

## COMPARATIVE STUDY TO ASSESS THE EFFICACY BETWEEN INTRAMUSCULAR AND VAGINAL MICRONIZED PROGESTERONE TO PREVENT THREATENED PREMATURE LABOUR

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**ABSTRACT:** Preterm birth remains a major clinical problem. Prematurity is not only a major cause of perinatal mortality but also leads to greater risk for short and long term complications including disability and impediments in growth and mental development. To compare vaginal with intramuscular progesterone administration to prevent preterm labor and to detect the effect of both on the uterine and foetal circulations. **STUDY DESIGN:** comparative interventional study. **POPULATION:** 100 pregnant women attending NRSMCH Kolkata, Obstetrics emergency with threatened preterm labour before 34 weeks of gestation. **STUDY PERIOD:** one year. **METHODS:** Gestational age was confirmed clinically and by USG of early weeks of gestation. Efficacy and tolerability of progesterone in two routes i.e., intramuscular and vaginal for prevention of threatened preterm labour were compared. **OUTCOME:** Ante partum, intrapartum and perinatal outcomes were compared between two groups by statistical analysis of data's using chi-square test and student-t test. **CONCLUSION:** Vaginal progesterone was as effective as intramuscular progesterone in reducing preterm birth with fewer side effects in favor of vaginal route.

**KEYWORDS:** Prematurity, Progesterone, Perinatal outcome.

**INTRODUCTION:** Prematurity is not only a major cause of perinatal mortality but also leads to greater risk for short and long term complications including disability and impediments in growth and mental development.<sup>1</sup> The contribution of these preterm births to overall perinatal morbidity and mortality is more than 50%.<sup>2</sup>

Rates for preterm birth has been reported between 6% and 12% .About 40% of all preterm births occur before 34 weeks and 20% before 32 weeks. Majority of morbidity and deaths occurs among those who delivered before 34 weeks.<sup>3</sup> Outcome depends on neonatal facility available.

Wide variety of tocolytic agents are being advocated for decades for prevention PTL.<sup>4-9</sup> and also been tried for management of threatened PTL.<sup>10</sup> Threatened PTL was diagnosed by:<sup>4</sup> a) Uterine contraction that are painful palpable occur with a frequency of at least once for every 10 minutes') May or may not be associated with cervical changes (Position, consistency, length and dilatation). Absence of cervical changes does not mean that patient complains of pain or the possibilities that she is in early labour may be ignored. Meta-analysis indicated that Ca-channel blocker and an oxytocin antagonist can delay delivery by 2-7 days,  $\beta_2$  - agonist drugs delay by 48 hrs. But carry more side effects.<sup>4-10</sup> Meta-analysis of magnesium sulfate administration failed to support it as a tocolytics agent. Above all, there are insufficient data on long term follow up for reliable conclusion about the effects on the baby of these tocolytic drugs. (RCOG Green top guidelines, 2011).<sup>11</sup>

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Progesterone is essential for maintenance of pregnancy and helps in prolongation of pregnancy.<sup>12-17</sup> Delaying delivery may reduce the rate of long term morbidity by facilitating maturity of vital organs, help in optimum action of the administered glucocorticoids, helps in transfer to higher centre with NICU facilities. Though exact mechanism of action until very recently,<sup>12-18</sup> suggested mechanisms were - 1. It acts primarily through establishing uterine quiescence and maintains cervical length. It has immunosuppressive activity against the activation of T-lymphocytes & blocks effects of oxytocin on myometrium.<sup>12</sup> 2. It is a potent inhibitor of formation gap junctions between myometrial cells.<sup>13</sup> 3. Local changes in progesterone or Estrogen/Progesterone ratio.<sup>14</sup> 4. Recent studies show suppression of calcium-calmodulin-myosin light chain kinase system, reducing calcium flux and altering the resting potential of smooth muscle are the basis of progesterone action.<sup>18</sup>

So different trials have been done to show the efficacy and safety of progesterone in prevention of recurrent preterm birth since 1960.<sup>19-30</sup> Progesterone can be administered oral capsule, vaginal gel or suppository, or intramuscularly. Oral administration has better patient compliance but there is variability in the plasma concentrations of the drug due to personal variation in gastric filling and enterohepatic circulation, also this route might be associated with side effects such as nausea, headache, sleepiness, etc. The vaginal route results in higher local concentrations in uterus but its blood levels are low, while progesterone administered intramuscularly results in optimal blood levels.<sup>31</sup> Very recently, on 3rd February'2011 injectable form of 17 $\alpha$  hydroxy progesterone (Mekena) has been approved by FDA to reduce the risk of PTL before 37 weeks of gestation.<sup>32</sup>

Local vaginal progesterone has some minor side effect like vaginal discharge, itching, irritation, yeast infection, rarely breast engorgement. Side effect of synthetic injectable progesterone are also mild and restricted to injection site, like pain, swelling, itching, bruising.<sup>33</sup> and systemic side effects like nausea, vomiting, pain abdomen, diarrhoea.

