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ORIGINAL ARTICLE

Role of Vaginal Progesterone in Prevention of Preterm Labour in Patients with History of Spontaneous Preterm Delivery

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ABSTRACT

Background: Preterm delivery (PTD) is defined as delivery before 37 weeks of gestation, and it raises the risk of perinatal mortality. Additionally, vaginal progesterone effectively improves newborn outcomes and lowers the chance of preterm delivery in these patients. This study aimed to evaluate the role of vaginal progesterone administration in the prevention of preterm labour in patient with history of spontaneous preterm delivery.**Methods:**A prospective cohort study was carried out at Department of Obstetrics and Gynecology, Faculty of Medicine, Zagazig University Hospital outpatient clinic, and ultrasound fetal medicine unit for a period of 6 months. included 50 patients with a history of spontaneous PTD and divided them into two groups. Patients in the first group were given progesterone (prontogest) 400mg vaginal suppository daily at night and whose cervical length was ≤25mm. The second group of women were not given any drugs with cervical length >25mm. **Results:** Mean cervical length at 18–24w of gestation showed significant difference between both groups, with a mean cervical length of 21.3±2.9mm for progesterone group and 29.9±3.3mm for control group, and the rate of PTL was significantly less in progesterone group (48%), compared to control group (80%). Neonatal deaths (2%, 16%) were significantly better in the progesterone group than in the control group. **Conclusions:** Vaginal progesterone is efficacious and safe for reducing the risk of preterm birth and neonatal morbidity and mortality in women with a singleton gestation with a mid-trimester sonographic short cervix.

Keywords: Spontaneous Preterm delivery; Vaginal progesterone ; Preterm Labour.

INTRODUCTION

Preterm delivery (PTD), or birth before 37 weeks of pregnancy, increases the risk of serious neonatal morbidity, perinatal mortality, and long-term effects such as cerebral palsy (CP) and cognitive impairment **[1]**. In 2014, PTD rates were anticipated to be 10.6% worldwide, with North Africa

accounting for 13.4% and Europe accounting for 8.7% of the total **[2]**.

It is believed that less than 10% of Egypt's population has PTD[3]. Regrettably, the most of premature births occur in Asia and Africa, where developing nations account for the majority of the 85% of preterm births (31% and 54%, respectively) **[3]**.

It is believed that there are several contributing elements, such as behavioral factors, environmental exposure and genetics, infertility treatments, societal and economic factors, and iatrogenic causes **[4].**

Past Spontaneous PTD, illness, numerous pregnancies, past late miscarriages, and cervical conization are common risk factors for postpartum depression (PTD) **[5].**

Preterm labor has a complex etiology, but there is one common mechanism that leads to an increase in prostaglandin and cytokine production in the cervix, fetal membranes, and myometrium. An infectious or inflammatory disease, uterine over distension (as in polyhydramnios and multiple pregnancies), or choriodecudidual hemorrhage (as in abruption) can all cause the release of prostaglandins **[6]**.

Despite the development of numerous risk-scoring systems, it is unknown if these methods can effectively detect women who are at risk and avert preterm delivery. The best course of action to avoid preterm delivery in the absence of such proof is to identify risks and then address relevant factors **[7]**. A key component of controlling and avoiding preterm labor is identifying patients who pose a high risk. With risk assessment and cervical length assessment, premature labor can be predicted **[8]**.

Progesterone is known to play a role in the continuation of the pregnancy. It keeps the uterus relaxed. Antenatally given progesterone whatever its dose and the route decreases the risk of giving birth to a low birth weight baby before term. Evidence shows that the local change in the level of progesterone and the progesterone and estrogen ratios in the placenta, Decidua , or fetal Membranes are important in starting labor in human beings**[9]**.

Cervical length can be measured by ultrasound in the general population to identify women who may be at risk of spontaneous preterm delivery. In these patients, vaginal progesterone effectively lowers the risk of preterm delivery and improves newborn outcomes. It is economical to do this screening in conjunction with vaginal progesterone therapy **[10].** This study aimed to evaluate the role of vaginal progesterone administration in the prevention of preterm labour in patients with history of spontaneous preterm delivery.

METHODS

This Prospective cohort study was conducted at the Department of Obstetrics and Gynecology, Faculty of Medicine, Zagazig University Hospital outpatient clinic and ultrasound fetal medicine unit for 6 months. The study was authorized by our local ethics commission (IRB # 10516-1-3-2023). Before the ladies were included in the study, they were informed of its goals. Consent was obtained in writing, and informed by each participant. The protocol for the study complied with the Helsinki Declaration (1975), which is the World Medical Association's guideline of ethics for research involving human subjects.

