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ORIGINAL ARTICLE

Early Vaginal Progesterone Versus Placebo in Twin Pregnancies for Prevention of Spontaneous Pre-Term Birth

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Abstract

Background: ***Preterm birth is defined as the delivery of a baby prior to thirty-seven weeks of gestation or less than 259 days following the first day of the woman's last menstrual period (LMP). Prematurity is a significant contributor to both neonatal deaths and health issues, as it is associated with long-term problems.***

Aim and objectives: ***To evaluate the impact of vaginal progesterone compared to a placebo in preventing spontaneous preterm delivery in twin pregnancies.***

Patients and methods: ***In this randomized, placebo-controlled study, which involved 120 patients and ran from the beginning of March 2023 to early December 2023, women with unchecked twin pregnancies at Al-Hussien Hospital A comparison was made between the administration of vaginal progesterone (four hundred mg per day) and a placebo, starting from weeks 11-14 to thirty-four weeks of gestation. Two groups of patients were formed: Group A comprised 60 cases whereby pregnant twin women were Administered a daily dosage of four hundred milligrams of vaginal progesterone.***

Results: ***The two study groups did not significantly differ in terms of age, BMI, parity, twin type, laboratory characteristics, or cervical length. Group A had a higher frequency of spontaneous births between 28 and 34 weeks and between 34 and 37 weeks than group B. However, there was no statistically significant difference. Although there was no statistically significant difference, group A experienced somewhat more outcomes and problems than group B.***

*Conclusion: T****his study concludes that vaginal progesterone had no effect in preventing unplanned preterm delivery in twin pregnancies.***

Keywords: Early vaginal progesterone; Twin pregnancies; Spontaneous pre-term birth

1. Introduction

The corpus luteum, whose lifespan has been estimated to be 12 ± 2 days, produces progesterone during the early stages of pregnancy. A crucial hormone for the biological process of reproduction is progesterone. In fact, it causes changes in the uterine lining's secretory function and is necessary for the embryo to implant successfully. Progesterone also improves uterine quiescence, reduces uterine contractions, and modifies the mother's immune response to prevent the embryo from being rejected. Thus, it is conceivable in theory that P supplementation could lower the chance of miscarriage among women who have a history of repeated miscarriages. Progesterone and related steroids, or progestogens, have been used in a number of trials to try and boost the rates of embryo implantation in assisted reproduction programs and reduce spontaneous miscarriages.[1]

A preterm birth, also known as a live delivery, takes place prior to 37 complete weeks of gestation or less than 259 days following the onset of the woman's last menstrual period (LMP) and is classified as preterm birth According to the World Health Organization (WHO). Preterm birth (PTB) can be further categorized into three distinct classifications: very preterm (28–32 weeks), moderate preterm (32–37 full weeks of gestation), and extremely preterm (less than 28 weeks). To concentrate on late preterm birth, moderate preterm birth (34–37 completed weeks) may be further divided.[2,3]

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If symptoms related to the abdomen or pelvis appear beyond between eighteen and twenty weeks of gestation, preterm labor needs to be taken into consideration. Indicators of impending preterm labor include persistent rather than severe symptoms such as pelvic pressure, menstrual-like cramps, back pain, and increasing vaginal discharge. When there are six or more contractions per hour, cervical dilatation of three centimeters or more, effacement of eighty percent or more, and rupture or bleeding of the membranes, the traditional criteria for labor—permanent uterine contractions coupled with dilatation or effacement of the cervix, or both—are rather accurate.[4]

When a pregnancy is twin, the uterus contains two fetuses. It is estimated that one in every 80 pregnancies will result in twin pregnancies on their own. Preterm labor and delivery is the most common issue associated with multiple pregnancies; over half of these cases result in deliveries before 37 weeks, primarily as a result of spontaneous preterm labor. Preterm birth that occurs spontaneously is caused by premature activation of contractility.[5]

The only method to find out if you are carrying more than one child when pregnant is to get an ultrasound examination with your doctor. Your doctor can verify the number of babies inside your uterus by viewing pictures taken during the test.[6,7]

Examining the impact of vaginal progesterone against a placebo in preventing spontaneous preterm delivery in twin pregnancies was the goal of this study.

