MAK HILL Publications Research Journal of Medical Sciences

Research Article
doi: 10.36478/makrjms.2024.9.647.651

OPEN ACCESS

Key Words
Preterm premature rupture of membranes, latency period, neonatal outcome, micronized progesterone

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Received: 15 August 2024
Accepted: 18 September 2024
Published: 23 September 2024

Citation: Anita Meena, Jagrati Gupta, Nisha Yadav and Pushpanjali Paraste, 2024. Impact of Micronised Progesterone as Maintenance Tocolytic in Affecting Fetal Outcome: A Cross Sectional Study. Res. J. Med. Sci., 18: 647-651, doi: 10.36478/makrjms.2024.9.647.651

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Impact of Micronised Progesterone as Maintenance Tocolytic in Affecting Fetal Outcome: A Cross Sectional Study

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ABSTRACT
Prediction of latency period for women with Preterm premature rupture of membranes (PPROM) is imprecise and duration of the latency period was inversely related to the gestational age at PPROM. This study evaluated the impact of latency period on maternal and fetal outcomes with PPROM. We conducted a cross sectional observational study of women aged 18-35 years with arrested preterm labour was enrolled. One group received vaginal micronized progesterone as maintenance tocolytic and second group not received any drug for maintenance tocolytic. We have followed all the patients and maternal and fetal outcomes were measured. Majority of the women (32.9%) latency period were 29-35 days, whereas in Group B most of the wowere 8-14 days, statistically significant (P<0.001). The birth weight was significantly higher in progesterone group as compared to control group. Frequency and duration of NICU admission of birth baby's was significantly lower in progesterone group as compared to control group (p<0.05). Low Birth Weight babies was higher in control group and neonatal morbidity due to Meconium aspiration syndrome and respiratory distress syndrome was significantly higher in control group (p<0.001). In progesterone group the majority of the women (74.3%) had no side effect and 12.9% complain of itching. Maternal and neonatal outcome were significantly correlated with the latency interval, increasing of latency period associated with the adverse maternal and neonatal outcomes.

INTRODUCTION

Preterm pre labour rupture of membranes (PPROM) is defined as rupture of the amniotic membranes before the onset of labour before 37 weeks of gestation[1]. PPROM complicates approximately 3% of pregnancies and leads to one third of preterm birth and leads to number of other perinatal and neonatal mortality and morbidity[2]. Latency period is defined as the interval between rupture of membranes and delivery[3]. The fetal and neonatal complications of PPROM include infections and fetal distress due to umbilical cord compression, Respiratory Distress syndrome (RDS), necrotizing enterocolitis, intraventricular hemorrhage, sepsis and pulmonary hypoplasia and an overall increase in the perinatal morbidity and mortality rate[4]. Prompt management in the mother along with early detection of sepsis and aggressive management in neonates significantly improves the neonatal outcome[5]. In cases of PPROM, antenatal exposure to clinical or sub-clinical infection appears to be an additional specific risk factor of neonatal mortality and respiratory or neurological complications[6]. When pregnant women present with PPROM, the management options, depending on gestational age, are induction of labour and delivery (an approach referred to as planned early delivery) or waiting for spontaneous labour to occur (termed expectant management)[7]. Expectant management of PPROM includes use of antibiotic treatment and steroids[3]. Basic aim of expectant management is to prolong the pregnancy for possible longer durations because of the strong association between perinatal outcome and gestational age. Arrested preterm is defined as a 12 hour contraction free period after tocolysis has been discontinued.

Latency period is the number of days of pregnancy gained after arresting preterm labor till delivery. The known factors that can influence the duration of the latency period include cervical length[8], presence of cervical funneling[9], amniotic fluid volume[8,10] and gestational age at PPROM[10,11].

Aims of this Study: This study is to identify the factors associated with prolonged duration of latency period and to determine the neonatal outcome associated with longer latency periods in pregnancy with PPROM.

