International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Kanal P et al. Int J Reprod Contracept Obstet Gynecol. 2026 Jul;15(7):2556-2559
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20262102

Original Research Article

Comparative efficacy of oral versus vaginal micronized progesterone in the prolongation of preterm labour: a prospective comparative study

Preeti Kanal, Neha Gupta*, Hema J. Shobhane, Smriti Agnihotri

[1]Department of Obstetrics and Gynecology, Maharani Laxmi Bai Medical College, Jhansi, Uttar Pradesh, India
[2]Department of Health Sciences Education and Pathology, University of Illinois College of Medicine, Peoria, Illinois

Received: 23 April 2026
Revised: 21 May 2026
Accepted: 01 June 2026

***Correspondence:**
Dr. Neha Gupta,
E-mail: nehakgmu47@gmaip.com

ABSTRACT

Background: Preterm labour is a leading cause of neonatal morbidity and mortality worldwide. Progesterone supplementation is an established strategy for preterm birth prevention; however, the optimal route of administration- oral or vaginal- remains debated, particularly regarding gestation prolongation. Objective was to compare the efficacy of oral versus vaginal micronized progesterone (200 mg daily) in prolonging gestation in women presenting with preterm labour.
Methods: A prospective comparative study was conducted at Maharani Laxmi Bai Medical College, Jhansi, from May 2025 to April 2026. One hundred pregnant women with preterm labour (24-36+6 weeks) were randomised to oral micronized progesterone 200 mg daily (group A, n=50) or vaginal micronized progesterone 200 mg daily (group B, n=50). Primary outcomes were mean prolongation of gestation (days) and mean gestational age at delivery (weeks).
Results: Both groups were comparable at baseline. The vaginal progesterone group demonstrated significantly greater mean gestation prolongation (20.14±4.58 versus 11.38±2.82 days; p=0.0001) and higher mean gestational age at delivery (35.81±1.09 versus 33.88±1.84 weeks; p=0.001). Deliveries at 33-36+6 weeks were more frequent in the vaginal group (94% versus 74%; p=0.02). Very preterm deliveries (24-29 weeks) occurred only in the oral group (2%).
Conclusions: Vaginal micronized progesterone is significantly more effective than oral progesterone in prolonging gestation in preterm labour, attributable to enhanced uterine bioavailability via the first uterine pass effect. It should be the preferred route in clinical management of preterm labour.

Keywords: Gestation prolongation, Micronized progesterone, Oral progesterone, Preterm birth prevention, Preterm labour, Vaginal progesterone

INTRODUCTION

Preterm birth, defined as delivery before 37 completed weeks of gestation, is the leading cause of neonatal morbidity and mortality globally, with an estimated 13.4 million preterm births annually, accounting for approximately 9.9% of all deliveries.[1,2] Direct complications of prematurity cause around one million neonatal deaths per year, and survivors face significant risks of respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, and long-term neurodevelopmental sequelae.[3,4]

Prolongation of gestation, even by a few days to weeks, yields clinically significant improvements in neonatal outcomes- particularly when delivery can be deferred beyond 34 weeks, at which point pulmonary maturity is largely achieved. Progesterone plays a fundamental physiological role in maintaining uterine quiescence through suppression of myometrial contractility, maintenance of cervical competence, and modulation of pro-inflammatory pathways implicated in labour initiation.[5] Progesterone supplementation is therefore a rational and evidence-based strategy for delaying preterm birth.

Progesterone may be administered intramuscularly (17-alpha-hydroxyprogesterone caproate), vaginally, or orally as micronized formulations. Vaginal administration is proposed to confer a pharmacokinetic advantage by bypassing hepatic first-pass metabolism, thereby achieving higher local uterine tissue concentrations- the "first uterine pass effect"- with reduced systemic exposure.[6] Published network meta-analyses consistently identify vaginal progesterone as the most effective intervention for reducing preterm birth in singleton pregnancies at high risk due to prior preterm birth or short cervix.[7,8]

However, most available comparative trials have used synthetic oral progestogens (e.g., dydrogesterone) rather than natural micronized progesterone, limiting direct pharmacological comparability. Comparative studies using identical doses of natural micronized progesterone via oral and vaginal routes, with gestation prolongation as the primary endpoint in women with established preterm labour, remain limited. This study was designed to address this gap in a tertiary care setting in northern India.

