International Journal of Clinical Obstetrics and Gynaecology

ISSN (P): 2522-6614
ISSN (E): 2522-6622

www.gynaecologyjournal.com
2019; 3(6): 294-298
Received: 16-09-2019
Accepted: 20-10-2019

Dr. Hemant Deshpande
Department of Obstetrics and Gynaecology, Dr. D. Y. Patil Medical College and Hospital, Pimpri, Pune, Maharashtra, India

Dr. Monika Maan Sharma
Department of Obstetrics and Gynaecology, Dr. D. Y. Patil Medical College and Hospital, Pimpri, Pune, Maharashtra, India

Dr. Afifa Reyaz
Department of Obstetrics and Gynaecology, Dr. D. Y. Patil Medical College and Hospital, Pimpri, Pune, Maharashtra, India

Dr. Chandrakant Madkar
Department of Obstetrics and Gynaecology, Dr. D. Y. Patil Medical College and Hospital, Pimpri, Pune, Maharashtra, India

Dr. Sarika Huzurbazar
Department of Obstetrics and Gynaecology, Dr. D. Y. Patil Medical College and Hospital, Pimpri, Pune, Maharashtra, India

Corresponding Author:
Dr. Monika Maan Sharma
Department of Obstetrics and Gynaecology, Dr. D. Y. Patil Medical College and Hospital, Pimpri, Pune, Maharashtra, India

Assessment of efficacy of micronized progesterone by vaginal route for prevention of preterm labour

Dr. Hemant Deshpande, Dr. Monika Maan Sharma, Dr. Afifa Reyaz, Dr. Chandrakant Madkar and Dr. Sarika Huzurbazar

DOI: https://doi.org/10.33545/gynae.2019.v3.i6e.429

Abstract
Preterm birth is a major health problem for neonates, family, country, and society in general. In our study 106 singleton pregnancies with no high risks were included to study the efficacy and safety of natural micronized progesterone in prevention of preterm labour.
Aim: To assess efficacy of natural micronized progesterone by vaginal route in prevention of preterm labour.
Material and Methods: It was a prospective study conducted at our tertiary care centre Dr. D. Y. Patil Medical College, Hospital & Research Center, Pimpri, from July 2018 to June 2019. The study population comprised of 106 pregnant females of 24 weeks to 37 weeks of gestation with singleton pregnancy with suspected risk of preterm labour who fulfilled the criteria were enrolled in the study. The total number of subjects were divided into two groups, Group A was the progesterone group (*n*=53) and Group B was the placebo group (*n*=53).
Result: It was observed in our study that the progesterone group delivered at a significantly later gestational age as compared to the placebo group [35.5±2.5 versus 33.1±2.7, p=0.001]. Also a significant rise in the birth weight of neonates was observed in the progesterone group as compared to the placebo group [2432±50 versus 1978±70, p=0.000].
Conclusion: Administration of vaginal progesterone significantly reduces the rate of preterm birth between 24-37 weeks of gestation among women with high risk factors for threatened preterm. In addition, the rates of NICU admissions, neonatal mortality and morbidity have been significantly decreased in infants of women supplemented with progesterone treatment.

Keywords: Preterm labour (PTL), vaginal micronized progesterone, cervical length, neonatal intensive care units (NICU) admission

Introduction
Preterm labour (PTL) is defined as the onset of labour in pregnancy from 28 weeks to 36 weeks and 6 days with intact membrane. One of the most challenging problems of an obstetrician in the era of modern obstetrics is the management of preterm labour and preterm births (PTB). According to World Health Organization (WHO), preterm is defined as gestationl age of <37 completed weeks (259 days) from the first day of the last menstrual period. PTL is defined by WHO as the onset of labour in a pregnancy before the completion of 37 weeks of gestation and after 20 weeks of gestation [1]. PTB causes perinatal morbidity and mortality and several chronic diseases in the long term despite of many advances [2]. In the lower-income countries, on an average, 12% of babies are born preterm compared with 9% in higher-income countries. Greatest number of preterm births is found in India. Incidence of preterm delivery has been estimated to be 14.5% in India.
Etiopathogenesis for PTB is due to interplay of maternal inflammatory, vascular dysfunctions, stress, preconceptional health, genetic causes, maternal genital tract infections, uteroplacental ischemia or vascular lesions, and uterine over distension [3] High circulating levels of inflammatory cytokines have a secondary role in the pathogenesis [4].
The risk factors of PTB include history of PTB, short cervical length (CL), poor socioeconomic status, multifetal pregnancy, polyhydramnios, advanced maternal age, infections like bacterial vaginosis, genetic factors, smoking, uterine anomaly, bleeding in early pregnancy, preterm premature rupture of membranes (PPROM), uteroplacental insufficiency, intra uterine vascular lesions and history of curettage or cervical conization, cervical incompetence [2, 5] History of

Preterm birth and short cervical length (<25mm) are the most important predictive factors.

