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Comparative study of oral and vaginal natural micronized progesterone 300mg in preventing preterm labor in semi urban population

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Abstract
Preterm deliveries is the major contributors of neonatal mortalities and under 5 age group morbidities. Excessive use of Progesterone and its supplements, antenatal steroidal cover and tocolysis prevents this. In this study, there has been made an attempt to study the perinatal outcome of both mother and neonate revolving around premature deliveries by using two different routes for progesterone administration. A prospective study was done on randomly selected 300 patients who complained of pain abdomen after 24 weeks of pregnancy, and were followed up till delivery after administration of progesterone, after dividing into 2 separate groups. This leads to collection of data for interpretation of association of variation in various parameters with relation to use of different routes for micronized progesterone. When compared, users of Oral micronized progesterone (OMP) presented at 31.37±1.94 weeks for delivery and that of Vaginal micronized progesterone (VMP) presented at 33.49±2.49 weeks of gestation. 78.7% neonates of Oral group were asymptomatic at birth than those 90.7% of vaginal neonates. Incidence of neonatal morbidity, like signs of birth asphyxia (16.7% vs 3.3%), mean APGAR Score of 1 min (7.77±2.11 vs. 8.07±1.63), mean birth weight (2.89±0.67 vs. 3.19±0.61), NICU admission (13.3% vs 3.3%) were found to be higher in Oral group than Vaginal group. Administration of Vaginal micronized progesterone helps in reduction of preterm labor and the rate of neonatal NICU admissions, neonatal mortality and morbidity as compared to oral micronized progesterone. Vaginal progesterone surpasses the first pass metabolism explaining the better outcome of the vaginal in preventing preterm labor.

Keywords: Preterm labor, oral micronized progesterone, vaginal micronized progesterone, neonatal morbidity

Introduction
In India, 3,341,000 babies are born too soon each year and 361,600 children under five die due to direct preterm complications.
Newborn are perhaps one of the most susceptible population worldwide. In the current scenario, prematurity is already playing a lead role for the prime cause of death among children under five age group and the cause of disability and low quality of life in later period all over the world.
Preterm labor (PTL) and delivery pose a significant impact on health of the baby, as they continue to be the principal cause of perinatal morbidity and mortality and its long term sequelae [1]. Preterm birth is an essentially rising global problem, however more than 60% of those occur in South Asia and Sub-Saharan Africa. In the developing countries, on average, 11.9% of babies are born preterm as opposed to 9.1% in higher-income countries [2]. With an estimation of 14.5% of risk of preterm delivery, India stands among among the top ten countries in the world [3-5].
A complex multifactorial etiopathogenesis for PTL occurs as a result of various maternal and fetal factors such as maternal demographic, socio-economic characteristics and obstetric history. The interplay between maternal physiological and fetoplacental parturition which triggers premature cervical dilatation, effacement and premature activation of uterine contractions resulting in preterm birth [6, 7].
Preterm births are managed by tocolysis and steroid coverage. With the advent of advanced NICU and obstetric facilities, in developed countries, the fetal survival is possible even at 20 weeks and in developing countries at best setups even at 28 weeks of gestation.
The incidence of PTL is 23.3% while in India being 10-69%. The current world stressors and ART techniques has added on to the risks associated with PTL.

"Prevention is better than cure" as said, in similar ways, prediction and prevention of risks associated with preterm birth is the most effective treatment. Progesterone and its supplements have been highly recommended method for prevention of preterm birth [8-10].
This current study, done at a reputed centre, compares oral and vaginal micronized progesterone effectivity in prevention of preterm birth and the impact of progesterone administration by two routes on new-born complications and admission to NICU.

Aim
To compare the effectivity of oral micronized progesterone to vaginal progesterone in prevention of PTL

Objectives
To compare the impact of progesterone administration by two routes on new-born complications and admission to neonatal intensive care unit

Materials and Methods
A prospective, randomized study was conducted with 300 patients who were randomly divided into two groups receiving OMP and VMP, for 18 months, who fulfilled the inclusion criteria.

Sample size determination
Formula used: $N = (Z^2 \times P \times (1 - P))/d^2$

Z^2= table value of alpha error from Standard Normal Distribution table = 1.96*1.96 = 3.84
Power (P) = 0.05, (1-P) =0.95, Precision error of estimation (d) = 4%, $d^2 = 0.0016$

$N = (3.84 \times 0.05 \times 0.95)/0.0016 = 134$

Hence, approximately 150 patients required per group to obtain a significant difference and thus sample size of 300 patients selected for this study.

