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Oral Micronized or Parenteral Progesterone versus Health Education in the Prevention of Preterm Birth: A Single Blinded Randomized Controlled Trial

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Abstract

Objective: The primary aim of this study was to evaluate the possible prophylactic role of progesterone in women with a history of spontaneous preterm birth (PTB) while the secondary aim was to compare oral or intramuscular progesterone versus health education in such cases. **Methods:** A randomized, single blinded interventional randomized controlled trial was conducted. It comprised 90 cases with a history of PTB who were divided into 3 equal groups who received oral micronized progestogen capsule 200 mg daily (group A), parenteral 17 α-hydroxyprogesterone caproate 250 mg weekly IM injections (group B) or received health education including rest (group C) starting from 20 weeks till the end of 34 weeks of gestation. **Results:** This study included eligible 90 pregnant women at high risk of PTB who continued follow-up. For socio-demographic characteristics, there were no significant differences between the groups in respect to age, residence, education level, occupation, gravidity, parity and number of living children apart from significant difference between group A and C regarding mean patients' age. Mode and place of delivery did not differ between the groups while gestational age at time of delivery was significantly better on using injectable than oral progesterone. Neonatal birth weight was significantly higher in group B if compared separately to groups A and C and was still significantly higher in group A if compared with group C. NICU admission rate was higher in group C if compared to group B or to the combined group A and B. Compliance was significantly higher in group B if compared to both group A and C and was significantly higher in the intervention group A and B if compared to group C. **Conclusions:** Progesterone supplementation has a significant role in prevention of PTB if compared with just health education. Progesterone

injections expressed significantly better results than oral micronized progesterone in terms of prolongation of gestational age, better neonatal birth weight and less admission rate to the NICUs.

Keywords

Preterm Birth, Oral, Injectable, Progesterone, Health Education

1. Introduction

Preterm birth (PTB) is the delivery prior to 37 weeks or 259 days of gestation. It represents a real challenge of all obstetricians and accounts for over 85% of all perinatal morbidity and mortality [1]. About 15 million babies are delivered preterm each year (5% to 18% of all deliveries) [2]. The chance of survival at less than 23 weeks is close to zero %, while at 23, 24 and 25 weeks, it is 15%, 55% and 80% respectively [3]. Premature infants are at greater risk for cerebral palsy, delays in development, hearing problems, and sight problems [4].

Since management of premature babies is costly and tedious work with limited success, much interest has been focused on preventive measures rather than treating established cases of PTB and premature babies.

The main preventive drugs of preterm birth are tocolytics, antibiotics and drugs that prevent fetal respiratory distress syndrome like corticosteroids [5]. The use of progesterone is associated with benefits in infant health following administration in women considered to be at increased risk of PTB. Synthetic or natural progesterone is helpful to allow pregnancy to reach its physiological full term as it blocks the oxytocin effect of prostaglandin F_2 alpha and α-adrenergic stimulation and therefore increases the α-adrenergic tocolytic response [6]. Supplemental progesterone decreases both the number of episodes of uterine contractions and the incidence of PTB in women at high risk for PTB [7]. However, progesterone prophylaxis is not a magic treatment as it was found to reduce the risk of PTB by just 20% despite proper dose and the absolute PTB rate would be reduced by only 0.01%, because most PTB are not recurrences and prophylaxis has limited efficacy [8]. Moreover, there is limited information available regarding long-term infant and childhood outcomes. So, further trials are required to assess the optimal timing, mode and dose of administration of progesterone therapy if given to women at risk of PTB [9]. The primary aim of this study was to evaluate the possible prophylactic role of progesterone in women with a history of spontaneous preterm birth (PTB) while the secondary aim was to compare oral or intramuscular progesterone versus health education in such cases.

2. Patients and Methods

This study was a randomized, single blinded (the researchers but not the subjects know which subjects are receiving the active treatment and which are not to eliminate the subjective bias), randomized controlled trial conducted at the