Inclusion Criteria were asymptomatic singleton pregnant women, aged between 20-35 years, gestational age from 18 – 24 weeks by last menstrual period at the time of examination, and history of spontaneous

preterm delivery, history of mid-trimester miscarriage. Exclusion Criteria**;** Fetal malformation. Uterine anomalies. Rupture of the membrane in a current pregnancy. Current use of progesterone. Cerclage in situ. Induced preterm birth. High-risk patients such as history of previous cervical procedures and dilatation and a history of PPROM.

All women were subjected to complete history taking, and clinical examination, and women were examined at the ultrasound unit by (Mindray Nuewa 19 Shinzen, China, 2022) at their routine ultrasound scan from 18-24 weeks for confirmed gestational age, fetal heart pulsation, detect fetal presentation, site of the placenta, determine Amniotic Fluid Index (AFI), exclude multiple pregnancies, exclude congenital anomalies in the fetus and the uterus and measure cervical length.

Based on vaginal progesterone administration they are divided into two groups;

First group (study group) women were given progesterone (prontogest) 400mg vaginal suppository daily at night. The women were instructed to limit their physical activity and continue progesterone vaginal suppositories until 36 weeks of gestation. In cases with recurrent uterine contraction, patients were instructed to return to the hospital.

Second group (control group) women were not given any drugs, followed up, and instructed to limit their physical activity. figure 2. In cases of recurrent uterine contractions, patients were instructed to return to the hospital and manage according to the fetal and maternal situations.

Transvaginal ultrasound was done for recruited patients with a history of PTD for cervical length measurement between 18+0 and 23+6 weeks gestation, and with the help of Transvaginal ultrasound, women were selected to receive vaginal progesterone. Those with a cervical length ≤ 25 mm Figure 1 will receive vaginal progesterone, and women with a cervical length >25mm Figure2 will not receive any drug.

FOLLOW-UP:

All the patients were followed up every 2 weeks by clinical and ultrasound examinations until the end of pregnancy in both groups.

Statistical analysis:

Data were entered, checked, and evaluated using Epi-Info version 6 and SPP for Windows version 8 (2022). To summarize the data, the arithmetic mean, standard deviation, student t-test, and X2 (chi-squared) (test of significance) were utilized. The p-value, or level of significance, is set at 5%.

RESULTS:

Table (1) Shows the basic characteristics of the studied groups. No significant differences regarding age or BMI were reported between both groups.

The past obstetric history of both groups is shown in Table (2). No significant differences were reported between both groups regarding mean parity, previous preterm deliveries, and abortion rates. The mean time since the last delivery was comparable between both groups with non-significant differences.

Table (3) Shows mean cervical length at 18-24 weeks gestation. A significant difference was reported between both groups with a mean cervical length of 21.3±2.9 mm for progesterone group and 29.9 ±3.3 mm for the control group.

The gestational age at delivery is shown in table (4). The rate of PTL was significantly less in progesterone group (48%) compared to (80%) in the control group.

Table (5) shows neonatal outcome: These outcomes were notably superior in the progesterone group compared to the control group.

Table (1): Demographic data of the studied groups

	Study group No= 25	**Control group No= 25**	**t**	**p**
Age (y) **Mean± SD** **Range**	26.9 ± 4.1 (20 – 35)	26.9 ±4.1 (20 – 35)	0.11	0.87
BMI (kg/m2) **Mean ± SD** **Range**	32.4 ± 5.3 (24.1– 35.7)	31.9 ± 4.9 (23.4 – 36.3)	0.56	0.77

t: student t test. p: p-value. BMI:body mass index.

Table (2): Past obstetric history of the studied groups

	Study group No= 25	**Control group No= 25**	**t**	**P**
Parity Mean ± SD Range	3.3 ± 0.5 (2 – 4)	2.5 ± 0.5 (1 – 4)	0.09	0.94
Previous full term deliveries Mean ± SD Range	1.3 ± 1.7 (0 – 4)	1.1 ± 2.1 (1 – 4)	0.11	0.92
Previous preterm deliveries Mean ± SD Range	0.8 ± 1.2 (1 – 2)	0.9 ± 1.3 (1 – 2)	0.24	0.84
	Study group No= 25	**Control group No= 25**	**t**	**P**
Previous abortions Mean ± SD Range	2.1 ± 0.9 (1 – 3)	1.4 ± 0.9 (1 – 2)	0.19	0.90
Last delivery since (ys) Mean ± SD Range	3.7 ± 1.5 (1 – 4)	3.6 ± 1.3 (2 – 5)	0.17	0.88

Table (3): Cervical length by TVUS of the studied groups

	Study group No= 25	**Control group No= 25**	**t**	**p**
CX length (mm) Mean± SD Range	21.3 ± 2.9 (20 – 25)	29.9 ± 3.3 (26– 35)	13.22	0.05

TVUS: transvaginal ultrasound. CX: cervix.