Recently progesterone supplement therapy is most commonly used in prevention of preterm birth in patients with history of PTB and/or short cervical length [6-8] Progesterone antagonizes uterine myometrial cells estrogen receptors, inhibits prostaglandin synthesis and inflammation [9].

There are 2 types of progesterone available:

1. Natural (Natural micronized progesterone)
2. Synthetic

- Dydrogesterone
- Hydroxy progesterone Caproate

This study has been planned to assess efficacy and safety of micronized progesterone in prevention of preterm labour. Oral, IM, vaginal routes were used in recent years. In our study we have chosen vaginal route.

Aim and Objectives

Aim:

- To assess efficacy of natural micronized progesterone by vaginal route in prevention of preterm labour.

Objective

- To determine incidence of pre-term labour in women.
- To determine the efficacy (prolongation of labour) while using the natural micronized progesterone (400 mg vaginal capsule) at bedtime.
- To compare our results with previous trials in the literature

Material and Methods

A hospital based prospective study was conducted with 106 patients to assess the efficacy of natural micronized progesterone by vaginal route in prevention of preterm labour.

Study design: A hospital based prospective study

Study duration: 1 years (July 2018-June 2019)

Study area: The study was done at our tertiary care centre at Dr D.Y. Patil Medical College, Hospital and Research Centre, Pimpri, Pune.

Study population: 106 pregnant females of 24 to 37 weeks of gestation with suspected risk of preterm labour who fulfilled the inclusion criteria.

Inclusion Criteria

1. Willing and able to provide written informed consent.
2. Pregnant women of weeks 24 to 37 weeks
3. Absence of any medical conditions like heart diseases.
4. All ANC patients with history of preterm birth, clinical findings (Short cervical length), & USG findings suggestive of preterm labour.
5. Women in whom prophylactic cervical encirclage is done with USG suggestive of short cervical length.
6. Multigravida with previous history of PPROM (Preterm premature rupture of membrane).

Exclusion criteria

1. Twin pregnancy
2. Premature rupture of membranes
3. Antepartum hemorrhage
4. Fetal growth restriction
5. Gross congenital anomalies
6. Rh incompatibility
7. With known medical disorders (Chronic Hypertension, Diabetes mellitus, active liver disease, heart disease) which may need preterm delivery.
8. Intra uterine fetal demise.
9. Patient is in established labour and >37 weeks.

Methodology

Study Drug-Micronized progesterone 400 mg cap for vaginal use.

Dosage -400 mg capsule to be inserted in vagina before sleeping at night.

Micronized vaginal progesterone used is a soft capsule (softule) containing gelatin, deeply inserted in vagina.

After taking written and informed consent the subjects were divided into two groups, Group A was the progesterone group which comprised of 53 subjects and received natural micronized vaginal progesterone capsules 400mg to be inserted in vagina at bedtime. Group B was the placebo group which comprised of 53 subjects and received identical vaginal capsules.

After admission of patients, investigations, clinical assessments and vaginal speculum examination for any cervical dilation, effacement, or ruptured membranes was done. Antibiotics like 3rd generation cephalosporins (Cefotaxime, Ceftriaxone, Cefpodoxime) were given to the patients for prevention of infection.

Corticosteroid [Inj Dexamethasone (6mg) 12 hourly 4 doses i.e. total 24mg] was given for fetal lung maturity along with Inj. Vit K for better perinatal outcomes. Patient's whose labour was arrested, micronized vaginal progesterone (400mg) at bedtime was started as a cold tocolytic. Other patients admitted to the OPD with risk factors were directly shifted on progesterone therepy.