2. Patients and methods

In this randomized, placebo-controlled study, which involved 120 patients and ran from the beginning of March 2023 to early December 2023, women with random twin pregnancies at Al-Hussien Hospital A comparison was made between the administration of vaginal progesterone (four hundred mg per day) and a placebo, starting from weeks 11 to 14 and continuing until thirty-four weeks of gestation. The United States followed up on the study. Two groups of patients were formed: Group A comprised 60 cases whereby pregnant twin women Administered a daily dosage of four hundred milligrams of vaginal progesterone, whereas Group B contained 60 cases wherein pregnant twin women received a daily vaginal placebo.

Inclusion criteria: BMI in the range of 18 to 30, age range of 18 to 40, history of no previous miscarriages or premature labor, dichorionic and monochorionic twin pregnancy, and two viable fetuses at 11 to 14 weeks of gestation.

Exclusion criteria: ladies who have had their cervical cerclages cut, women who suffer from long-term illnesses, significant fetal anomaly, Women having a history of premature labor or repeated miscarriages. At the 11–13 week scan, nuchal translucency thickness measuring more than 3·5 mm was found. An intolerance to progesterone, Ladies who were gravely ill or unconscious, severe impairment of the liver, cancer of the breast or genitalia, Thromboembolic diseases, such as thrombophilia, and cerebral hemorrhage.

Patients in this study were subjected to the following: Comprehensive medical history (individual, menstrual, early, familial, obstetric, and parity history; current chronic illness and medication history; previous history of hypertension, diabetes mellitus, and history of medication allergies)., Abdominal and local clinical examination, auscultation, evaluation of the membranes, and locating the presenting part were all included in the general examination. During pregnancy, the abdomen was palpated to determine the fundal width (level), fundal grip, lateral or umbilical grip, pelvic grip, and first and second pelvic grip. Ultrasound examinations of the abdomen and pelvis, laboratory work, bilateral exams, and local pelvic exams (to detect any anomalies, infections, or ulcers).

The ultrasound machine: We used the ultrasound machine model GE LOGIQ V3 ULTRASOUND.

Figure 1. The ultrasound machine used in the study.

Fundal height (level): Comprehensive medical background (personal,

Weeks of gestation were calculated starting at 16 weeks of pregnancy. (The fundus reached the level of the symphysis pupis at 12 weeks. It was at the umbilicus level at 24 weeks. The fundus height reached the xiphisternum at 36 weeks.

Fundal grip: Gently use your entire hand to

identify the specific fetal portion at the uterine fundus, such as the breech, which is soft, wide, and uneven, and the Head, which has a hard, rounded, homogeneous contour.

Lateral or umbilical grip: To ascertain the fetus's location and lay, as well as its back, in order to osculate FHS.

Pelvic grip: In order to ascertain if the presenting part was engaged or not, the first pelvic grip was used to feel for mobility. In order to ascertain whether the head was extended (face) or flexed (vertex), the second pelvic grip was used. The forehead, or cephalic prominence, The sensation was perceived on the contralateral side of the occiput, or the prominent part of the head, when it was flexed, and on the contralateral side of the fetal back when the head was extended.

Auscultation: A sonic aid or fetal stethoscope was used to auscultate the fetal heart sound. As early as the tenth week of pregnancy, Sonicaid detected FHS. Following the 20th week of pregnancy, the fetal stethoscope, or Pinard, detected FHS.

Assessment of the membranes: If there was alcohol drainage, the rupture of the membranes might be seen. Nonetheless, it is important to constantly feel for membranes covering the area that's being seen. In most cases, feeling intact membranes was easy if the presenting portion was high. If the presenting portion was properly put to the cervix, it could be challenging to feel the membranes. In this instance, it is best to wait for a contraction, as this is when the membranes can be felt because alcohol frequently appears directly in front during the presenting portion. Occasionally, the part being presented could feel the umbilical cord (a cord presentation).

Determining the position of the presenting part: Position describes the angle at which the mother's pelvic symphysis pubis is in respect to a fixed point on the presenting part, also known as the denominator or point of reference. During a vaginal exam, the position was established. The sacrum of the fetus served as the point of reference in a breech presentation, the chin served as the point of reference in a face presentation, and the posterior fontanelle, or occiput, served as the point of reference in a vertex presentation.

The primary outcome: The outcome assessed spontaneous birth inclusively between 28 and 34 weeks of gestation in situations where one fetus died (by termination, miscarriage, or stillbirth) at a gestational age prior to the second fetus's birth.

Secondary outcome: Stillbirth, miscarriage, intrauterine fetal death (IUFD), neonatal birth weights between 1500 and 2500 g, spontaneous premature birth between 34 and 37 weeks gestation.

