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The Efficacy of Vaginal Progesterone in Reducing Preterm Birth in High-Risk Pregnancies

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Abstract

Preterm birth is a leading cause of perinatal mortality and morbidity and has adverse long –term consequences for the child health. The vast majority of morbidity and mortality relates to early delivery before 32 weeks. to evaluate whether the prophylactic administration of vaginal progesterone would reduce the preterm birth rate in singleton high-risk pregnancies. This prospective,observational study included 100 cases of high risk pregnant women admitted to Obstetrics and Gynaecology Departments in Benha University and El Bagour General Hospital. Participants were divided into two groups: a Study Group including 50 pregnant women under treatment by prophylactic progesterone vaginal suppository [prontogest 400mg vaginal suppository from period of 28 – 34 weeks and a Control Group:- including 50 pregnant women not treated by progesterone vaginal suppository. The incidence of preterm deliveries in the study group was significantly lower than that of the control group [38% versus 56%], the postnatal morbidity was significantly lower [6% versus 15%] while the postnatal mortality was significantly different. Our results indicate that the progesterone therapy significantly reduces the incidence of preterm delivery. The study concludes that vaginal progesterone reduces the risk of PTB,NICU admission,RDS in singleton high-risk pregnancies.

Keywords: Vaginal Progesterone , Preterm Birth, High- Risk Pregnancies.

1.Introduction

Preterm birth [PTB] is defined as delivery of a viable pregnancy at less than 37 completed weeks of gestation. The lower limit of viability exoutri generally accepted to be at 23 completed weeks. Birth before 23 completed weeks of gestation is classified as either miscarriage or abortion [1].

Preterm birth is an important perinatal health problem all over the world as its rates have been reported to range from 5% to 7% of live births in some develoed countries and higher in developing countries [2].

Preterm birth is due to one of three clinical conditions: medically indicated [iatrogenic] preterm birth, preterm premature rupture of membranes [PPROM] and spontaneous [idiopathic] preterm birth. Medically indicated preterm birth in the absence of PPROM or spontaneous preterm labor occurs in about 25% of all preterm births with variations from 8.7% - 35.2 % according to reports and studied populations [3].

The incidence of iatrogenic preterm birth is increasing with decrease in the incidence of spontaneous preterm birth. There are attempts to analyze, interpret and decrease preterm birth rates which consider spontaneous and iatrogenic preterm births separately [4].

Preterm birth is a leading cause of perinatal mortality and morbidity and has adverse long –term consequences for the child health [5]. The vast majority of morbidity and mortality relates to early delivery before 32 weeks [6].

Economically, PTB has a major and significant direct and indirect cost. There is a direct cost in terms of clinical resources use, as Intensive and prolonged neonatal care as in- patient followed by higher rate of re hospitalization following discharge and emotional, psychological, and financial burden to the parents. There is also have indirect cost where scarce public resources are utilized for long term care of the handicapped premature child [7].

Primary prevention of preterm birth is always by detection of the cause and the pathphsiological mechanism of preterm birth therefore ; the early detection of women at high risk of preterm delivery could be the gold way to prevent preterm birth [8].

There are two sources of progesterone: Endogenous progesterone which is gestational vital support steroid hormone produced by the adrenal glands, corpus luteum and placenta [9]. Exogenous progesterone has been used to support assisted reproduction protocols, such as in vitro fertilization [IVF], while progesterone receptor antagonist such as mifepristone have Contraceptive and abortificient effect [10].

Moreover, progesterone supplementation has been reported to reduce the incidence of preterm delivery in women at risk for premature labor [11].

2.Patients and Methods

This prospective, observational, cohort study was conducted in Obstetrics and Gynaecology outpatient clinic and departments of El-Bagour general hospital and Benha University Hospital, during the period from June 2018 to June 2019.

Approval of the study was obtained from the Ethical Committee of Scientific Research, Faculty of Medicine, Benha University. Written informed consent was taken from the patients enrolled in this study.

The study included 100 cases of high risk pregnant women admitted to the department and candidates for progesterone therapy for possible preterm birth.

The study included patients with singleton pregnancy, gestational age of pregnancy between 28 - 34 weeks, pregnancies with history of previous one or more spontaneous preterm labor and no serious maternal or fetal problems

While loss of follow up, ruptured membranes., Multiple pregnancies., Symptoms of preterm labor, Serious maternal or fetal problems, Placenta previa, fetal congenital anomalies, Polyhydraminos, Any woman who had to be delivered before term for medical or obstetric indications were excluded from the study.

