

## A Hospital Based Study to Assess the Role of Intravaginal Micronized Progesterone in Preterm Labor in Prolonging the Pregnancy Up to Term

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Conflict of interest: Nil

### Abstract

**Aim:** The aim of the present study was to assess the role of intravaginal micronized progesterone in preterm labor in prolonging the pregnancy up to term.

**Methods:** A retrospective study was conducted in the Department of Obstetrics and Gynecology, IGIMS, Patna, Bihar, India for one year. Patients were randomly divided into two groups having 100 women in each group by computer generated randomization tables.

**Results:** There was no significant difference between the two groups in their demographic characteristics. The randomly allocated groups were comparable in terms of age, parity, region at the time of inclusion in study. Age varied from 19-35 yrs, mean age being  $23.67 \pm 2.68$  and  $24.66 \pm 3.57$  in group I & II respectively. Parity varied from 0-4, median parity observed in both groups was 1. Majority belonged to rural area. Period of gestation at admission varied from 26 to 34 weeks but maximum patients presented at 30-34 weeks gestation in both groups. Mean gestation age was  $31.82 \pm 1.80$  &  $31.55 \pm 1.81$  weeks in the two groups respectively. The mean number of uterine contractions per ten minutes was  $2.17 \pm 0.37$  and  $2.13 \pm 0.32$  in Group I & II respectively ( $p = 0.56$ ). No significant difference in cervical dilatation ( $1.48$  vs  $1.42$  cm;  $p=0.27$ ) and cervical effacement ( $43.4\%$  vs  $41.6\%$ ;  $p= 0.15$ ) was seen between the two groups. In Group I, the mean gestational age at delivery was  $35.805 \pm 1.70$  weeks whereas in Group II, it was found to be  $34.974 \pm 1.81$  weeks. In Group I, 60% of the patients delivered at more than 37 weeks as compared to 14% in Group II. Significant difference was found between the two groups. The difference between the mean birth weight of the two groups was statistically significant.

**Conclusion:** In patients of preterm labour vaginal micronized progesterone when used along with tocolytics and supportive therapy significantly prolongs the pregnancy and hence gestational age at delivery. Progesterone therapy leads to higher number of women reaching term and delivering beyond 37 weeks and also better neonatal outcome in terms of higher birth weight and fewer complications.

**Keywords:** Prematurity, Preterm Labor, Tocolytics, Micronized Progesterone.

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### Introduction

Preterm birth is the leading cause of perinatal mortality and morbidity worldwide [1,2] and the leading cause of death before the age of 5 years. [3,4] Moreover, preterm birth is a major cause of long-term morbidity in adult life. Therefore, predicting and preventing preterm birth is a major healthcare priority. [1,5,6] Irregular contractions, lower backache, vaginal discharge, or bleeding are indicators of threatened preterm labor that may or may not lead to preterm birth. In addition, threatened preterm labor may appear with or without cervical changes, and a sonographic short cervix is the most powerful method for predicting preterm birth. [7] Vaginal progesterone reduces the rate of preterm birth in women with a short cervix, and the treatment

is effective regardless of history of preterm birth. [8,9] Cervical cerclage is also effective in the subgroup of patients with a short cervix and a history of preterm birth. [10] Cervical pessary has also been proposed as a viable intervention, and its effectiveness is the subject of ongoing studies. [11]

In developed countries, the incidence of preterm birth is about 7-12% of all deliveries and among these 1/3rd occur before 34 completed weeks. The prevalence in developing countries is even higher. In India, the incidence of preterm delivery is 10%-69%. [12] The mechanism responsible for preterm labor is not known. Concurrent obstetrical abnormalities like abruptio placenta, placenta previa, multiple gestation, hypertensive disorders,

IUGR etc. are identifiable only in 40% of cases, but the remainder occur unexpectedly and without any cause. [13] Progesterone treatment for preventing preterm birth has been the subject of several relatively small trials beginning in 1960s.

The aim of the present study was to assess the role of intravaginal micronized progesterone in preterm labor in prolonging the pregnancy up to term.

### Materials and Methods

A retrospective study was conducted in the Department of Obstetrics and Gynecology, IGIMS, Patna, Bihar, India for one year. Patients were randomly divided into two groups having 100 women in each group by computer generated randomization tables. Women enrolled as cases [Group I (n=100)] received daily doses of 200 mg natural micronized progesterone administered vaginally from the time of randomization until 36 weeks gestation or until the delivery of the fetus if sooner. Group II (n=100) were included as control subjects and received no drug.

