# Role of Oral Progesterone in Pre Term Labour

**Hina Ilyas,[1] Safia Perveen,[2] Zareen Akhter,[3] Azra Yaseen,[4] Mariam Rafiq[5] Suleiman Azhar,[6] Fizza Mahmood[7]**

**Abstract**

**Objective:** Our study aims at determining safety and efficacy of oral micronized progesterone in preventing preterm labor.

**Method:** Study conducted at Sahiwal Teaching Hospital from June 2018-July 2019 including 180 participants with preterm labor. Oral micronized progesterone give 200 microgram twice daily till preterm labor settled.

**Results:** 12.5% were ⩽ 20 years. 31% were 20-25 years. 35% were from 25-30 years. While 36(22%) were ⩾ 35 years. Primigravida were 27% and multigravida 73%. In 76% cases preterm labor settled and 24% had labor ⩽ 37 weeks. Latency period ⩽ 24 hours in 15% ,2-6 days in 18%, 1-3 weeks in 24%, 4-8 weeks in 32%, 9-12 weeks in 7%, ⩾ 12 weeks in 5% respectively. 78% had vaginal delivery, C-Sec in 22% of patients. Gestational age at delivery ⩽ 28 weeks in 7%, ⩽ 32 weeks in 20%, ⩽ 36 weeks in 25% and ⩾ 37 weeks in 48% respectively. Birth weight, ⩾ 3.0 kg in 25%, 2.0-2.5 kg in 50%, ⩽ 2.0 kg 18%, ⩽ 1.5 kg 7%. NICU admission 25%. RDS seen in (22%), Sepsis (10%), IVH (3%), NEC (1%). neonatal deaths were 12.

**Conclusion:** Oral micronized progesterone is found to be safe, effective and well tolerated therapy for prevention and treatment of preterm birth.

**Keywords:** Progesterone, Preterm birth, latency period

**How to cite:** *Ilyas H, Perveen S, Akhter Z, Yaseen A, Rafiq M, Azhar S, Mahmood F. Role of Oral Progesterone in Pre Term Labour. Esculapio - JSIMS 2022;18(02):204-208*

**DOI: *https://doi.org/10.51273/esc22.2518221***

## Introduction

Globally 3 in 4 neonatal deaths occur due to preterm births complications. Incidence of neonatal mortality due to preterm birth is 28%. Annually about fifteen million babies are born before 37 weeks of pregnancy. That is more than 1 in 10 babies. Approximately one million children die due to complications of preterm. Global prevalence of preterm birth is 9.6%, in Pakistan 15.7% whereas in Australia it is 6.6%. Preterm birth is one of major contributor to infant mortality and morbidity.[1,2]

Preterm birth is defined as birth of baby before 37 completed weeks of pregnancy. Preterm labor is further divided into late preterm (35-36 weeks), moderately preterm (32-34 weeks), early preterm (28-31 weeks) and severely preterm (28 weeks). It accounts for more than 50% neurological disabilities. Complications include respiratory distress syndrome, retrolental fibroplasias, necrotizing enterocolitis, cerebral palsy and learning disabilities. All these complications lead to increase in neonatal and child mortality less than five years.[3,4]

Preterm birth is a considerable source of financial burden on government and families. In developing countries situation is even graver due to lack of provision of neonatal facilities and services uniformly all over the country. Although remarkable changes are being made in public sector but there is a lot to do more as burden

*1-7. Department of Obstetrics and Gynaecology, Sahiwal Teaching Hospital, Sahiwal.*

**Correspondence:**
Dr. Hina Ilyas *Assistant Professor Obst. and gynae department, Sahiwal Teaching Hospital, Sahiwal. Pakistan E-mail. Hinailyasobg@gmail.com*

Submission Date: 19-02-2022
1st Revision Date: 17-03-2022
Acceptance Date: 24-04-2022

of prematurity is considerably high in Pakistan.[1,5]

A lot of interventions have been made to decrease the incidence of preterm labor. Amongst these progesterone seems to be most promising, easy to administer and cost effective with high safety profile. Progesterone has a pivotal role in containing pregnancy till term due to its anti-inflammatory role. American college of Obstetrician and Gynecologists recommended progesterone as a prophylaxis to prevent preterm labor in women with previous preterm labor and short cervical length.[6,7,8]

