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The Effectiveness of Progestogens in Reducing Preterm Birth Risk

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ABSTRACT

Objective: The study aims to evaluate the effectiveness of prophylactic vaginal progesterone in preventing preterm birth among women with a history of spontaneous preterm birth.

Methodology: This study was conducted at the Department of Gynecology & Obstetrics, Ayub Teaching Hospital Abbottabad, from February 2022 to August 2022. The study was approved by the Institutional Review Board (IRB). A total of 125 women with a history of spontaneous preterm birth were enrolled. Baseline demographic, medical, and obstetric data were recorded before initiating treatment. Participants self-administered vaginal progesterone daily and attended follow-up visits every two weeks for monitoring. The treatment was continued until 36 weeks of gestation, with standard preterm labor management provided as needed. Data were documented using a standardized form.

Results: The mean age of participants was 29 years (SD±8.631), with 38% being first-time mothers and 62% having had prior births. The administration of prophylactic vaginal progesterone was associated with a successful pregnancy outcome in 88% of participants. The average gestational period at delivery was 34 weeks (SD±3.455). While these findings indicate a promising trend, the absence of a control group limits the ability to determine statistical significance. The observed 88% success rate suggests a potential benefit, reinforcing the current clinical practice of using prophylactic vaginal progesterone for women with a history of spontaneous preterm birth. However, further research with a control group is essential to confirm its efficacy and establish statistical significance.

Conclusion: Prophylactic vaginal progesterone appears to significantly reduce the risk of preterm birth in women with a prior history, demonstrating its potential to improve pregnancy outcomes in this high-risk population. Nevertheless, individual variability in response to treatment underscores the need for personalized medical guidance, emphasizing the importance of discussing risk factors and treatment options with healthcare providers.

Keywords: Cervical Length**,** Drug Therapy, Progesterone**,** Preterm Birth**,** Pregnancy Complications**,**

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Introduction

Preterm birth, defined as delivery before 37 weeks of gestation, is a leading cause of perinatal morbidity and mortality worldwide.[1,2] It contributes to over one-third of neonatal deaths and is associated with long-term health complications, including respiratory distress syndrome, necrotizing enterocolitis, and intraventricular hemorrhage.[3] These conditions often necessitate prolonged neonatal intensive care, placing emotional and financial strain on families. Moreover, infants born preterm, particularly those before 32 weeks, face a heightened risk of developmental impairments,

chronic health conditions, and social challenges in adulthood.

Accurate prediction of preterm birth is crucial for timely intervention. Among symptomatic women, the fetal fibronectin (fFN) test has been shown to predict preterm birth risk with approximately 40% accuracy within seven days. Additionally, cervical length (CL) measurement via ultrasound between 21 and 24 weeks of gestation is a more reliable and cost-effective predictor of preterm labor than multiple scans conducted before 20 weeks.[4] A systematic review evaluating the combined use of fFN and CL concluded that this approach enhances sensitivity and positive predictive value while maintaining a high negative predictive value.[5]

While various treatment strategies have been explored, progesterone remains the only intervention consistently supported by evidence for the prevention of preterm birth in high-risk populations.[6-8] Progesterone maintains pregnancy by reducing uterine contractility through multiple mechanisms, including inhibition of oxytocin and alpha-adrenergic receptor activity, suppression of prostaglandin synthesis, and modulation of myometrial structure.[9,10]

Given the substantial burden of preterm birth and its associated consequences, identifying effective and accessible interventions is imperative. This study evaluates the efficacy of prophylactic vaginal progesterone as a cost-effective and scalable intervention, particularly in resource-limited settings where access to advanced neonatal care is constrained. By assessing its impact in a population served by Ayub Teaching Hospital, where preterm birth risk factors are prevalent, this research aims to provide evidence that could directly inform clinical practice and public health policy.

Despite the well-documented effectiveness of progesterone in reducing preterm birth rates, its long-term benefits for infant health remain underexplored. Current research predominantly focuses on immediate neonatal outcomes, overlooking critical long-term concerns such as cerebral palsy, developmental delays, and chronic lung diseases. This study seeks to bridge this knowledge gap by examining the impact of progesterone prophylaxis on the long-term health and developmental outcomes of children born to mothers with a history of spontaneous preterm birth.

By employing a cohort design with defined comparison groups and rigorous follow-up, this study aims to provide comprehensive insights into both the short- and long-term effects of prophylactic vaginal progesterone. The findings have the potential to refine clinical guidelines, enhance neonatal care strategies, and improve the overall prognosis for preterm infants.