Woman's Health University hospital of Assiut Faculty of Medicine, Assiut, Egypt between July 2017 and May 2018. It was approved by the Research Ethics Committee of the Faculty of Medicine, Assiut University. The methods were performed in accordance with approved guidelines. Written informed consent was obtained from all participants. This clinical trial was registered at ClinicalTrials.gov (Clinical trials registration: NCT 03343795). The study consecutively recruited 152 asymptomatic pregnant women at 20 - 34 weeks of gestation identified to be at increased risk to have spontaneous PTB based on the presence of prior history of spontaneous PTB. PTB was defined as delivery of a potentially viable fetus between 28 and 37 gestational weeks. As shown in **Figure 1**, 48 cases were not included in this study. Women on tocolytic drugs, women having current cervical cerclage, multiple gestation or women with a picture of established preterm labor were excluded from this study. Major fetal congenital malformations as proved by level II ultrasonography were also excluded from this study. On the other hand, 104 cases fulfilling the inclusion criteria were included. Women should have a singleton pregnancy with a past history of one or more PTB. Among the included patients, 14 declined to participate. Starting from 20 weeks till the end of 34 weeks of gestation, the remaining 90 cases were randomly divided into 3 equal groups according to the management plan using sequentially numbered opaque sealed envelopes. Group A received oral micronized progestogene capsule 200 mg daily at bed time (Hysterogest Globe International Pharm, Cairo, Egypt). Group B received parenteral 17 α-hydroxyprogesterone caproate 250 mg weekly deep intramuscularly gluteal injections (Cidolut Depot, Cid Co, Cairo, Egypt). Group C received health education which included clear instructions of rest as much as possible, sleeping at least 8 hours daily, minimization of travelling or carrying heavy objects, avoiding sexual intercourse particularly if she feels colic during it, drinking excessive amounts of oral fluids to keep the level of antidiuretic hormone at least (which has an oxytocin like action), proper treatment of any concomitant vaginal or urinary infections, avoiding travelling or direct trauma to the abdomen and avoid smoking, alcohol or drug intake. After initial clinical and sonographic evaluation of all cases, they were allocated in one of the 3 groups and were asked to come for follow-up visits every 2 weeks. During every visit, women were asked about occurrence of pelvic heaviness, cramps, abdominal colic, painful fetal movements, passage of excessive mucoid with or without blood vaginal discharge, sudden gush of vaginal fluid or any other alarming symptoms of PTB. All cases were subjected to uterine contraction monitoring using external tocodynamomerer in the left lateral position for 60 minutes by an external monitor, from 28 to 34 weeks of gestation. A positive test was considered when there were four or more contractions per hour, before the 30th week of gestation, and from 30 weeks onward, 6 or more contractions per hour [10].

The primary outcome was to assess the occurrence of definite uterine contractions or PTB. Secondary outcomes were assessment of gestational age at the time of delivery, course of delivery and pregnancy outcome, neonatal outcome, com-

pliance and side effects. Neonatal outcomes included birth weight, Apgar scores, neonatal intensive care unit (NICU) admission rate and for how long, transient tachypnea of neonate, respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH) as diagnosed by ultrasonography or CT scan, necrotizing enterocolitis (NEC), neonatal sepsis or neonatal death. Moreover, the need for assisted respiration and intubation was recorded.

Data were collected, revised, stratified and analyzed using SPSS (SPSS Inc, Chicago, IL, USA) program version 22. Data were presented as mean and SD or number and percentage. Chi-square test and Fisher-exact test for categorical variables, independent *t*-test for continuous variables, and Mann-Whitney U test for nonparametric variables were used when appropriate. A $p < 0.05$ was considered statistically significant.

3. Results

This study included eligible 90 pregnant women at high risk of PTB after exclusion of 48 cases and 14 cases who declined to participate. They were randomly assigned to three groups: Group A received oral micronized progestogene capsule 200 mg daily at bed time, Group B received parenteral 17 α- hydroxyl-progesterone caproate 250 mg weekly deep intramuscularly gluteal injections and Group C received health education (**Figure 1**). None of the eligible women were lost to follow-up. For socio-demographic characteristics, there were no significant differences between the groups in respect to age, residence, education level, occupation, gravidity, parity and number of living children apart from significant difference between group A and C regarding mean patients' age (**Table 1**).

Mode and place of delivery did not differ between the groups while gestational age at time of delivery was significantly better on using injectable than oral progesterone. Regarding maternal complications, postpartum hemorrhage was more significantly common in group C if compared to both groups A and B separately or if combined. The same applies for puerperal sepsis if compared to group B or combined group A and B (**Table 2**). Main neonatal outcomes are shown in **Table 2**. Neonatal birth weight was significantly higher in group B if compared separately to groups A and C and was still significantly higher in group A if compared with group C. The same occurred if combined results of groups A ns B were compared to group C. Apgar scores < 7 at 1 and 5 min did not differ between the groups. Additionally, differences between groups in respect to RDS, IVH, NEC, sepsis, apnea of prematurity, transient tachypnea of new born (TTNB), and days of neonatal hospitalization were not significant. There was no neonatal mortality in this study. NICU admission rate was higher in group C if compared to group B or to the combined group A and B as shown in **Table 2**. **Table 3** demonstrates side effects and patient satisfaction. Compliance was significantly higher in group B if compared to both groups A and C and was significantly higher in the intervention groups A and B if compared to group C.

