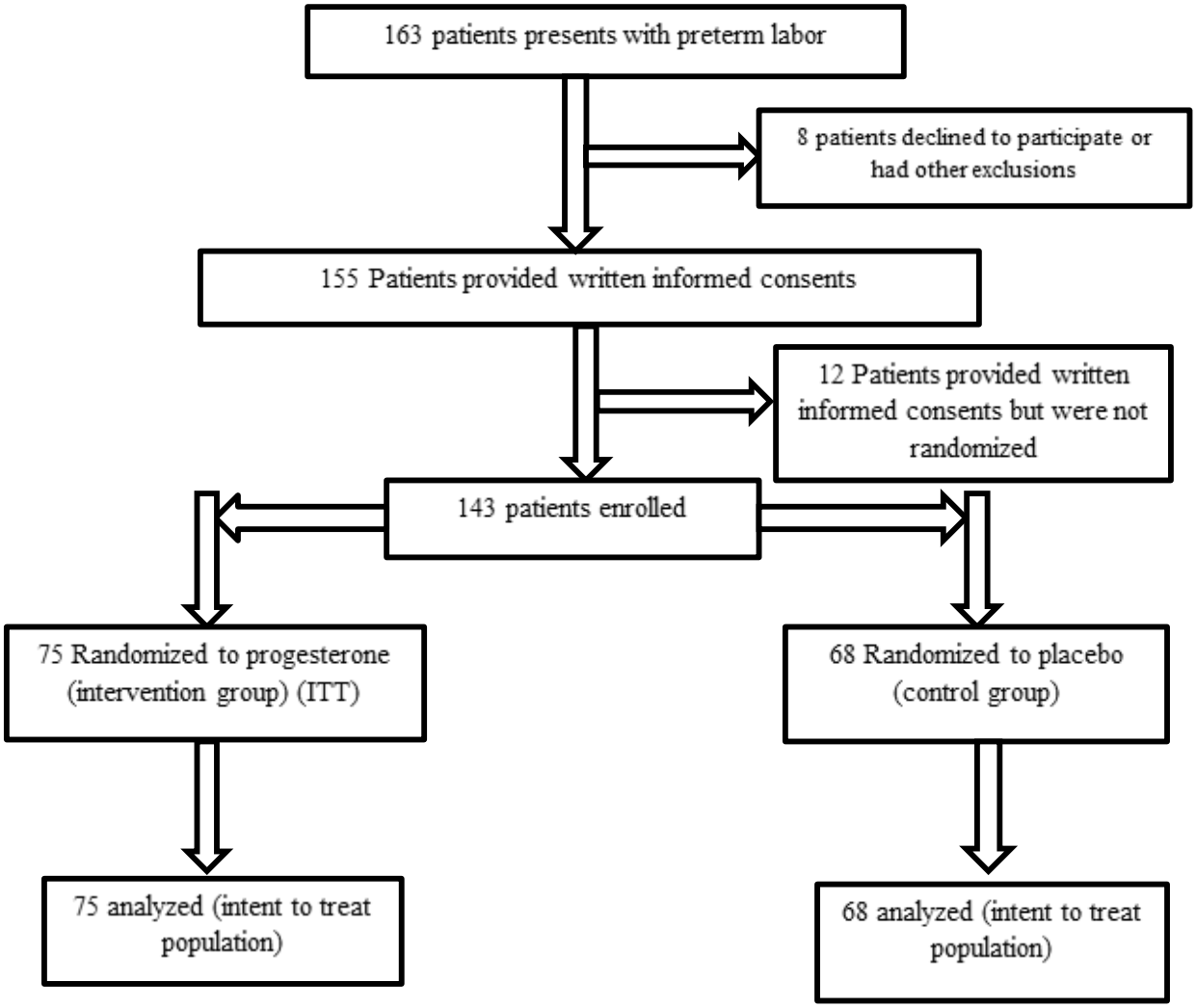
An individual data for most patients were the major strength of this study, the overall compliance was 100% for both progesterone and control group, and this point was another potential strength.

Although one of the potential limitations is small study population, but we were able to stratify the exposure by the close follow up (twice weekly) and also the recording of other events like Hospital admissions for threatened preterm labor and use of different modalities of treatment (tocolytics, steroids, antibiotics or magnesium sulfate) and also detection of delivery methods (Spontaneous vaginal delivery, cesarean section in labor or pre-labor cesarean section).

4. RESULTS:

A total of 163 women were seen at the beginning of the study, 8 patients declined to participate or had other exclusions and the remaining 155 gave oral consent, of whom12 were not randomized. The causes of non-randomization were a multiple gestation, cerclage, medical complications (e.g. hypertension) in pregnancy and raptured membrane. A total of 143 patients were deemed fit for attribution in this study, with 143 being distributed to the two treatment groups. Patients who received study medication were included in the ITT population.

