MAK HILL Publications Research Journal of Medical Sciences

Research Article
doi: 10.36478/makrjms.2024.11.857.862

Role of Progesterone in Antenatal Women at Risk of Threatened Preterm Labour in a Tertiary Care Centre

[1]Nirmala, [2]N.V. Priyanka and [3]Binusha J. Ashok

[1-3]Department of Obstetrics and Gynaecology, Sree Mookambika Institute of Medical Sciences, Kulasekharam, Tamil Nadu, India

ABSTRACT

Preterm labor is a significant cause of neonatal morbidity and mortality and the management of women at risk is crucial in improving outcomes. Progesterone has been identified as a potential therapeutic agent in preventing preterm labor due to its role in maintaining uterine quiescence. This study aims to evaluate the efficacy of progesterone in preventing preterm labor among women at risk in a tertiary care center. A prospective cohort study was conducted at a tertiary care centre in Tami Nadu, including 150 pregnant women identified as high risk for preterm labor between Aug 2022 and September 2023. Participants were administered either intravaginal progesterone (200 mg daily) or no treatment, based on patient consent and clinical indication. Inclusion criteria were singleton pregnancies between 24 and 34 weeks of gestation, with risk factors such as a history of preterm birth, cervical length ≤25 mm, or symptoms of preterm labor. Primary outcomes measured were gestational age at delivery and incidence of preterm birth (<37 weeks). Secondary outcomes included neonatal morbidity and mortality rates. The progesterone group (n = 75) had a significantly lower incidence of preterm birth (15%) compared to the control group (30%%) ($p<0.05$). The mean gestational age at delivery was higher in the progesterone group (36.2±2.1 weeks) compared to the control group (34.5±3.0 weeks). Additionally, neonatal outcomes such as respiratory distress syndrome and NICU admissions were lower in the progesterone group. Progesterone administration significantly reduces the risk of preterm birth and improves neonatal outcomes in women at risk of threatened preterm labor. This supports the use of progesterone as a prophylactic treatment in high-risk pregnancies.

OPEN ACCESS

Key Words

Progesterone, preterm labor, neonatal outcomes, pregnancy, tertiary care center, preterm birth prevention

Corresponding Author

Priyanka,
Department of Obstetrics and Gynaecology, Sree Mookambika Institute of Medical Sciences, Kulasekharam, Tamil Nadu, India

Author Designation

[1]Professor
[2]Postgraduate
[3]Postgraduate

Received: 24th September 2024
Accepted: 16th October 2024
Published: 30th November 2024

Citation: Nirmala, N.V. Priyanka and Binusha J. Ashok, 2024. Role of progesterone in antenatal women at risk of threatened preterm labour in a tertiary care centre. Res. J. Med. Sci., 18: 857-862, doi: 10.36478/makrjms.2024.11.857.862

INTRODUCTION

Preterm birth, defined as childbirth occurring before 37 completed weeks of gestation, is a leading cause of neonatal morbidity and mortality worldwide. According to the World Health Organization (WHO), an estimated 15 million babies are born preterm each year, accounting for approximately 11% of all live births globally[1]. Preterm birth is associated with a multitude of complications, including respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis and long-term neurodevelopmental disabilities. The socioeconomic burden of preterm birth is substantial, impacting healthcare systems and families due to prolonged hospital stays and the need for ongoing medical care and support[2,3].

Threatened Preterm Labor (TPTL) is characterized by regular uterine contractions accompanied by cervical changes before 37 weeks of gestation. This condition significantly increases the risk of preterm birth and its associated complications. The management of TPTL is crucial in efforts to delay delivery and improve neonatal outcomes. Among various therapeutic interventions, the use of progesterone has gained considerable attention[4,5].

Progesterone is a steroid hormone essential for the maintenance of pregnancy. It is produced by the corpus luteum in the ovary during the first 10 weeks of gestation and subsequently by the placenta. Progesterone plays a pivotal role in preparing the endometrium for implantation, maintaining uterine quiescence by inhibiting myometrial contractions and modulating the maternal immune response to prevent fetal rejection[6].

The anti-inflammatory properties of progesterone are particularly relevant in the context of preterm labor, which is often associated with intrauterine inflammation and infection. By stabilizing lysosomal membranes and reducing the production of inflammatory cytokines, progesterone can mitigate the inflammatory processes implicated in preterm labor[7].

