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Effect of progesterone on preventing preterm birth and adverse perinatal outcomes in women in the risk group: A prospective clinical trial

Pareshan Faris Asaad *
Ariana Khalis Jawad**

Abstract

Background and Objective: Preterm labor is a significant reason for perinatal mortality and morbidity. This study was conducted to determine the effect of two regimens of progesterone to avoid preterm labor and the adverse perinatal outcomes in the two groups.

Methods: A prospective clinical trial was performed in Maternity Teaching Hospital and Hawler Private Hospital in Erbil city, Kurdistan region, Iraq over a one-year period from 1 May 2019 until 1 May 2020. The study sample was 200 pregnant women with a short cervix and a risk of preterm birth; the sample was divided into two groups. Group I of 100 pregnant women received 400 mg progesterone vaginally once daily, and group II of 100 pregnant women received it twice daily, started from 16 weeks of gestation up to the time of delivery in both groups.

Results: The rate of term pregnancy (≥ 37 weeks) was 87% among women in group II and 55% in women in group I. Accordingly, the rate of neonatal intensive care admission was significantly higher in group I than in group II (30% and 11%, respectively). The rate of respiratory distress syndrome was also significantly higher in group I (31%) than in group II (7%).

Conclusion: The administration of progesterone 400 mg vaginally twice a day appears to be more effective than progesterone 400 mg vaginally once a day in preventing preterm birth and reducing the risk of adverse neonatal complications.

Key words: Clinical study, Neonatal outcomes, Preterm birth, Progesterone.

Introduction

Preterm birth (PTB) is a well-known factor for short- and long-term adverse outcomes for newborns, and it is one of the main causes for death of neonates and an increased rate of under-five-year mortality.[1-2] Being born preterm puts infants at great risk of dying during their first year of life. Surviving infants are at an elevated risk of repeated admission to the hospital as a result of short-term health complications such as vision and hearing problems, infection, central nervous system, gastrointestinal problems, acute respiratory problems, long-term neurodevelopmental disabilities (including visual disorders, impaired learning, and cerebral palsy), and chronic diseases in adulthood.[3] Every year, 5-18% of babies are born preterm, accounting for 15 million babies worldwide. This percentage in developed European countries is lower than that in poor African countries.[4-5] Preterm birth can occur due to risk factors such as a history of curettage or cervical conization, uterine anomaly, smoking, genetic factors, infectious diseases, advanced maternal age, multifetal pregnancy, short cervical length (CL), and

* MBChB, KHCMS trainee in Obstetrics and Gynecology, Maternity teaching hospital, Erbil, Kurdistan –Iraq. Email: Pareshan.jaff@gmail.com
** CABAG, FICMS, Professor in Obstetrics and Gynecology. Kurdistan Higher Council of Medical Specialties. Erbil, Kurdistan -Iraq.

history of preterm birth.[6] Among these risk factors, the most significant predictive factors are a short cervical canal and a history of preterm birth. Preterm birth can be effectively reduced by predicting and preventing its risks. Currently, therapy with progesterone supplementation is the most effective method to prevent preterm birth in women with a short cervical canal and/or a history of preterm birth.[7] The administration of vaginal progesterone has been associated with a remarkably decreased risk of preterm birth at <28 and <35 weeks of gestation.[8] Regarding the safety of vaginal administration of progesterone, no evidence of short- or long-term harm has been reported to the newborn or the mother.[9] In addition, clinical trials have shown no harmful effect of exposure to progesterone in children.[10] However, scarce information is available concerning the optimal progesterone dose, administration mode, and gestation to start therapy or its duration. More trials are required to evaluate and answer these queries.[11] preterm birth can be effectively treated by predicting and preventing its risks, which include the history of curettage or cervical conization, uterine anomaly, smoking, ethnicity, multiple pregnancies, short cervical length, and history of preterm birth. The history of preterm birth is the most significant prescient factor. It has been shown that the progesterone supplement treatment may help to prevent preterm birth in women with a short cervix and a history of incautious preterm birth.[12] A prospective clinical trial was performed to evaluate the effect of two regimens of vaginal progesterone on preventing preterm birth and improving the perinatal and neonatal outcomes in high-risk women.