Figure 1:- Participant flow diagram



The ITT population of preterm labor patients included 75 patients in the progesterone group and 68 patients in the control group. Table 1 shows the baseline characteristics for the population.The groups were identical for maternal age; smoking rate difference was 1.1% between both groups. At randomization, gestational age (mean (SD)) was 32.34 (2.134) and 32.91 (1.834) weeks for the progesterone and control groups, respectively. The percentage of one previous spontaneous preterm labor in patients assigned to the progesterone and control groups was comparable (84%) and (86.76%) respectively, while the frequency of previous spontaneous miscarriage was (24%) and (29.41%) respectively.

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Table -1-

Table -1- demographic criteria of study groups			
Characteristic	Progesterone (n= 75) 52.45%	control (n = 68) 47.55%	Mean difference or odds ratio (95% CI) *
	N(%) or mean (SD)	N(%) or mean (SD)	
Maternal Age	30.1 (7.8)	31.5 (8.5)	1.4 (-1.2947 to 4.094)
Smoking	3 (4%)	2 (2.9%)	1.1% (-6.5133% to 8.5186%)
BMI	25.5 (6.3)	24.8 (7.20)	-0.7(-2.9321 to 1.5321)
Obstetric history (n (%))			
Nulliparous	22 (29.3%)	18 (26.47%)	2.83% (-11.8569% to 17.1376%)
≥ 1 prior preterm birth (*n* (%))	63 (84%)	59 (86.76%)	2.76% (-9.2616% to 14.4102%)
≥ 1 previous spontaneous miscarriage (*n* (%))	18 (24%)	22 (29.41%)	5.41% (-8.9528% to 19.7188%)
History of stillbirth (*n* (%))	5 (6.67%)	3 (4.41%)	2. 257 % (-6.3905% to 10.7741%)
GA at time of study (weeks, mean, (SD))	32.34 (2.134)	32.91 (1.834)	0.334 (-0.0911 to 1.2311)
Cervical length at time of the study(cm, mean (SD))	2.952 (0.5007)	3.008 (0.3017)	(0.070) (-0.0822 to 0.1946)
Compliance (*n* (%))	75 (100%)	68 (100%)	1.62 % (-4.5965% to 8.8707%)

* Calculation for mean difference = Progesterone—control, with 95% CI for the difference (significant if zero not included in the range).

The research drug compliance rates were comparable between groups: 100 % for women in the progesterone and control group participants.

Table -2- Analysis of reported data on the quality of evidence for any indicator of outcome				
Outcomes	Vaginal progesterone (N=75)	Control (N=68)	Relative risk (95% CI)	P value

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	N(%) or mean (SD)	N(%) or mean (SD)		
Primary outcome				
Preterm birth < 35 weeks (n (%))	7 (9.333%)	15 (22.05%)	0.7552% to 24.8754%	**P = 0.0359**
Preterm birth (35- 37 weeks) (n (%))	21 (28%)	33 (48.529%)	4.6025% to 35.1764%	**P = 0.0117**
Neonatal morbidity or death (n (%))	19 (25.33%)	18 (26.47%)	-12.9907% to 15.4540%	P = 0.8769
Components of the obstetric outcome (n (%))				
Fetal death (n (%))	1(1.33%)	3 (4.41%)	-3.4383% to 10.9315%	P = 0.2661
Live born delivery before 34 weeks (n (%))	3 (4%)	12 (17.64%)	3.4821% to 24.6707%	**P = 0.0081**
Birth weight (1500-2499g) (n (%))	7 (9%)	10 (14.70%)	-5.1078% to 16.9832%	P = 0.2915
Birth weight ≤ 1500 g (n (%))	1(1.33%)	6 (8.82%)	-4.6045% to 8.8562%	**P = 0.0388**

In Table -2- we summarized the result of each outcome measures, the rate of preterm labor (< 35 weeks and from 35-37 weeks) was significantly higher in control group (P=0.0359), (P=0.0117), respectively. There was no significant statistical difference in the Neonatal morbidity or death rate for the progesterone and control group, in our study, we find significant statistical difference between rate of Live born delivery before 34 weeks between the progesterone and control group (P = 0.0081). While there is no statistical difference in the birth weight (1500-2499g) between both groups (P = 0.2915), progesterone seems to decrease birth weight < 1500 g (P = 0.0388).