MATERIALS AND METHODS

This cross sectional interventional study was carried out in the Department of Obstetrics and Gynaecology in Kamla Raja and associated group of Hospitals in central India. The study duration was 18 months. Women aged 18-35 years with arrested preterm labour who provided written informed consent for the study were included.

Women with PPROM, Multiple gestations, Patients on progesterone therapy or Allergic to progesterone and women who not provide consent were excluded. All the study subjects were randomly divided into two groups (70 in each).

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

Group B: Not received any drug for maintenance tocolytic.

Arrested preterm labor will be defined as patients who will have been admitted with an episode of preterm labor or threatened preterm labor, contractions will have been successfully treatment by acute tocolysis given for 48 hours.

The woman in group a will be asked to self administer the 400mg micronized progesterone vaginally once a day at bed time until 36 weeks 07 days of gestation, rupture of membrane or until preterm delivery whichever will occur first. Patient will be followed twice weekly till 36 weeks and then weekly till delivery.

The Following Outcomes Should be Measured:

Obstetric Outcome: Latency period (Latency period is the number of days of pregnancy gained after arresting preterm labor till delivery), Episodes of recurrence of preterm labor and Birth Prior to 34 completed weeks

Neonatal Outcome: Birth weight of the baby, Neonatal morbidity and mortality.

Statistical Analysis: Analysis was done by using statistical package for the social sciences (SPSS version 22.0). Frequency and percentage was calculated. P-value <0.05 was considered as statistically significant

RESULTS AND DISCUSSIONS

A total of 140 women of arrested pre term labour were randomly divided into two groups. Group A: received micronized progesterone maintenance therapy for tocolytic and Group B: not received progesterone therapy.

Among Group A: Majority of the women (32.9%) latency period were 29-35 days followed by 22.9% women's latency period were 36-42 days and 17.1% women's latency period were >42 days, whereas in Group B most of the women (25.7%) latency period were 8-14 days followed by 20.0% women's latency period were 15-21 days. Differences was statistically significant (P<0.001) in both the group.

Table 1: Latency Period (Days) of Cases in Both the Groups.

Latency Period (days)	Group A	Group B	p-value
Up to 7 days	3 (4.3%)	18 (25.7%)	<0.001
8-14 days	7 (10.0%)	18 (25.7%)	
15-21 days	4 (5.7%)	14 (20.0%)	
22-28 days	5 (7.1%)	14 (20.0%)	
29-35 days	23 (32.9%)	3 (4.3%)	
36-42 days	16 (22.9%)	3 (4.3%)	
> 42 days	12 (17.1%)	0 (0.0%)	

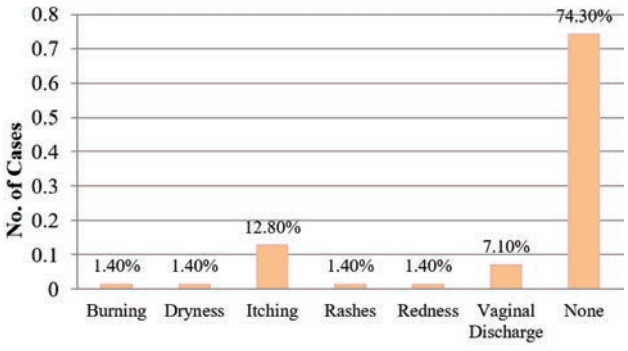
In group A majority of the baby's (74.3%) birth weight was 2.6-3.0 kg followed by 8.1% of baby's birth weight was 3.1-3.5 kg, whereas in group B, 45.7% baby's birth weight was 2.6-3.0 kg followed by (25.7%) baby's birth weight was 2.1-2.5 kg. The birth weight was significantly higher in group A as compared to group B. Frequency and duration of NICU admission of birth baby's was significantly lower in group A as compared to group B ($p<0.05$).

Low Birth Weight babies was higher in group B and neonatal morbidity due to Meconium aspiration syndrome and respiratory distress syndrome was significantly higher in group B ($p<0.001$).

Table 2: Comparison of Neonatal Outcomein Both the Groups.