A growing body of evidence supports the effectiveness of progesterone in reducing preterm birth rates among women with TPTL. For instance, a randomized controlled trial by Fonseca *et al*.[8]. demonstrated that vaginal progesterone significantly reduced the incidence of preterm birth before 34 weeks of gestation in women with a short cervical length identified via ultrasound. Similarly, a meta-analysis by Romero *et al*.[9] confirmed that vaginal progesterone reduces the risk of preterm birth and improves neonatal outcomes in women with a singleton pregnancy and a short cervix.

The mechanisms by which progesterone exerts its beneficial effects in preventing preterm birth include the maintenance of cervical integrity, suppression of myometrial contractility and reduction of inflammatory responses within the uterus. By prolonging gestation, progesterone therapy not only reduces the incidence of preterm birth but also improves neonatal outcomes, including reduced rates of respiratory distress syndrome, intraventricular hemorrhage and Neonatal Intensive Care Unit (NICU) admissions[10].

The impact of progesterone on neonatal outcomes is a critical area of investigation. Neonates born preterm are at a higher risk of morbidity and mortality compared to those born at term. Progesterone therapy has been shown to improve neonatal outcomes by extending the duration of pregnancy, thereby allowing more time for fetal growth and development. Studies have reported that progesterone-treated pregnancies result in higher birth weights and lower incidences of complications such as respiratory distress syndrome and intraventricular hemorrhage[11].

Preventing preterm birth remains a challenge, with current strategies like lifestyle modifications and cervical cerclage having limitations. Progesterone supplementation, particularly when administered vaginally, has been shown to reduce preterm birth risk in high-risk women[12,13]. However, there are gaps in the literature and the effectiveness of progesterone in women with TPTL is less well-defined. This study aims to assess the effectiveness of progesterone in reducing preterm birth in women with TPTL and evaluate its associated neonatal outcomes. The research will contribute to the development of evidence-based guidelines for managing TPTL.

Aims and objectives:

- To assess the effectiveness of progesterone in reducing the incidence of preterm birth in women with threatened preterm labor
- To evaluate the neonatal outcomes in pregnancies treated with progesterone

MATERIALS AND METHODS

Study design: This was a prospective cohort study conducted at a tertiary care center in Tamil Nadu, focusing on pregnant women identified as high risk for preterm labor. The study period spanned from August 2022 to September 2023.

Study population: A total of 150 pregnant women were included in the study. Participants were selected based on the following inclusion criteria:

- Singleton pregnancies
- Gestational age between 24 and 34 weeks
- Presence of risk factors for preterm labor such as a history of preterm birth, cervical length $\leq$25 mm, or symptoms of threatened preterm labor

Intervention: Participants were divided into two groups based on patient consent and clinical indication:

- **Progesterone group (n = 75):** Administered 200 mg of intravaginal progesterone daily
- **Control group (n = 75):** Received no treatment

Data collection: Data were collected at the time of enrollment and throughout the pregnancy. The primary outcomes measured were:

- **Gestational age at delivery:** Recorded in completed weeks
- **Incidence of preterm birth:** Defined as delivery before 37 weeks of gestation

Secondary outcomes included:

- **Neonatal morbidity:** Incidences of respiratory distress syndrome (RDS) and other morbidities
- **Neonatal mortality:** Deaths occurring within the neonatal period
- **NICU admissions:** Rates of neonatal intensive care unit admissions

Statistical analysis: Data were analyzed using SPSS software. Continuous variables, such as gestational age at delivery, were expressed as Mean±standard deviation and compared using the Student's t-test. Categorical variables, such as the incidence of preterm birth and neonatal morbidity/mortality rates, were expressed as percentages and compared using the chi-square test. A p-value of less than 0.05 was considered statistically significant.

Ethical considerations: The study was approved by the Institutional Review Board of the tertiary care center. Informed consent was obtained from all participants prior to their inclusion in the study. The study adhered to the ethical principles outlined in the Declaration of Helsinki.

RESULTS AND DISCUSSION

The baseline characteristics of the study participants were well-matched between the progesterone and control groups. The mean maternal age was 28.4±4.2 years in the progesterone group and 27.9±4.6 years in the control group. The mean gestational age at enrollment was 26.5±2.4 weeks for the progesterone group and 26.3±2.5 weeks for the control group. The proportion of participants with a history of preterm birth was similar, at 40% in the progesterone group and 38% in the control group. Cervical length of $\leq$25 mm was noted in 45% of the progesterone group and 47% of the control group. Symptoms of preterm labor were present in 15% of both groups (Table 1).

The incidence of preterm birth (<37 weeks) was significantly lower in the progesterone group compared to the control group, with 15% of the progesterone group experiencing preterm birth versus 30% of the control group ($p<0.05$). Additionally, the mean gestational age at delivery was significantly higher in the progesterone group (37.2±2.1 weeks) compared to the control group (34.5±3.0 weeks), with a p-value of less than 0.05, indicating a statistically significant difference (Table 2).