METHODS

Study design and setting

This was a hospital-based, prospective, open-label, randomised comparative study conducted in the department of obstetrics and gynecology, Maharani Laxmi Bai Medical College and Hospital, Jhansi, Uttar Pradesh, India, from May 2025 to April 2026. Ethics approval was granted by the Institutional ethics committee (human studies), MLB Medical College (Reference No. 6700/IEC/PG-23-74/2026/SC1). Written informed consent was obtained from all participants prior to enrolment.

Inclusion and exclusion criteria

Eligible women were pregnant with preterm labour between 24 and 36+6 weeks of gestation, confirmed fetal cardiac activity on recent ultrasonography, cervical length ≤25 mm on transvaginal ultrasound, a history of prior preterm labour or abortion, no serious maternal comorbidities, and willingness to provide informed consent. Women were excluded if they had premature rupture of membranes, multiple gestation, intrauterine growth restriction, congenital fetal anomalies, severe preeclampsia or eclampsia, placenta praevia or abruption, or any contraindication to progesterone (hormone-sensitive malignancy, undiagnosed vaginal bleeding, or thromboembolic disorders).

Sample size

Sample size was estimated using $n = Z^2p(1-p)/d^2$, with Z=1.96 (95% confidence), p=0.235 (preterm recurrence rate from prior literature), and d=0.10 (margin of error), yielding a minimum of 69 per group. A final sample of 50 per group (n=100 total) was enrolled to ensure adequate statistical power and account for potential attrition.

Randomisation and interventions

Participants were randomly allocated to group A (oral micronized progesterone 200 mg once daily, n=50) or group B (vaginal micronized progesterone 200 mg once daily, n=50). Treatment was initiated at enrolment and continued until delivery or 36+6 weeks, whichever occurred earlier. All women underwent standardised baseline assessment: obstetric history, general and obstetric examination, hemogram, blood grouping, blood glucose, urine analysis, and obstetric ultrasonography for gestational age confirmation, fetal biometry, and cervical length measurement.

Outcome measures

Primary outcomes: (i) mean prolongation of gestation (days from enrolment to delivery), and (ii) mean gestational age at delivery (weeks). Secondary outcome: gestational age distribution at delivery (24-29, 30-32, and 33-36+6 weeks).

Statistical analysis

Data were analysed using IBM SPSS Statistics version 21.0. Continuous variables are reported as mean±standard deviation and compared by the independent samples t-test. Categorical variables are reported as frequencies and percentages and compared by the chi-square test or Fisher's exact test. A two-tailed p value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

Both groups were well-matched at baseline (Table 1). The majority of participants were aged 25-29 years (44% oral versus 64% vaginal; p=0.23). Multigravida women predominated in both groups (92% oral versus 96% vaginal; p=0.40). No statistically significant differences were observed for any baseline variable, confirming comparability.

Primary outcomes: gestation prolongation and gestational age at delivery

The vaginal progesterone group achieved significantly greater mean gestation prolongation compared to the oral group (20.14±4.58 versus 11.38±2.82 days; p=0.0001). Correspondingly, the mean gestational age at delivery was significantly higher in the vaginal group (35.81±1.09 versus 33.88±1.84 weeks; p=0.001). These results are presented in Table 2.

Table 1: Baseline characteristics of study participants.

Variables		Oral group (n=50)	Vaginal group (n=50)	P value
Age years, (%)	20-24	20 (40)	14 (28)	0.23
	25-29	22 (44)	32 (64)	
	≥30	8 (16)	4 (8)	
Primigravida, (%)		4 (8)	2 (4)	0.40
Multigravida, (%)		46 (92)	48 (96)	

Table 2: Gestation prolongation and gestational age at delivery.

Parameters	Oral group (n=50) Mean±SD	Vaginal group (n=50) Mean±SD	P value
Gestation prolongation (days)	11.38±2.82	20.14±4.58	0.0001
Gestational age at delivery (weeks)	33.88±1.84	35.81±1.09	0.001

Table 3: Gestational age distribution at delivery.