Study Group Composition
- Age: 18 to 40 years
- Gestational age between >24 week to <36 weeks
- Presence of one or more risk factor for PTL
- Multiple gestations
- Polyhydramnios
- Past history of PTL
- Previous history of multiple abortions
- Short duration between two pregnancies (<6 months)
- Clinical diabetes or Gestational diabetes
- Obese or undernourished

Omitting Factors
- Vaginal bleeding
- Placenta praevia
- Low lying placenta
- Foetal congenital anomalies
- Pregnancy from in-vitro fertilization
- Diagnosed clotting disorders
- Uterine anomalies

With due consents from ethical committee and patients, data was recorded from those women who presented with complaints of abdominal pain? Uterine contractions and cervical length less than 30 mm which is suggestive of PTL. Patients randomised into two groups and followed up on fort-night basis for detection of any PTL. Pregnancies continuing beyond 36 weeks were assessed for intervention for delivery. In neonates, APGAR score at 5 minutes were recorded. Number of neonates who required NICU admission from two groups were also noted. Comparison done with unpaired t test and association assessed with the help of Fisher test, student't' test and Chi-Square test. Significance measured by 'p' value less than 0.05. Results were graphically represented where deemed necessary.

Results
Number of patients vs Age
The mean age in OMP group came to be 26.12 ± 5.04 years and that in VMP group was 27.02 ± 5.09 years.

Number of patients vs Gestational Age
The mean gestational age of patients in OMP group and VMP group was 31.37 ± 1.94 weeks and 33.49 ± 2.49 weeks respectively. The comparison showed significant values.

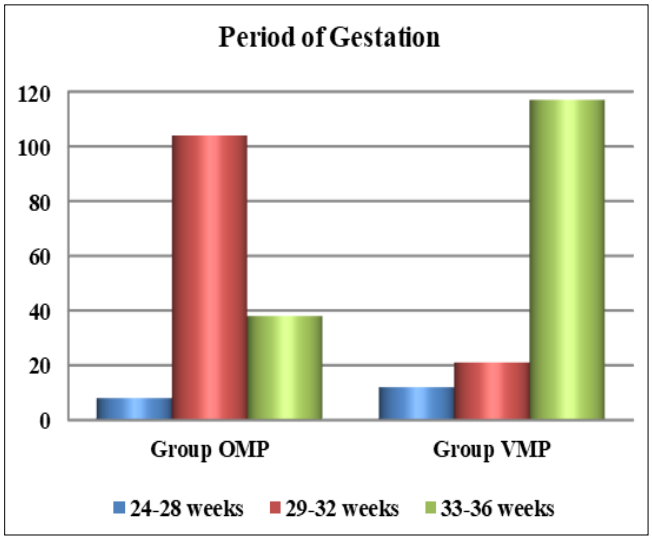

Fig 1: Distribution of patients according to Gestational Age showing the prevalence of use of OMP in earlier gestational age than that of VMP

Number of patients vs perinatal outcome
118 (78.7%) neonates in OMP group group were asymptomatic at birth compared to 136 (90.7%) neonates in VMP group, holding the comparison significant. Incidence of meconium aspiration syndrome (2.7% vs. 0.7%), neonatal sepsis (2% vs. 1.3%) and Hypoxemic ischaemic encephalopathy (2% vs. 1.3%) was comparable between the groups while the incidence of birth asphyxia was noticably higher in OMP group compared to VMP group (16.7% vs. 3.3%).

Table 1: Number of patients as per the respective perinatal outcome

Perinatal outcome	OMP group		VMP group		p Value
	N	%	N	%	
Asymptomatic at birth	118	78.7%	136	90.7%	<0.05
Meconium aspiration syndrome	4	2.7%	1	0.7%	>0.05
Birth asphyxia	25	16.7%	5	3.3%	<0.05
Neonatal sepsis	3	2%	2	1.3%	>0.05
Hypoxemic ischaemic encephalopathy	3	2%	2	1.3%	>0.05

Comparison of APGAR Score at 1 min and 5 mins between groups

The mean APGAR score at 1 min was lower in OMP group compared to VMP group as per Student t-test (7.77±2.11 vs. 8.07±1.63) while the mean APGAR score at 5 mins was comparable between the groups (7.93±1.74 vs. 8.13±1.51; *p*>0.05). Hence, the data of APGAR of 1 min is significant, and not that of 5 min.