Ethical Consideration: The patients gave their verbal informed consent, and information confidentiality was guaranteed. The director of the obstetrics and gynecology department, the hospital management, the dean of the medical faculty at Al-Azhar University, and an official written administrative approval letter were acquired. To secure their cooperation, patients were informed about the study's purpose and title. The institutional review board (IRB) and the faculty of the medical ethical committee both gave their permission.

Data management and statistical analysis: Microsoft Excel is used to code, enter, and analyze historical data, as well as perform basic clinical examinations, laboratory tests, and outcome measurements. After that, The data were imported into a statistical program for social science researchers (SPSS version 20.0) software for analysis. The following tests were employed to examine differences for significance: Pearson's correlation and Spearman's correlation. The qualitative data were represented as numbers and percentages, while the quantitative group was represented by mean ± SD. For significant results, the P value was set at <0.05, and for highly significant results, at <0.001. After being gathered, the data were statistically analyzed. The following parameters and statistical tests were applied: The mean, standard deviation, and predictive value of sensitivity specificity.

3. Results

Table 1. Demographic data of the two studied groups.

	GROUP A (N=60)	GROUP B (N=60)	T	P
AGE (YEARS) MEAN ± SD	28.52 ± 2.47	28.38 ± 2.74	.280	.780
BMI (KG/M^2) MEAN ± SD	27.02 ± 1.93	27.18 ± 1.82	.478	.634
PARITY				
NULLI	28 (46.7%)	30 (50%)	.223	.895
PRIMI	18 (30%)	18 (30%)		
MULTI	14 (23.3%)	12 (20%)		

This table showed that there was no significant difference between the two studied groups regarding age, BMI, and parity.

Table 2. Twins type distribution between the two studied groups.

	GROUP A (N=60)	GROUP B (N=60)	χ^2	P
MONOCHORIONIC	16 (26.7%)	13 (21.7%)	.409	.522
DICHORIONIC	44 (73.3%)	47 (78.3%)		

The table indicated that there existed no

statistically significant distinction between the two groups under study with respect to the type of twins.

Table 3. Laboratory characteristics comparing the two groups under study

	GROUP A (N=60)	GROUP B (N=60)	T	P
HB (G/DL) MEAN ± SD	10.25 ± 1.12	10.8 ± 1.5	.688	.493
TLC (X 10^3/L) MEAN± SD	7.19 ± 0.953	7.45 ± 0.871	1.54	.126
PLT (X 10^3/L) MEAN± SD	265.6 ± 92.77	288.1 ± 93.14	1.33	.188
ALT (U/L) MEAN± SD	34.22 ± 8.66	34.58 ± 9.6	.220	.827
AST (U/L) MEAN± SD	33.52 ± 10.54	36.83 ± 9.63	1.56	.121
ALBUMIN (G/DL) MEAN ± SD	4.1 ± 0.449	4.22 ± 0.454	1.37	.173
CREATININE (MG/DL) MEAN ± SD	0.729 ± 0.106	0.728 ± 0.103	.070	.944
UREA (MG/DL) MEAN ± SD	19.83 ± 3.01	19.62 ± 3.07	.391	.696
RBS (MG/DL) MEAN ± SD	121.34 ± 8.34	119.21 ± 10.9	1.2	.232
CRP (MG/L) MEAN ± SD	7.26 ± 2.99	6.19 ± 2.88	MW 1434	.055
PROGESTERONE (NG/ML) MEAN ± SD	25.89 ± 2.85	25.37 ± 2.16	1.45	.148

The data shown in this table indicate that there was no statistically significant distinction between the two groups under study in terms of laboratory parameters.

Table 4. Cervical length distribution between the two studied groups.

	GROUP A (N=60)	GROUP B (N=60)	T	P
CERVICAL LENGTH (MM) MEAN ± SD	32.75 ± 3.65	33.3 ± 3.62	.879	.381

This table demonstrated that there had been no discernible variation in cervical length between the two study groups.

Table (5): Spontaneous birth distribution between the two studied groups.

	GROUP A (N=60)		GROUP B (N=60)		χ^2	P
	N	%	N	%		
SPONTANEOUS BIRTH BETWEEN 28-34 WEEKS	7	11.7%	5	8.3%	.370	.543
SPONTANEOUS BIRTH BETWEEN 34-37 WEEKS	9	15%	5	8.3%	1.29	.255

The data from this table demonstrates that group A had a greater occurrence of spontaneous deliveries among twenty-eight and thirty-four weeks as well as between 34 and 37 weeks compared to group B. However, it is important to note that this difference was not statistically significant.

