e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(11); 1244-1251

Original Research Article

Evaluation of Role of Oral Micronized Progesterone in Prevention of Preterm Labor.

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Received: 18-09-2023 / Revised: 19-10-2023 / Accepted: 28-11-2023
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Conflict of interest: Nil

Abstract:

Background: More and more people are learning that progesterone may prevent premature births by reducing the risk of recurring preterm births. The impetus for this acceptance is growing. The major goal of this study was to find out whether oral micronized progesterone (OMP) may help avoid preterm birth (PTB).

Materials and Methods: One hundred participants were randomly allocated to one of two groups: fifty people took progesterone and fifty people took a placebo for this study. Each day, 200 mg of oral micronized progesterone were administered to the progesterone-treated group. Women who were likely to go into labor too soon were part of this category. Starting around the fourteenth to eighteenth week of pregnancy, this continued until the baby was born or until the 36th week and six days of gestation. The pregnant women in the placebo group also received a tablet that had no active ingredient other than a placebo. Additionally, they could have gone into labor sooner than anticipated.

Results: The progesterone group had a later gestational age at birth and a significantly longer interval between tocolysis and delivery compared to the other group. The relative risk of spontaneous preterm birth was therefore decreased to 0.66 due to this adjustment. The cervical cerclage rate was significantly lower in the progesterone group compared to the other groups. There was no statistically significant difference in the rates of surgical delivery or postpartum complications between the two groups. No postpartum problems occurred in either group. Using progesterone during pregnancy was linked to a number of unpleasant side effects, including drowsiness and vertigo. Improved mean birth weight, decreased rates of respiratory distress syndrome and infant mortality, shorter hospitalizations in the neonatal intensive care unit, and lower rates of low birth weight were additional benefits. The total infant mortality rate fell as a result of all of these variables.

Conclusion: After careful consideration, it is possible to conclude that the utilization of progesterone supplements might be an appropriate choice for women who have been recognized as being at a high risk for premature delivery.

Key words: Drowsiness, Preterm Birth, Oral Micronized Progesterone, Gestation, Progesterone, Placebo.

Introduction

Premature births of newborns are increasing everywhere in the world. Due to the fact that its frequency has grown over the course of the last several decades, it is now the leading cause of mortality associated with neonates as well as long-term health problems. [1, 2]. Furthermore, it continues to be a substantial source of economic difficulty for people as well as for public institutions. Developing countries have a greater incidence of this problem, which is connected to insufficient and restricted neonatology care [3]. This problem is made worse by the increase in prevalence. There are between 10 and 69 percent of preterm births that occur in India. [4].

Preterm labor is caused by complicated physiological and molecular processes that are still poorly understood. The presence of concomitant obstetrical defects, such as abruptio placenta, placenta praevia, multiple gestation, hypertensive diseases, and intrauterine growth restriction, is only observed in forty percent of cases. The other instances, on the other hand, are characterized by spontaneous occurrences that lack any discernible cause [5]. There is some evidence that a premature decline in the efficacy of progesterone is connected

with preterm labor [2]. The changes that occur in progesterone receptors and the transcriptional activity of these receptors are more likely to be the source of this phenomenon than a reduction in the quantity of progesterone that is present in the bloodstream [6, 7]. Furthermore, it has been proven that the weekly injectable dosage of 17-alpha-hydroxyprogesterone-caproate (17OHP-C) is less effective in encouraging pregnancy as the gestational age at which it begins grows. This is the case because its effectiveness decreases with increasing gestational age. [8].

Some evidence suggests that progesterone may help lower the probability of preterm birth (PTB) [9–13]. Randomized controlled trials and meta-analyses are the sources of these numbers. Clinical trials often use the intramuscular administration of 17-alpha hydroxyprogesterone caproate (17-OHPC), a progestational medication, to prevent preterm birth (PTB). Furthermore, there is evidence from a study that used vaginal administration of micronized progesterone. [13]. We will go more into this subject later on. But since medical personnel are required to provide the medication via painful intramuscular injections, patients may be less likely to comply with their treatment plans. Although 17-OHPC has shown encouraging outcomes in clinical trials, this method of pharmaceutical administration is more difficult. For the treatment of early pregnancy losses and luteal phase anomalies, micronized progesterone has been administered orally and vaginally [14]. Regardless, most patients have a negative experience with the vaginal approach, and it is associated with an unpleasant vaginal discharge [15]. This research aims to evaluate the efficacy of oral micronized progesterone in preventing preterm labor. This is due to the lack of research on the efficacy of micronized progesterone taken orally to avoid premature delivery.

