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Original Research

Assessment of prophylactic use of oral micronized progesterone in prevention of preterm labour in high risk pregnancy

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ABSTRACT:

Objective: To assess the effect of prophylactic use of oral micronized progesterone (OMP) in prevention of preterm labour(PTL) in high risk pregnancy. **Methods:** this present case control study was conducted at OBGY Department 120 women with at least one PTB who received 100 mg of OMP or no drug twice a day from recruitment (18–24 weeks) until 36 weeks or delivery. **Results:** PTB occurred in 29 women in the OMP group (n= 60) compared with 60 in the control group (n= 60, P = 0.002). Mean gestational age at delivery was higher in the OMP group (36.1 vs 34.0 weeks, P b 0.001). Fewer preterm births occurred between 28 and 31 weeks plus 6 days in the OMP group (RR 0.20; 95% CI, 0.05–0.73, P b 0.001). Neonatal age at delivery (34 vs 32 weeks, P b 0.001), birth weight (2400 vs 1890 g, P b 0.001), NICU stay (N 24 h, P b 0.001), and Apgar scores (P b 0.001) were more favorable in the OMP group, and fewer neonatal deaths occurred (3 vs 7, P = 0.190).**Conclusion:** In high risk patients, OMP decreased the risk of PTB between 28 and 31 weeks plus 6 days, NICU admissions, and neonatal morbidity and mortality.

Keywords: Oral micronized progesterone, Preterm delivery, Prevention of preterm birth

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INTRODUCTION

The World Health Organization (WHO) defines preterm birth as giving birth before 37 full weeks of pregnancy. Approximately 85% of these preterm births take place between 32 and 36 weeks of gestation, 10% at 28 to 31 weeks, and 5% at less than 28 weeks (extremely preterm babies).

Each year, premature birth is a significant factor in infant mortality, and many preterm infants suffer from long-term impairments. Preterm birth rates are on the rise globally, with an estimated 15 million preterm births occurring each year [1-3]. Progesterone may be helpful in high-risk pregnancies to prevent preterm birth, according to mounting research. Progestogen use has been thoroughly investigated over the years, and it continues to be a subject of interest in current research [4–13]. The prophylactic use of progesterone, according to expert researchers, may help lower the rate of PTB, particularly in women with high risk factors like a history of spontaneous preterm birth and those who had transvaginal ultrasounds that showed they had short cervical lengths (CL) [14]. Reliable prediction is difficult due to the preterm labour activation's complex pathogenesis [15]. The best predictor is thought to be an obstetric history of spontaneous preterm birth (sPTB). In 35 to 50% of pregnancies, s PTB recurs, and the likelihood of a recurrent event increases in direct proportion to the number of previous spontaneous preterm births. Other risk factors include non-Hispanic Black race, low socioeconomic status, mid trimester cervical length of less than 25 mm, cervical-vaginal infections, history of cervical surgery procedures, maternal smoking, inadequate or no prenatal care, uterine over distension, deciduasl haemorrhage, and short inter pregnancy interval. Multiple pregnancies,

pregnancies resulting from ART, periodontal disease, maternal anaemia, environmental factors, and epigenetics are additional conditions that may be linked to spontaneous preterm birth [16]. Experts have recently argued that there may be a link between the environment and preterm birth. However, some researchers have shown the likely impact of air pollution on epigenetic effects. It is still unclear how pollution and other contaminants may induce maternal-fetal effects. Epigenetics may also be related to preterm labour, according to other recent scientific evidence [17].

The long and fascinating chronological steps that make up the history of progesterone (PG) are indicative of its "never-ending history," as was recently discussed in a paper [18,19]. The oldest hormone that is currently known to science is probably progesterone. Progestation-inducing chemical substances, whether natural or artificial, are referred to as "progestogens" or "progestagens." Progesterone's pharmacokinetic and pharmacodynamic properties are well known today. The evidence that progesterone relaxes the uterus throughout pregnancy by inhibiting the expression of oestrogen receptor alpha (ER-a) and decreasing sensitivity to oestrogen is the foundation for our understanding of the pharmacodynamics of progesterone in preterm labour prevention [20]. Progesterone has been shown to have a variety of effects on the myometrium, including the ability to inhibit the growth of connexin 43-based channels called gap junctions, increase levels of cyclic adenosine monophosphate (cAMP), and stimulate nitric oxide synthetase (NOS) in a time-dependent manner. By interacting with nuclear and membrane P4 receptors and inducing low levels of the inflammatory prostaglandins (via cyclooxygenase), oxytocin, and intracellular calcium, natural progesterone (P4) and its metabolites promote uterine quiescence [21–24]. In order to achieve the desired clinical effects and determine P4's ideal pharmacody- namic profile, the route of administration appears to be essential. The majority of the body of scientific research focuses on the oral, intramuscular, and vaginal routes, which are all covered below. The development of the micronization process, which allowed for further optimization of the clinical effects and goals resulting from its use, represents the most significant advancement in the field of progesterone. In order to improve the absorption of progesterone when taken orally, it was first studied in the late 1970s to micronize progesterone and suspend it in oil-filled capsules [18]. Today, micronized progesterone products are widely preferred and used in obstetrics (and not just in this field) for a variety of medical conditions, such as threatened miscarriage, repeated pregnancy loss, and PTB prevention [18,25,26]. According to the majority of reliable studies, vaginal administration is the best method to use because it delivers higher concentrations to the uterus for the "first uterine pass effect" and prevents unpleasant side effects like nausea, headaches, and sleepiness that can result from oral administration [18,27].

