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To Assess the Role of Vaginal Micronised Progesterone as a Tocolytic Therapy in Arrested Preterm Labour

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ABSTRACT
Women with preterm labour that is arrested with tocolytic therapy are at increased risk of recurrent preterm labour. The efficacy of progesterone tocolytic therapy after successful arrest of preterm labour remains controversial Aim of this study to evaluate role of vaginal micronized progesterone in arrested preterm labour. Pregnant women who were arrested with acute tocolysis as evidenced by a 12 hour contraction free period were randomized into study and control groups. The study group received 400 mg of vaginal micronized progesterone daily, while the control group did not receive any drug. The patients were followed up till 37 completed weeks. Maternal and fetal outcomes were compared in both the groups In the present study majority of the women were 21-25 years age in both the groups, the period of gestation at delivery was significantly ($p<0.05$) high in progesterone group (37-40 weeks) as compared to that in control group (34-36.6 weeks). Lower segment cesarean sections (LSCS) was higher in progesterone group (57.1%) as compared to control group (34.3%). In Recurrence rate of preterm labour was significantly lower (75.7%) in progesterone group as compared to control group (82.8%). Vaginal micronized progesterone as a tocolytic therapy following an episode of arrested pre-term labor significantly increased the duration to delivery interval., reduces the recurrence of preterm labour and also reduced the rate of Preterm birth.

INTRODUCTION

Preterm birth remains a significant public health problem and a leading cause of long-term disability in developing country[1]. Approximately 15 million babies are born preterm annually worldwide, indicating a global preterm birth rate of about 11%. With 1 million children dying due to preterm birth before the age of 5 years, preterm birth is the leading cause of death among children, accounting for 18% of all deaths among children aged under 5 years and as much as 35% of all deaths among newborns (aged <28 days)[2]. Risk factors include psycho-social stress, malnutrition, low and high maternal age, multiple pregnancy, decidual bleeding, ascending pathogen invasion of the amniotic sac and uterus and alterations in the vaginal microbiome[3-5]. In India, among the total 27 million babies born annually, 3.6 million babies are born preterm, and over 300,000 of these preterm babies die each year because of associated complications. India, with its highest number of PTBs and the highest number of preterm deaths worldwide, contributes 25% of the overall global preterm related deaths[6]. Progesterone was found to be useful to prevent PTB in 2 at risk categories: a) women with a prior history of PTB and/or late pregnancy loss[7] and b) women with short cervix at mid gestation[9]. In 2012, both the American College of Obstetricians and Gynaecologists (ACOG) and the Society for Maternal-Fetal Medicine recommended the administration of vaginal progesterone to women with a singleton gestation, no history of spontaneous pretermbirth and a transvaginal cervical length ≤20 mm at ≤24 weeks of gestation[9,10]. In 2021, the ACOG updated its guidelines, which were endorsed by the SMFM and recommended the administration of vaginal progesterone to women with a singleton gestation, no history of spontaneous preterm birth, and a transvaginal cervical length <25 mm at 18-22 weeks of gestation[11]. Vaginal administration of progesterone is well tolerated by the patients and has only minor maternal side effects, whereas intra muscular injections of 17 Alpha-Hydroxy-progesterone caproate are associate with a significant higher rate of side effects. Based on the success of progesterone in preventing preterm delivery in high risk groups, we planned a study to evaluate the effectiveness of progesterone as maintenance tocolytic in another high risk group i.e. women with arrested preterm labor.

Aims and Objectives: To study the role of vaginal micronized progesterone as a tocolytic therapy after arrested preterm labor in prolonging the latency period till delivery.

MATERIALS AND METHODS

This was a comparative interventional study conducted in the Department of Obstetrics and Gynaecology, Kamla Raja and J.A. Group of Hospitals, Gwalior (M.P.), for 18 months duration.

Inclusion Criteria:

- Women of 18-35 years of age group.
- Women with singleton pregnancies, Gestational age between 28-34 completed weeks and Intact membranes.
- Women with arrested preterm labor.
- Women who provide consent for the study.

Exclusion Criteria:

- Preterm premature rupture of membranes or Multiple gestation.
- History of recurrent preterm labor or History of recurrent mid trimester abortions.
- Uterine antomic malformation, Abruption Placentae, Placenta Previa, Intrauterine fetal demise, Cervical encerclage or Chorioamnionitis.
- Patients already on progesterone or Allergic reaction to progesterone.
- Patients who not provide consent for the study.