Observations and Results

Table 1: Baseline characteristics of the progesterone and placebo groups

	Progesterone group (Group A)	Placebo group (Group B)	p-value
Maternal age (years)	28±4.3	28.2±4.5	0.815
Parity			
Para 1	19(36%)	18(34%)	1.000
Multipara	34(64%)	35(66%)	
Previous preterm delivery			
Once	24(45%)	20(38%)	0.554
More than once	29(55%)	33(62%)	
Previous history of PPROM (preterm premature rupture of membrane)	13(25%)	14(26%)	1.000
Gestational age at previous deliveries (weeks)	31.9±2.1	32.2±3	0.552
Mean birth weight at previous deliveries (grams)	1524±50	1610±54	0.000

In our study, the two groups (53 women each) matched well for baseline characteristics with a similar maternal age of [28±4.3 in progesterone group versus 28.2±4.5 in placebo group]. The other risk factors of history of previous preterm delivery, previous history of PPROM (preterm premature rupture of membranes), and mean birth weight at previous deliveries were also similar (Table 1).

Table 2: Maternal predictors of preterm delivery

	Progesterone group (Group A)	Placebo group (Group B)	P-value
Cervical length(mm)	25.2±8.2	24.1±9.8	0.53
Elective cervical encerclage	13(25%)	12(23%)	1.000
History of PPROM (preterm premature rupture of membranes)	13(25%)	12(23%)	1.000

In our study it was observed that during the current pregnancy, their cervical lengths were statistically similar (25.2±8.2 in the progesterone group ranging from 13 to 40 mm versus 24.1±9.8 in the placebo group, ranging between 13 to 44 mm, p=0.53). Also the two groups underwent cervical encirclage at similar rates, electively at the end of first trimester (Table 2).

Table 3: Maternal outcomes of current pregnancy

	Progesterone group (Group A)	Placebo group (Group B)	P-value
Gestational age at delivery (weeks)	35.5±2.5	33.1±2.7	0.001
PPROM (preterm premature rupture of membrane)	17(32%)	21(40%)	0.543
Preterm delivery	21(40%)	29(55%)	0.173
Chorioamnionitis	4(8%)	5(9%)	1.000
Postpartum haemorrhage	2(4%)	3(6%)	0.983
Postpartum sepsis	1(2%)	2(4%)	1.000

In our study it was observed that the gestational age at delivery was significantly higher in the progesterone group as compared to the placebo group (35.5±2.5 in progesterone group versus 33.1±2.7 in placebo group, p=0.001). It was also noted that lesser number of women were likely to be admitted for preterm deliveries in the progesterone group 21(40%) as compared to women in the placebo group 29(55%). The number of women with PPROM (preterm premature rupture of membrane) was also noted to be lesser in the progesterone group 17 (32%) as compared to women in the placebo group 21(40%). (Table 3)

Table 4: Fetal and neonatal outcomes of the current pregnancy

	Progesterone group (Group A)	Placebo group (Group B)	P-value
Birth weight (grams)	2432±50	1978±70	0.000
LBW(<2.5 kg)	12(23%)	25(47%)	0.014
Admission to NICU	7(13%)	18(34%)	0.022
Duration of stay in NICU(days)	15.2±5.4	19.6±5.9	0.000
Neonatal mortality rate	2(4%)	6(11%)	0.270

It was observed in our study that a significant rise in the birth weight of the neonates was observed in the progesterone group as compared to the placebo group (2432±50 gm in progesterone group versus 1978±70 gm in the placebo group with p=0.000 which is highy significant). The rate of low birth weight (LBW) was also found to be lesser in the progesterone group 12(23%) as compared to the placebo group 25(47%) with a significant p value (p=0.014).

On the other hand the placebo group had higher rates of NICU admission 18(34%) as compared to progesterone group 7((13%) with a significant p value, p=0.022. The duration of NICU stay was also significantly lesser in progesterone group as compared to placebo group [15.2±5.4 versus 19.6±5.9, p=0.000]. (Table 4).

Table 5: Side effects in progesterone group

Vaginal Dryness	7(13%)
Itching	6(11%)
Abnormal vaginal discharge	9(17%)
Constipation	13(25%)
Dizziness	4(8%)