**AIMS AND OBJECTIVES:** In the present study we want to compare the efficacy and tolerability of vaginal micronized progesterone and intramuscular 17 $\alpha$ OH-P for management of threatened preterm labour before 34 weeks of gestation. The aim of this study is to assess the efficacy and tolerability of vaginal micronized progesterone compared to intramuscular 17  $\alpha$  OH progesterone caproate in management of threatened preterm labour before 34 weeks' gestation

**MATERIALS & METHODOLOGY:** It is a comparative interventional study. 100 pregnant women attending NRSMCH Obstetrics emergency with threatened preterm labor before 34 weeks of gestation and fulfilling the inclusion criteria were enrolled for the study within 1 year study period.

**Inclusion Criterion:**

1. Threatened PTL at <34 weeks of gestation.
2. Singleton pregnancy.

**Exclusion Criterion:**

1. Multiple gestations.
2. P/V Dribbling.
3. Any evidence of chorioamnionitis.
4. Active stage of labor-cervical dilatation >4cm.
5. Diabetes.
6. Foetal anomaly.
7. Hypertension.

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8. Active liver-disease, thrombo-phlebitis, active thrombo-embolism.
  1. Maternal general examination done, temperature, pulse, blood pressure etc. were noted.
  2. Gestational age was confirmed clinically and by USG of early weeks of gestation.
  3. Per abdominal examination regarding uterine activity, tone and tenderness, liquor volume, fundal height and presentation, FHS pattern were thoroughly noted.
  4. Pelvic examination was done with aseptic precaution. Per speculum examination were done to exclude any dribbling or bleeding P/V, and to see the position and length of cervix. Per vaginal examination were done to detect position, consistency, length, dilatation of cervix, head station, presentation of fetus, membrane status.
  5. Threatened PTL is diagnosed by the specific criteria mentioned earlier.
  6. Patients were screened for exclusion criteria by clinical examination.
  7. Those cases fulfilling the inclusion criteria were counseled regarding the study and written consent were taken.
  8. Detailed history were taken to find out risk factors for preterm labours.

**RESULTS AND ANALYSIS:** Efficacy and tolerability of progesterone in two different routes for prevention of threatened preterm labour were compared. Antepartum, intrapartum and perinatal outcomes were compared between two groups by statistical analysis of data using chi square test and student-t test.

	<b>GROUP RECEIVING VAGINAL PROGESTERONE (n=50)</b>	<b>GROUP RECEIVING IM PROGESTERONE (n=50)</b>	<b>STATISTICAL ANALYSIS P value</b>
AGE OF MOTHER (AVERAGE In years) ±SD	23.72±5.5219	23.36±5.32518	0.9143
MEAN GESTATIONAL AGE AT ADMISSION(days)± SD	230.4±8.005927	228.96±9.930288	0.4278
PARITY	1.0823±1.1149	.78±1.03588	
CERVICAL DILATATION>1cm	16	18	

Below poverty line	26	28	0.8410
H/O spontaneous preterm birth present	10	12	0.8092
H/O UTI	6	5	
Culture positive vaginal swab	2	1	

**Table 1: Comparison Between two Groups Regarding Epidemiology and Risk Factors**

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OUTCOME	GROUP RECEIVING VAGINAL PROGESTERONE (n=50)	GROUP RECEIVING IM PROGESTERONE (n=50)	STATISTICAL ANALYSIS P value
MEAN GESTATIONAL AGE AT DELIVERY(days)±SD	236.82±8.589719	235.82 ±10.45826	0.6025
MEAN LATENCY(days) ± SD	7.02±3.755214	6.9 ± 4.087063	0.8788
MEAN BIRTH WEIGHT (kg)±SD	2.094±0.299258	2.048±0.335176	0.4709
Occurrence of PPRM	5	3	0.7124
Occurrence of chorioamnionitis	1	-	1.00
Side effect	3	11	0.0407
Prolonged labour	1	2	0.9580
Fetal distress	15	18	0.6706
NICU admission	16	17	1.00
Apgar Score <7 at 1min	12	14	0.8197
Neonatal sepsis	5	3	0.7124
RDS	7	8	1.00
Mechanical ventilation	8	9	1.00
Convulsion	3	1	0.6098
NICU stay >7days	5	7	
Neonatal death	9	11	0.7967

**Table 2: Comparison between two Groups Regarding Major outcome Variables**

**DISCUSSION:** Though there are many studies on role of different tocolytic drugs.<sup>4-10</sup> and progesterone for prevention of preterm labour in high risk gr.<sup>19-30</sup> But there are few studies regarding role of progesterone in threatened PTL.<sup>34-39</sup> Most of the studies compared the effect of progesterone as a maintenance tocolytic with placebo after initial tocolysis with other agents. There are very few studies comparing the different routes of use of progesterone.<sup>33</sup>

Erny R et al in 1986.<sup>4</sup> showed oral progesterone decreases uterine activity in 75% to 88% of cases, depending on the initial severity of the menace of premature delivery. The tocolytic effect of oral progesterone is not as intense or as rapid as the effect of intravenous beta-mimetics but is sufficient in 80% of cases, on the average, to stop the premature labor without any detectable side effects.