Materials and Methods:

Over two years, beginning in January 2021 and ending in December 2022, the Obstetrics and Gynecology department at VIMSAR, Burla, conducted a prospective observational study between January and December 2022. Based on the following calculation, the required sample size was determined to be one hundred, with the assumption that there was a prevalence of premature delivery in the high-risk group of thirty-six percent, that there was a statistical power of eighty percent to detect a fifty percent decrease in the risk of preterm labor, and that there was a zero percent dropout rate.

Sample size = $2(Z\ \alpha/2 + Z\ \beta)^2\ P(1-P)/ (P\ 1 - P\ 2)^2$

$Z\ \alpha/2 = Z\ 0.05/2 = Z\ 0.025 = 1.96$ (from Z table) at type 1 error of 5%

$Z\ \beta = Z\ 0.020 = 0.84\ 2$(from Z table) at 80% power

P 1 -P 2 =difference in proportion of event in two groups

P=Polled Prevalence= {prevalence in case group (P1) + prevalence in control group(P2)}/2

P 1 =36%, P 2 =18%, P= (P 1 +P 2)/2=27%

Participants in the study were outpatients who visited the Department of Obstetrics and Gynecology at the VIMSAR, Burla facility before taking part in the research. The participants in the trial were assigned to either the progesterone or placebo groups via the use of random assignment. Both groups received the identical amount of the medicine at their prescribed dose. A single daily dose of 200 milligrams of oral micronized progesterone was supplied after meals to women who were at risk of preterm labor beginning between 14 and 18 weeks of pregnancy and continuing until either 36 weeks and 6 days of gestation or birth. This treatment was offered to women who were at risk of experiencing premature labor. Those ladies who were in the progesterone group were given this treatment.

On the other hand, the placebo group consisted of pregnant women who were at danger of going into labor before their due date. The oral micronized progesterone tablet and the placebo pill that was administered to these women were identical in terms of their size, shape, and color from one another. In order for participants to be eligible to take part in the research, it was necessary to verify that they were pregnant women who were carrying a single child and that their gestational age was between 14 and 18 weeks. The following prerequisites must be taken into consideration as part of the inclusion criteria: either a singleton asymptomatic pregnancy with a cervical length of less than 25 millimeters prior to the 24th week of gestation, or a singleton asymptomatic pregnancy with a history of spontaneous premature birth. Both of these conditions must be met in order to be considered for inclusion. Multifetal gestation, intrauterine fetal death, placenta previa or low-lying placenta, coagulation disorders, uterine anomalies, congenital anomalies of fetus incompatible with life, chronic liver, heart, or kidney disease, and chronic hypertension of the mother were some of the criteria that were used to exclude patients from the study. A further factor that was taken into consideration throughout the screening process for patients was whether or not they had premature labor or had persistent uterine contractions.

With regard to the instances that we recruited, patients in both groups were permitted to have cervical cerclage removal. The implementation of this ethical strategy was performed with the intention of offering mothers in the control group a certain degree of protection against the arrival of their babies prematurely. All of the women who took

part in the research project were required to provide their informed consent before being included in the study.

Every patient who qualified for the trial chose from among the identical, numbered, opaque, and tightly sealed bags. Either the actual medication or a similar placebo was put in each bag. The codes for each of the one hundred distinct bag numbers were produced using a confidential computer-generated random number list.