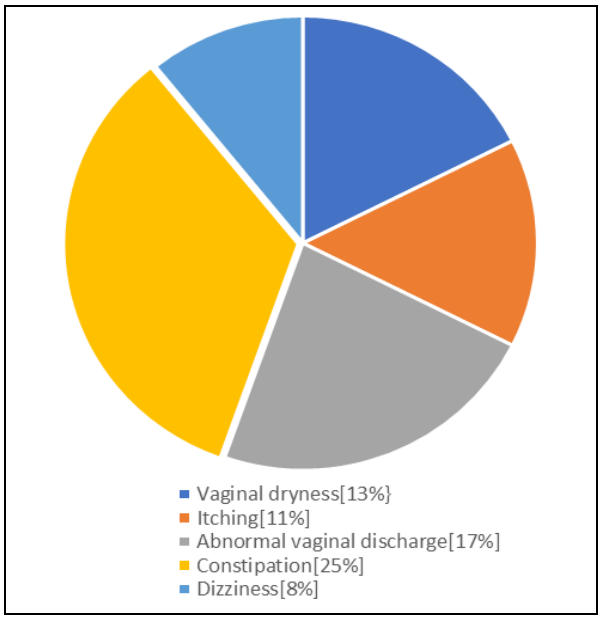

Fig 1: Side effects in progesterone group

In our study it was observed that women receiving progesterone treatment were more likely to complain of vaginal dryness, itching, constipation, dizziness, abnormal vaginal discharge (Table 5) However these symptoms were classified as mild to moderate.

Discussion

Despite the recent advances in knowledge, PTL continues to have high incidence in Indian population. It is imperitive to diagnose PTL and intervene so as to prolong delivery. Buying this time helps steroids to aid in fetal lung maturity.

It was observed in the present study that 24(45%) patients had 1 previous preterm delivery while 34(64%) had more than one preterm delivery. 13(25%) patients had PPROM in previous delivery. This is concordant to the studies of Fernandes SF *et al* [10] and Kuppusamy N *et al*. [11].

In our study, the mean cervical length of patients in progesterone group was 25.2 ± 8.2 mm and in the placebo group was 24.1±9.8 mm. Ashoush S *et al*. [12] and Dekker GA *et al*. [13] noted similar observations in their studies.

It was observed in the present study that 21(40%) patients had preterm delivery and the mean gestational age at delivery was 35.5±2.5 weeks in the progesterone group. This finding was consistent with the studies of Patra K *et al*. [14], Wajid R *et al* [15] and Abdou AM [16].

In the present study, 2(4%) patients had postpartum haemorrhage. 1(2%) patient had postpartum sepsis. This is similar to the study of Ashoush S *et al* [12].

In our study, 12(23%) neonates had low birth weight (<2.5kg), while 7(13%) neonates were admitted in NICU. This is comparable to the studies of Patra K *et al*. [14], Ashoush S *et al*. [12], Choudhary M *et al*. [17], Khan S *et al*. [18] and Abdou AM, [16].

In our study, the mean birth weight was significantly higher in the progesterone group as compared to the placebo group [2432±50 gm versus 1978±70 gm, p=0.000]. This is comparable to the study of Abdou AM [16].

It was observed in the present study that 7(13%) patients had vaginal dryness, 13(25%) patients had constipation, 4(8%) patients had dizziness. This is concordant to the studies of Erny R *et al*. [19], Patra K *et al*. [14], Ashoush S *et al*. [12], Maher MA *et al*. [20] and El-Gharib MN *et al*. [21].

Progesterones may entail many side effects such as mood swings, dyspepsia, headache, constipation, dyspareunia, drowsiness, fatigue, genital itching. The synthetic progesterones (17α-OHPC) has lower rates of side effects as compared to natural micronized progesterone. Vaginal administration of micronized progesterone helps in avoiding metabolism by liver, thereby markedly reducing these side effects.

It was observed in our study that the mean gestational age at delivery was 35.5±2.5 in the progesterone group. Similar observations were noted in the studies of Borna S *et al*. [22], Arikan I *et al*. [23], Ashoush S *et al*. [12], Wajid R *et al*. [15], Choudhary M *et al*. [17] and Ming-Xia D *et al*. [24].

Conclusion

To conclude, it was observed in our study that the gestational age at delivery was significantly higher in the progesterone group as compared to the placebo group.

Administration of vaginal progesterone significantly reduces the rate of neonatal NICU admissions, neonatal mortality and morbidity.