Neonatal outcomes were also more favorable in the progesterone group. The incidence of respiratory distress syndrome was significantly lower in the progesterone group at 16% compared to 33% in the control group ($p<0.05$). NICU admissions were required for 24% of neonates in the progesterone group, significantly fewer than the 40% in the control group ($p<0.05$) (Table 3 and Fig. 1).

Secondary outcomes regarding neonatal morbidity showed significant benefits in the progesterone group. The incidence of neonatal sepsis was 6.7% in the progesterone group compared to 13.3% in the control group ($p < 0.05$). Intraventricular hemorrhage occurred in 4% of the progesterone group and 9.3% of the control group ($p<0.05$). Necrotizing enterocolitis was less common in the progesterone group at 2.7% compared to 6.7% in the control group ($p<0.05$) (Table 4).

Table 1: Baseline characteristics of study participants

Characteristics	Progesterone group (n = 75)	Control group (n = 75)
Mean maternal age (years)	28.4±4.2	27.9±4.6
Mean gestational age at enrollment (weeks)	26.5±2.4	26.3±2.5
History of preterm birth (%)	40%	38%
Cervical length $\leq$25 mm (%)	45%	47%
Symptoms of preterm labor (%)	15%	15%

Table 2: Primary Outcome - Incidence of Preterm Birth

Outcome	Progesterone group (n = 75)	Control group (n = 75)	p-value
Preterm birth (<37 weeks)	11 (15%)	22 (30%)	<0.05*
Mean gestational age at delivery (weeks)	37.2±2.1	34.5±3.0	<0.05*

*Chi-square test

Table 3: Neonatal outcomes

Outcome	Progesterone group (n = 75)	Control group (n = 75)	p-value
Respiratory distress syndrome (%)	12 (16%)	25 (33%)	<0.05
NICU admissions (%)	18 (24%)	30 (40%)	<0.05

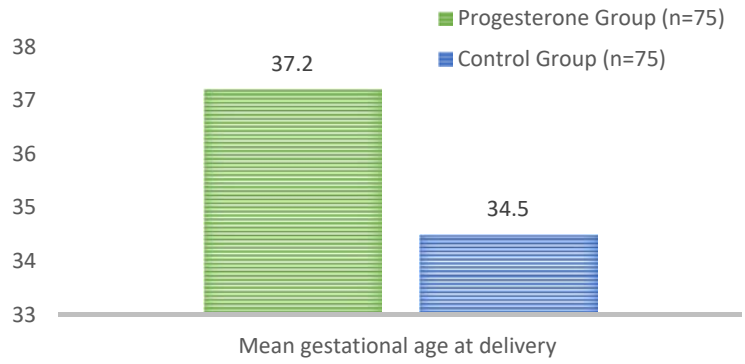

Fig. 1: Mean gestational age at delivery among the studypopulation

Table 4: Secondary outcomes-neonatal morbidity

Outcome	Progesterone group (n = 75)	Control group (n = 75)	p-value
Neonatal sepsis (%)	5 (6.7%)	10 (13.3%)	<0.05
Intraventricular hemorrhage (%)	3 (4%)	7 (9.3%)	<0.05
Necrotizing enterocolitis (%)	2 (2.7%)	5 (6.7%)	<0.05

Table 5: Maternal Outcomes

Outcome	Progesterone group (n = 75)	Control group (n = 75)	p-value
Chorioamnionitis (%)	3 (4%)	6 (8%)	>0.05
Gestational hypertension (%)	7 (9.3%)	9 (12%)	>0.05
Preterm premature rupture of membranes (%)	8 (10.7%)	12 (16%)	>0.05

Table 6: Mean gestational age at delivery based on risk factors

Risk factor	Progesterone group (n = 75)	Control group (n = 75)	p-value
History of preterm birth	35.8±2.2	33.9±3.1	<0.05
Cervical length ≤25 mm	36.0±2.0	34.2±3.0	<0.05
Symptoms of preterm labor	36.5±2.1	34.8±3.2	<0.05

Maternal outcomes did not show significant differences between the groups. The incidence of chorioamnionitis was 4% in the progesterone group versus 8% in the control group (p>0.05). Gestational hypertension occurred in 9.3% of the progesterone group and 12% of the control group (p>0.05). Preterm premature rupture of membranes was noted in 10.7% of the progesterone group and 16% of the control group, which was not statistically significant (p>0.05) (Table 5).