Women whose gestational ages varied from 14 to 18 weeks provided a thorough history. The women's menstrual history, prior obstetric history, family history, personal history, surgical history, and medical history were all included in this history. The patient's age, socioeconomic situation, parity, and any other information that would have signaled cervical incompetence were all taken into account when gathering the patient's history. The patient had an obstetric checkup in addition to the standard physical and systemic examinations that were done. By examining a variety of parameters, such as the location of the placenta, the weight of the fetus, the gestational age, and the amount of amniotic fluid, obstetric ultrasonography was used to discover any possible fetal abnormalities that may have been present. Progesterone was the treatment that was administered 14–18 weeks after enrollment, and progesterone levels were evaluated between 20 and 28 weeks of pregnancy. The placebo was the treatment that was administered. At the twenty-week mark, a transvaginal ultrasound (TVS) was performed in order to determine the length of the cervical canal. Patients who had a cervical length of fewer than 15 millimeters were candidates for either an emergency or rescue cervical cerclage for their condition. Additionally, up to the 28th week, follow-up scans were performed (weekly for those with shorter cervical lengths and twice monthly for those whose cervical length was between 20 and 25 millimeters). These scans were performed weekly for individuals with shorter cervical lengths.

To make sure the patients were adhering to the study procedure, they were routinely watched closely. They were urged to visit the hospital right away if they had severe vaginal bleeding, ruptured membranes, or constant uterine contractions. They were also told to show up for their scheduled prenatal care appointments. It was advised that women who were admitted to the hospital for whatever reason—including tocolysis or obstetric or medical issues—keep taking the prescription medicine. Additionally, all infants received ongoing medical care until they became seven days old.

Results:

Table 1: **Baseline characteristics of the participants between two groups**

	Placebo (N=50)	Progesterone (N=50)	P value
Parity			0.43
1	10 (20.0%)	10 (20.0%)	
2	13 (26.0%)	19 (38.0%)	
3	13 (26.0%)	13 (26.0%)	
4	14 (28.0%)	8 (16.0%)	
Previous preterm delivery			0.64
1	22 (44.0%)	26 (52.0%)	
2	18 (36.0%)	17 (34.0%)	
3	10 (20.0%)	7 (14.0%)	
Previous pprom			0.072
No	29 (58.0%)	20 (40.0%)	
Yes	21 (42.0%)	30 (60.0%)	
GA previous delivery			0.44
Mean (SD)	31.26 (1.96)	31.56 (1.88)	
Range	27.00 - 35.00	28.00 - 36.00	
Birth weight previous delivery			0.34
Mean (SD)	1494.15 (44.27)	1503.01 (47.42)	
Range	1431.50 - 1609.30	1419.50 - 1624.30	

Table 1 shows that the two groups' basic characteristics were different. Ten were in the first parity, thirteen in the second, thirteen in the third, and fourteen in the fourth of the fifty women who took part in the placebo group. A total of fifty women were included in the progesterone study; ten (20%) were in the first trimester, nineteen (38%), thirteen (26%), and eight (16%) were in the second,

third, or fourth trimester, respectively. A p-value of 0.43 indicates that the two groups were statistically equivalent, according to the results of the study. Of the women in the placebo group, 22 (or 44% of the total) had reported having given birth prematurely before. Thirty-six percent, or 18 women, had given birth earlier than expected, whereas twenty percent, or 10 women, had done the same in the past. The progesterone group consisted of seven women with a history of three preterm deliveries, seventeen with a history of two preterm births, and twenty-six with a history of one preterm delivery. Premature delivery had a history for 52% of the women in the progesterone group. For the total number of preterm births in the past, the computed p-value was 0.64, showing that the two categories were statistically indistinguishable. Fifteen women (or 42% of the total) in the placebo group had a history of PPROM from a prior pregnancy.

The progesterone group, on the other hand, reported that 30 out of 60 women had PPROM in a previous pregnancy. The observed difference does not meet the criteria for statistical significance, as indicated by the p-value of 0.072. With a standard deviation of 1.96 weeks, the last baby in the placebo group was born at an average gestational age of 31.26 weeks. The gestational ages ranged from twenty-seven to thirty-five weeks. With a standard deviation of 1.88 weeks, the ultimate birth age in the progesterone-treated group averaged 31.56 weeks. Additionally, the gestational ages ranged from 28 to 36 weeks. With p-values of 0.44 for both groups, it's safe to say that they were in agreement on the gestational age during the prior delivery. Among those who received a placebo, the most recent delivery weight was 1494.15 g, with a standard deviation of 44.27 g. Between 1431.50 and 1609.30 grams in weight were the grams. With a standard deviation of 47.42 grams, the most recent delivery in the progesterone-treated group had an average birth weight of 1503.01 grams. From 1419.50 to 1624.30 grams was the weight range. It would indicate that the birth weights of the two groups were statistically highly similar, as the calculated p-values for the birth weight of the prior delivery were 0.34.