Subjects and methods

A prospective clinical trial was conducted on 200 pregnant women was performed in Maternity Teaching Hospital and Hawler Private Hospital in Erbil city, Kurdistan region, Iraq. Data collection was performed over a one-year period from the 1st of May 2019 to the 1st of May 2020. The inclusion criteria were singleton gestation, prior preterm birth, and mid-trimester sonographic short cervix length (less than 25 mm). The exclusion criteria were multiple gestations, ruptured membranes and uterine anomalies. The data collection was performed by the researcher through direct interviews with the selected women in the risk group and completion of a prepared questionnaire. The study population included two groups of pregnant women with a history of previous preterm birth and history of short cervix or examination revealed short cervix. The patients were observed while visiting an obstetrician private clinic. After confirming the eligibility based on the inclusion and exclusion criteria and obtaining written consent to participate in the study, we selected a convenient sample of 200 pregnant women with risks of preterm birth and short cervix and divided them into two groups. The first group (group I) of 100 pregnant women was selected at a private clinic and received 400 mg vaginal progesterone once daily. The second group (group II) was 100 other pregnant women at the private clinic, but they received 400 mg vaginal progesterone twice daily, started from 16 weeks of gestation up to the time of delivery in both groups. At labor, the studied pregnant women were delivered in a labor room or operating room with the help of a researcher. The gestational age was calculated at the time of delivery. Follow-up was performed by the researcher through their regular antenatal visit and phone calls. After these two groups of women delivered, the following data were collected on all newborns: viability of fetus, birth weight, APGAR score, respiratory distress syndrome, jaundice and admission to the neonatal intensive care unit. The delivered neonates were examined by the pediatrician and followed for seven days of life. Approval was taken

from the Kurdistan Higher Council of Medical Specialties on the 3rd of December 2019 no. 2074. Written informed consent was obtained from the women enrolled in the study. The data of the women were analyzed using the Statistical Package for Social Sciences (SPSS, version 25). Chi square tests of association were used to compare the proportions. Fisher's exact test was used when the expected frequency (value) was less than 5 of more than 20% of the table's cells. A p value of ≤ 0.05 was considered statistically significant.

Results

Two hundred women were included in the study. One hundred women were given one dose of progesterone per day (Group I), and the other group was given two doses of progesterone (Group II). Table (1) shows that the largest proportion of the women (48%) were young adults, and only 2.5% were aged ≥ 40 years. No significant difference was present in the age distribution between the two groups (p >0.999). Approximately two-thirds (66%) of the women were housewives with no important contrast between groups I and II (p = 0.370). The majority (79%) of the sample was of normal weight, and only 19.5% were overweight, with no significant difference between groups I and II (p = 0.080). The rate of smoking among the women in group II (14%) was significantly higher (p <0.001) than that among the women in group I (1%).

Table (1): Basic characteristics of the studied sample by progesterone dose.

Progesterone dose							
	group I		group II		Total		
	No.	%	No.	%	No.	%	P value
Age (years)							
< 20	6	(6)	6	(6)	12	(6)	
20-29	48	(48)	48	(48)	96	(48)	
30-39	43	(43)	44	(44)	87	(43)	
≥ 40	3	(3)	2	(2)	5	(2.5)	> 0.999*
Occupation							
Housewife	69	(69)	63	(63)	132	(66)	
Employee	31	(31)	37	(37)	68	(34)	0.370
Body mass index (kg/m^2)							
< 18.5	0	(0)	1	(1)	1	(0.5)	
18.5-24.9	85	(85)	73	(73)	158	(79)	
25-29.9	14	(14)	25	(25)	39	(19.5)	
≥ 30	1	(1)	1	(1)	2	(1)	0.080*
Smoking							
Yes	1	(1)	14	(14)	15	(7.5)	
No	99	(99)	86	(86)	185	(92.5)	< 0.001
Total	100	(100)	100	(100)	200	(100)	

No significant differences were detected between the two groups regarding the parity (p = 0.096) and cervical trauma (p = 0.369). The rate of term pregnancy (≥ 37 weeks) was 87% in group II and 55% in group I (p <0.001). None of the women in group II delivered babies before 32 weeks gestation Table (2).

Table (2): Obstetric history by progesterone dose.

Progesterone dose							
	group I		group II		Total		
	No.	%	No.	%	No.	%	p value
Parity							
Multiparous	90	(90)	96	(96)	186	(93)	
Grand multiparous	10	(10)	4	(4)	14	(7)	0.096
Cervical trauma							
Yes	1	(1)	4	(4)	5	(2.5)	
No	99	(99)	96	(96)	195	(97.5)	0.369*
Gestational age at delivery (weeks)							
< 28	1	(1)	0	(0)	1	(0.5)	
28-< 32	12	(12)	0	(0)	12	(6)	
32-< 37	32	(32)	13	(13)	45	(22.5)	
≥ 37	55	(55)	87	(87)	142	(71)	< 0.001*
Total	100	(100)	100	(100)	200	(100)	

*By Fisher's correct test. The other p values were obtained by the Chi square test.

The rate of low birth weight (below 2500 g) was 35% among the women in group I and only 7% among the women in group II (p < 0.001). A significantly (p < 0.001) higher APGAR score of 4-6 was detected among the women in group I (28%) than among those in group II (4%). Accordingly, the rate of NICU admission was significantly (p = 0.001) higher in group I than in group II (30% and 11%, respectively). The rate of respiratory distress syndrome was suggestively (p <0.001) higher in group I (31%) than in group II (7%). The rate of neonatal jaundice was significantly (p = 0.003) higher in the first group (15% vs. 3%). There were no significant differences regarding the sex of the baby (p >0.999) or outcome, whether dead or alive (p >0.999), as shown in Table (3).