Role of progesterone in preventing preterm labor was characterized in 1934 and first reported in literature in 1954. Since then a lot of research is going on different routes and preparation of progesterone including vaginal, intramuscular and oral rotes. Different formulations available are 17 hydroxy progesterone, dydrogesterone and oral micronized progesterone.[8,9]

A lot of research available on vaginal progesterone though it was associated with difficulty in administration and unpleasant vaginal discharge. Oral progesterone was studied first in preventing preterm labor but lagged behind in research. It was not due to decreased efficacy of oral progesterone but rather lack of preference of oral progesterone by researching bodies. Even in Pakistan there is scarcity of research in role of oral micronized progesterone preventing preterm birth.[10]

## Material and Methods

This study was conducted at Sahiwal teaching hospital Sahiwal for a period of one year from June 2018 till June 2019. It was quasi experimental study. 180 women participated in study after informed consent and fulfilling inclusion criteria. Preterm labor was defined as onset of regular uterine contractions at least 3 in 10 minutes for 20-25 seconds (between 24-36+6 weeks). All patients underwent detailed history and examination. Sterile speculum and pelvic examination done to assess cervical changes and dilatation. Patients having premature contractions given oral micronized progesterone 200 mg twice a day till labor settled and discharged to home. Treatment continued till 36 weeks and patients were called on regular follow up visits. At each visit patients were assessed for signs and symptoms of labor and any complications related to progesterone treatment including headache, nausea, vomiting, constipation and dizziness. During course of study 18 patients lost follow up so at end of study there were total 162 participants.

**Inclusion criteria:** All women with single preterm labor from 24 weeks till 36+6 weeks.

**Exclusion criteria:**

- Multiple pregnancies
- Thromboembolic disease current or history
- Breast /genital tract malignancy
- Presence of fever or sepsis
- Heavy vaginal bleeding requiring surgical intervention
- Active labor (Cervical dilatation 4cm)

## Results

12.5% were years. 31% were 20-25 years. 35% were from 25-30 years. While 36(22%) were 35 years. Primigravida were 27% and multigravida 73%. In 76% cases preterm labor settled and 24% had labor 37 weeks. Latency period 24 hours in 15% ,2-6 days in 18% , 1-3 weeks in 24%, 4-8 weeks in 32%, 9-12 weeks in 7%, 12 weeks in 5% respectively. 78% had vaginal delivery, C-Sec in 22% of patients. Gestational age at delivery 28 weeks in 7%, 32 weeks in 20%, 36 weeks in 25% and 37 weeks in 48% respectively. Birth weight, 3.0 kg in 25%, 2.0-2.5 kg in 50%, 2.0 kg 18%, 1.5 kg 7%. NICU admission 25%. RDS seen in (22%), Sepsis (10%), IVH (3%), NEC (1%) neonatal deaths were 12.

## Discussion

More than 60% of births occur in Africa and South Asia, but preterm birth is truly a global problem. In the lower

**Table 1:** *Maternal Characteristics*

| Characteristics | N=162 | % |
|---|---|---|
| **Age** | | |
| ⩽20 years | 20 | 12 |
| 20-25 years | 50 | 31 |
| 26-30 years | 56 | 35 |
| ⩾ 30 years | 36 | 22 (mean=27±8) |
| **Gravidity** | | |
| Primigravida | 44 | 27 |
| Multigravida | 112 | 73 |
| **History of preterm labor** | | |
| Yes | 30 | 18 |
| No | 132 | 82 |
| **BMI** | | |
| 25-30 | 150 | 93 |
| ⩾ 30 | 12 | 7 |

**Table 2:** *Obstetrical outcome*

| Outcome | N=162 | % |
|---|---|---|
| Preterm labor | | |
| Settled | 124 | 76 |
| Not settled | 38 | 24 |
| Tocolysis to delivery interval | | |
| ⩽1 day(24 hours) | 24 | 15 |
| 2-6days | 28 | 18 |
| 1-3 weeks | 38 | 24 |
| 4-8 weeks | 52 | 32 |
| 9-12weeks | 12 | 7 |
| ⩾12 week | 8 | 5 |
| Meconium staining of liquor | 40 | 25 |
| Mode of delivery | | |
| SVD | 126 | 78 |
| Cesarean section | 36 | 22 |
| Gestational age at delivery | N=162 | % |
| ⩽28 weeks | 13 | 7 |
| 28-32 weeks | 31 | 20 |
| 33-36 weeks | 40 | 25 |
| ⩾37 weeks | 78 | 48 |

