Effectiveness of vaginal administration of natural progesterone for prevention of preterm labor

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Abstract: Suppositories in patients at high risk of preterm birth. **Patients and Methods:** This randomized controlled double-blinded clinical trial involved 146 pregnant women at high risk of preterm labor. All women had singleton pregnancy before 20 weeks of gestation with a past history of one or more spontaneous preterm labor. They were randomized into two groups; progesterone and placebo groups. Women in the progesterone group received Utrogestan capsules containing 100 mg of natural progesterone vaginally once a day at bedtime. Women of placebo group received similar capsules the same way as the progesterone group. Medication was started at 20 weeks and stopped at the end of 34 weeks. The primary outcome measure was delivery before 34 and 36 weeks. **Results:** Four patients were lost to follow up; results are presented for 142 patients. Progesterone treated group have significantly reduced frequency of preterm deliveries before 36 weeks ($p = 0.017$) and before 34 weeks ($p = 0.008$) compared to placebo group. Progesterone is protective against preterm delivery before 36 weeks with an Odds Ratio (OR) of 0.39 (95%CI: 0.18-0.86) and against preterm delivery before 34 weeks with an OR 0.23 (95%CI: 0.07-0.73). **Conclusion:** Natural progesterone seems effective in reduction of the rate of preterm deliveries if administered vaginally starting from mid trimester for women with prior preterm births with minimal adverse effects.

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1. Introduction:

Preterm labor is defined as delivery before 37 completed weeks of gestation[1]. It is a significant perinatal health problem worldwide, butdeveloping countries suffer the highest burden of the problem. In a systematic review, it was estimated that in 2005, 9.6% of all births were preterm; 85% of them was concentrated in Africa and Asia. The highest rates occurred in Africa (11.9%) and North America (10.6%)[2].

Preterm birth is the leading cause of neonatal morbidity and mortality accounting for 70% of these complications such as cerebral palsy, sensory deficits and respiratory illnesses[3]. About 28% of early neonatal deaths not related to congenital malformations are due to preterm birth[4]. The morbidity associated with preterm birth extends to childhood and adolescence resulting in massive physical, psychological and economic costs[5].

The exact etiology of preterm birth is not completely understood; however it is thought to be multifactorial. Causal factors include medical diseases of the mother, genetic factors, environmental exposure, treatments of infertility and socioeconomic factors[6]. In nearly half of preterm births, there is no definite cause and in 30% of cases, labor is preceded by preterm rupture of membranes (PROM). In addition, 15-20% are attributed to medically indicated deliveries[7]. Also, the exact mechanisms of preterm labor are essentially unknown. These are believed to comprise cervical incompetence, cervical inflammation, uterine distortion, decidual hemorrhage, uteroplacental insufficiency and hormonal changes[6].

This mystery in the etiology and mechanisms of preterm labor in addition to the absence of a precise method for prediction of the problem - including suggested scoring systems - hinders the development and implementation of effective prophylactic and therapeutic measures. However, prevention should be considered in high-risk women and in response to screening tests as cervical ultrasound[8,9], fetal fibronectin[10] or uterine electromyography[11].

Medical prevention consists of administration of antibiotic and/or progesterone. The use of antibiotics in women at high risk of preterm birth was based on association of infection in a significant proportion of preterm birth. However, prophylactic antibiotics have not been shown to be beneficial in preterm birth prevention; even some trials reported a trend towards an increased risk[12]. At present, progesterone prophylaxis is a key research focus in prevention of preterm birth.

Many studies reported the beneficial effect of progesterone by intramuscular injection or in the form of vaginal suppositories in reduction of the rate of preterm labor[13-15]. Mainly, two types of

progesterone were used; natural and synthetic[16]. Natural progesterone is administered mainly vaginally, one study reported the use of oral micronized progesterone[17]. On the other hand, 17-α-hydroxy-progesterone is a synthetic progesterone given exclusively by the IM route with limited side effects[13].

The **aim** of the study is to test theprophylacticefficiency of progesterone vaginal suppositories in patients at high risk of preterm birth.