Table -3- Hospital admissions

	Vaginal progesterone (N=75)	Control (N=68)	odds ratio (95% CI)	P value
	N(%) or mean (SD)	N (%) or mean (SD)		
Antenatal hospital admissions per woman				
Hospital admissions for threatened preterm labor	52 (69.33%)	48 (70.59%)	1.26% (-13.6693% to 15.9140%)	P = 0.8701
With tocolytics	30 (40%)	42 (61.67%)	21.67% (5.2631% to 36.5019%)	P = 0.0099
With steroid	73 (97.33%)	67 (98.53%)	1.20% (-5.4859% to 7.8573%)	P = 0.6184

With antibiotic	19 (25.33%)	23 (33.82%)	8.49% (-6.3590% to 23.0486%)	P = 0.2673
With magnesium sulfate	3 (4%)	6 (8.82%)	4.82% (-3.7141% to 14.3111%)	P = 0.2375
Delivery method				
Spontaneous vaginal delivery	58 (77.33%)	51 (75%)	2.33% (-11.4778% to 16.2919%)	P = 0.7446
LSCS in labor*	14 (18.67%)	12 (17.65%)	1.02% (-11.8935% to 13.5873%)	P = 0.8750
LSCS pre-labor	3 (4%)	5 (7.35%)	3.35 % (-4.8954% to 12.4690%)	P = 0.3856

*LSCS lower segment cesarean section

Table -3- Antenatal hospital admission rate for both groups with use of other types of managements, there were no significant variations between the progesterone and the control groups in the proportions with safety or other, with exception for use of other tocolytics e.g. Ca^{++} channel blockers, it was higher in control group than in progesterone group (61.67%),(40%), respectively. There were no obvious differences in the proportions of pre-labor and in labor LSCS between both groups.

Table -4- Birth Outcome				
	Vaginal progesterone (N=75)		Control (N=68)	
	N	Median	N	Median
Median Apgar score (1 min) (IQR) *	75	9.0 (7.0–9.0)	68	8.0 (6.0–9.0)
Median Apgar score (5 min) (IQR)	75	9.0 (9.0–10.0)	68	9.0 (9.0–10.0)
Median length of hospital admission, days (IQR)	75	3.0 (1.0–6.0)	68	5.0 (2.0–10.0)

*(IQR) interquartile range

In Table -4- We find that there is no difference between the median Apgar score at 1 and 5 minute between both groups, while for the Median length of hospital stay days, it was 3 days for progesterone group and 5 for control group with range of (1.0–6.0) and (2.0–10.0), respectively.

5. DISCUSSION

Preventing premature birth is a top priority in health care, the overarching goal of interventions is premature birth reduction and improve infant outcomes [(7)]

In our study we find that the use of vaginal progesterone suppositories by women with preterm uterine contraction was associated with a significant reduction in percentage of preterm brirth<35 weeks (primary endpoint), and <37 weeks of gestation (secondary endpoint); also associated with a substantial increase in the rate of Live born delivery before 34 weeks, but it associated with a comparable rate of unwanted events associated with treatment in patients assigned to progesterone or control group. The primary end point result agreed with another study done by da Fonsecaet al.[4] as they found that vaginal progesterone significantly lowered the frequency of uterine contractions and the proportion of preterm delivery. Another study done by ElcinCetingoz et al.[36] also found the similar relationship between the use of vaginal progesterone and the significant reduction in the rate of preterm labor. Another study done by Saccone G et al.[37] found that lower rates of SPTB < 34 weeks in women who used vaginal progesterone. This result was different from result found by Nelson et al. as they find that the median gestational age was identical in both groups at delivery [38] This result also found by O'Brien.[6]

Besides the primary and secondary endpoints linked with gestational age, vaginal progesterone suppositories administration to women with preterm uterine contraction was associated with a substantialincrease in the rate of live born delivery before 34 weeks of gestation, but there was no significant statistical difference in the Neonatal morbidity or death rate for the progesterone and control group, this result agreed with Norman et al.[39] as there study displayed no significant effect on the final neonatal composite results, and the same result was found by Nelson et al.[38] Opposite result was found by Hassan et al.[7] as they found that there is substantial decrease in the rate of infants with any morbidity/mortality event, and a substantial improvement in neonatal outcome after use of vaginal progesterone.

Reducing early premature birth (about 32 weeks) is more likely to be associated with a lowering the rate of neonatal morbidity and mortality than would be associated with a decrease in premature birth defined as < 37 weeks. In fact, Dodd et al. [40] noted that no sufficient evidence exists to promote routine progestin use to decrease neonatal morbidity.

In our study, we find that there is no statistical difference in the birth weight (1500-2499g) between both groups (P = 0.2915), but progesterone seems to decrease birth weight < 1500 g (P = 0.0388), the same result was found by Hassan et al.[7] and by Ding et al.[41]

In this study we find no significant difference in the rate of fetal death between both groups (P = 0.2661), the same result was found by ElcinCetingoz et al.[36] while Nelson et al.[38]found that no significant difference in infants and neonatal outcomes.

The rate of cesarean section seems to be similar in both groups, in accordance with a study done by Combs CA.[42]

In accordance with this study, Saccone G et al.[37] found that vaginal progesterone was related to a lower rate of neonatal admission to intensive care unit, the same result was found in meta-analysis of individual patient data published at 2017 done by Romero R. [43]

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6. CONCLUSION:

Maintenance tocolysis with vaginal progesterone suppositories is associated with decreased frequency of uterine contractions and the proportion of preterm laborand improve perinatal outcomes in singleton pregnancy.

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