Table (4): Rate of spontaneous preterm labour & GA at delivery of the studied groups

	Study group No= 25	**Control group No= 25**	**X^2**	**P**
Spontaneous preterm labor< 37weeks	12 (48%)	20 (80%)	10.16	0.001 HS
GA (w) **<34w** **34-37** **>37**	 3(12%) 9(36%) 13(52%)	 8(32%) 12(48%) 5(20%)	17.38	<0.001 (HS)

GA: gestational age. X^2: chi-squared. P: p-value.

Table (5): Neonatal outcome at delivery of the studied groups

	Study group No= 25	**Control group No= 25**	**X^2**	**P**
BW(g) Mean ±SD	3000.g 18±500.	2000.g 6±500	16.91	0.01 (HS)
NICU	3 (12%)	5 (20%)	12.19	0.04 (S)`
APGAR 1min <7 >7	 (8%) 23 (92%)	 8 (32%) 17 (68%)	10.70	0.05 (S)
APGAR 5min <7 >7	 1 (4%) 24 (96%)	 6 (24%) 19 (76%)	15.50	0.01 (HS)
RDS	4 (16%)	7 (20%)	8.41	0.01 (HS)
Sepsis	1 (4%)	3 (12%)	10.22	0.01 (HS)
Neonatal death	1 (4%)	6 (24%)	11.54	0.03 (S)

BW: birth weight. **APGAR score**: activity, pulse, grimace, appearance, respiration. **RDS**: respiratory distress syndrome.

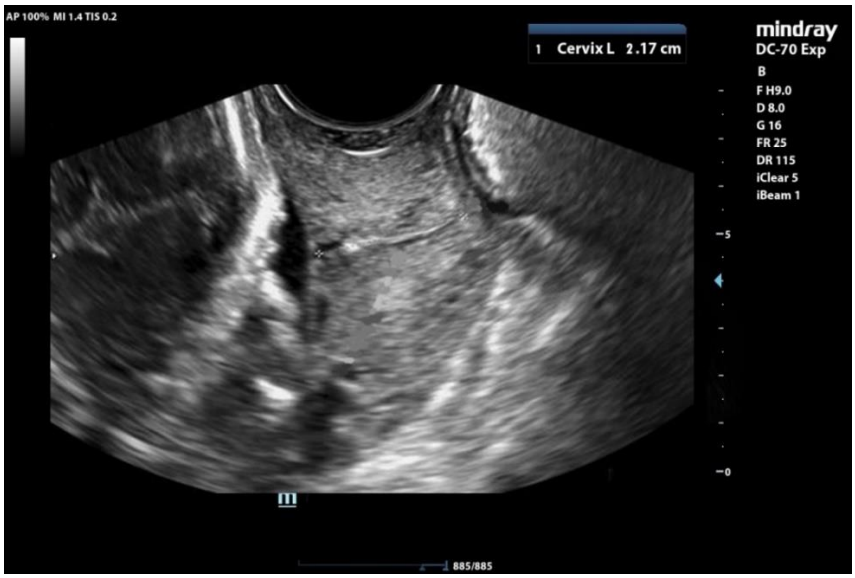

Figure 1: Second trimester transvaginal ultrasound cervical length measurement in patient with history of spontaneous preterm delivery, show cervical length = 2.17cm

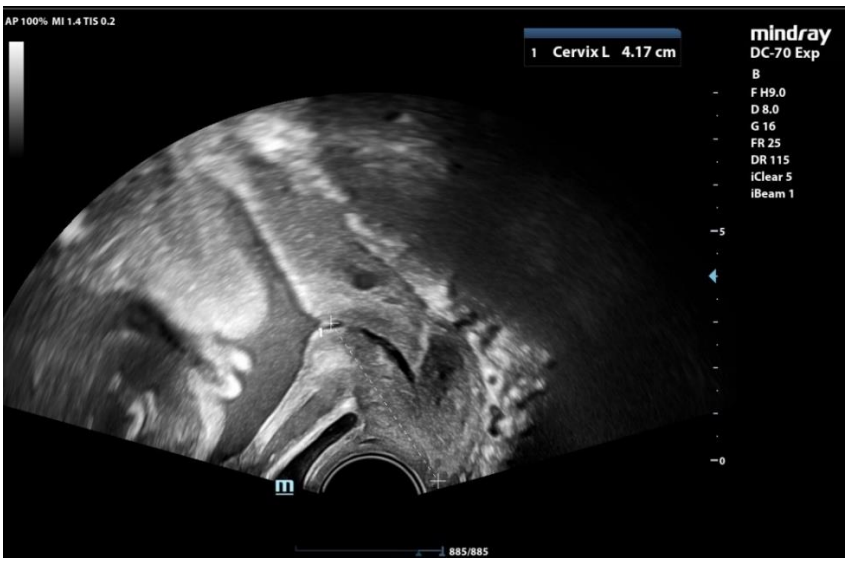

Figure 2: Second trimester transvaginal ultrasound cervical length was >25 measurement in patient with history of spontaneous preterm deliveryshow cervical length = 4.17cm

DISCUSSION

In the current work, we discovered that there was no discernible difference between the two groups under study, as regards maternal age, parity, or BMI at the start of the examination.