**Table 3:** *Neonatal outcome*

| Characteristics | N=162 | % |
|---|---|---|
| **Birth weight(Kg)** | | |
| ⩽1.5 | 12 | 7 |
| 1.5-2.0 | 30 | 18 |
| 2.0-3.0 | 80 | 50 |
| ⩾3.0 | 40 | 25 |
| APGAR Score ⩽7 | 42 | 26 |
| At 1min | 10 | 6 |
| At 5 min | 110 | 68 |
| APGAR Score ⩾7 | | |
| **Neonatal** complications | 58/162 | 36 |
| RDS | | |
| IVH | | |
| NEC | | |
| Sepsis | | |
| **NICU Admissions** | 40 | 25 |
| **Neonatal deaths** | 12 | 7.5 |

income countries, on average 12% of babies are born too early compared with 9% in higher income countries. Pakistan is at 4th number in having preterm births. There is a dramatic difference in survival of premature babies in developed and underdeveloped countries. About 90% of babies born at 28 weeks die in low income countries and only 10% of babies born at this gestation die in developed and high income countries. Each day 600 newborn die due to complications related to birth asphyxia, prematurity and sepsis (UNICEF).[1,11]

Progesterone is a key factor in controlling preterm birth. The first and foremost study on role of oral micronized progesterone in a multicentre RCT including 57 patients. Our study showed the efficacy of oral progesterone in treatment of preterm labor. Research conducted in our department showed mean age of patients was 27±8. In other National and international studies mean age was relatively high and was around 29-30±6. It showed that teen age pregnancies contributed to preterm labor in our study.[8,9,12]

Most of patients presenting to sahiwal teaching hospital gynae department were multigravida about 2/3rd (67%) while 1/3rd (33%) were Primigravida. While RCT conducted at Bangkok hospital showed number of Primigravida presenting with preterm labor were more than multigravida. Gestational age range in our study was 24-36 weeks contrary to research carried out by cheung et al where pregnancy between 14-23 weeks were also included and they included cervical cerclage in patients presenting with short cervical length (⩽2.5cm).[13,14]

Regarding BMI 150(93%) women had BMI less than 30Kg/m$^2$ and only 12(7%) had BMI more than 30kg/m$^2$. In contrary to study carried out at Nishter hospital where obesity was found in 24% of population. Meis et al showed that mean BMI in patients was 26±7, which is also contradictory to our statistics. It showed that obesity was not a risk factor for patients presented to our setup.[15,16]

Progesterone showed promising results in controlling preterm births in our study, about (124) 76% preterm labors settled and only (38) 24% deliver preterm. Some national and international studies showed efficacy of progesterone in controlling preterm labor ranging from 61-68%. Ibraheem et al and Ahmad et al showed efficacy of about 64% and 68% respectively.[17,18] Rai et al showed 61% efficacy in controlling preterm labor. High success rate in our study may be due to the fact that previous history of preterm labor was in less than 20% of patients. Whereas in other studies patients with history of recurrent preterm labor were recruited in studies.[19,23] Our study showed similar results in successfully controlling preterm labor to the first study carried out at France randomizing 57 patients in placebo controlled trial where 80% of pregnancies were treated successfully.[12] Regarding latency period i.e; tocolysis to delivery interval oral micronized progesterone has shown promising results at increasing the period from onset of preterm labor and delivery of fetus. Minimum interval was 6 hours and maximum interval was 13 weeks delaying

delivery. About 1/3rd of cases 52(32%) pregnancy prolonged for up to 8 weeks (2 months). In 1/4th of pregnancies having preterm labor, uterine contractions settled and pregnancy prolonged for about 3 weeks. Pregnancy prolonged for up to 24 hours and till one week in 15% and 18% cases respectively. Our study showed even more success rates as compared to national and international studies in controlling preterm labor and increasing latency period. Research conducted by international journal showed that micronized progesterone was effective to prolong latency period for about 8 weeks .24 Study carried out at PIMS Islamabad showed role of progesterone in postponing pregnancy upto 32 days.[13] In contrast to micronized progesterone randomized controlled trial including Dyderogesterone versus placebo couldn't show any significant result in prolonging pregnancy in both groups.[14]