References

1. World Health Organization (WHO). International statistical classification of disease and related health problems. 10th Revision II. Gineva Switzerland, 1993.
2. Goldenberg RL, Culhane JF, Iams JD *et al*. Epidemiology and causes of preterm birth. Lancet. 2008; 371(9606):75-84.
3. Kramer MR, Hogue CR. what causes racial disparities in very preterm birth? A Biosocial perspective. Epidemiol rev. 2009, 31:84-98.
4. Nold C, Anton L, Brown A *et al*. Inflammation promotes a cytokine response and disrupts the cervical epithelial barrier: a possible mechanism of premature cervical remodeling and preterm birth. Am J Obstet Gynecol. 2012; 206:208.
5. Harrison MS, Goldenberg RL. Global burden of prematurity. Semin Fetal Neonatal Med. 2016; 21:74-79.
6. Newnham JP, Dickinson JE, Hart RJ *et al*. Strategies to prevent preterm birth. Front Immunol. 2014; 5:584.
7. da Fonseca EB, Bittar RE, Damião R *et al*. Prematurity prevention: the role of progesterone. Curr Opin Obstet Gynecol. 2009; 21:142-147.
8. Romero R, Yeo L, Chaemsaithong P *et al*. Progesterone to prevent spontaneous preterm birth. Semin Fetal Neonatal Med. 2014; 19:15-26.
9. How HY, Sibai BM. Progesterone for the prevention of preterm birth: indications, when to initiate, efficacy and safety. Ther Clin Risk Manag. 2009; 5:55-64.
10. Fernandes SF, Chandra SA. Study of risk factors for preterm labour. Int J Reprod Contracept Obstet Gynecol. 2015; 4:1306-12.
11. Kuppusamy N, Vidhyadevi A. Prevalence of Preterm Admissions and the Risk Factors of Preterm Labor in Rural Medical College Hospital. Int J Sci Stud. 2016; 4(9):125-128
12. Ashoush S, El-Kady O, Al-Hawwary G *et al*. The value of oral micronized progesterone in the prevention of recurrent spontaneous preterm birth: a randomized controlled trial. Acta Obstetricia et Gynecologica Scandinavica. 2017; 96:1460-1466.
13. Dekker GA, Lee SY, North RA *et al*. Risk Factors for Preterm Birth in an International Prospective Cohort of Nulliparous Women. PLoS ONE. 2012; 7(7): Fernandes SF, Chandra SA. Study of risk factors for preterm labour. Int J Reprod Contracept Obstet Gynecol. 2015; 4:1306-12.
14. Patra K, Chattopadhyay S, Munsi S *et al*. "Comparative Study to Assess the Efficacy between Intramuscular and Vaginal Micronized Progesterone to Prevent Threatened Premature Labour". Journal of Evolution of Medical and Dental Sciences 2015; 4(87):15243-15250.
15. Wajid R, Zafar M, Waheed F. Effectiveness of Vaginal versus Intramuscular Progesterone for the Prevention of Preterm Delivery. Annals. 2016; 22(4):284-289.
16. Abdou AM. Role of Vaginal Progesterone in Prevention of Preterm Labor in Women with Previous History of One or More Previous Preterm Births. Open Journal of Obstetrics and Gynecology. 2018; 8:329-337.
17. Choudhary M, Suneja A, Vaid N *et al*. Maintenance tocolysis with oral micronized progesterone for prevention of preterm birth after arrested preterm labour. Int J Gynecol Obstet. 2014; 126(1):60-63.
18. Khan S, Gupta D, Premi HK. Role of micronized progesterone in women with arrested Preterm labor. Indian Journal of Basic and Applied Medical Research. 2018; 7(4):106-110.
19. Erny R, Pigne A, Prouvost C *et al*. Am J Obstet Gynecol. 1986; 154(3):525-9.

20. Maher MA, Abdelaziz A, Ellaithy M *et al*. Prevention of preterm birth: a randomized trial of vaginal compared with intramuscular progesterone. Acta Obstet Gynecol Scand. 2013; 92:215-222.
21. El-Gharib MN, El-Hawary TM. Matched sample comparison of intramuscular versus vaginal micronized progesterone for prevention of preterm birth. J Matern Fetal Neonatal Med. 2013; 26:716-9.
22. Borna S, Sahabi N. p rogesterone as maintenance tocolytic therapy after threatenend preterm labour; a randomized controlled trial. Aust N Z J Obstet Gynaecol. 2008; 48:58-63.
23. Arikan I, Barut A, Harma M *et al*. Effect of progesterone as a tocolytic and in maintenance therapy during preterm labor. Gynecol Obstet Invest. 2011; 72(4):269-73.
24. Ming-Xia D, Luo X, Xue-Mei Z *et al*. Progesterone and nifedipine for maintenance tocolysis after arrested preterm labor: A systematic review and meta-analysis of randomized controlled trial. Taiwanese Journal of Obstetrics and Gynecology. 2016; 55(3):399-404.