Methodology

Study Design

This study utilized a prospective cohort design to assess the effectiveness of prophylactic vaginal progesterone in preventing spontaneous preterm birth among women with a history of prior preterm delivery. The study was conducted at the Department of Obstetrics and Gynecology, Unit A, Ayub Teaching Hospital, Abbottabad, over a six-month period from February to August 2022.

Study Setting

The study was conducted at Ayub Teaching Hospital, Abbottabad, a tertiary care hospital that serves a diverse patient population, particularly high-risk obstetric cases. Recruitment and follow-up took place in the hospital's antenatal clinic, where women at risk of preterm birth received routine prenatal care and were screened for study eligibility. The facility was equipped with ultrasound services, laboratory testing, and neonatal intensive care units, ensuring comprehensive maternal and neonatal care.

Inclusion criteria

- All pregnant women with age 18 to 45 years
- All pregnant women with gestational age18 to 23 weeks (by LMP).

- All pregnant women with a history of spontaneous preterm singleton birth between 20 and 35 weeks in the immediately preceding pregnancy.

Exclusion criteria

- Patients with other co-morbid condition e.g., uncontrolled diabetes, heart disease, renal impairment, chronic liver disease, suspicion of thromboembolic disease or other major illness. These are confounding factors.
- History of preterm labor due to chorioamnionitis, cervical cerclage or planned cervical cerclage during current pregnancy, preterm birth without spontaneous preterm labor, preterm premature rupture of membranes, preterm labor in multiple pregnancy, placenta previa and pregnancy induced hypertension.
- Major fetal anomaly diagnosed on ultrasound and maternal mullerian duct anomaly.
- History of allergy to progesterone and progesterone treatment within four weeks before enrollment.

Variables

The study captured both maternal and pregnancy-related variables to assess the effectiveness of vaginal progesterone treatment including maternal age, parity, gestational age at enrollment and at delivery, cervical length, prior preterm birth history, incidence of spontaneous preterm birth before 37 weeks, neonatal birth weight and adverse maternal or fetal outcomes related to progesterone use.

Data Source & Measurement

Baseline data, including maternal demographic characteristics, obstetric history, and cervical length, were collected at enrollment. Cervical length was measured using transvaginal ultrasound at the hospital's imaging center, following standardized protocols.

Participants were instructed to self-administer vaginal progesterone gel daily in the morning from the time of enrollment until 36 weeks of gestation, spontaneous rupture of membranes, or delivery whichever occurred first. Compliance was monitored through biweekly follow-up visits, where participants were interviewed regarding adherence, side effects, and any obstetric symptoms.

Adverse events and pregnancy outcomes were recorded during routine prenatal visits and hospital admissions. Data were recorded in pre-designed case report forms (CRFs) by trained research personnel.

Bias Considerations

Several strategies were implemented to minimize bias, selection bias was addressed by enrolling all eligible women within the specified gestational window. Recall bias was minimized through real-time data collection at scheduled follow-ups.

Study Size

A total of 125 participants were enrolled in this pilot study based on feasibility and availability of eligible patients at the hospital. While a formal power calculation was not performed, the sample size was deemed adequate for a preliminary assessment of vaginal progesterone's effectiveness.

Statistical Methods

Data were analyzed using SPSS version 22.0. Descriptive statistics were calculated to summarize the characteristics of the study population. Post-stratification chi-square test was performed, with p-values ≤ 0.05 considered statistically significant.

Ethical Considerations

Ethical approval for the study was obtained from the institutional review board of Ayub Teaching Hospital Abbottabad, (Ref. No ERC/ATH/171) Dated. 20-04-2021.

Written informed consent was secured from all participants after a thorough explanation of the study's purpose, procedures, potential risks, and benefits. To protect patient confidentiality, data were anonymized and stored securely, accessible only to authorized research personnel. Participants were informed about potential side effects of vaginal progesterone, such as vaginal irritation and

discharge, and were monitored regularly for adverse events. They retained the right to withdraw from the study at any stage without any impact on their routine medical care. The study adhered to the Declaration of Helsinki and all relevant ethical guidelines for research involving human subjects.

Results

Participants

A total of 125 women were included in this study, with a mean age of 29 years (SD ± 8.631). The majority of participants (77%) were between 18 and 35 years old, with 42% in the 18-25 age group and 35% in the 26-35 age group. The remaining 23% were aged 36-45 years. The age distribution of participants is summarized in Table I.