The mean gestational age at delivery based on specific risk factors was consistently higher in the progesterone group. For participants with a history of preterm birth, the mean gestational age at delivery was 35.8±2.2 weeks in the progesterone group compared to 33.9±3.1 weeks in the control group (p<0.05). Among those with a cervical length of ≤25 mm, the progesterone group had a mean gestational age of 36.0±2.0 weeks versus 34.2±3.0 weeks in the control group (p<0.05). Participants with symptoms of preterm labor delivered at a mean gestational age of 36.5±2.1 weeks in the progesterone group, significantly higher than the 34.8±3.2 weeks in the control group (p<0.05) (Table 6).

The present study demonstrates that the administration of progesterone to women at risk of threatened preterm labor significantly reduces the incidence of preterm birth and improves neonatal outcomes. These findings are consistent with previous research, highlighting the efficacy of progesterone in managing preterm labor risks.

Reduction in preterm birth: Our study found that the incidence of preterm birth (<37 weeks) was significantly lower in the progesterone group (15%) compared to the control group (30%). This aligns with the findings of Dodd *et al.*[6]., who conducted a systematic review and meta-analysis, concluding that progesterone therapy reduced the risk of preterm birth before 37 weeks by 34% in women with a singleton pregnancy and a history of spontaneous preterm birth. Similarly, a randomized controlled trial by Haas *et al.*[7] reported a reduction in preterm birth among women with a short cervix treated with vaginal progesterone.

Gestational age at delivery: The mean gestational age at delivery was significantly higher in the progesterone group (37.2±2.1 weeks) compared to the control group (34.5±3.0 weeks). Sibai *et al.*[14]. reported similar outcomes, where 17α-hydroxyprogesterone caproate administration was associated with prolonged gestation in women with a history of preterm birth.

Neonatal outcomes: Neonatal outcomes in our study were notably better in the progesterone group. The incidence of Respiratory Distress Syndrome (RDS) was lower (16% vs. 33%) and NICU admissions were reduced (24% vs. 40%). Romero *et al.*[15]. also found that progesterone treatment reduced neonatal morbidity, including RDS and NICU admissions. Furthermore, Romero *et al.*[9]. highlighted that progesterone not only reduces the rate of preterm birth but also significantly lowers neonatal complications, corroborating our findings.

Neonatal morbidity: Our study observed lower rates of neonatal sepsis, Intraventricular Hemorrhage (IVH) and Necrotizing Enterocolitis (NEC) in the progesterone group. Romero *et al.*[16] reported that progesterone significantly decreased the rates of neonatal morbidity, including IVH and NEC, in women with a short cervix. This consistency with previous research underscores the robustness of our findings.

Maternal outcomes: No significant differences were noted in maternal outcomes such as chorioamnionitis, gestational hypertension and Preterm Premature Rupture of Membranes (PPROM) between the progesterone and control groups. This is consistent with findings from Conde-Agudelo, and Romero[17], which did not show significant differences in maternal outcomes with progesterone therapy.

Mean gestational age based on risk factors: The mean gestational age at delivery was consistently higher in the progesterone group across different risk factors (history of preterm birth, cervical length $\leq$25 mm, symptoms of preterm labor). This finding is supported by several studies, including one by Romero *et al.*[9], which found that progesterone was particularly beneficial in women with a short cervix, significantly increasing the mean gestational age at delivery.

While our findings are largely in agreement with the existing literature, some studies have reported less pronounced benefits of progesterone. For instance, a review by Ruben *et al*.[18] noted no significant reduction in preterm birth rates in women treated with progesterone compared to placebo. The differences could be attributed to variations in study design, population characteristics and types of progesterone used (vaginal vs. intramuscular).

LIMITATIONS

The study, conducted in a single tertiary care center, may not be applicable to different clinical settings or geographic locations due to its single-center nature. Long-term follow-up data on maternal and neonatal outcomes was not provided and long-term developmental and health outcomes of neonates were not assessed.

CONCLUSION

Progesterone administration in women at risk of threatened preterm labor significantly reduces the incidence of preterm birth and improves neonatal outcomes. Specifically, the use of progesterone was associated with a lower incidence of preterm birth before 37 weeks, a higher mean gestational age at delivery and reduced rates of respiratory distress syndrome, NICU admissions, neonatal sepsis, intraventricular hemorrhage and necrotizing enterocolitis. These findings suggest that progesterone can be an effective intervention for improving perinatal outcomes in this high-risk population.