In agreement with our results, **Mohamed et al [3]** revealed that there was no statistically significant difference in age, BMI, or parity between the groups under study.

Not in agreement with what we found, **Wikström et al [1]** stated that there were notable differences in age and BMI between research groups (p<0.001).

Regarding prior abortions, there is no discernible difference between the two groups in our study, the mean time since the last delivery and previous PTL.

Consistent with our findings, **Wikström et al [1]** demonstrated that there was no discernible difference between the groups under study regarding age, and parity. Previous abortion, the mean time since last delivery, and previous PTL.

In our study, as regards mean cervical length at 18-24weeks gestation, a significant difference was reported between both groups with a mean cervical length of 21.3±2.9mm for the progesterone group and 29.9 ±3.3mm for the control group.

In agreement with our findings, **Conde-Agudelo & Romero[11]** giving women who have a transvaginal sonographic cervical length progesterone intravaginally (CL) ≤25 mm is linked to a notable and substantial decrease in the incidence of the preterm birth from before 25 weeks of gestation <28 to <35 weeks of gestation.

Also, by **Romero et al [12]** Data from 974 women with a cervical length were available (498 assigned to vaginal progesterone, 476 to placebo) ≤25 mm taking part in five excellent trials. Preterm birth risk was significantly lower when vaginal progesterone was used <33 weeks of gestation (relative risk, 0.62; 95% confidence interval, 0.47–0.81; P= .0006; high-quality evidence).

In the present study Preterm birth rates <37wk were significantly less in the Progesterone group (48 %) compared to (80 %) in the control group.

These results are in accord with many RCTs and meta-analyses investigating the preventive effect of progestogens on preterm labor.

In agreement with our findings, **Phillips et al[13]** evaluated 30 women with a history of PTL, 17-hydroxy progesterone 250mg IM weekly was linked to results starting at 20–30

weeks and ending at 34 weeks with significantly lower rates of PTB less than 35 weeks compared to placebo (45%. VS 35%). As well as there were decreased infant mortality and morbidity rates in comparison to placebo.

In addition, Randomized clinical trials **(RCTs)** in singleton pregnancies have shown that antenatal progestogens (including vaginal In women who are at high risk of premature delivery, progesterone and semi-synthetic progestogens (such as injectable 17-hydroxy progesterone caproate, or 17pc) lower the rate of preterm delivery **[14].**

Also, a RCT by **Romero et al[15]** It is found that using daily vaginal progesterone suppositories at a dose of 100 mg between 24-34 weeks significantly decreased the risk of PTB <37 weeks (51%vs 79%) but not <34weeks (10% vs 25%) compared to placebo.

In addition, in contrast to **Norman et al**[16], vaginal progesterone gel 90 mg daily starting at 24 weeks and continuing for a minimum of 10 weeks did not appear to have a significant impact on the incidence of PTB (19.4% in the placebo group and 24.7% in the progesterone group) in 500 women. Furthermore, there were no differences in perinatal morbidity or mortality when compared to the placebo **[16].**

Also, a Cochrane review by **Dodd et al [17]** pooled data from 5 trials of vaginal progesterone found no significant benefit over placebo on Preterm birth rate at less than 34 weeks gestation. Moreover, a pooled analysis of 7 trials discovered that progesterone does not considerably lower the rate of perinatal death.

These differences with our study may be because of variations in sample size, dose, and route of progesterone administrations.

Our secondary outcome was adverse perinatal outcomes (NICU admission-Apgar score). In the present study, we revealed that neonatal outcome was notably superior in the progesterone group compared to the control group. The progesterone group had a considerably greater mean birth weight at delivery. these findings agreed with that of **Mohammed et al [3]**.

In agreement with our results Wikström et al[1] demonstrated that progesterone use concurrently with other treatments was strongly linked with improved perinatal outcomes (significantly higher mean birth weight, higher mean Apgar score, and lower rate of NICU admission), as well as a significant reduction in the risk of PTL.

In disagreement also with our results O'Brien and Lewis[14] found that, in 677 cases, progesterone 200 mg medication, commencing at 20–24 weeks and continuing until 34 weeks, had no discernible effect on the incidence of PTL or perinatal problems as compared to placebo.

CONCLUSIONS:

We conclude that in women with a history of spontaneous preterm birth, a mid-trimester sonographic short cervix, and a singleton gestation, vaginal progesterone is safe and effective at lowering the risk of preterm birth and neonatal morbidity and mortality.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors are responsible for the content and writing of the paper.

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None declared

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