Descriptive Data

The study analyzed various demographic and clinical characteristics of participants, including parity, gestational age, cervical length, and history of preterm birth. Among the 125 women, 38% were primiparous, and 62% were multiparous. The gestational period ranged from 28 to 36 weeks, with a mean of 34 weeks (SD ± 3.455). Cervical lengths varied between 2 and 5 cm, with an average of 3 cm (SD ± 2.118). All participants had experienced at least one preterm birth, with an average of two preterm births per woman (SD ± 1.872).

Outcome Data

The primary outcome of the study was the efficacy of prophylactic vaginal progesterone in preventing preterm birth, defined as delivery before 37 weeks of gestation. The treatment was considered effective if the participant delivered at or beyond 37 weeks of gestation after receiving vaginal progesterone, while delivered before before 37 weeks despite receiving the intervention was considered non-effective.

Among 125 participants, 110 women (88%) successfully reached at least 37 weeks of gestation, indicating the intervention was effective. However, 15 women (12%) still experienced preterm birth despite treatment. The distribution of treatment effectiveness is presented in Figure 1.

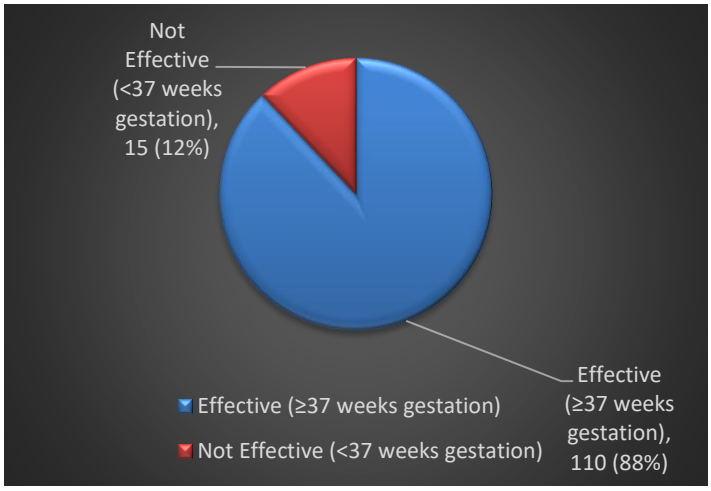

Figure 1: Efficacy of Prophylactic Vaginal Progesterone

Table I. Participant Characteristics

Variables		N (%)
Age (Years)	18-25	52(42)
	26-35	44(35)
	36-45	29(23)
Parity	Primiparous	48(38)
	Multiparous	77(62)
Gestational Age (Weeks)	28-34	52(42)
	34-36	73(58)
Cervical Length (cm)	2-3	50(40)
	4-5	75(60)
Number of Prior Preterm Births	One	25(20)
	Two	44(35)
	Three	56(45)

Main Results

The efficacy of vaginal progesterone was further stratified by parity, gestational age, and cervical length at the time of randomization. The effectiveness of progesterone remained consistent across subgroups, as detailed in Table II. The findings suggest that prophylactic vaginal progesterone is highly effective in reducing the risk of preterm birth in women with a history of spontaneous preterm

delivery. The consistency of efficacy across different age groups, parity statuses, and gestational age at initiation suggests its broad applicability. However, recognizing subgroup differences is essential for optimizing treatment strategies. For instance, if multiparous women were to exhibit slightly lower efficacy rates, closer monitoring or alternative interventions might be warranted. These insights contribute to personalized obstetric care and provide a foundation for further research into optimizing progesterone therapy in high-risk pregnancies.

Table II: Comparison of Treatment Efficacy across parity, gestational age, and cervical length.

Variables		Effective n (%)	Not Effective n (%)	p-value
Parity	Primiparous	42 (87.5%)	6 (12.5%)	0.007
	Multiparous	68 (88.3%)	9 (11.7%)	
Gestational Age (Weeks)	28-34	46 (88.5%)	6 (11.5%)	0.034
	34-36	64 (87.7%)	9 (12.3%)	
Cervical Length (cm)	2-3	44 (88%)	6 (12%)	0.101
	4-5	66 (88%)	9 (12%)	

Discussion

Preterm labor, as defined by the World Health Organization (WHO), refers to the onset of labor before 37 weeks of gestation and is characterized by regular uterine contractions, rupture of fetal membranes, and cervical changes, such as cervical shortening of less than 1 cm or dilation greater than 2 cm. When uterine contractions occur without cervical changes, the condition is classified as threatened preterm labor.[11-13]