Table 2: **Maternal predictor of pre-term labor among the participants between two groups**

	Placebo (N=50)	Progesterone (N=50)	P value
progesteron_level_20wks			**<0.001**
Mean (SD)	15.81 (1.41)	30.68 (3.85)	
Range	12.28 - 18.65	16.09 - 36.63	
progesteron_level_28wks			**<0.001**
Mean (SD)	16.72 (2.86)	33.85 (4.15)	
Range	9.93 - 23.37	20.75 - 41.77	
cervical_length			0.85
Mean (SD)	24.95 (8.34)	25.29 (9.71)	
Range	11.22 - 42.40	-0.29 - 44.36	
total_cervial_circlage			**0.029**
No	30 (60.0%)	40 (80.0%)	
Yes	20 (40.0%)	10 (20.0%)	
elective_cervical_circlage			0.78
No	42 (84.0%)	43 (86.0%)	
Yes	8 (16.0%)	7 (14.0%)	
rescue_circlage_20wks			0.081
No	43 (86.0%)	48 (96.0%)	
Yes	7 (14.0%)	2 (4.0%)	
rescue_circlage_beyong_20wks			0.092
No	45 (90.0%)	49 (98.0%)	
Yes	5 (10.0%)	1 (2.0%)	

Table 2 shows, by comparing two groups of research participants, the maternal predictor of preterm labor. Whether the operation was done as an emergency or rescue procedure at 20 weeks or later, or as an elective therapy at the end of the first trimester, there was no discernible difference in the incidence of cervical cerclage between the two groups. At 20 and 28 weeks, progesterone levels were determined, and it was evident that the progesterone group had much higher levels than the other group.

Additionally, throughout the third trimester, the progesterone group's levels remained much higher.

Table 3: **Maternal outcome of current pregnancy among the participants between two groups**

	Placebo (N=50)	Progesterone (N=50)	P value
GA_delivery			**0.013**
Mean (SD)	33.68 (3.45)	35.30 (2.89)	
Range	27.00 - 41.00	30.00 - 43.00	
mid_trimester_miscarriage			0.20
No	38 (76.0%)	43 (86.0%)	
Yes	12 (24.0%)	7 (14.0%)	
admission_tocolytic			**0.032**
No	29 (58.0%)	39 (78.0%)	
Yes	21 (42.0%)	11 (22.0%)	
tocolysis_delivery_interval			**<0.001**
Mean (SD)	36.39 (12.44)	86.29 (30.86)	
Range	12.70 - 70.50	30.90 - 152.00	
pprom			0.68
No	30 (60.0%)	32 (64.0%)	
Yes	20 (40.0%)	18 (36.0%)	
preterm_delivery			**0.046**
No	20 (40.0%)	30 (60.0%)	
Yes	30 (60.0%)	20 (40.0%)	
cesarian_delivery			0.68
No	31 (62.0%)	33 (66.0%)	
Yes	19 (38.0%)	17 (34.0%)	
chorioamnionitis			0.56
No	42 (84.0%)	44 (88.0%)	
Yes	8 (16.0%)	6 (12.0%)	
PPH			0.30
No	39 (78.0%)	43 (86.0%)	
Yes	11 (22.0%)	7 (14.0%)	
post_partum_sepsis			0.24
No	45 (90.0%)	48 (96.0%)	
Yes	5 (10.0%)	2 (4.0%)	

Table 3 contrasts the two sets of subjects and shows how the mothers' pregnancies turned out. When comparing the progesterone group to the placebo group, the progesterone group had a significantly higher average gestational age at birth.