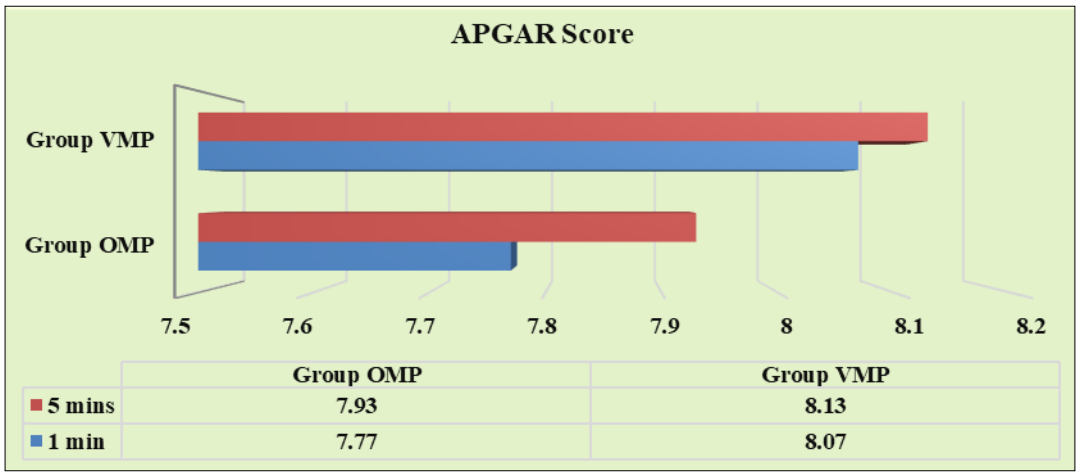

Fig 2: APGAR Score at 1 min and 5 mins comparison between groups showing the need of resuscitation in the respective groups

Distribution of neonates according to Requirement of NICU Admission

20 (13.3%) and 5 (3.3%) neonates in OMP group and VMP group respectively required NICU admission. The mean NICU stay of neonates in OMP group was significantly higher compared to VMP group as per Student t-test (21.20 ± 5.02 days vs. 6.20 ± 1.30 days; p<0.05).

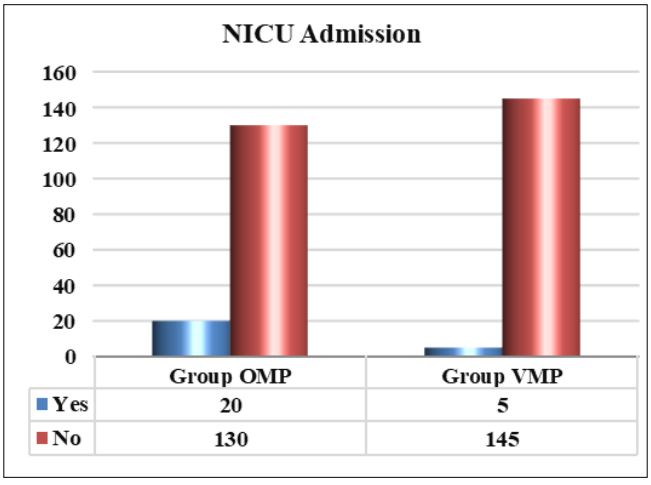

Fig 3: Distribution of neonates according to Requirement of NICU Admission with respect to use of OMP vs VMP.

Comparison of Birth Weight of Neonates between groups

In OMP group, 40 (26.7%) and 56 (37.3%) neonates weighed <2.5 kgs and 2.5–3.0 kgs respectively while 54 (36%) neonates weighed >3.0 kgs. In VMP group, 15 (10%) and 38 (25.3%) neonates weighed<2.5 kgs and 2.5–3.0 kgs respectively while 97 (64.7%) neonates weighed >3.0 kgs. The mean birth weight was considerably lower in OMP group compared to VMP group (2.89±0.67 kgs vs. 3.19 ± 0.61 kgs; p<0.05).

