Original Article

To Determine the Frequency of Preterm Birth with Oral Progesterone in Female Presenting with Risk of Preterm Delivery

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Abstract

Background: Preterm Birth (PTB) is the foremost reason of morbidity and mortality in newborns. Intramuscular 17-hydroxyprogesterone has been demonstrated to lower the risk of subsequent premature delivery. The potential of oral natural progesterone to prevent repeated preterm births has not been well investigated.

Objective: To determine the frequency of preterm birth (<37 weeks) among pregnant women at risk of preterm birth receiving oral progesterone from 28-34 weeks gestation over a period of 6 months.

Methods: The Department of Obstetrics and Gynecology at Madina Teaching Hospital Faisalabad conducted this Descriptive case series. The study comprised 100 pregnant women presented in Gynae OPD & Emergency of Madina Teaching Hospital who satisfied the selection criteria. Patients were given oral progesterone twice daily till 36-37 weeks of gestation or delivery whichever occurs first. During follow-up, females were advised to present in situation of active labor and primary outcome measure is documented that is Frequency of preterm delivery <37 weeks of gestation.

Results: The patients average age was 28.61 + 3.72 years.

Frequency of PTB with oral progesterone in female presenting with risk of PTB shows that 14% had preterm birth whereas 86% had Term birth. Distribution of cases by gestation age shows that 57% were between 28-30 weeks whereas 43% (n=43) were between 31-34 weeks of gestation, mean Gestational age was 30.46+2.11 weeks. Mean BMI of the patients was calculated as 30.49+2.01kg/m2.

Conclusion: Oral progesterone administration in females at risk of preterm delivery significantly reduces the frequency of preterm birth and may serve as an effective preventive strategy in high-risk pregnancies.

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Introduction

In resource-rich countries, preterm birth (PTB) accounts for 5% to 10% of all births; but, in recent years, the frequency appears to have grown in certain nations.[1] Despite various risk factors, low cervical length determined by transvaginal ultrasonography is the utmost realistic, risk factor that is both practical and sensitive for predicting spontaneous PTB.[2] Approximately 75 percent of PTB cases occur after spontaneous preterm labor, which is occasionally preceded by preterm premature membrane rupture. Babies born preterm are at higher risk of a number of undesirable short-term

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and long-term problems.[3]

When utilized in singleton pregnancies for women who have previously had a labor, progesterone prevents PTB. Progesterone has been used in reproductive medicine for decades with no reported effect on the incidence of congenital malformations. The reported greater likelihood of fetal hypospadias does not appear to be verified in currently utilized progestogens.[4] Hydroxyl progesterone caproate has just received US Food and Drug Administration approval to be used in women having a history of PTB to avoid preterm. Progesterone lowers the chances of preterm birth before 32 weeks in women who have had a singleton pregnancy and a prior preterm delivery. progesterone may also help women who have a short cervix or who give birth prematurely.[5,6] One study reported that with oral progesterone, the frequency of PTB was 39.2%.[7]

The purpose of this study was to determine the prevalence of PTB in women who were at risk of preterm birth while using oral progesterone. Progesterone is given intravaginal, intramuscular or intravenous route. But high-risk females usually present in second trimester and to follow these patients with administration of progesterone is long. So, all these routes have low compliance and ultimately PTB occurs. Research has demonstrated that oral progesterone can also effectively lower the incidence of PTB in women at high risk. There is no local evidence available in literature which could help us in determining the beneficial role of oral progesterone in women at risk for premature labor. So, this research was conducted to get evidence available in literature which could help us in determining the beneficial role of oral progesterone in females with risk of preterm delivery.