2. Patients and methods:

This randomized controlled double-blinded clinical trial involved 146 pregnant women diagnosed to be at high risk of preterm labor recruited from the maternity hospital of Ain Shams University during the period from June 2009 to May 2010. Using closed envelop method, women were randomized into two groups; progesterone and placebo groups. Progesterone and placebo vaginal capsules were identical in shape, color and weight. Both the patients and the researcher were blinded to the study medication allocation. Treatment assignment was blinded till delivery of the last pregnant woman in the study.

Women were selected for this study if they have singleton pregnancy before 20 weeks of gestation with a past history of one or more spontaneous preterm labor.Exclusion criteria were multiple gestations, congenital malformations, tocolytictherapy or having cervical cerclage in the current pregnancy.

Gestational age was confirmed on the basis of the date of the last menstrual period and ultrasonography up to12 weeks or by two concordant scans between 12 and 20 weeks. At recruitment, full history taking and general and obstetric examination was done for all women who were advised about the benefit of the drug used. A written informed consent to join the study was taken from each woman before enrollment in the study

All women received prophylactic medical treatment for bacterial vaginosis and chlamydial infection just before starting progesterone therapy in the form of Azithromycin tablets 500 mg once a day for 3 days and Metronidazole tablets 250 mg three times/day for 7 days.

Women in the progesterone group received Utrogestancapsules containing 100 mg of natural progesteronevaginally once a day at bedtime. Women of the placebo group received similar capsules the same way as the progesterone group. Medication was started at 20 weeks and stopped at the end of 34 weeks.

At the follow up visits, women were submitted to uterine contraction monitoring by an external tocodynamometer every other week for 60 minutes by an external monitor from 28 to 34 weeks of gestation while in left lateral position. A positive test was considered when there were ≥ 4 contractions/hour before the 30th week of gestationor≥ 6 contractions/hour from 30 weeks onward. Women were asked about symptoms of preterm labor as heaviness, cramps, abdominal colic, and sudden gush of fluid.

Statistical methods:

Data was analyzed using IBM SPSS Advanced Statistics version 20.0 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation (SD) or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. For quantitative data, comparison between two groups was done using independent sample t-test or Mann-Whitney test. Odds ratio (OR) with its95% confidence interval (CI) were used for risk estimation. A p-value < 0.05 was considered significant.

3. Results

Four patients (3 in the progesterone group and 1 in the placebo group) were lost to follow up; thus outcome data are available for 142 of the 146 admitted women (97.3%). Table 1 shows that there was no significant difference between progesterone and placebo groups in age, parity and body mass index as well as history of preterm labor.

Table 1: Demographic and Clinical characteristics of the two studied groups

	Progesterone Group (n = 70)	Placebo Group (n = 72)	p value
Age, mean±SD (years)	27.5±3.5	27.9±2.8	0.453
Parity, median (range)	2 (1-4)	1 (1-4)	0.509
Body mass index, mean±SD (years)	24.1±2.6	23.8±2.8	0.510
Work, working/housewife	23/47	28/44	0.454
Previous preterm labors, median (range)	1 (1-3)	1 (1-3)	0.283

Progesterone treated group have significantly reduced frequency of preterm deliveries before 36 weeks (p = 0.017) and before 34 weeks (p = 0.008) compared to placebo group. Progesterone is protective against preterm delivery before 36 weeks with an Odds Ratio (OR) of 0.39 (95%CI: 0.18-0.86) and against preterm delivery before 34 weeks with an OR 0.23 (95%CI: 0.07-0.73).

Gestational age at delivery was significantly longer in the progesterone group in all women (p = 0.003) and in those born before 36 weeks (p < 0.001). Symptoms of preterm labor were more frequent in the placebo group, with a trend towards statistical significance (p = 0.066). Occurrence of uterine contractions was more significantly frequent in the placebo group (p = 0.028) (Table 2). Progesterone is protective against preterm uterine contractions with an Odds Ratio (OR) of 0.45 (95%CI: 0.22-0.92).