In this study, the mean maternal age was 29 years (SD±8.63), with 38% being first-time mothers and 62% having had prior births. The average gestational period at the time of delivery was 34 weeks (SD±3.45). Prophylactic vaginal progesterone was found to be beneficial for 88% of participants, but it did not improve outcomes in 12% of cases. The effectiveness of progesterone in preventing preterm birth is attributed to its multifaceted mechanisms, including cervical ripening, immune modulation, and decidualization. However, despite its well-established role, progesterone is not universally effective. Several factors, such as maternal infection, multiple gestation, placenta previa, and fetal anomalies, may contribute to its limited efficacy in certain populations.

A randomized, double-blind trial involving 458 asymptomatic women with singleton pregnancies assessed the efficacy of vaginal progesterone gel. Participants were randomly assigned to receive either vaginal progesterone (n=235) or a placebo (n=223).[14] The study found a significantly lower rate of preterm birth before 33 weeks in the progesterone group (8.9% vs. 16.1%; p=0.02), demonstrating a 45% reduction in risk.[15] Similarly, another trial found that women receiving progesterone had a lower risk of preterm birth before 37 weeks (14% vs. 29%) and before 34 weeks (3% vs. 19%). Weekly monitoring of uterine contractions revealed fewer contractions in the progesterone group, suggesting that progesterone may exert its protective effects by promoting uterine quiescence and preventing premature labor.[16]

However, some studies have reported conflicting results. A large randomized controlled trial involving 659 women with a history of preterm birth assessed the impact of daily vaginal progesterone gel (90 mg) versus placebo, administered between 18 and 23 weeks of gestation until 37 weeks.[17] Despite a high incidence of preterm birth in the study population, with approximately 25% delivering before 35 weeks and 40% before 37 weeks, progesterone did not significantly reduce the risk of preterm birth at any gestational age. Additionally, no significant

differences were observed between the groups in maternal or neonatal outcomes.[18]

While multiple studies suggest that progesterone significantly reduces the risk of recurrent preterm birth, the magnitude of its impact varies. The estimated rate of recurrent preterm birth is between 25% and 31% with progesterone, compared to 33% to 47% with placebo.[19,20] However, its effect on perinatal mortality and long-term neonatal morbidity remains unclear due to limited study power. Given these findings, further research is needed to determine which subpopulations are most likely to benefit from progesterone therapy, the optimal dose and mode of administration, and the long-term neonatal outcomes, including neurological development, respiratory health, and the risk of chronic conditions.

This study contributes to the growing body of literature on preterm birth prevention, emphasizing the potential role of prophylactic vaginal progesterone in reducing preterm deliveries. However, the findings also underscore the need for individualized treatment strategies, particularly in populations with limited access to advanced neonatal care. Future studies should explore combination therapies and assess biomarkers that predict progesterone responsiveness to optimize patient selection and improve clinical outcomes.

Conclusion

This study underscores the clinical significance of prophylactic vaginal progesterone in reducing the recurrence of preterm births, a pressing public health concern associated with significant neonatal morbidity, mortality, and long-term health complications. By demonstrating an 88% success rate in preventing preterm birth recurrence, these findings contribute to the growing body of evidence supporting progesterone therapy for high-risk women. Beyond its immediate health benefits, preventing preterm births has substantial economic implications by reducing the need for costly neonatal intensive care. From a policy standpoint, these results advocate for the integration of prophylactic vaginal progesterone into clinical guidelines for women with a history of spontaneous preterm birth. Broadening its implementation could lead to meaningful reductions in preterm birth rates, improved neonatal outcomes, and significant healthcare cost savings. Future research should focus on optimizing implementation strategies, assessing long-term benefits, and conducting cost-effectiveness analyses across diverse populations.

Limitations: It is important to acknowledge the limitations of the current study, especially the lack of a control group. Without a control group, it is difficult to determine whether the 88% success rate is truly attributable to progesterone or if it would have been similar in the absence of treatment.

Suggestions: A crucial area for future research is the evaluation of long-term neurodevelopmental outcomes in children exposed to prophylactic progesterone *in utero*. While this study focused on the prevention of preterm birth itself, it's essential to understand the long-term impact, if any, of progesterone on cognitive function, motor skills, and behavior in these children. A prospective cohort study design with long-term follow-up would be ideal for addressing this question.

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