Methods:

The descriptive case series was carried out at the Madina Teaching Hospital's Obstetrics and Gynecology Department, affiliated with the University Medical and Dental College Faisalabad. Sample size of 100 cases was calculated by taking expected percentage of PTB i.e. 39.2% with oral progesterone[7] by using WHO sample size calculator. Patients who met the inclusion and exclusion criteria were added to the research. Criteria for selection included singleton pregnancy, age between 18-40 years, gestational age between 28-34 weeks, history of previous spontaneous preterm birth or Transvaginal cervical length < 25mm), and informed consent. Patients with multiple pregnancy (on ultrasound), polyhydramnios (AFI >25 cm) , gestational or chronic hypertension, patients with Diabetes, Asthma, Cardiac problems were excluded.

After receiving ethics committee permissions, Patients demographic data were documented and informed consent was acquired. Then females were given oral progesterone[7] twice a day till delivery and were followed up to 36+6 weeks. During follow up, females were advised to present in case of active labour. To minimize loss to follow up, counselling was done regarding importance of regular visits and telephonic reminders were offered. Compliance and adverse effects were monitored. Non probability consecutive sampling Technique was used.

Patient demographics (age, parity, BMI, obstetric history) were recorded, cervical length measured by transvaginal ultrasound and informed consent was obtained. SPSS 21 was used to enter and analyze the data. Mean and standard deviation for quantitative variables (age and gestational age). Frequency and percentage for qualitative variables (preterm birth) PTB in stratified groups was compared using the Chi square test. A significant P value was less than 0.05. Primary outcome measure is frequency of preterm delivery (<37 completed weeks of gestation).

Results

One hundred (100) patients in all were included in the research.

Average age of patients was 28.61+3.72 years, 69% (n=69) females from age 18 to 30 years and 31% (n=31) from 31 to 40 years.

Gestational age shows that 57% were between 28-30 weeks whereas 43% (n=43) were between 31-34 weeks of gestation, Mean gestational age was 30.46+2.11 weeks.

Mean BMI of the patients was calculated as 30.49 + 2.1kg/m^2.

Table 1: *Demographic Details of Patients*

	Frequency	Percentage
Age		
18-30	69	69
31-40	31	31
G. Age (in weeks)		
28-30	57	57
31-34	43	43
Parity		
1-2	54	54
>2	46	46

Frequency of preterm birth with oral progesterone in

female presenting with risk of preterm delivery shows that 14% (n=14) had preterm birth whereas 86% (n=86) had term birth.

Table 2: *Frequency of preterm birth*

Preterm birth	No. of patients	%
Yes	14	14
No	86	86
Total	**100**	**100**

The data was stratified for age, gestation age at presentation, gestational age at delivery, BMI and parity.

Table 3: *Stratification of Preterm Birth with respect to Age, Gest Age and Parity*

		Preterm Birth		Total	P Value
		Yes	No		
Age (years)	18-30	10(14.5%)	59(85.5)	69(100%)	0.83
	31-40	4(12.9%)	27(87.1%)	31(100%)	
G. Age (weeks)	28-30	8(14%)	49(86%0	57(100%)	1.45
	31-34	6(14%)	37(86%)	42(100%)	
Parity	1-2	9(16.7%)	45(83.3%)	54(100%)	0.41
	>3	5(10.9%)	41(89.1%)	46(100%)	
BMI	≤ 30	8(13.8%)	50(86.2%)	58(100%)	0.96
	>30	6(14.3%)	36(85.7%)	42(100%)	