In addition, compared to the placebo group, the progesterone group had a far reduced risk of hospital admissions for tocolysis treatment. This stood out when contrasted with the placebo group. The time it took for the progesterone group to go from the beginning of tocolysis until the baby was born was significantly longer than the placebo group. It was like this for the women who had gone into premature labor.

In addition, the rate of preterm birth was reduced in the progesterone group compared to the placebo group.

Table 4: **Fetal and neonatal outcomes of current pregnancy**

	Placebo (N=50)	Progesterone (N=50)	P value
Birthweight			**<0.001**
Mean (SD)	1890.89 (66.89)	2309.38 (79.98)	
Range	1695.10 - 2007.60	2108.50 - 2470.70	
LBW			**0.026**
No	23 (46.0%)	34 (68.0%)	
Yes	27 (54.0%)	16 (32.0%)	
admission_NICU			**0.002**
No	24 (48.0%)	39 (78.0%)	
Yes	26 (52.0%)	11 (22.0%)	
duration_stay_NICU			**0.019**
N-Miss	24	39	
Mean (SD)	19.46 (4.47)	15.82 (3.09)	

Range	12.00 - 29.00	10.00 - 22.00	
RDS			0.050
No	30 (60.0%)	39 (78.0%)	
Yes	20 (40.0%)	11 (22.0%)	
ICH			0.50
No	44 (88.0%)	46 (92.0%)	
Yes	6 (12.0%)	4 (8.0%)	
NEC			0.24
No	45 (90.0%)	48 (96.0%)	
Yes	5 (10.0%)	2 (4.0%)	
NMR			**0.029**
No	38 (76.0%)	46 (92.0%)	
Yes	12 (24.0%)	4 (8.0%)	

Table 4 displays the results of the current pregnancy for the fetus and newborn.

Neonatal problems, mostly related to low birth weight and respiratory distress syndrome, were more common in the placebo group. They also had greater rates of newborn death and longer hospitalizations in neonatal intensive care units (NICUs). Despite being higher in the placebo group than in the progesterone group, the incidence of necrotizing enterocolitis and cerebral hemorrhage did not achieve statistical significance.

Table 5: **Side effects of progesterone use during the current pregnancy**

	Placebo (N=50)	Progesterone (N=50)	P value
dizziness			**0.026**
No	41 (82.0%)	31 (62.0%)	
Yes	9 (18.0%)	19 (38.0%)	
constipation			0.42
No	43 (86.0%)	40 (80.0%)	
Yes	7 (14.0%)	10 (20.0%)	
somnolence			**0.029**
No	40 (80.0%)	30 (60.0%)	
Yes	10 (20.0%)	20 (40.0%)	
vaginal_dryness			0.084
No	46 (92.0%)	40 (80.0%)	
Yes	4 (8.0%)	10 (20.0%)	

Table 5 It has been demonstrated that using progesterone throughout this pregnancy has negative effects. Researchers discovered that women using progesterone pills were more likely to report feeling fatigued and lightheaded. It's crucial to remember, too, that none of the women discontinued taking their medication due to side effects.

Discussion:

Preterm delivery is associated with increased incidence of newborn health complications and mortality in both high-income and low-income countries [16–18]. Few studies have shown that antibacterial treatment, tocolytic medications, or any of the other several methods can avert preterm birth [19, 20]. During uterine relaxation, progesterone acts as a buffer by encouraging relaxation. For this to happen, it's likely necessary to block certain receptors, such as those for prostaglandin F2 alpha and alpha-adrenergic, as well as genes that cause the uterine muscles to contract, oxytocin receptors, intracellular gap junction formation, and systems that induce uterine relaxation, such as nitric oxide [21–27].