Gestational age at delivery	Oral group (%)	Vaginal group (%)	P value
24-29 weeks	1 (2.0)	0 (0)	0.02
30-32 weeks	12 (24.0)	3 (6.0)	
33-36+6 weeks	37 (74.0)	47 (94.0)	

Gestational age distribution at delivery

The gestational age distribution at delivery differed significantly between groups (p=0.02) (Table 3). Deliveries at 33-36+6 weeks were markedly more frequent in the vaginal group (94% versus 74%). Deliveries at 30-32 weeks were four times more common in the oral group (24% versus 6%). Critically, very preterm deliveries at 24-29 weeks occurred exclusively in the oral group (2%), with none in the vaginal group.

DISCUSSION

This prospective randomised study demonstrates that vaginal micronized progesterone prolongs gestation significantly more effectively than oral micronized progesterone when administered at an equivalent dose of 200 mg daily in women presenting with preterm labour. The vaginal group achieved nearly double the mean gestation prolongation (20.14 versus 11.38 days) and a mean gestational age at delivery approximately two weeks higher (35.81 versus 33.88 weeks). These differences are clinically significant: each additional week of gestation near term substantially reduces neonatal respiratory morbidity, NICU admission, and mortality, particularly when delivery is deferred beyond 34 weeks.

The superior gestation prolongation with vaginal progesterone is best explained by the first uterine pass effect. Vaginal progesterone bypasses hepatic first-pass metabolism and is absorbed directly by the uterus and cervix, achieving markedly higher local tissue concentrations than the oral route.[6] These elevated uterine tissue levels more effectively suppress myometrial contractility via progesterone receptor-mediated inhibition of calcium-calmodulin-myosin light chain kinase pathways, and maintain cervical integrity by reducing collagen degradation and inhibiting prostaglandin synthesis.[5,6] Oral progesterone, despite achieving higher systemic concentrations due to extensive hepatic metabolism, delivers comparatively lower progesterone levels to uterine tissue- limiting its ability to maintain uterine quiescence.

The three-arm randomised controlled trial by Srisutham et al in 231 women with threatened preterm labour reported that vaginal progesterone 200 mg daily achieved a significantly longer median latency period (43.0 days versus 36.5 days in control; p=0.012) and reduced preterm birth before 34 weeks (5.2% versus 16.0%; p=0.030), while oral dydrogesterone 30 mg daily showed no significant benefit over control.[10] Iqbal et al reported mean pregnancy prolongation of 30.7±5.47 days with vaginal micronized progesterone pessary versus 18.22±6.33 days with oral progesterone in 112 high-risk women, consistent with our findings.[11]

Deshpande et al compared 400 mg oral versus vaginal natural micronized progesterone in 140 women with threatened preterm labour, finding a higher proportion of term deliveries in the vaginal group (81.42% versus 68.57%), further corroborating the advantage of vaginal administration in prolonging gestation.[12] Abdelaziz also demonstrated higher mean gestational age at delivery in the vaginal group (37 versus 36 weeks) in 138 high-risk women.[13]

The gestational age distribution data in our study underscore the clinical relevance of these differences. The virtual elimination of very preterm deliveries in the vaginal group (0% versus 2%) and the fourfold reduction in 30-32-week deliveries (6% versus 24%) translate directly into reduced neonatal mortality risk. In low- and middle-income settings, delivery at 30-32 weeks carries an

approximately five- to tenfold higher neonatal mortality risk compared to delivery at 34-36 weeks, making even modest gestation prolongation of major public health significance.

A particular strength of this study is the use of natural micronized progesterone- rather than synthetic dydrogesterone- at an identical dose in both arms, ensuring observed differences reflect route of administration rather than pharmacological differences between progestogen types. The prospective design, standardised inclusion criteria, and complete follow-up further strengthen internal validity.

Limitations include the open-label single-centre design, as blinding was not feasible given the different routes of administration. The modest sample size of 50 per group limits subgroup analyses. The absence of serum and uterine tissue progesterone assays precludes direct pharmacokinetic confirmation of the first uterine pass effect in this cohort. Future multicentre, double-dummy, blinded randomised trials with pharmacokinetic sub studies are recommended.