Table 6. Outcome distribution between the two studied groups.

	GROUP A (N=60)		GROUP B (N=60)		χ^2	P
	N	%	N	%		
MISCARRIAGE	5	8.3	4	6.7	.120	.729
STILLBIRTH	2	3.3	2	3.3	--	1
IUFD	2	3.3	1	1.7	.342	.559
BIRTHWEIGHT						
<1500 GM	6	10	5	8.3	.100	.752
<2500 GM	20	33.3	17	28.3	.352	.553
NEONATAL RD	5	8.3	4	6.7	.120	.729
NECROTIZING ENTEROCOLITIS	1	1.7	0	--	1.01	.315
NEONATAL SEPSIS	2	3.3	1	1.7	.342	.559
NICU	13	21.7	11	18.3	.208	.648

The data from this table indicates that, while not statistically significant, group A had somewhat higher outcomes or complications compared to group B.

4. Discussion

Our recent analysis revealed that there were no noticeable disparities in their ages, BMI, or parity across the two groups being studied. Furthermore, our findings proved that there was no discernible variation in the twins' types between the two groups under investigation.

Our findings were corroborated by Rehal et al.[8] We sought to determine how well vaginal progesterone compared to a placebo, prevented unplanned preterm delivery in a pair of pregnancies. In their trial, 582 participants took progesterone, while 587 received a placebo. Progesterone or a placebo was given to women in a 1:1 random assignment. According to their findings, The groups under research did not exhibit any notable disparities in terms of age, BMI, or parity.

Moreover, Serra et al.,[9] Researchers sought to ascertain whether two distinct daily dosages of vaginal natural progesterone (200 and 400 mg) were safe and effective in preventing preterm delivery in unselected twin pregnancies when compared to a placebo. They included in their investigation. The researchers demonstrated that there were no noticeable disparities in their ages, BMI, or parity among the groups being examined.

Regarding laboratory parameters, we discovered no discernible difference between the two groups under investigation. Furthermore, our results demonstrated no discernible variation in cervical length between the two groups under study.

Our findings are consistent with those of Rehal et al.[8] who stated that there was no discernible variation in cervical length between the two groups under study.

Moreover, Cetingoz et al.,[10] The study revealed that there was no statistically significant disparity in cervical length measures between the groups that received progesterone and the groups that received a placebo (34.61 ± 6.75 vs. 34.26 ± 6.06,

p > 0.05). There was no noticeable distinction observed among the two groups when comparing the cervical length measurements of women who had undergone preterm birth (PTB) and women who were now pregnant with twins.

Also, Brizot et al.,[11] Which researcher demonstrated that there was no noticeable distinction in the cervical length measures between the groups receiving progesterone and those receiving a placebo?

Our research findings revealed that group A had a higher frequency of spontaneous births over the time periods of 28-34 weeks and 34-37 weeks compared to group B. Nevertheless, it is crucial to acknowledge that this discrepancy did not achieve statistical significance.

Also, Norman et al.[12] found no difference between the groups under study in spontaneous deliveries between 28 and thirty-four weeks and between 34 and 37 weeks.

Furthermore, cetingoz et al.[10] They stated that the progesterone group had a lower rate of preterm delivery (40.2% vs. 57.2; OR 2; 95% CI, 1.-3.83) than the placebo group did. Between these groups, there was a statistically significant difference (p < 0.05). The progesterone group had a significantly lower incidence of deliveries before 34 weeks of gestation (24.3 vs. 8.8%; OR 3.35; 95% CI, 1.3-8.63; p < 0.05). In the progesterone group, the mean gestational age at birth was 36w6d ± 2w3d, while in the placebo group, it was 35w6d ± 3w2d (w, week; d, day; p < 0.05).

Based on our research, group A had somewhat higher outcomes and complications than group B; however, the difference was not statistically significant.

Brizot et al.,[11] The study demonstrated that there was no significant distinction among the progesterone (15.5%) and placebo (15.9%) groups in terms of composite newborn morbidity and death. The odds ratio was 1.01, with a 95% confidence interval ranging from 0.58 to 1.75.