All participants were subjected to the following:- History taking included: personal history, detailed obstetric history, past history, family history. Estimation of gestional age was calculated according to the date of the last normal menstrual period and confirmed by first trimester ultrasound. if there is adiscrepancy [more than five days], early ultra sound will be used to determine gestional age. General, obstetrics and abdominal examination. CTG .Routine antenatal laboratory investigations including [blood group, Rh typing, full blood count and urine analysis]. Routine obstetric ultrasound scanning for gestional age, fetal biometry, presentation, aminotic fluid volume, placental location and exclusion of fetal anomalies [using 7-10MHZ?? Probe –Voluson 730 PRO, GE Health care, USA]

Participants were divided into two groups: Study Group:- including 50 pregnant women under treatment by progesterone vaginal suppository [prontogest 400mg vaginal suppository from period of 28 – 34 weeks. Control Group:- including 50 pregnant women not treated by prontogest vaginal suppository

2.1Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 [SPSS Inc., Chicago, Illinois, USA]. Quantitative data were expressed as mean± standard deviation [SD]. Qualitative data were expressed as frequency and percentage.

2.1.1The following tests were done

Independent-samples t-test of significance was used when comparing between two means. Chi-square [χ^2] test of significance was used in order to compare proportions between qualitative parameters. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: Probability [P-value] P-value <0.05 was considered significant. P-value <0.001 was considered as highly significant. P-value >0.05 was considered insignificant.

3.Results

Table (1) Comparison between study group and control group according to age [years].

Age [years]	Study Group [n=50]	Control Group [n=50]	t-test	p-value
Mean±SD	**27.35±5.88**	27.56±7.14	0.412	0.605
Range	**20-32**	19-33		

Using: t-Independent Sample t-test; p-value >0.05 NS
This table shows no statistically significant difference between study group 27.35±5.88 and control group 27.56±7.14 according to age [years].

Table (2) Comparison between study group and control group according to no. of previous preterm delivery.

No of previous preterm	Study Group [n=50]	Control Group [n=50]	x2	p-value
1 preterm cases	33 [66%]	27 [54%]	4.682	0.174
2 preterm cases	17 [34%]	20 [40%]		
3 preterm cases	0 [0%]	3 [6%]		

Using: x^2-Chi-square test; p-value >0.05 NS
This table shows no statistically significant difference between study group and control group according to no. of previous preterm.

Table (3) Comparison between study group and control group according to gestational age of previous preterm delivery.

Gestational age of previous preterm delivery	Study Group [n=50]	Control Group [n=50]	t-test	p-value
Gest age of first /week	29.7±2.8	28.2±2.6	3.648	0.019*
Gest age of second /week	29.7±3.4	31.5±1.9	2.622	0.037*
Average gest. Age/week	29.7±3.1	29.9±2.3	0.366	0.715

Using: t-Independent Sample t-test; p-value <0.05 S
This table shows statistically significant difference between study group 29.7±2.8 and control group 28.2±2.6 according to gestational age of first/week.
Also, statistically significant difference between study group 29.7±3.4 and control group 31.5±1.9 according to gestational age of second/week.

Table (4) Comparison between study group and control group according to mean cervical length at first time of examination.

Mean Cervical length [cm]	Study Group [n=50]	Control Group [n=50]	t-test	p-value
Mean±SD	3.60±0.60	3.37±0.77	1.912	0.085
Range	2.81-4.39	2.7-4.04		

Using: t-Independent Sample t-test; p-value >0.05 NS
This table shows no statistically significant difference between study group 3.60±0.60 and control group 3.37±0.77 according to mean cervical length.

Table (5) Comparison between study group and control group according to incidence of preterm delivery in current pregnancy from <32 wks.

Preterm delivery (<32 wks.)	Study Group (n=17)	Control Group (n=25)	x2	p-value
No	10 (58.8%)	10 (40%)	6.227	0.025*
Yes	7 (41.2%)	15 (60%)		

Using: x2-Chi-square test; *p-value <0.05 S
This table shows statistically significant difference between study group 7 (41.2%) and control group 15 (60%) according to incidence of preterm delivery in recent pregnancy <32 weeks.

Table (6) Comparison between study group and control group according to incidence of preterm delivery in current pregnancy from 32-34 weeks.

Preterm delivery (32-34wks.)	Study Group (n=33)	Control Group (n=25)	x2	p-value
No	21 (63.6%)	12 (48%)	1.163	0.568
Yes	12 (36.4%)	13 (52%)		

Using: x2-Chi-square test; p-value >0.05 NS
This table shows no statistically significant difference between study group 12 (36.4%) and control group 13 (52%) according to incidence of preterm delivery in current pregnancy from 32-34 weeks.