CONCLUSION

Vaginal micronized progesterone 200 mg daily prolongs gestation significantly more effectively than oral micronized progesterone 200 mg daily in women presenting with preterm labour, achieving nearly double the mean gestation prolongation (20.14±4.58 versus 11.38±2.82 days; p=0.0001) and a significantly higher mean gestational age at delivery (35.81±1.09 versus 33.88±1.84 weeks; p=0.001). The pharmacokinetic advantage of vaginal administration via the first uterine pass effect- delivering higher progesterone concentrations directly to uterine and cervical tissue- provides the mechanistic basis for this superiority. Vaginal micronized progesterone should be the preferred route of administration for gestation prolongation in preterm labour, and its incorporation into standard clinical protocols for threatened preterm labour is strongly recommended.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee MLB Medical College, Jhansi (Ref. No. 6700/IEC/PG-23-74/2026/SC 1; 23 January 2026)

REFERENCES

1. Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller AB, et al. Born too soon: the global epidemiology of 15 million preterm births. Reprod Health. 2013;10(Suppl 1):S2.
2. Cao G, Liu J, Li M. Global, regional, and national incidence and mortality of neonatal preterm birth, 1990–2019. JAMA Pediatr. 2022;176(8):787-96.
3. Harrison MS, Goldenberg RL. Global burden of prematurity. Semin Fet Neonat Med. 2016;21(2):74-9.
4. Blencowe H, Lee AC, Cousens S, Bahalim A, Narwal R, Zhong N, et al. Preterm birth–associated neurodevelopmental impairment estimates at regional and global levels for 2010. Pediatr Res. 2013;74(1):17-34.
5. Norwitz ER, Caughey AB. Progesterone supplementation and the prevention of preterm birth. Rev Obstet Gynecol. 2011;4(2):60-72.
6. Velez Edwards DR, Likis FE, Andrews JC, Woodworth AL, Jerome RN, Fonnesbeck CJ, et al. Progestogens for preterm birth prevention: a systematic review and meta-analysis by drug route. Arch Gynecol Obstet. 2013;287(6):1059-66.
7. Jarde A, Lutsiv O, Beyene J, McDonald SD. Vaginal progesterone, oral progesterone, 17-OHPC, cerclage, and pessary for preventing preterm birth in at-risk singleton pregnancies: an updated systematic review and network meta-analysis. Obstet Gynecol Surv. 2019;74(9):545-7.
8. Care A, Nevitt SJ, Medley N, Donegan S, Good L, Hampson L, et al. Interventions to prevent spontaneous preterm birth in women with singleton pregnancy who are at high risk: systematic review and network meta-analysis. BMJ. 2022;376.
9. Ashoush S, Elkady OS, Al-Hawwary G, Othman A. The value of oral micronized progesterone in the prevention of recurrent spontaneous preterm birth: a randomized controlled trial. Acta Obstet Gynecol Scand. 2017;96(12):1460-6.
10. Srisutham K, Wuttikonsammakit P, Chamnan P. Efficacy of vaginal and oral progesterone after tocolytic therapy in threatened preterm labor: a 3-arm parallel-group randomized controlled trial. J Med Assoc Thai. 2021;104(5):705-11.
11. Iqbal SZ, Hanif S, Nisa ZU, Shabbir A, Anwar K, Afridi N. Comparison of the effectiveness of oral progesterone and micronized progesterone pessary in reducing the spontaneous preterm birth incidences. Pak J Med Health Sci. 2023;17(2):395-7.
12. Deshpande HG, Dhedia RA, Katakdhond S. A comparative study of oral 400 mg natural micronized progesterone versus vaginal 400 mg natural micronized progesterone in threatened preterm labour and perinatal neonatal outcomes. J Neonat Surg. 2025;14:46.
13. Abdelaziz MH. Oral versus vaginal progesterone in preterm labor. Evid Based Womens Health J. 2018;8(1):141-9.

Cite this article as: Kanal P, Gupta N, Shobhane HJ, Agnihotri S. Comparative efficacy of oral versus vaginal micronized progesterone in the prolongation of preterm labour: a prospective comparative study. Int J Reprod Contracept Obstet Gynecol 2026;15:2556-9.