Study by Fabio Facchinetti et al in 2007. revealed shortening of the cervix in the observation group (30 cases) was higher than in the 17P group (30 cases) both at day 7(2.37±2.0 mm Vs. 0.83±1.74 mm; P=.002) and day 21(4.60±2.73 mm Vs. 2.40±2.46 mm; P= .002).

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	Study groups after randomization	Gestational age at admission (mean±SD) in weeks		Gestational age at delivery (mean±SD) in weeks		Latency of delivery	
Borna and Sahabi in Iran(n=70), 2008. <sup>36</sup>	TPTL after tocolysis treated with 400mg prog suppository	31.1±2.9		36.7±1.5	P value 0.041	36.1±17.9 (days)	P Value 0.03
	TPTL after tocolysis not/t given	32.4±2.1		34.5±1.2		24.5±27.2 (days)	
Mohan and Regmi et al, Nepal 2009-10 (n=60). <sup>37</sup>	TPTL after tocolysis treated with weekly IM progesterone	32.62±1.72	P value 0.552	36.59±1.94	P value 0.004	25.48 ±14.64 (days)	P value 0.003
	TPTL after tocolysis not/t	32.90 ±1.94		34.30±1.47		16.42±9.82 (days)	
Mohamed Ahmed Hussein et al 2009-10 (n=315). <sup>33</sup>	H/O spontaneous PTB treated with vaginal progesterone	14.9±1.1	P value 1.00	No significant difference when delivered <24 weeks, 24-28 weeks, 32-34 weeks, 34-37weeks, >37 weeks except 28-<32 weeks vaginal group had less % of delivery (P=0.02)			
	H/O spontaneous PTB treated with IM progesterone	15.1±1.0					
Bomba opon DA 2007-10. <sup>38</sup> (n=190)	TPTL after tocolysis treated with vaginal progesterone	27weeks (mean)				7.6 weeks (mean)	P value 0.039
	TPTL after tocolysis no t/t	28weeks (mean)				6.3 weeks (mean)	
Arican et al RCTin2011 InTurkey. <sup>39</sup> (n=83)	TPTL after acute tocolysis treated with vaginal progesterone	24 to 34 weeks		50% preterm delivery (<37wks) in prog group and 68% in placebo group		32.1 ±17.8	P value <0.05
	TPTL after tocolysis with no treatment		21.2 ±16.3				

A 2012 open-label multicenter RCT by Rozenberg and colleagues.<sup>40</sup> in France including 188 mothers analysis did not find a statistically significant difference between groups in the study's primary efficacy outcome, time to delivery (From randomization).

In our study there is no significant difference between vaginal and IM progesterone groups regarding baseline characteristics like maternal age, parity, gestational age at admission, cervical dilatation, risk factors. Efficacy of both routes are similar as determined by primary outcome like gestational age at delivery (P value=0.6025), admission delivery interval (P value=0.8788) and birth weight (P value=0.4709). On the other hand study by Borna and Sahabi, Bomba opon DA, Arican et al shows the efficacy of vaginal progesterone as a maintenance tocolysis than placebo. Whereas Mohan and Regmi et al found IM progesterone more effective as maintenance tocolysis than placebo.

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The admission – deliver interval of these studies were significantly large than our study because majority of them used acute tocolysis before use of progesterone. There is also no significant difference in comparison to duration of labour (P value-0.9580), foetal distress (P value-0.6706), mode of delivery (P value-0.7832), NICU admission (P value-1.00), apgar score <7 at 1min (P value-0.8197), occurrence of neonatal sepsis (P value-0.7124), RDS (P value-1.00), mechanical ventilation (P value-1.00), convulsion (P value-0.6098), period of NICU stay (P value-0.6721), neonatal death (P value-7967). Mohamed Ahmed Hussein et al also founds similar outcome between two groups regarding foeto maternal adverse outcomes.

6% of vaginal and 22% of IM progesterone receiving mothers have complained of various side effects i.e. vaginal group has significantly lesser side effects in comparison to IM group. (P value=0.0407).

Study by Mohamed Ahmed Maher HUSSEIN et al 2011, reported side effects in 19.1% in intramuscular group but only in 7.6% in vaginal group.<sup>33</sup>

**CONCLUSION:** Vaginal progesterone is as effective as intramuscular progesterone in reducing preterm birth with fewer side effects in favor of vaginal route.

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