Hence in this study we did Assessment of Prophylactic use of oral micronized progesterone in prevention of preterm labour in high risk pregnancy.

METHODS

This present case control study was conducted at Obst& Gynecology Department at SRI AUROBINDO MEDICAL COLLEGE AND POST GRADUATE INSTITUTE, INDORE and who satisfy the inclusion criteria will be studied from 1st April 2021 to 30th September 2022 (18 months).after approval from Institutional ethical committee. Each patient fulfilling the inclusion criteria will be included in the study. Informed written consent shall be taken. The control group is identical with the cases

A prestructured proforma will be used to collect the baseline data. Detailed clinical examination and biochemical tests will be done on all patients as per the protocol.

INCLUSION CRITERIA

Singleton pregnancy with at least one risk factor for preterm delivery, Primi with short cervical length < 25 mm and Present pregnancy between 20-34 weeks period of gestation.**Exclusioncriteria-** Documented evidence of uterine malformation, prophylactic cerclage operation, multiple gestation, foetal malformation, patients with PROM, abnormal vaginal bleeding.The patient underwent systemic, obstetric, and general physical exams. The last menstrual period, the length of the crown-rump before 12 weeks, and/or the biparietal diameter in the early second trimester were used to determine gestational age. At the time of recruitment, a per-speculum examination was done, and endocervical and high vaginal swabs were taken for culture and sensitivity. Every two weeks, women were asked to come in for a check-up; if they failed to do so, they were lost for follow-up. The study medication allocation was kept a secret from the patients and the medical team until the last patient had given birth and the study was over. Preterm labour patients were treated in accordance with hospital protocol.

RESULTS

60 women were assigned to each group out of the 120 total women in the study. Age, gestational stage, number of first- and second-trimester abortions, total number of pregnancies lost, gestational age at last preterm birth, and socioeconomic status of the patients in the two groups were all closely matched (Table 1).

Table 1Patient characteristics at recruitment			
Characteristic	**OMP group (n= 60)**	**Control group (n= 60)**	**P value**
Age, y	26.07 ± 3.24	25.72 ± 3.42	0.53
Gestational age, wks	20.69 ± 2.83	20.73 ± 1.78	0.92
No. of first trimester abortions	0.71 ± 0.93	0.64 ± 0.75	0.63
No. of second trimester abortions	0.69 ± 0.85	0.68 ± 0.77	0.92
No. of preterm births	1.21 ± 0.53	1.31 ± 0.52	0.27
Total number of pregnancy losses	2.61 ± 1.13	2.63 ± 1.05	0.94
Abbreviation: OMP, oral micronized progesterone. Values are given as mean±SD unless otherwise indicated.			

In the OMP group, fewer women delivered prematurely than in the control group (29 vs 44 women, P = 0.002; Table 2). When compared to the control group, the OMP group's mean gestational age at delivery was older (36.1 2.66 vs. 34.0 3.25 weeks, P b 0.001). OMP was protective in preventing PTB between 28 and 31 weeks plus 6 days, according to further analysis (RR 0.20; 95% CI, 0.05-0.73; Table 2). The OMP group's pregnancy was prolonged.

Table 2Gestational age at delivery					
Gestational age at delivery(wk+d)	**OMP group**	**Control group**	**Total no. of patients**	**RR (95% CI)**	**p- value**
<28wk	0	3	3	-	0.25
28–31+6	2	15	17	0.20(0.05-.73)	0.001
32–33+6	20	19	39	0.86(0.60–1.22)	0.85
34–36+6	7	7	14	0.83(0.48–1.45)	1.000
Abbreviations: OMP, oral micronized progesterone; RR, relative risk; CI, confidence interval.					

(15.57 7.38 vs. 11.10 7.01 weeks; P 0.001) when compared to the control group. The index pregnancy was extended by 14.68 3.53 weeks in the OMP group versus 12.23 3.17 weeks in the control group when compared to previous deliveries (P 0.001).