Table 1. Sociodemographic data of the studied cases.

	Oral progesterone (n = 30)		Injectable progesterone (n = 30)		Health Education (n = 30)		P-value[1]	P-value[2]	P-value[3]	P-value[4]
	No.	%	No.	%	No.	%				
Age: (years)										
Mean ± SD	32.83 ± 5.24		31.76 ± 4.92		29.83 ± 5.71		0.430	0.046*	0.179	0.059
Range	20.0 - 42.0		21.0 - 40.0		20.0 - 39.0					
Residence:										
Rural	19	63.3	21	70.0	17	56.7	0.353	0.598	0.284	0.353
Urban	11	36.7	9	30.0	13	43.3				
Education:										
Illiterate	22	73.3	27	90.0	23	76.7	0.576	0.766	0.166	0.576
Literate	8	26.7	3	10.0	7	23.3				
Occupation:										
Working	7	23.3	5	16.7	6	20.0	1.000	0.754	0.739	1.000
Not working	23	76.7	25	83.3	24	80.0				
Gravidity:										
Mean ± SD	4.35 ± 2.14		3.89 ± 1.86		4.14 ± 2.77		0.340	0.749	0.690	0.953
Range	3.0 - 9.0		3.0 - 8.0		2.0 - 9.0					
Parity:										
Mean ± SD	3.81 ± 1.40		3.56 ± 1.66		3.72 ± 1.53		0.540	0.817	0.706	0.494
Range	2.0 - 6.0		2.0 - 7.0		2.0 - 8.0					
Living children:										
Mean ± SD	3.49 ± 1.32		3.27 ± 1.23		3.30 ± 1.13		0.517	0.561	0.924	0.914
Range	2.0 - 5.0		2.0 - 6.0		2.0 - 6.0					

P-value[1]: significance between group A and group B. P-value[2]: significance between group A and group C. P-value[3]: significance between group B and group C. P-value[4]: significance between combined group A and B (intervention) and group C (health education).

Table 2. Peripartum and neonatal outcomes of the studied groups.

	Oral (n = 30)		Injection (n = 30)		Health education (n = 30)		P-value[1]	P-value[2]	P-value[3]	Pvalue[4]
Gestational age (weeks) at time of delivery										
Mean ± SD	34.97 ± 5.02		37.87 ± 2.93		34.90 ± 3.50		0.032*	0.951	0.028*	0.599
Range	22.0 - 40.0		29.0 - 40.0		22.0 - 39.0					
Mode of delivery										
Vaginal	17	56.7	19	63.3	15	50.0	0.598	0.605	0.297	0.367
C.S.	13	43.3	11	36.7	15	50.0				
Place of delivery										
Governmental hospital	12	40.0	9	30.0	13	43.3	0.417	0.793	0.284	0.462
Private clinic	18	60.0	21	70.0	17	56.7				

Continued

Puerperal sepsis										
Yes	5	16.7	3	10.0	12	40.0	0.706	0.045*	0.007*	0.046
No	25	83.3	27	90.0	18	60.0				
Post-partum hemorrhage										
Yes	9	30.0	4	13.3	12	40.0	0.117	0.417	0.020*	0.034*
No	21	70.0	26	86.7	18	60.0				
Need for blood transfusion										
Yes	6	20.0	4	13.3	7	23.3	0.488	0.754	0.317	0.190
No	24	80.0	26	86.7	23	76.7				
Duration of lactation (ms)										
Mean ± SD	16.54 ± 3.56		16.97 ± 4.12		18.22 ± 5.11		0.674	0.157	0.314	0.243
Range	6.0 - 24.0		8.0 - 24.0		6.0 - 24.0					
Breast complications:										
Yes	6	20.0	5	16.7	9	30.0	0.739	0.371	0.222	0.612
No	24	80.0	25	83.3	21	70.0				
NICU:										
Yes	13	43.3	9	30	18	60.0	0.284	0.196	0.020*	0.036*
No	17	56.7	21	70	12	40.0				
Birth weight (Kg)										
Mean ± SD	2.23 ± 0.51		2.64 ± 0.43		2.07 ± 0.49		0.015*	0.035*	0.007*	0.007*
Range	1.9 - 2.6		1.9 - 2.8		1.8 - 2.4					

P-value[1]: significance between group A and group B. P-value[2]: significance between group A and group C. P-value[3]: significance between group B and group C. P-value[4]: significance between combined group A and B (intervention) and group C (health education).