Table (7) Comparison between study group and control group according to incidence of preterm delivery.

Preterm delivery	Study Group (n=50)	Control Group (n=50)	x2	p-value
No	31 (62%)	22 (44%)	4.194	0.037*
Yes	19 (38%)	28 (56%)		

Using: x2-Chi-square test; *p-value <0.05 S
This table shows statistically significant difference between study group 28 (56%) and control group 19 (38%) according to incidence of preterm delivery.

Table (8) Relation between incidence of preterm and the cervical length in the study group.

Mean cx length [cm]	Incidence of Preterm		t-test	p-value
	Preterm	No preterm		
Study group	3.28±0.45	3.69±0.49	3.864	<0.001**
Control group	3.14±0.53	3.37±0.57	2.782	0.013*

Using: t-Independent Sample t-test;
*p-value <0.05 S; **p-value <0.001 HS

The no of preterm cases was [19] with mean cervical length 3.28±0.45. The no of full-term cases was [31] with mean cervical length 3.69±0.49. There was significant difference in mean cervical length between preterm and full term pregnancy within treatment group.

The no of preterm cases was [28] with mean cervical length 3.14±0.53 The no of full-term cases was [22] with mean cervical length 3.37±0.57 There was significant difference in mean cervical length

between preterm and full term pregnancy within control group

Table (9) Comparison between study group and control group according to need for NICU admission, RDS and fate of the baby.

	Study Group [n=50]	Control Group [n=50]	x2	p-value
Need for NICU admission				
Yes	14 [28%]	24 [48%]	7.482	0.009*
No	36 [72%]	26 [52%]		
RDS				
Yes	6 [12%]	15 [30%]	3.858	0.049*
No	44 [88%]	35 [70%]		
Fate of the baby				
Died	7 [14%]	8 [16%]	0.478	0.387
Alive	43 [86%]	42 [84%]		

Using: x^2-Chi-square test;
p-value >0.05 NS; *p-value <0.05 S
This table shows statistically significant difference between study group 14 [28%] and control group 24 [48%] according to need for NICU admission.
This table shows statistically significant difference between study group 6 [12%] and control group 15 [30%] according to RDS.
This table shows no statistically significant difference between study groups died 7 [14%] compared to control group died 8 [16%] according to fate of the neonate.

4.Discussion

Every year, an estimated 15 million babies are born preterm worldwide with rates ranging from 5% in several European countries to 18% in some African countries In 2015, the preterm birth rate in the United States, which was declined over 2007- 2014, increased slightly to 9.63% [12]. Globally, preterm birth complications are the leading cause of child mortality, and was responsible for nearly 1 million deaths in 2013. In addition, surviving preterm babies are at greater risk for short-term health complications including acute respiratory, gastrointestinal, infectious, central nervous system, hearing, and vision problems. Long- term neurodevelopmental disabilities such as cerebral palsy, impaired learning and visual disorders, as well as chronic diseases in adulthood are also recorded that [13].

There are many factors cause preterm labor either Spontaneous [70%] as [Infection, Spontaneous rupture of the membranes, Idiopathic contractions, Multiple pregnancy, Cervical dysfunction, Antepartum haemorrhage, Stress and Malnutrition] and Iatrogenic [30%] as [Hypertension, Diabetes, Intrauterine growth restriction] [14].

Progesterone has a role in maintaining pregnancy, by suppression of the calcium–calmodulin–myosin light chain kinase system. Additionally, progesterone has recognized anti-inflammatory properties, raising a possible link between inflammatory processes, alterations in progesterone receptor expression and the onset of preterm labor. Systematic reviews of randomized controlled trials evaluating the use of intramuscular and vaginal progesterone in women considered to be at increased risk of preterm birth have been published, with primary outcomes of preterm birth <34 weeks, perinatal death,and neurodevelopmental handicap in childhood [15].

The purpose of this study was to evaluate whether the prophylactic administration of vaginal progesterone would reduce the preterm birth rate in high-risk singleton pregnancies.

The study will include 100 cases of high risk pregnant women admitted to the department and candidates for progesterone therapy for possible preterm birth. Our patient characteristics were age [19-33] years, mean cervical length [36 ± 0.7 mm] and mean gestational age of previous preterm delivery [29.8±2.7 week].