Discussion

The efficacy of progesterone in reducing preterm birth has been well documented with vaginal and intramuscular formulations: however data regarding the oral route remain limited. The findings of our study add to the evidence that oral progesterone can provide comparable benefits in women at risk of preterm delivery. A history of spontaneous preterm birth is one of the primary risk factors for preterm delivery. IM 17-OHPC starting at 16-20 weeks gestation has been shown to reduce the chance of a future preterm birth as well as neonatal complications compared with placebo group. Not much of research has been done on oral natural progesterone for preventing repeated preterm births. Progesterone contributes to the natural progression of pregnancy to the full term by inhibiting the oxytocin effect of prostaglandin F2α and α adrenergic stimulation in the myometrium at adequate concentrations, thereby enhancing the alpha adrenergic tocolytic response.[8] Progesterone is administered by vaginal, intramuscular or intravenous routes. However, high-risk females frequently come in the second trimester, and following these patients with the injection of progesterone is lengthy. So, use of progesterone through these routes is not feasible most of the time and ultimately PTB occurs because of low compliance. The micronization of progesterone and its suspension in oil filled capsules allowed progesterone to be absorbed more efficiently thru oral route.[9] But not much work has seen been done on effectiveness of oral progesterone in such cases. So, we conducted this study for determining the beneficial role of oral progesterone in females with risk of preterm delivery. Another study showed that with oral progesterone, PTB occurred in 25% females.[10]

The mean gestational age was 30.46+2.11 weeks, and the average age was 28.61+3.72 years. Mean BMI of patients was calculated as 30.49+2.01kg/m^2. These features are in accordance with other studies.[10,11] In a recent study Rupsa C. Boeli and others conducted a review comparing oral progesterone to placebo or other therapies for PTB prevention with previous spontaneous preterm delivery. The search method turned up 79 distinct studies. No studies comparing oral progesterone to any other intervention met the inclusion criteria, however three trials comparing oral progesterone to a placebo did. A meta-analysis found that comparing oral progesterone to a placebo, the odds of giving birth at less than 37 weeks were significantly lower (42% vs.63%), at less than 34 weeks (29% vs.53%) and at a later gestational age. A considerably lower risk of perinatal death was linked to oral progesterone (5% vs. 17%; P 0.001), neonatal intensive care unit hospitalization, respiratory distress syndrome, and greater birth weight. Additionally, oral progesterone was associated with a higher prevalence of maternal adverse effects, such as dizziness. In pregnancies with a history of spontaneous preterm delivery, they showed that oral progesterone was superior to a placebo in preventing recurrent preterm birth and lowering perinatal morbidity and death rates. Compared to the placebo, oral progesterone therapy had greater side effects, however none of them were severe. To prevent recurrent preterm birth, a randomized trial comparing oral progesterone to other existing treatments is necessary.[12]

In our study, frequency of preterm birth with oral progesterone in female presenting with risk of preterm delivery shows that 14%(n=14) had preterm birth. Although an oral micronized form of natural progesterone exists, few research has been conducted to examine its effectiveness. A daily dosage of 400 mg is common, although amounts have varied greatly. Sleepiness and weariness are among the reported adverse effects of synthetic progesterone, which are less severe.[12,13] In one study, there was no difference between oral progesterone and 17-OHPC when it came to preventing preterm labor and improving perinatal outcomes, Even yet, oral pro-

gesterone and 17OHPC both outperformed a placebo in these areas.[13]

Another different research examined the effects of oral and vaginal natural micronized progesterone 300 mg on avoiding preterm labor in a community that is semi-urban. In contrast, those who used vaginal micronized progesterone (VMP) presented at 33.49±2.49 weeks of gestation, while those who used oral micronized progesterone (OMP) did so at 31.37±1.94 weeks for delivery. A study compared the spontaneous preterm births incidence. In this study rate of preterm C-section was higher in oral progesterone as compared to micronized progesterone.[14]

The percentage of preterm deliveries before 34 weeks varied significantly among the three treatment groups, with the control, oral progesterone, and vaginal progesterone groups experiencing rates of 16.0%, 12.0%, and 5.2%, respectively, according to Srisutham K et al.'s 3-arm randomized control trial assessing oral and vaginal progesterone, emphasizing on the fact that progesterone when used vaginally proved to be more useful than the oral route in preventing preterm birth before 34 weeks than the control group.[15]

Compared to a placebo, oral progesterone significantly decreased the risk of PTB at <37 weeks (42% vs. 63%), PTB at <34 weeks (29% vs.53%), and increased gestational age of birth, according to a meta-analysis. A considerably lower risk of perinatal death was linked to oral progesterone (5% vs. 17%; P 0.001), neonatal intensive care unit hospitalization, respiratory distress syndrome, and greater birth weight. Oral progesterone was associated with a higher incidence of maternal adverse effects, such as lightheadedness. In pregnancies with a history of spontaneous PT delivery, they showed that oral progesterone was superior to a placebo in preventing repeat PTB and lowering perinatal morbidity and death rates. To prevent recurrent PTB, a randomized study comparing oral progesterone to different treatments is necessary.