Table 3. Side effects and patient satisfaction of the studied cases.

	Oral (n = 30)		Injection (n = 30)		Health education (n = 30)		P-value[1]	P-value[2]	P-value[3]	P-value[4]
	No.	%	No.	%	No.	%				
Side effects:										
Nausea/vomiting	2	6.6	0	0	0	0	-	-	-	-
Drowsiness	7	23.3	0	0	0	0				
Injection site problems	0	0	6	20	0	0	-	-	-	-
Interference with daily activities	0	0	0	0	11	36.6	-	-	-	-
Women satisfaction score:										
Mean ± SD	71.30 ± 11.44		83.46 ± 14.71		59.13 ± 10.45		0.011*	0.004*	0.001*	0.001*
Range	62 - 82		67 - 93		43 - 70					

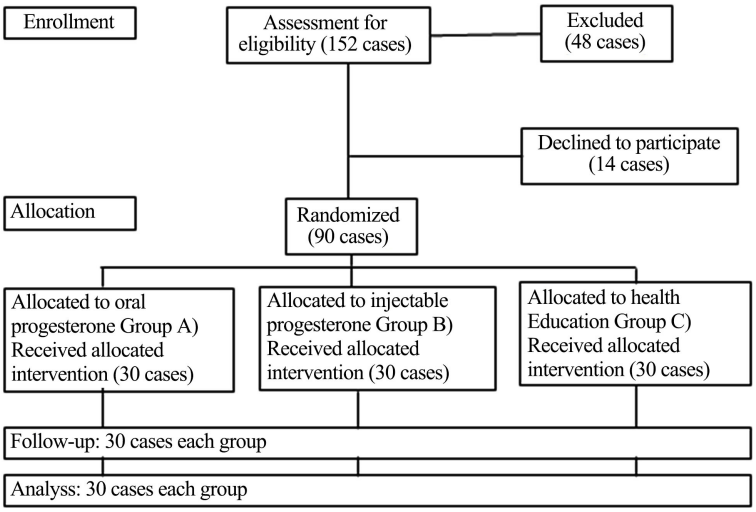

Figure 1. Flow chart of the studied cases.

4. Discussion

Despite great advances in neonatal care, the burden of established PTB is still high. Prevention of PTB is a continuous dilemma in modern obstetric practice. Some authors proved the efficacy of one intervention while others denied the role of the same intervention. Nowadays, there is a bad need for high-quality research in this area of obstetrics. In a recent Cochrane review, it was stated that there is no evidence for the clinically important interventions of cervical pessary, cervical length assessment and vaginal progesterone for prevention of PTB [11]. Centrally, vaginal progesterone was proved to be significantly effective for prevention of PTB in high risk cases [12]. Currently, no evidence exists on which progesterone supplementation can maximize the preventative effects while minimizing the side effects. Therefore, further researches are still required to define the optimal type, dose and duration of progesterone depending on various indications of treatment [13].

The first aim of this study was to test if there is a role of progesterone for prevention of PTB. We tested two routes of progesterone administration. Oral micronized natural progesterone 200 mg capsules were used in group A while weekly IM injection of 250 mg of 17-α hydroxyprogesterone caproate (a synthetic derivative of 17 hydroxyprogesterone) with a half-life of 7.8 days was used in group B. Both routes were compared to each other and were combined and compared with health education including rest (group C). We tried to make study cases homogenous and excluded 62 cases from assessed 152 cases (40.7%) due to strict inclusion and exclusion criteria used. Socio-demographic data of the 3 groups were more or less similar. The mean age of all cases was 31.4 years. It is well known that maternal age under 18 years (OR 1.70, 95% CI 1.02 - 3.08) or over 35 years is the risk factor for PTB [14]. Some authors compare progesterone supplementation versus no intervention [15] [16]. The ethics committee of our institution refused to make group C with no intervention. It seems unethical

to subject a group of high risk of PTB to no treatment. We relied on regulation of life style and rest. Rest has been tested before but no definite studies support its role in the prevention or management of PTB. There has not been any randomized trial of bed rest in the prevention or treatment of PTB in single pregnancy [17], and a trial of bed rest in twin pregnancies revealed no benefit [18]. Moreover, the greater the degree of immobilization, the higher the risk of maternal complications such as thrombosis and muscle atrophy [19]. Likewise, this study detected inferiority of rest and health education if compared to progesterone therapy in all neonatal and some maternal aspects.