Most prior studies on progesterone injections for preterm delivery prevention have concentrated on the intramuscular and vaginal routes[28,29], although the oral approach was the first to get extensive investigation. French researchers were the first to use oral micronized progesterone (OMP) in a clinical trial. Positive results were seen in a placebo-controlled trial including 57 individuals hospitalized for preterm labor. Contrasted with the 42% of women in the placebo group who were instructed to rest in bed, 80% of those in the therapy group reported that their contractions had ceased [28]. In addition, favorable results were seen in a randomized controlled study (RCT) including 44 pregnant women hospitalized for tocolysis in France between the ages of 32 and 35 weeks. Progesterone considerably decreased the necessary dose, therapy duration, and tocolysis-related expenditures in the group that received progesterone [29]. The use of progestins as a therapy has been demonstrated in several

randomized controlled trials and meta-analyses to significantly reduce the incidence of preterm births [9–13]. The meta-analysis by Keirse et al. [10] focused on six studies that utilized 17-OHPC. The treatment groups had a lower incidence of preterm delivery as compared to the placebo groups. Consistent with previous research, Sanchez-Ramos et al. [30] used 17-OHPC in their meta-analysis. Keep in mind that the one study that employed naturally occurring progesterone given vaginally found a 13.8% risk of premature delivery in the treatment group and a 28.5% risk in the placebo group [13]. Results from our most recent OMP-based study are consistent with those from earlier investigations into injectable progestins and vaginal micronized progesterone formulations.

Ashous et al. found that normal blood progesterone levels were significantly higher in the progesterone-treated group compared to the placebo-treated group at both 20 and 28 weeks [31]. Our study revealed a statistically significant decrease in the overall cervical cerclage rate (p-value = 0.029) in the group that was administered progesterone. Our findings contradict those of a prior research by Ashous et al. [31], which found no significant difference between the two sets of data. The results of our study suggest that oral micronized progesterone (OMP) might help decrease the need for cervical cerclage, a commonly performed surgical procedure. The results of the study by Rai et al. [32] showed that compared to the placebo group, the group given oral micronized progesterone (OMP) had a longer gestational age at delivery. Consistent with the findings of the placebo group, this is the outcome. Preterm birth rates are much lower among women who use progesterone medication. Rai et al. [32] found that compared to the control group, the one given oral micronized progesterone (OMP) had a lower rate of premature births. Preterm birth rates were significantly lower in the OMP group compared to the placebo group, as reported by Ashoush et al. [31]. Meis et al. [12] performed a randomized controlled experiment and found that 17-OHPC decreased the risk of preterm delivery (defined as delivery before 35 weeks of gestation) and preterm birth (defined as delivery before 32 weeks of gestation). Similarly, a study conducted by da Fonseca et al. [13] found that although the placebo group had an early delivery rate of 18.6%, the therapy group had a rate of 2.6% before 34 weeks. There was a 34% cesarean section rate in the progesterone group and a 38% rate in the placebo group. The results of the statistical analysis showed that the rates of cesarean sections were not significantly different between the two groups. According to Ashoush et al. [31], this finding contradicts their findings. The risk of cesarean sections was much greater in the placebo group compared to the other group in the experiment. Our data revealed that fetal distress was the leading cause of cesarean sections, with a history of cesarean sections coming in second. This is rather intriguing. Our perinatal results were quite similar to the ones reported in the study by Rai et al. [32] [32]. In addition to a lower rate of baby mortality, the OMP group exhibited better outcomes, according to the research, including greater birth weights, shorter NICU stays, and better Apgar ratings. A study by Ashoush and colleagues [31] also found that the OMP group achieved better outcomes. Among these outcomes were shorter NICU stays, fewer newborn deaths, an increase in mean birth weight, a decrease in the frequency of low birth weight, and an increase in the rates of admission to the NICU. Infants in the placebo group were delivered weighing less than 2500 grams in 41.1% of instances, compared to 27.2% of neonates in the treatment group, according to Meis et al. [12]. In a similar vein, Sanchez-Ramos et al. [30] discovered that mothers who received 17-OHPC had a lower incidence of newborns weighing less than 2500 grams at delivery. The findings of this current study are consistent with those of these two preliminary studies. In addition, the findings of our investigation regarding the adverse effects of progesterone use throughout this pregnancy are highly consistent with those of the study by Ashoush et al. [31].

Conclusion:

Based on the results of this investigation, it is feasible to draw the conclusion that progesterone supplementation might be considered a suitable intervention for women who are classified as having a high risk of premature delivery. This is particularly true for women who have previously given birth prematurely for unclear reasons. Progesterone can also raise the newborn's weight and reduce the incidence of neonatal illness.

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