The use of serum progesterone as a possible pharmacokinetic and pharmacodynamics endpoint in oral progesterone allows for more investigation into the optimal dose and threshold serum levels for therapeutic effectiveness. The dosages of vaginal progesterone and 17-OHPC were determined by experimentation; pharmacologic principles have not yet been used to adjust dosages for increased effectiveness. Research on oral progesterone of this type enables the development of such a medication that can be tracked using a standard laboratory test and modified to maximize its efficacy.[16]

The efficacy of progesterone therapy in preventing recurrent spontaneous preterm birth has been widely studied, with growing interest in the use of oral and vaginal formulations. Mazza et al. (2024) reported that oral progesterone was associated with a reduced incidence of preterm birth in a minority population, suggesting its potential as an effective and more accessible alternative to injectable options[17]. Bell et al. (2022) emphasized the importance of reducing extreme prematurity and improving long-term outcomes, reinforcing the need for reliable prophylactic options.[18]

The historical reliance on injectable 17-alpha hydroxyprogesterone caproate (17-OHPC) has recently been questioned. Nelson et al. (2021) outlined the limitations and controversy surrounding 17-OHPC in preventing preterm birth, calling attention to the need for alternative approaches.[19] The PROLONG trial by Blackwell et al. (2020) similarly failed to show a significant benefit of 17-OHPC compared to placebo, prompting a shift in focus toward other formulations.[20]

In contrast, Conde-Agudelo and Romero (2022) presented compelling evidence through a meta-analysis that vaginal progesterone significantly reduces the risk of recurrent preterm birth in women with singleton pregnancies and a history of spontaneous preterm birth.[21] These findings suggest a stronger efficacy profile for vaginal progesterone compared to the injectable form. Additionally, oral progesterone remains an attractive option due to its ease of use, cost-effectiveness, and potential for improved patient compliance, especially in underserved populations.[17,21]

Adjunctive preventive strategies like cervical pessary have also been explored, but progesterone therapy remains a key intervention.[22] Collectively, these data support a clinical move away from injectable forms and toward more effective and acceptable alternatives like vaginal and oral progesterone. While the findings are encouraging, they should be interpreted with caution due to limited sample size and absence of control group.

Conclusion

The frequency of preterm delivery among females at risk who received oral progesterone in this study was relatively low (14%). Based on current evidence, progesterone therapy remains a cornerstone in the prevention of recurrent spontaneous preterm birth. This study demonstrates that oral progesterone has beneficial role in reducing the incidence of preterm birth.[17,21] The treatment is well tolerated and easy to administer, offering a practical alternative to injectable or vaginal formulations.

Although further large-scale randomized trials are necessary to validate these findings, the results of this study emphasize the importance of timely identification and management of high-risk pregnancies to improve perinatal outcome.

Ethical Approval: The Research & Ethical Review Committee, University Medical & Dental College, The University of Faisalabad approved this study vide letter No UMDC/Dean/008/12.

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Authors' Contribution:

AY: Acquisition of data, analysis & interpretation of data, drafting of article

MT: Acquisition of data, analysis & interpretation of data, drafting of article

MN: Acquisition of data, drafting of article, critical revision for important intellectual content, final approval of the version to be published

HZ: Acquisition of data, critical revision for important intellectual content, final approval of the version to be published

UF: Acquisition of data, analysis & interpretation of data, drafting of article, final approval of the version to be published

AF: Acquisition of data, drafting of article

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