Regarding gestational age at delivery approximately 50% (78) patients delivered at more than 37 weeks thus improving neonatal outcome.1/4th (40) pregnancies ended up in delivery between 33-36 weeks. 31(20%) delivered at gestation ranging from 28-32 weeks. A very few 13(7%) were very very preterm, that is below 28 weeks of gestation. A double blind randomized controlled trial carried out including 150 women with previous history of preterm births and oral micronized progesterone was given to one group. This trial revealed encouraging results regarding prolonging period from onset of preterm labor till delivery. It was 36 weeks in trial group as compared to below 34 weeks in placebo group. Meconium staining of liquor was seen in 40(25%) of pregnancies. It is significantly high but not mentioned in other studies. It resulted in more NICU admissions in spite of well controlled preterm labor. No significant risk factor was seen for meconium staining.[13,22]

Most promising fact about our study was that about 126(78%) patients had spontaneous vaginal delivery and only 36(22%) had cesarean section.It may be due to the fact that most of our participants (78%) were multi gravid with previous vaginal deliveries. It was Contrary to other studies where cesarean section rates were between 66-78%.[23,24,25]

Regarding gestational age at delivery nearly half of participant (48%) in our study delivered at gestation at or more than 37 weeks. One fourth (25%) delivered at 34-36 weeks, 20% at 28-32weeks and only 7% delivered at less than 28 weeks gestation. It was comparable to studies carried out internationally and at local levels where mean gestational age at deliver was 36 weeks. In a study conducted internationally it was 35+ 2weeks. Another randomized controlled trial at America showed success rate of oral micronized progesterone in reducing preterm birth and gestational age at delivery was 37+ 2 weeks .[25,10]

As most of participants delivered beyond 36 weeks encouraging results regarding neonatal outcome seen. 50 % of neonates have birth weight ranging 2-3 kg, 25% were of more than 3 kg, low birth weight (2.0 kg) and very low birth weight (1.5 kg ) were 18% and 17% respectively. It was comparable to other studies where birth weight was 2.5+0.7 kg. Admission in NICU was seen in 25% of cases. It was similar to research conducted at Hong Kong. A national study showed neonatal admissions in 5% with micronized progesterone and 22% with nifedipine. Similar results regarding neonatal admissions were seen in some international studies where neonatal admissions were 22%, but these were mostly due to very low birth weight babies. In our study most admissions were result of meconium staining of liquor. APGAR score was 7 at 1 and 5 minutes similar to other studies. Number of neonatal deaths was 12 in our study, while in other studies it was less. Increased neonatal mortality in our research was due to unavailability of optimal facilities in NICU.[16,18,22]

Very few studies are available regarding oral use of micronized progesterone most of work done on vaginal progesterone. Few randomized controlled trials were conducted at America but draw back was small number of patients so they were stopped due to failure of statistical significance. Best role of oral micronized progesterone was shown in study conducted, in which its role was observed in recurrent preterm births. This study reduced the rate of false positive results.[22]

## Conclusion

Our study showed promising role of oral micronized progesterone in reducing preterm births in both spontaneous and recurrent preterm labor. Oral route was most accepted and was not associated with discomfort related to vaginal or intramuscular preparations. It was well tolerated and showed encouraging neonatal outcome.

**Conflict of interest:** *None*

## References

1. Blencowe H, Cousens S, Ostergaard M et al. National, regional and worlwideestimates of preterm birth. The Lancet, June 2012.9;379(9832):2162-72.Estimates from 2010.