Table 2: Comparison between the two studied groups as regards presence of preterm labor (< 36 weeks)

	Progesterone Group (n = 70)	Placebo Group (n = 72)	p value
Frequency of preterm labor < 36 weeks, No.(%)	12 (17.1%)	25 (34.7%)	0.017
Frequency of preterm labor < 34 weeks, No.(%)	4 (5.7%)	15 (20.8%)	0.008
GA at delivery, mean±SD (weeks)	37.2±1.7	36.0±2.8	0.003
GA at delivery in neonates born before 36 weeks, mean±SD (weeks)	34.3±1.4	32.6±2.1	< 0.001
Frequency of symptoms of preterm labor, No.(%)	31 (44.3%)	43 (59.7%)	0.066
Frequency of uterine contractions, No.(%)	17 (24.3%)	30 (41.7%)	0.028

GA: gestational age

Pregnancy was complicated by intrauterine feral death in only 1 case of progesterone group. Also, one case in each group was complicated by antepartum hemorrhage.

4. Discussion:

This study demonstrated that vaginal suppositories of 100 mg natural progesterone are effective in prophylaxis of preterm delivery before 36 and 34 weeks in women with prior history of preterm births. Immediate adverse effects after delivery are minimal.

In the current study, we depend on the single greatest risk factor for preterm delivery which is a previous preterm delivery. The risk of preterm delivery is 15% following one and 41% after a second preterm delivery[18]. We used natural progesterone in the form of vaginal suppositories which bypasses hepatic effects resulting in better bioavailability. It has been reported that endometrial bioavailability is higher after vaginal progesterone compared to the intramuscular route in spite of lower serum levels[19], which is attributed to the so-called uterine first-pass effect, i.e. direct transport of progesterone from the vagina to the uterus[20]. Compared to oral use, vaginal administration is nearly free of side effects as sleepiness, fatigue, and headache[15,19].

The role of progesterone in myometrial quiescence was first reported in 1954 [26]. During the last decade, several randomized trials were done for evaluation of the effect of intramuscular 17-α-hydroxy-progesterone caproate or natural progesterone administered vaginally or orally for prevention of preterm birth. Different studies involved different populations regarding singleton or multiple gestation, history of previous preterm births and length of uterine cervix.

In a group of 142 women with singleton gestations and past history of preterm birth, da Fonseca et al. [14] reported significant reduction in the incidence of preterm delivery before 37 and 34 weeks using vaginal progesterone 100 mg from 24-34 weeks compared to placebo. In a similar study, vaginal progesterone 90-mg gel reduced the rate of preterm labor as well as neonatal morbidity and mortality[19]. A large prospective randomized trial involving 518 women with a prior history of preterm birth found that 90 mg of vaginal progesterone gel is more effective than intramuscular progesterone for prevention of preterm birth with fewer adverse effects[21].

An adjusted indirect meta-analysis of 4 randomized controlled trials performed an indirect comparison of vaginal progesterone vs. cerclage. Conde-Agudelo *et al* [22] found that vaginal progesterone is equally effective as cerclage in the prevention of preterm birth in the presence of a short cervix in the mid trimester.Vaginal progesterone gel was also successful in cases of mid-trimester short cervix where it resulted in 45% reduction in the rate of preterm birth before 33 weeks of gestation in a

multicenter, randomized, double-blind, placebo-controlled trial involving 458 women[23].

The exact mechanism of action of progesterone in preventing preterm birth is not known. However, many studies suggested several possibilities. Generally, two mechanisms seem to be more probable; an anti-inflammatory effect, and a local increase in progesterone concentration in the gestational tissues which neutralizes the functional decrease in progesterone that leads to preterm delivery[19,24].

A recent study found no effect of vaginal or intramuscular progesterone on several pathways known to be involved in uterine contractility or quiescence or cervical remodeling[25].

Conclusion:

Natural progesterone seems effective in reducing the rate of preterm deliveries if administered virginally starting from mid trimester among women with prior preterm births with minimal adverse effects.

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