This study clearly addresses the effective and significant role of progesterone for the prevention of PTB in high risk cases as the results of combined group A and B were superior to group C as regards some maternal complications (puerperal sepsis and postpartum haemorrhage) and neonatal admission to NICU and birth weight. These results go hand in hand with some recommendations that the most important single advance of the past decade has been the introduction of progesterone supplementation for the prevention of PTB [20]. Moreover, it can also be used for secondary prevention after tocolysis in singleton pregnancy [21]. The available evidence supports the recommendation that all pregnant women who have either a prior history indicating increased risk or current, asymptomatic cervical insufficiency should receive progesterone supplementation until the end of 34 weeks. Prophylactic progesterone administration is an evidence-based method for the prevention of preterm birth in women with a previous preterm birth and in pregnant women with a sonographically short cervix (≤25 mm) before 24 weeks of gestation [22]. On the other hand, some randomized controlled trials failed to define any role of progesterone for this purpose [16]. The role of oral progesterone is not well established in literature. Oral dedrogesterone was ineffective in a randomized controlled trial [16]. In this study, we used oral micronized natural progesterone for group A in dose of 200 mg daily. We selected 200 mg dose as it is commercially available at our country in this form (Hysterogest). Others used 100 mg daily twice a day versus placebo in women with history of spontaneous PTB. The treatment group had lower rates of PTB < 37 weeks of gestation and PTB at 28 to 32 weeks of gestation [23]. Another randomized controlled trial included 212 singleton pregnancies with past history of spontaneous preterm delivery at <37 weeks, into a progesterone group (receiving 100 mg oral micronized progesterone, six-hourly, starting at 14 - 18 weeks until 37 weeks or delivery) and an identical placebo group. They documented significant efficacy of 400 mg oral progesterone for prevention of PTB. The progesterone group delivered at a later gestational age, and needed longer tocolysis-to-delivery intervals (35.4 weeks vs. 33.9 weeks, $p = 0.01$, and 87 days vs. 36 days, $p < 0.001$, respectively). The relative risk of spontaneous preterm delivery was 0.7 (95% confidence interval 0.54 - 0.92, $p = 0.01$) [24]. However, no difference was noted in the rate of recurrent PTB and neonatal outcome between the use of high dose of 400-mg oral progesterone group and placebo

group in another study [25]. These conflicting results regarding oral natural progesterone in addition to increased incidence of nausea and drowsiness (occurred in 30% of cases in this study) call for more extensive large sample sized studies to define its role in modern practice.

In this study, we utilized 17-alpha-hydroxyprogesterone caproate (17-OHPC) 250 IM weekly injections for group B. Our results encourage its use as a preferred progesterone due to its better and significant results if compared to oral progesterone and with health education. Initial studies suggested a potential benefit for 17-alpha-hydroxyprogesterone caproate (17-OHPC) in decreasing the risk of recurrent preterm birth women with a singleton gestation. However, the use of 17-OHPC has not conferred benefit for other categories of women at high risk for preterm delivery (twins, triplets, and short cervical length) [26]. In this study, patient satisfaction with its use was significantly better than oral progesterone despite injection site problems in 20% of cases. This can be explained by efficacy, weekly use and avoidance of oral route with its side effects. However, some studies denied the role of 17-alpha-hydroxyprogesterone caproate (17-OHPC) whenever cervical length is shortened < 25 mm [27]. Moreover, its addition to cerclage in women with three or more second trimester pregnancy losses didn't improve results [28]. These results are not consistent with some recommendations that all pregnant women who have either a prior history indicating increased risk or current, asymptomatic cervical insufficiency should receive progesterone supplementation until the end of 34 weeks [20]. Vaginal progesterone was thought to be superior to intramuscularly applied 17-OHPC, especially because of the lower rate of maternal side effects [22]. Actually, there are missing well-constructed studies to address which type of progesterone should be the first choice for prevention of PTB. The main limitations of this study are small sample size which may be attributed to high exclusion rate up to 40% of cases and lack of correlation with cervical length by ultrasonography which was excluded due to performing the study in two different hospitals with variable experience of the sonographers. More studies with bigger sample size and variable progesterone doses and routes are recommended. From this study, it is concluded that progesterone supplementation has a significant role in prevention of PTB if compared with just health education. Progesterone injections expressed significantly better results than oral micronized progesterone in terms of prolongation of gestational age, better neonatal birth weight and less admission rate to the NICUs.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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