This current results showed that the incidence of preterm delivery in the Study Group was significantly lower than that of the Control Group [38% versus 56%], the postnatal morbidity was also significantly lower [6% versus 15%] while the postnatal mortality was not significantly different. Our results indicate that the progesterone therapy significantly reduced the incidence of preterm delivery.

The same results were reported by a previous study by [16] Society for Maternal-Fetal Medicine Publications Committee (2012) reported that vaginal progesterone administration was associated with a reduction in the risk of admission to the neonatal intensive care unit [NICU], respiratory distress syndrome [RDS], composite neonatal morbidity and mortality in many studies.

Even with a shorter cervical length than we reported in our study [mean was 36 mm in our study], vaginal progesterone achieve a statically significant effect difference between study group and control group according to preterm labor. Data were available from 974 women in [17] study [498 assigned to vaginal progesterone, 476 assigned to placebo] with a cervical

length ≤25 mm participating in five high-quality trials. Vaginal progesterone was associated with a significant reduction in the risk of preterm birth <33 weeks of gestation [RR 0.62, 95% CI 0.47-0.81, P=0.0006; high-quality evidence]. Moreover, vaginal progesterone significantly decreased the risk of preterm birth <36, <35, <34, <32, <30 and <28 weeks of gestation, spontaneous preterm birth <33 and <34 weeks of gestation, respiratory distress syndrome, composite neonatal morbidity and mortality, birth weight <1500 and <2500 g, and admission to the neonatal intensive care unit [RRs from 0.47 to 0.82; high-quality evidence for all]. There were seven [1.4%] neonatal deaths in the vaginal progesterone group and 15 [3.2%] in the placebo group [RR 0.44, 95% CI 0.18-1.07, P=0.07; low-quality evidence]. Maternal adverse events, congenital anomalies, and adverse neurodevelopmental and health outcomes at 2 years of age did not differ between groups.

A.Abdou et al. [18] showed that the administration of vaginal suppository progesterone [200 mg, daily] beginning at 20 - 24 wks of gestation and continued to 36 wks of gestation can significantly reduce the rate of preterm birth before 37, 32 and 28 wks of gestation among women with previous spontaneous preterm birth specially in earlier gestational ages and increase the mean birth weight. In addition, the rates of RDS and admission to NICU were significantly decreased among infants of women assigned to progesterone treatment. Also, there was an additional benefit of vaginal progesterone for prevention of preterm birth in women who had prior spontaneous preterm birth and cervical length < 25 mm. This result was in the same line with [19] where there was no statistically significant difference between study group and control group according to no. of previous preterm in women with This was a multicenter, randomized, double-blind, placebo-controlled trial that enrolled asymptomatic women with a singleton pregnancy and a sonographic short cervix [10–20 mm] at 19 + 0 to 23 + 6 weeks of gestation.

In the opposite side, the findings of the OPPTIMUM study (2016)were reported. This was a randomized controlled trial comparing vaginal progesterone versus placebo in women at risk of preterm birth because of previous spontaneous preterm birth <34 weeks of gestation, or a cervical length ≤25 mm, or because of a positive fetal fibronectin test combined with other clinical risk factors for preterm birth. The results of that trial showed that vaginal progesterone did not significantly reduce the risk of preterm birth or perinatal morbidity and mortality in the entire population, or in the subgroup of women with a cervical length ≤25 mm. This study clearly says that vaginal progesterone was not associated with reduced risk of preterm birth or composite neonatal adverse outcomes, and had no long-term benefit or harm on outcomes in children at 2 years of age [20].

In J. M. O'Brien et al. [21] found that prophylactic treatment with vaginal progesterone did not reduce the frequency of recurrent preterm birth [</= 32 weeks] in women with a history of spontaneous preterm birth. The effect of progesterone administration in patients at high risk for preterm delivery as determined by methods other than history alone [e.g. sonographic cervical length] requires further investigation.

There was many different between study group properties between this study and ours. This study group age was [18-45] years old and the mean age of previous preterm labor was only 19.9 weak. And that may explain the difference of results between the two studies

E. B. Fonseca et al. [22] reported that progesterone was associated with a not significant reduction in neonatal morbidity [8.1% vs. 13.8%; relative risk, 0.59; 95% CI, 0.26 to 1.25; P=0.17]. There were no serious adverse events associated with the use of progesterone.

This study discussed much more serious factors to estimate fetal morbidity than in our study like [intra ventricular hemorrhage,, retinopathy of prematurity, or necrotizing enterocolitis] which isn't included in our study.

5.Conclusion

From this study we concluded that vaginal progesterone reduces the risk of PTB,NICU admission, RDS in singleton pregnancies at high-risk of preterm labour.

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