A total of 140 cases were randomly divided into two equal groups (70 each)

Group A: Received vaginal micronized progesterone, 400 mg daily as maintenance tocolysis.

Group B: Not received any drug for maintenance tocolysis.

A detailed history and clinical examination was done. Patient will be followed twice weekly till 36 weeks and then weekly till delivery. Baseline characteristics of women in both groups will be compared Hemodynamic parameters, Obstetric outcome, maternal outcome and neonatal outcomes were compared in both the groups.

Statistical Analysis: Statistical analysis was performed using statistical package for the social sciences (SPSS version 22.0). Outcomes will be evaluated using the Chi-square test for binary outcomes and the Student's' test for continuous outcomes. P<0.05 was considered as statistically significant

RESULTS AND DISCUSSIONS

Study participants divided into two groups, group A (received vaginal progesterone) and group B ((not received progesterone). Majority of women were 21-25 years of age in both the groups Most of the cases are booked. In both groups majority of women residing at rural area, belonged to upper lower socioeconomic class and educated up to secondary school. The above association was statistically not significant (p>0.05) which shows that both groups are comparable with respect to their age, residential status, socio-economic class and educational status. In Group A, majority of the women (71.4%) were between G2-G4 and 27.1%

were primigravida, whereas in Group B, 68.6% was between G2-G4 and 30% women were primigravida, the association found to be statistically not significant (p>0.05).

Table 1: Socio-Demographic Characteristics of Study Participants among Both the Groups

Socio-demographic characteristics		Group A	Group B	p-value
Age (years)	<20 years	3 (4.3%)	6 (8.6%)	0.270
	21-25 years	34 (48.6%)	39 (55.7%)	
	26-30 years	31 (44.3%)	21 (30.0%)	
	31-35	1 (1.4%)	4 (5.7%)	
	More than 35 years	1 (1.4%)	0 (0.0%)	
Residence	Rural	40 (57.1%)	39 (55.7%)	0.865
	Urban	30 (42.9%)	31 (44.3%)	
Socio-economic Class	Lower	24 (34.3%)	29 (41.4%)	0.194
	Upper Lower	30 (42.9%)	33 (47.1%)	
	Lower Middle	16 (22.9%)	8 (11.4%)	
Educational Status	Primary	32 (45.7%)	22 (31.4%)	0.066
	Secondary	38 (54.3%)	45 (64.3%)	
	Higher Secondary	0 (0.0%)	3 (4.3%)	
Booking status	Booked	53 (75.7%)	50 (71.4%)	0.565
	Unbooked	17 (24.3%)	20 (28.6%)	
Parity	G1	19 (27.1%)	21 (30.0%)	0.932
	G2-G4	50 (71.4%)	48 (68.6%)	
	> G4	1 (1.4%)	1 (1.4%)	

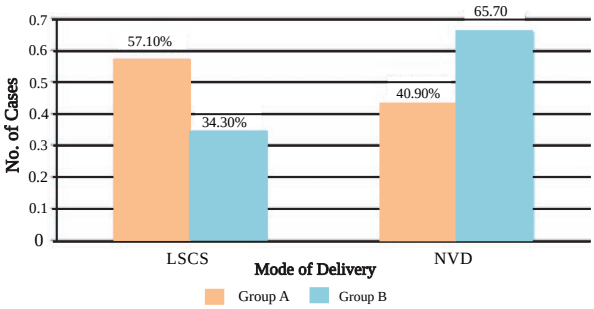
In both the groups majority of women were fall in gestational age 32-34 weeks on admission, most of the women belonged to Cervical Effacement in 10% Effaced. The above association found to be statistically not significant (p>0.05) which shows that both groups are comparable with respect to their gestational age at admission and Cervical Effacement

In Group A, majority of the women's (52.9%) gestational age at delivery was 37-40 weeks, whereas in Group B, most of the women's (57.1%) gestational age at delivery was 34-36.6 weeks, the association found to be statistically significant (p<0.001).

Table 2: Gestational Parameter of Study Participants in Both the Groups.