The pregnant women with period of gestation between 26 to 34 weeks, who were admitted with preterm labor, formed the eligible population. They were evaluated by a thorough history, general physical, systemic and obstetric examination and routine antenatal investigations including obstetric ultrasound were done. Preterm labor was defined as the presence of regular and painful uterine contractions at the rate of more than or equal to 2 contractions in 10 minutes with evidence of cervical changes such as effacement and/or dilatation, by manual examination. All patients were initially managed for preterm labor with tocolytics, steroids and antibiotics prophylaxis. Once the labor got arrested, which was defined as a 12hour contraction free period with tocolytics, these patients were

enrolled in study after applying inclusion and exclusion criteria. Informed consent was taken after counseling the patients. Inclusion criteria were singleton pregnancy, intact fetal membranes and cervical dilatation less than 3 cms. Exclusion criteria were multiple pregnancy, placenta previa, Preterm premature rupture of membranes at presentation, pre-existing hypertension, maternal seizure disorder, active or history of thromboembolic disease, maternal liver disease, known sensitivity to progesterone and fetus with congenital malformations

Once the subjects in both the groups became stabilized and had relaxed uterus, they were discharged and monitored on outdoor basis by regular antenatal checkups till delivery. During the study period, no patient received oral tocolytics. They were contacted telephonically also to ensure compliance with progesterone. Various outcomes to be monitored were recorded from case records of mother and baby.

Primary outcome variable were inclusion in study to delivery interval and gestational age at delivery. Secondary variables were neonatal birth weight, need for NICU admission and neonatal complications.

All Statistical analysis were performed using statistical package for social science, version 13 (SPSS– 13). Normality of distribution of continuous variables was first tested and unpaired student t-test was applied for baseline quantitative variables if data follows normal distribution otherwise Mann-Whitney test was applied. Chi square/fisher exact (where applicable) was applied for qualitative outcome variables. P value <0.05 was considered as statistically significant.

### Results

**Table 1: Demographic profile**

	Group 1	Group 2	P value
Age Mean Age $\pm$ SD	23.67 $\pm$ 2.68	24.66 $\pm$ 3.57	0.07
Rural/ Urban	75 (75%)	80 (80%)	0.743
Urban	25 (25%)	20 (20%)	
Parity Range	0-3	0-4	0.525
Median	1	1	

There was no significant difference between the two groups in their demographic characteristics. The randomly allocated groups were comparable in terms of age, parity, region at the time of inclusion in study. Age varied from 19-35 yrs, mean age being 23.67  $\pm$  2.68 and 24.66  $\pm$  3.57 in group I & II respectively. Parity varied from 0-4, median parity observed in both groups was 1. Majority belonged to rural area.

**Table 2: Baseline Presentation Characteristics at the time of inclusion in the Study**

	Group 1	Group 2	P value
Period of gestation Mean $\pm$ SD	31.82 $\pm$ 1.80	31.55 $\pm$ 1.81	0.12
No. of Uterine contractions Mean $\pm$ SD	2.17 $\pm$ 0.37	2.13 $\pm$ 0.32	0.52

Cervical Dilatation Mean $\pm$ SD	1.48 $\pm$ 0.50	1.42 $\pm$ 0.49	0.22
Cervical Effacement Mean $\pm$ SD	43.4 $\pm$ 10.02	41.6 $\pm$ 7.102	0.17

Period of gestation at admission varied from 26 to 34 weeks but maximum patients presented at 30-34 weeks gestation in both groups. Mean gestation age was 31.82  $\pm$  1.80 & 31.55  $\pm$  1.81 weeks in the two groups respectively. The mean number of uterine contractions per ten minutes was 2.17  $\pm$  0.37 and

2.13  $\pm$  0.32 in Group I & II respectively ( $p = 0.56$ ). No significant difference in cervical dilatation (1.48 vs 1.42 cm;  $p=0.27$ ) and cervical effacement (43.4% vs 41.6%;  $p= 0.15$ ) was seen between the two groups.

**Table 3: Gestational age at delivery**

POG at delivery	Group I		Group II	
	Frequency	percentage	Frequency	Percentage
26.1 - 30	0	0	0	0
30.1 – 34	8	8	24	24
34.1 - 37	32	32	62	62
> 37	60	60	14	14
Total	100	100	100	100
Mean	35.805		34.974	
Std. Dev	1.70		1.81	
p-value	0.00			

In Group I, the mean gestational age at delivery was 35.805  $\pm$  1.70 weeks whereas in Group II, it was found to be 34.974  $\pm$  1.81 weeks. In Group I, 60% of the patients delivered at more than 37 weeks as compared to 14% in Group II. Significant difference was found between the two groups.

**Table 4: Neonatal Birth Weight**

Birth weight (in grams)	Group I		Group II	
	Frequency	percentage	Frequency	percentage
< 1500	2	2	2	2
1500 – 2000	2	2	12	12
2000 - 2500	26	26	50	50
> 2500	70	70	36	36
Total	100	100	100	100
Mean	2670.5		2395.5	
Std. Deviation	380.22		376.04	
p-value	0.00017			

The difference between the mean birth weight of the two groups was statistically significant.