The neonatal results are shown in Table 3. The OMP group's neonates' mean age at delivery (Ballard score [15]) was significantly higher than that of the control group, and these neonates also had significantly higher Apgar scores at 1 and 10 minutes after birth (P 0.001). The neonates of women in the OMP group also had significantly higher mean birth weights (P 0.001). 48 neonates in total, including 10 from the OMP group and 38 from the control group, needed admission to the neonatal intensive care unit (NICU). One new born from the OMP group's three neonates (mean birth weight: 1160–290 g) who were admitted to the NICU for longer than 24 hours passed away from respiratory distress syndrome (RDS), and the other two from RDS with hyperbilirubinemia and septicemia. For RDS with septicemia (n= 16), RDS with hyperbilirubinemia (n= 9) and RDS with hyperbilirubinemia and septicemia (n= 6), 31 neonates in the control group required NICU admission for longer than 24 hours. Of these, RDS with hyperbilirubinemia (n=5) and RDS with septicemia (n=2) resulted in 7 neonatal deaths (mean birth weight: 1240360 g). The remaining neonates were discharged home when they were in a satisfactory condition.

Table 3 Neonatal outcome			
Neonatal outcome	**OMP group(n= 60)**	**Control group(n= 60)**	**P value**
Neonatal age at delivery, wk (Ballard Score)	34.26 ± 2.88	32.95 ± 3.20	0.001
Birth weight, g	2400 ± 650	1890 ± 560	0.001
NICU stay			
b 24 h	7	7	0.001
24 h – 1 wk	1	20	
N 1 wk	2	11	
Apgar score at 1 min			
< 6	10	40	0.001
>6	54	20	

Apgar score at 10 min			
< 6	8	29	0.001
>6	52	31	
Neonatal deaths	3	7	0.190

DISCUSSION

In both high- and low-income nations, preterm birth is a major contributor to neonatal morbidity and mortality [28-30]. Preterm birth has not yet been prevented by the use of tocolytic drugs, antibiotic therapy, or other methods [31,32].

By obstructing prostaglandin F2 alpha and alpha-adrenergic receptors, suppressing contractile genes required for uterine contractility, lowering the concentration of oxytocin receptors in the myometrium, up-regulating systems like nitric oxide that cause myometrial relaxation, and blocking the development of intracellular gap junctions, progesterone protects against uterine relaxation [33-39]. 17-OHPC, a synthetic progestogen administered intramuscularly, is the progestin for preventing PTB that has been the subject of the most research. Da Fonseca et al. [40] used vaginal progesterone in a trial.

Progestin use has been the subject of numerous randomised controlled trials and meta-analyses, all of which have significantly decreased the rate of preterm birth [41,42,43,44,40]. In a meta-analysis limited to six trials using 17-OHPC, Keirse et al. [42] discovered a lower incidence of preterm birth in the treatment group compared to the placebo group (OR 0.05; 95% CI, 0.30-0.85). In a recent meta-analysis using 17-OHPC, Sanchez-Ramos et al. [45] reported findings that were similar (PTB in the treatment group was 26% vs. 35.9% in the placebo group [OR 0.45; 95% CI, 0.25-0.80]). The incidence of PTB was 13.8% in the treatment group compared to 28.5% in the placebo group (P = 0.03) in the one study that used natural progesterone administered vaginally [40]. The findings of the current study using OMP are consistent with those of earlier investigations using vaginal micronized progesterone and intramuscular progestins.

An intervention with 17-OHPC decreased the risk of delivery before 35 weeks of gestation (20.6% vs. 30.7%, RR 0.67; 95% CI, 0.48-0.93) and delivery before 32 weeks (11.4% vs. 19.6%, RR 0.58; 95% CI, 0.32-0.91), according to the findings of a randomised controlled trial conducted by Meis et al. In a study by da Fonseca et al. [40], the frequency of preterm delivery before 34 weeks was 2.6% in the treatment group as opposed to 18.6% in the placebo group. Women in the OMP group in the current study had significantly fewer preterm deliveries (2.7% vs. 24.3%) than women in the control group. Meis et alresearch .'s [44] revealed that 17-OHPC recipients required less tocolysis (17.3% vs 15.9%; RR 1.09; 95% CI, 0.70-1.69). However, the number of women who received tocolysis did not significantly differ between the groups according to the current study (P = 0.686).

Meis et al. [44] found that 27.2% of newborns in the treatment group had birth weights under 2500 g, compared to 41.1% in the placebo group (RR 0.66; 95% CI, 0.51-0.87). The same goes for Sanchez-Ramos et al[45] revealed that 17-OHPC treatment caused fewer neonates to be born under 2500 g (20.3% vs 28.4%; OR 0.50; 95% CI, 0.36-0.71). The results of this study concur with those of these two studies (Table 3). Meis et al. [44] demonstrated in their trial that treatment with 17-OHPC resulted in significantly lower rates of oxygen supplementation (RR 0.62; 95% CI, 0.42-0.92), necrotizing enterocolitis (P = 0.01), and intraventricularhaemorrhage of any grade (RR 0.25; 95% CI, 0.8-0.82).

In order to evaluate the effectiveness of therapeutic interventions, randomised controlled trials are considered to be the most reliable method. Although we saw better outcomes in the OMP group, a significant drawback of our study was that it was only conducted in one hospital. The findings show that OMP treatment has significant short-term advantages, but further research is required to ascertain whether the medication has any long-term negative effects. To confirm its efficacy and safety, a significant multicenter study with a larger patient population and a longer follow-up is required.

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