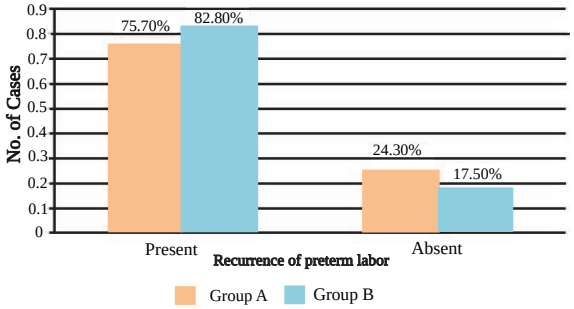
Gestational parameter				
Gestational age		Group A	Group B	p-value
(weeks)	28-29.6 weeks	7 (10.0%)	5 (7.1%)	0.829
	30-31.6 weeks	16 (22.9%)	17 (24.3%)	
	32-34 weeks	47 (67.1%)	48 (68.6%)	
Cervical Effacement	10% Effaced	32 (45.7%)	24 (34.3%)	0.553
	20% Effaced	14 (20.0%)	18 (25.7%)	
	30% Effaced	2 (2.9%)	03 (4.3%)	
	Early Effaced	22 (31.4%)	25 (35.7%)	
Gestational age at delivery	<34 weeks	5 (7.1%)	24(34.3%)	<0.001
	34-36.6 weeks	23 (32.9%)	40 (57.1%)	
	37-40 weeks	37 (52.9%)	6 (8.6%)	
	> 40 weeks	5 (7.1%)	0 (0.0%)	

In Group A there were, 57.1% women's mode of delivery was LSCS and 42.9% was normal vaginal delivery, whereas in Group B, 34.3% women's were LSCS and 65.7% was normal vaginal delivery, statistically significant (p<0.05) association.



Graph 1: Comparison of Mode of Delivery in Both the Groups

In Group A, recurrence of preterm labour was present in 75.7% of women's, whereas in Group B, recurrence of preterm labour was present in 82.8% of women.



Graph 2: Recurrence of Preterm Labor in Both the Groups

Administration of vaginal progesterone to women was found to increase the duration of randomization to delivery interval (primary endpoint) and also led to substantial reduction in the rate of pre term delivery <32 weeks and <37 weeks of gestation. Use of progesterone as maintenance tocolysis led to a higher mean birth weight and lower neo natal morbidities and mortality associated with pre term labor as shown by lower incidence of neo natal RDS and the rate of NICU admissions[12].

In the present study, majority of the patients were in the age group 21-25 years the distribution was comparable in both the groups (48.6% vs. 55.7%), in agreement with the Yadav[13] and Mishra[14]. Our study observed that most of women were from rural areas and upper-lower class, accordance to the Bajaj[15].

Majority of women was multiparous in both the groups, in current study, similar results was found in study done by Ferrari[16].

Our observation reported that the majority of women with preterm labour admitted at gestational age in between 30-34 weeks in both groups, The gestational age at enrollment was comparable in both the groups (P>0.05). Consistent finding also reported by Mishra[17] and K Rundell[18].

There was significant difference (p<0.05) between the progesterone group and the control group in respect of gestational age at delivery in this study, comparable with the other studies done by Cetingoz[19] and Jane[20]. Bomba-Opon[21] also observed a significant reduction in delivery before 34 weeks with vaginal progesterone, whereas[22] observed there were no significant differences between progestational agents and placebo/no treatment in terms of delivery.

A large multi center, randomized, double-blind, placebo controlled trial conducted by Tejada[23] showed that the maintenance treatment of 200 mg of daily vaginal progesterone suppository in women after an episode of arrested pre term labor did not significantly

reduce the rates of PTB <37 and <34 weeks of gestation.

In present study, rate of caesarean delivery was significantly higher in progesterone group as compared to control group, concordance with the Vladic[24].

Recurrence rate of preterm labor was higher in non progesterone group as compared to progesterone group, but it's not significant statistically (p>0.05), similar findings are reported by many other researchers: Di Renzo[25], S Borana[26] and V Pradyuman[27].

CONCLUSION

We conclude that, maintenance tocolytic therapy with micronized progesterone up-to 37 weeks of gestation in patients with arrested preterm labor had significantly reduces the rate of recurrence of preterm labor. It also increased duration of randomization to delivery interval and favorable peri-natal outcomes by an increase in gestational age at delivery. Self vaginal progesterone in arrested pre-term labor can improve compliance with decreased health care burden. However, further larger studies are required in the future for establishing the role of vaginal progesterone in preventing pre-term labor

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