Neonatal outcome		Group A	Group B	p-value
Birth weight (kg)	1.5-2.0 kg	2 (2.9%)	15 (21.4%)	<0.001
	2.1-2.5 kg	5 (7.1%)	18 (25.7%)	
	2.6-3.0 kg	52 (74.3%)	32 (45.7%)	
	3.1-3.5 kg	6 (8.6%)	5 (7.1%)	
	> 3.5 kg	5 (7.1%)	0 (0.0%)	
Duration (days)	1-7 days	4 (5.7%)	10 (14.3%)	0 .007
	8-14 days	2 (2.9%)	7 (10.0%)	
	15-21 days	0 (0.0%)	4 (5.7%)	
	>21 days	0 (0.0%)	2 (2.9%)	
	None	64 (91.4%)	47 (67.1%)	
NICU admission	Yes	6 (8.6%)	23 (32.9%)	<0.001
	No	64 (91.4%)	47 (67.1%)	
Morbidity	Very Low Birth Weight (<1.5kg)	0 (0.0%)	1 (1.4%)	0.007
	Low Birth Weight (<2.5kg)	1 (1.4%)	10 (14.3%)	
	Meconium aspiration syndrome1	(1.4%)	4 (5.7%)	
	Respiratory distress syndrome	4 (5.7%)	8 (11.4%)	
	None	64 (91.4%)	47 (67.1%)	

In Group A the majority of the women (74.3%) had no side effect, 12.9% complain of itching, 7.1% vaginal discharge and 1.4% each women complain of burning, dryness, rashes, redness respectively.



Graph 1: Maternal Side effects in group A

Prediction of latency period for women with PPROM is imprecise and therefore consulting women with PPROM about their predicted latency period is a difficult task. PPROM remains the leading cause of PTB and adverse neonatal outcomes. The main cause of PPROM is still unknown and delivery strategies for PPROM treatment remain controversial. In the absence of other cases, labor induction is not recommended for women with PPROM during 28-34 gestational weeks due to the increase of neonatal morbidity and cesarean section[12-13]. In the present study latency period was significantly longer until delivery in progesterone group as compared to control group, in agreement with the S. Fatima[14]. Borna[15] reported difference in prolongation of pregnancy by 11.5 days while Gargari[16] reported it to be 2.6 weeks. Walker[17] was found that latency in PPROM of three weeks was associated with high mortality and reduced likelihood of morbidity-free interval in all subgroups irrespective of gestational age. The impact of age of mother is directly related to the duration of latency and pregnancy outcome.

Current study confirmed the positive effects of administration of vaginal progesterone on increasing neonatal birth weight our result similar with the many other researchers. Mishra[18], Yadav[19] and Bomba[20].

The NICU admission rate was significantly lower in patients with vaginal progesterone in this study comparable as found in a study performed by Saccone[21] and Romero[22].

In our study neonatal complication like respiratory distress syndrome, sepsis and meconium aspiration syndrome was significantly less in group A, which shows positive effect of progesterone on reducing admission to NICU and reducing perinatal morbidity, constant results seen by Singhal[23] and Akbarian Rad[24]. We observed that micronized vaginal progesterone had lesser side effect that intramuscular progesterone, accordance with the Chandra[25].

A study done by Ilhan[26] reported that latency period of 7 days or more had statistically significant chances of miscarriages and other adverse neonatal outcomes. This study observed maternal and neonatal outcome were significantly correlated with the latency interval, increasing of latency period associated with the adverse maternal and neonatal outcomes, our finding consistent with the Kamlesh[27] and Raina[28].

In a research conducted by Frenette[29], reported that longer latency periods were associated with decreased prematurity-related morbidity in both gestational age groupings without a corresponding increase in serious maternal or neonatal infectious morbidity.

CONCLUSION

We have concluded that maintenance tocolytic therapy with vaginal micronized progesterone up to 34 weeks of gestation in patients with arrested preterm labour significantly prolongs latency period, increase gestational age of delivery, improves with weight at delivery and reduce need for NICU administrations. It significantly reduces the maternal and neonatal mortality.

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