2. Beck S, Wojdyla D, Say L, Betran AP, Merialdi M, Requejo JH, et al. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. Bull World Health Organ 2010; 88: 31–38.
3. Lawn J, Gravett M, Nunes T, Rubens C, Stanton C; GAPPS Review Group. Global report on preterm birth and stillbirth (1 of 7): definitions, description of the burden and opportunities to improve data. BMC Pregnancy Childbirth. 2010;10(Suppl 1):S1
4. Liu L, Oza S, Hogan D et al. Global, regional and National causes of under 5 mortality in 200-15: an updated systematic analysis with implications for the sustainable development Goals. Lancet .2016;388(10063);3027-35.
5. Asif Hanif, Tahira Ashraf et al. Prevalence of Preterm Birth in Pakistan: A Systematic Review and Meta-Analysis. ANNALS VOL 23, ISSUE 2, APR. – JUN. 2017.
6. Csapo A, Goodall M. Excitability, length tension relation and kinetics of uterine muscle contraction in relation to hormonal status.J Physiol 1954:126:384-95.Level ll-2
7. Nobolt G. Audra P et al. The use of Progesterone in treatment of menace preterm delivery.Eur J Obstet GynecolReprod Biol 1991:40:203-9.Level l.
8. American college of Obstetrician and Gynecologists. Use of Progesterone to reduce preterm birth.ACOG Committee opinion no.419. Obstet Gynecol 2008: 112: 963-5. Level lll
9. Ning A, Vladutiu CJ, Dotters-Katz SK, Goodnight WH, Manuck TA. Gestational age at initiation of 17-alpha hydroxyprogesterone caproate and recurrent preterm birth. Am J Obstet Gynecol. 2017;217:371.e1–7.
10. Sherrif Ashoushe, Osama Al kedy , Ahmad Othman. The value of oral micronized progesterone in the prevention of recurrent preterm birth: A randomized controlled trial. 2017 Nordic Federation of Societies of Obstetrics and Gynecology, Acta Obstetricia et Gynecologica Scandinavica 96 (2017) 1460–1466.
11. Vogel JP, Lee ACC, Souza JP. Maternal morbidity and preterm birth in 22 low- and middle-income countries: a secondary analysis of the WHO Global Survey dataset. BMC Preg Childbirth. 2014;14(1):1-14
12. Erny R, Pigne A, Prouvost C, Gamerre M, Malet C, Serment H, et al. The effects of oral administration of progesterone for premature labor. Am J Obstet Gynecol. 1986;154:525–9
13. Suparudeewan Thongchan and Vorapong Phupong. Oral Dydrogesterone as an adjunctive therapy in management of preterm labor: a randomized double blinded, placebo- controlled trial.BMC Pregnancy and child birth (2021)21;90.
14. Lim K, Butt K, Crane J M.SOGC . Clinical practice guide line.Ultrasonographic of cervical length assessment in predicting preterm birth in singleton pregnancies. J Obstet Gynecol Can 2011:33(5):486-99. [Practice Guide line].
15. Kizra M, Hira A. Role of oral progesterone therapy in prevention of preterm labor. Journal of Medicine, Physiology and Biophysics. ISSN-2422-8427. An International peer reviewed journal. Nol.55-2019. DOI: 10.7176/JMPB
16. Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med. 2003 Jun 12;348(24):2379-85. 20. Rai P, R
17. Ahmed F, Yasir S, Naeem NK, Amin A. Efficacy of 17 alpha hydroxy progesterone in prevention of preterm labour in high risk patients. Ann King Edward Med Uni. 2012;18(2):158-62.
18. Rai P, Rajaram S, Goel N, Ayalur Gopalakrishnan R, Agarwal R, Mehta S. Oral micronized progesterone for prevention of preterm birth. Int J Gynaecol Obstet. 2009 Jan;104(1):40-3. Spongy CY. Prediction and prevention of recurrent spontaneous birth. Obstet Gynecol 2007:110 (2 pt 1):405-15.
19. Eman F, Yasir S, Norah H. Use of progesterone during pregnancy to prevent preterm birth. 2020 Apr; 41(4): 333–340.doi: 10.15537/smj.2020.4.25036
20. Arikan I, Barut A. Effect of progesterone as a tocolytic and in maintenance therapy during preterm labor. Gynecol Obstet Invest. 2011:7294):269-73.
21. Borna S, Sahabi N. Progesterone for maintenance tocolytic therapy after threatened preterm labor. A randomized controlled trial. AUST NZ J Obstet Gynecol. 2008:48(1)58-63.
22. Nataranjan G, Shankaran S. Short and long term outcomes of moderate late preterm infants. Am J Perinatol. 2016:33:305-317.
23. Harrison M, Golden Berg R L.Global burden of prematurity . Semin Fetal Neonatal Med.2016:21;74-79.
24. Brien J M et al . Effect of progesterone on cervical shortening in women at risk for preterm birth: Secondary analysis from a multinational randomized double blind placebo controlled trial. Ultrasound Obstet Gynecol 2009:34:653-9.

## Authors Contribution

**HI:** Conceptualization of Project
**HI, MR, FM:** Data Collection
**ZA, HI:** Literature Search
**ZA:** Statistical Analysis
**SP, HI:** Drafting, Revision
**ZA, AY, SA:** Writing of Manuscript