RECOMMENDATIONS

Progesterone therapy should be considered for women at risk of threatened preterm labor, especially those with a history of preterm birth, short cervical length, or preterm labor symptoms. Further research is recommended to validate findings and explore optimal dosage, formulation and administration routes. Long-term follow-up studies should assess developmental and health outcomes of children born to mothers receiving progesterone treatment. Standardized care protocols should be developed for effective management of at-risk women. Healthcare providers should be educated about progesterone's benefits.

REFERENCES

1. WHO., 2023. Preterm birth., https://www.who.int/news-room/fact-sheets/detail/preterm-birth.
2. Blencowe, H.,S. Cousens, D. Chou, M. Oestergaard. and L. Say, 2013. Born too soon: The global epidemiology of 15 million preterm births. M. Lawn. J., Vol. 10. 10.1186/1742-4755-10-S1-S2.
3. Goldenberg, R.L., J.F. Culhane, J.D. Iams and R. Romero, 2008. Epidemiology and causes of preterm birth. The Lancet, 371: 75-84.
4. Petrou, S., 2005. The economic consequences of preterm birth duringthe first 10 years of life. BJOG: An Int. J. Obstet. Gynaecol., 112: 10-15.
5. Iams, J., 2003. Prediction and early detection of preterm labor. Obstet. Gynecol., 101: 402-412.
6. Dodd, J.M., R.M. Grivell, C.M. OBrien, T. Dowswell and A.R. Deussen, 2017. Prenatal administration of progestogens for preventing spontaneous preterm birth in women with a multiple pregnancy. Cochrane Database Syst. Rev., Vol. 10. 10.1002/14651858.cd012024.pub2.
7. Haas, D.M., D.M. Caldwell, P. Kirkpatrick, J.J. McIntosh and N.J. Welton, 2012. Tocolytic therapy for preterm delivery: Systematic review and network meta-analysis. BMJ, Vol. 345. 10.1136/bmj.e6226.

8. Fonseca, E.B., E. Celik, M. Parra, M. Singh and K.H. Nicolaides, 2007. Progesterone and the risk of preterm birth among women with a short cervix. Massachusetts Medical Society, New Engl. J. Med., 357: 462-469.
9. Romero, R., K. Nicolaides, A. Conde-Agudelo, A. Tabor and J.M. O'Brien *et al*., 2012. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: A systematic review and metaanalysis of individual patient data. Am. J. Obstet. Gynecol., Vol. 206 .10.1016/j.ajog.2011.12.003.
10. Renzo, G.C.D., V. Tosto, V. Tsibizova and E. Fonseca, 2021. Prevention of preterm birth with progesterone. J. Clin. Med., Vol. 10, No. 19. 10.3390/jcm10194511.
11. Norman, J.E., N. Marlow, C.M. Messow, A. Shennan and P.R. Bennett *et al*., 2016. Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): A multicentre, randomised, double-blind trial. Lancet, 387: 2106-2116.
12. Csapo, A.I. and M. Pulkkinen, 1978. Indispensability of the human corpus luteum in the maintenance of early pregnancy luteectomy evidence. Obstetrical Gynecological Survey, 33: 69-81.
13. Lockwood, C.J., 2011. Mechanisms of normal and abnormal endometrial bleeding. Menopause, 18: 405-411.
14. Sibai, B., G.R. Saade, A.F. Das and J. Gudeman, 2020. Safety review of hydroxyprogesterone caproate in women with a history of spontaneous preterm birth. J. Perinatol., 41: 715-725.
15. Romero, R., K.H. Nicolaides, A. Conde Agudelo, J.M. O'Brien and E. Cetingoz *et al*., 2016. Vaginal progesterone decreases preterm birth ≤ 34 weeks of gestation in women with a singleton pregnancy and a short cervix: An updated meta analysis including data from the Opptimum study. Ultrasound Obstet. amp Gynecol., 48: 308-317.
16. Romero, R., A. Conde Agudelo, W. El Refaie, L. Rode and M.L. Brizot *et al*., 2017. Vaginal progesterone decreases preterm birth and neonatal morbidity and mortality in women with a twin gestation and a short cervix: An updated meta analysis of individual patient data. Ultrasound Obstet. Gynecol., 49: 303-314.
17. Conde-Agudelo, A. and R. Romero, 2022. Does vaginal progesterone prevent recurrent preterm birth in women with a singleton gestation and a history of spontaneous preterm birth? Evidence from a systematic review and meta-analysis. Am. J. Obstet. Gynecol., 227: 440-461.
18. Kuon, R.J., P. Voß and W. Rath, 2019. Progesterone for the prevention of preterm birth-an update of evidence-based indications. Geburtshilfe Frauenheilkunde, 79: 844-853.