Table (3): Outcome by progesterone dose.

Progesterone dose							
	group I		group II		Total		
	No.	%	No.	%	No.	%	p value
Birth weight (g)							
< 2500	35	(35)	7	(7)	42	(21)	
2500-3999	65	(65)	92	(92)	157	(78.5)	
≥ 4000	0	(0)	1	(1)	1	(0.5)	< 0.001*
APGAR score in the 5th minute							
7-10	72	(72)	96	(96)	168	(84)	
4-6	28	(28)	4	(4)	32	(16)	< 0.001
Admission to NICU							
Yes	30	(30)	11	(11)	41	(20.5)	
No	70	(70)	89	(89)	159	(79.5)	0.001
Respiratory distress syndrome							
Yes	31	(31)	7	(7)	38	(19)	
No	69	(69)	93	(93)	162	(81)	< 0.001
Jaundice							
Yes	15	(15)	3	(3)	18	(9)	
No	85	(85)	97	(97)	182	(91)	0.003
Sex							
Female	50	(50)	50	(50)	100	(50.0)	
Male	50	(50)	50	(50)	100	(50.0)	>0.999
Outcome							

Alive	98	(98)	99	(99)	197	(98.5)	
Early neonatal death	2	(2)	1	(1)	3	(1.5)	> 0.999*
Total	100	(100.0)	100	(100.0)	200	(100.0)	

Discussion

Preterm birth is still the main reason for increased early neonatal comorbidities and mortalities.[13] Currently, treatment with progesterone is accompanied by a decline in uterine contractions. As a result, there was a decline in preterm birth incidence for pregnant women with a risk of preterm birth.[14] The present study shows a significant difference in gestational age at delivery between the two groups of pregnant women (p<0.001). The vaginal administration of 400 mg progesterone twice daily was associated with fewer preterm births than vaginal progesterone 400 mg once daily (13% and 45%, respectively). This finding is consistent with the results of the Khazaali study.[15] Their participants included 252 pregnant women with preterm birth risk who were treated with 400 mg vaginal progesterone in the 2nd trimester and 240 pregnant women with preterm birth risk who were not treated with progesterone. Their results showed that early administration of progesterone decreased the rate of preterm birth. The mechanism of action for progesterone in inhibiting preterm birth was multiple and distributed at several levels. At the myometrial and cervical levels, it reduces the myometrial contractility and cervical effacement.[16] At the placental level, it regulates the labor timing[17]. At the amniotic level, it is important to anticipate the generation of prostaglandins [18]. At the level of fetal sides as it hinders the apoptosis.[19] In the current study, neonatal NICU admission was significantly higher for pregnant women who received vaginal progesterone 400 mg once daily (p=0.001). Consistently, in his double-blind, randomized placebo-controlled study, Azargoon ET al[20] showed that the prophylactic progesterone treatment at early pregnancy decreased the preterm birth and neonatal risk morbidities, specifically neonatal NICU admission, among pregnant women at risk of preterm birth. Our study also showed that the low APGAR score of neonates after 5 minutes was significantly higher for pregnant women who received vaginal progesterone 400 mg once daily (p< 0.001) than for those who received it twice daily (28% vs. 4%). This finding coincides with Norman's study, [21] which stated that the early intramuscular progesterone treatment for pregnant women at risk of preterm birth decreased the chance of preterm birth and the risk of neonatal low APGAR score after 5 minutes. This study shows that the rate of low birth weight was significantly higher in group I (pregnant women who received vaginal progesterone 400 mg once daily) than in group II (those who received vaginal progesterone two times daily) (35% vs. 7%). This finding is similar to the result of Azam Azargoon Amir-AL-Momenin Hospital in Iran, who demonstrated that the use of vaginal progesterone 400 mg by pregnant women with a history of previous preterm birth decreased the rate of birth weight below 2500 g.[22] In our study, the neonatal respiratory distress syndrome stayed importantly higher in group I (women who received vaginal progesterone 400 mg once daily) than in group II (those who received vaginal progesterone twice daily) (p=0.001). This result is similar to Dodd et al[23], who reported that the antenatal treatment of pregnant women with a history of preterm birth by progesterone decreased the risk of breathing distress syndrome in subsequent pregnancies. Inconsistently, another multi-center randomized placebo-controlled trial study in Australia by Crowther et al [24] did not find any major difference in the incidence of respiratory distress syndrome among neonates of pregnant women treated with progesterone and those treated with placebo.

Conclusion

The findings of this study indicate that vaginal administration of 400 mg progesterone twice a day is more effective than vaginal progesterone once a day. It also decreases the percentage of babies with birth weight below 2500 g, respiratory distress syndrome, admission to the NICU, low APGAR score, and jaundice.

Conflicts of interest

The author reports no conflicts of interest.

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