**Table 5: Neonatal Parameters**

	Group I		Group II	
	Frequency	%	Frequency	%
Nursery Admission	15	15	25	25
Nursery stay in days	Mean	SD	Mean	SD
	7.71	2.870	8.41	4.461
Neonatal Complications	Frequency	%	Frequency	%
RDS	11	11	19	19
Sepsis	5	5	9	9
MV	5	5	7	7

More neonates needed admission to NICU in group II (25% in group II and 15% in group I) and length of nursery stay was also more in group II, mean stay being 8.41 + 4.461 in group II and 7.71 + 2.870 in group I. Neonatal complications were more in group II RDS (18% vs 10%), sepsis (8%vs 4%) and need for mechanical ventilation (7% vs 5%).

### Discussion

Prematurity as a consequence of preterm labor accounts for 75-80% of neonatal morbidity and mortality. [14] Of the survivors, 10% to 15% have significant handicaps. [15] Survival of the preterm infant is related directly to the gestational age at delivery. [16] The incidence of preterm labor has remained at 9-11% of all live births despite the use of tocolytic agents. [17] According to world health organization, a preterm birth is defined as birth before 37 completed weeks of gestation. [15] Traditionally preterm labor is defined as uterine contractions that result in cervical changes at less than 37 weeks gestation. [17]

Tocolytic drugs are the corner stone of primary pharmacological management of preterm labour. [18] It is clear from the literature, that these drugs are effective in delaying delivery for at least 24-48 hours. Unfortunately, this modest delay may not be sufficient to produce a reduced perinatal mortality. Therefore, many of these patients subsequently develop recurrent premature labor and deliver prematurely. Adjuvant therapy to prevent this could be a missing element in the treatment of these women. [19]

There was no significant difference between the two groups in their demographic characteristics. The randomly allocated groups were comparable in terms of age, parity, region at the time of inclusion in study. Age varied from 19-35 yrs, mean age being 23.67 ± 2.68 and 24.66 ± 3.57 in group I & II respectively. Parity varied from 0-4, median parity observed in both groups was 1. Majority belonged to rural area. Period of gestation at admission varied from 26 to 34 weeks but maximum patients presented at 30-34 weeks gestation in both groups. Mean gestation age was 31.82 ± 1.80 & 31.55 ± 1.81 weeks in the two groups respectively. Borna et al [20] reported difference in prolongation of pregnancy by 11.5 days while Saleh Gargari S et al [21] reported it to be 2.6 weeks. Bomba-Opon et al observed a significant reduction in delivery before 34 weeks with vaginal progesterone (9.8% in progesterone group versus 35.3% in control group; p = 0.002). Their results were comparable to our study (8% versus 24%). This much difference in gestation age makes significant impact on neonatal prognosis and societal economic burden. Of all early neonatal deaths (deaths within the first 7 days of life) that are not related to congenital malformations, 28% are due to preterm birth.

The mean number of uterine contractions per ten minutes was 2.17 ± 0.37 and 2.13 ± 0.32 in Group I & II respectively (p = 0.56). No significant difference in cervical dilatation (1.48 vs 1.42 cm; p=0.27) and cervical effacement (43.4% vs 41.6%; p=0.15) was seen between the two groups. In Group I, the mean gestational age at delivery was 35.805 ± 1.70 weeks whereas in Group II, it was found to be 34.974 ± 1.81 weeks. In Group I, 60% of the patients delivered at more than 37 weeks as compared to 14% in Group II. Significant difference was found between the two groups. The difference between the mean birth weight of the two groups was statistically significant. In our study in progesterone group neonatal birth weight was higher by approximately 300 gm. (2675.2 gm in group I vs 2393.2 gm in group II) Vaginal progesterone was associated with birth weight of more than 2500 gm in 70% cases as compared to 36% in control group. The results were comparable to that observed in literature. In various studies improvement in birth weight ranged from 290-490 gms. [20-22]

More neonates needed admission to NICU in group II (25% in group II and 15% in group I) and length of nursery stay was also more in group II, mean stay being 8.41 + 4.461 in group II and 7.71 + 2.870 in group I. Neonatal complications were more in group II RDS (18% vs 10%), sepsis (8%vs 4%) and need for mechanical ventilation (7% vs 5%). There was one case of neonatal death in Group II. The results were comparable to the previous studies. [23-25]

### Conclusion

In patients of preterm labor vaginal micronized progesterone when used along with tocolytics and supportive therapy significantly prolongs the pregnancy and hence gestational age at delivery. Progesterone therapy leads to higher number of women reaching term and delivering beyond 37 weeks and also better neonatal outcome in terms of higher birth weight and fewer complications.

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