Table 3: Comparison of Birth Weight of Neonates between groups

Birth Weight	OMP group		VMP group		p Value
	N	%	N	%	
<2.5 kgs	40	26.7%	15	10%	<0.05
2.5 – 3.0 kgs	56	37.3%	38	25.3%	
>3.0 kgs	54	36%	97	64.7%	
Total	150	100%	150	100%	
Mean ± SD	2.89 ± 0.67		3.19 ± 0.61		

Discussion

In the present study, majority of the patients (65.3%) in OMP group were in the age group of 21-30 years, the mean age in OMP group was 26.12 ± 5.04 years. Majority of the patients (61.4%) in VMP group were in the age group of 21-30 years, the mean age in VMP group was 27.02 ± 5.09 years. The results obtained show than the use of progeterones both orally and vaginally, are comparable to parity. This is similar to the studies of Mostafa AH [11] and Deshpande H *et al.* [12]. Mostafa AH[11] study found mean age for oral group was (28.7±7.2) and for the vaginal group was (28.1±8) which showed insignificant difference statistically. Deshpande H *et al.* [12] prospective study assessing efficacy of natural micronized progesterone by vaginal route in prevention of PTL found maternal age was 28±4.3 in progesterone group versus 28.2±4.5 in placebo group.

The mean gestational age of patients in OMP group and VMP group was 31.37 ± 1.94 weeks and 33.49 ± 2.49 weeks respectively. Parveen R *et al.* [13] randomized controlled trial found mean gestational age was 9.3+2.7 weeks.

It was observed in the present study that 118 (78.7%) neonates in OMP group were asymptomatic at birth compared to 136 (90.7%) neonates in VMP group. Incidence of meconium aspiration syndrome (2.7% vs. 0.7%), neonatal sepsis (2% vs. 1.3%) and Hypoxemic ischaemic encephalopathy (2% vs. 1.3%) was comparable between the groups while the incidence of birth asphyxia was substantially higher in OMP group compared to VMP group (16.7% vs. 3.3%; p<0.05). Srisutham K *et al*. [14] 3-arm randomized control trial evaluating oral and vaginal progesterone made a notice that proportion of preterm delivery before 34 weeks was significantly different across the three treatment groups at 16.0%, 12.0%, and 5.2% in control, oral progesterone, and vaginal progesterone groups, respectively, emphasising on the fact that progesterone when used vaginally proved to be more useful than the oral route in preventing preterm birth before 34 weeks than the control group.

It was noticed that the mean APGAR score at 1 min was significantly lower in OMP group compared to VMP group (7.77±2.11 vs. 8.07±1.63; p<0.05) while the mean APGAR score at 5 mins was comparable between the groups (7.93±1.74 vs. 8.13±1.51; p>0.05).Mostafa AH [11] study showed Apgar score at one minute post-delivery was more than 7 in majority of the patients (73.6% and 90.9%) in the oral and vaginal group respectively and significant difference between both group). The APGAR score at five minutes post-delivery was more than 7 in majority of the patients (81.9% and 90.9%) in the oral and vaginal group respectively and was insignificant difference between both groups.

In the present study, in OMP group, 40 (26.7%) and 56 (37.3%) neonates weighed <2.5 kgs and 2.5–3.0 kgs respectively while 54 (36%) neonates weighed >3.0 kgs. In VMP group, 15 (10%) and 38 (25.3%) neonates weighed<2.5 kgs and 2.5–3.0 kgs respectively while 97 (64.7%) neonates weighed >3.0 kgs. The mean birth weight was lower in OMP group than in VMP group (2.89±0.67 kgs vs. 3.19 ± 0.61 kgs; p<0.05). Similarly Mostafa AH[11] found that mean of birth weight was 2.9±0.3 Kg (2.87 ± 0.378 and 3±0.24 Kg) for the oral and vaginal group respectively and most delivered average-weight newborns (83.3% and 100%) for the oral and vaginal group respectively.

In our study, 20 (13.3%) and 5 (3.3%) neonates in OMP group and VMP group respectively required NICU admission. The mean NICU stay of neonates in OMP group was significantly higher compared to VMP group (21.20 ± 5.02 days vs. 6.20 ± 1.30 days; p<0.05). Boelig RC *et al*. [15] metaanalysis showed significantly lower rate of perinatal death (5% vs 17%), neonatal intensive care admission, respiratory distress syndrome, and higher birth weight (mean difference, 435.06 g) with oral progesterone.

Conclusion

Administration of natural micronized vaginal progesterone 300 mg plays a vital role in the reduction of PTL and also significantly reduces the rate of neonatal NICU admissions, neonatal mortality and morbidity as compared to oral progesterone. The risk of preterm birth, neonatal morbidity and mortality, NICU admissions can be reduced by using Progesterone, as it appears to be potent and safe. As per our study, vaginal mode of administration is considered more efficacious which could be possibly explained as it surpasses first pass metabolism.

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