Moreover, Rehal et al.[8] They reached their conclusion. They revealed there was no noticeable disparity in the rates of inadequate fetal growth, neonatal therapies, neonatal difficulties, or stillbirth between the two therapy groups. Among the women in the progesterone group, 1.4% (8 out of 582) experienced at least one serious adverse event, while among the fetuses in the same group, the rate was 1.9% (22 out of 1164). In comparison, the placebo group had a rate of 1.2% (7 out of 587) for women and 3.2% (37 out of 1174) for fetuses. The statistical significance for these differences was P=.80 and P=.06, respectively.

On the other hand, O'Brien JM, Adair CD, Lewis DF et al.[13] The administration of a daily medication consisting of a moderate dose (ninety mg) of progesterone vaginal gel did not result in a decrease in the occurrence of early preterm delivery. This conclusion was drawn from a randomized, double-blind, placebo-controlled trial involving 659 pregnant women who had previously had spontaneous preterm birth.

Schuit et al.[14] that comprised research using both 17P and natural vaginal progesterone, also demonstrated that vaginal progesterone significantly improved neonatal outcomes in the group with a short cervix (25 mm).

4. Conclusion

This study findings indicate that vaginal progesterone does not have a significant impact in preventing spontaneous preterm birth in twin pregnancies.

Disclosure

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References

1. Di Renzo GC, Mattei A, Gojnic M, Gerli S. Progesterone and pregnancy. Curr Opin Obstet Gynecol. 2005;17(6):598-600.
2. Howson CP, Kinney MV, McDougall L, Lawn JE; Born Too Soon Preterm Birth Action Group. Born too soon: preterm birth matters. Reprod Health. 2013;10 Suppl 1(Suppl 1):S1.
3. Quinn JA, Munoz FM, Gonik B, et al. Preterm birth: Case definition & guidelines for data collection, analysis, and presentation of immunisation safety data. Vaccine. 2016;34(49):6047-6056.
4. Behrman RE, Butler AS, Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes, eds. Preterm Birth: Causes, Consequences, and Prevention. Washington (DC): National Academies Press (US); 2007.
5. Turton P, Neilson JP, Quenby S, Burdyga T, Wray S. A short review of twin pregnancy and how oxytocin receptor expression may differ in multiple pregnancy. Eur J Obstet Gynecol Reprod Biol. 2009;144 Suppl 1:S40-S44.
6. Morin L, Lim K; DIAGNOSTIC IMAGING COMMITTEE; SPECIAL CONTRIBUTOR; GENETICS COMMITTEE; MATERNAL FETAL MEDICINE COMMITTEE. Ultrasound in twin pregnancies. J Obstet Gynaecol Can. 2011;33(6):643-656.
7. Dias T, Arcangeli T, Bhide A, Napolitano R, Mahsud-Dornan S, Thilaganathan B. First-trimester ultrasound determination of chorionicity in twin pregnancy. Ultrasound Obstet Gynecol. 2011;38(5):530-532.
8. Rehal A, Benkő Z, De Paco Matallana C, et al. Early vaginal progesterone versus placebo in twin pregnancies for the prevention of spontaneous preterm birth: a randomized, double-blind trial. Am J Obstet Gynecol. 2021;224(1):86.e1-86.e19.

9. Serra V, Perales A, Meseguer J, et al. Increased doses of vaginal progesterone for the prevention of preterm birth in twin pregnancies: a randomised controlled double-blind multicentre trial. BJOG. 2013;120(1):50-57.
10. Cetingoz E, Cam C, Sakallı M, Karateke A, Celik C, Sancak A. Progesterone effects on preterm birth in high-risk pregnancies: a randomized placebo-controlled trial. Archives of gynecology and obstetrics. 2011 Mar;283:423-9.
11. Brizot ML, Hernandez W, Liao AW, et al. Vaginal progesterone for the prevention of preterm birth in twin gestations: a randomized placebo-controlled double-blind study. Am J Obstet Gynecol. 2015;213(1):82.e1-82.e9.
12. Norman JE, Mackenzie F, Owen P, et al. Progesterone for the prevention of preterm birth in twin pregnancy (STOPPIT): a randomised, double-blind, placebo-controlled study and meta-analysis. Lancet. 2009;373(9680):2034-2040.
13. O'Brien JM, Adair CD, Lewis DF, 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):687-696.
14. Schuit E, Stock S, Rode L, et al. Effectiveness of progestogens to improve perinatal outcome in twin pregnancies: an individual participant data meta-analysis. BJOG. 2015;122(1):27-37.