Scholars Journal of Applied Medical Sciences (SJAMS)
Abbreviated Key Title: Sch. J. App. Med. Sci.
ISSN 2320-6691 (Online)
ISSN 2347-954X (Print)

A Unit of Scholars Academic and Scientific Society, India
www.saspublishers.com

Obstetrics & Gynaecology

Prophylactic Use of Micronised Progesterone in Prevention of Preterm Labuor

Prof. Dr. Archana Maurya*, Pooja Khetpal
Gajra Raja Medical College, Gwalior, Madhya Pradesh, India

Original Research Article

***Corresponding author**
Prof. Dr. Archana Maurya

Article History
Received: 01.11.2018
Accepted: 05.11.2018
Published: 30.11.2018

DOI:
10.36347/sjams.2018.v06i11.044

Abstract: Preterm labor is defined as the presence of uterine contractions of sufficient frequency and intensity to effect progressive effacement and dilation of the cervix prior to term gestation. Preterm labour occurs in approximately 12% of pregnancies and is the leading cause of neonatal mortality. To assess the efficacy of micronized progesterone in prevention of preterm labor. To assess the incidence of preterm in terms of need of tocolysis. To know about period of gestation at which delivery occurs. To study the mean birth weight and perinatal outcome. To study the maternal complications. The present prospective study has been conducted in the Department of Obstetrics & Gynaecology at Kamlaraja Hospital, Gajra Raja Medical College, Gwalior for a period of 1 year from September 2014 to October 2015. Result and conclusion: It is concluded from the present study that by using micronized progesterone in mothers with previous spontaneous preterm birth and bad obstetrics history we can reduce the incidence of preterm birth and prolong the period of gestation till term thus alleviating mental trauma to mother and reduces maternal morbidity.
Keywords: Preterm labour, prevention of preterm labour, Micronized progesterone prophlactic sue of micronized progesterone.

INTRODUCTION

Preterm labor is defined as the presence of uterine contractions of sufficient frequency and intensity to effect progressive effacement and dilation of the cervix prior to term gestation. Preterm labour occurs in approximately 12% of pregnancies and is the leading cause of neonatal mortality [1].

Preterm labour is the number one cause of neonatal morbidity and mortality, and a leading cause of long-term disability in the United States and elsewhere.[2,3] Overall, PTL accounts for up to 12.7% of births in the developed world & 20-25 % in developing countries; the vast majority of these (~ 75%) occur spontaneously.[1,2] Although secondary or tertiary interventions such as antenatal corticosteroids, postnatal surfactant and improved neonatal care have led to reduced morbidity and mortality caused by PTL, effective primary preventive interventions have remained elusive.

Goals of obstetric case management of preterm labor should include

- Early identification of risk factors associated with preterm labour,
- Timely diagnosis of preterm labor,
- Identifying the etiology of preterm labor,
- Evaluating fetal well-being,
- Providing prophylactic pharmacologic therapy to prolong gestation and reduce the incidence of respiratory distress syndrome (RDS) and intra-amniotic infection.
- Initiating tocolytic therapy when indicated.
- Establishing a plan of maternal and fetal surveillance with case/ provider education to improve neonatal outcome.

AIMS AND OBJECTIVES

- To assess the efficacy of micronized progesterone in prevention of preterm labor.
- To assess the incidence of preterm in terms of need of tocolysis.
- To know about period of gestation at which delivery occurs.
- To study the mean birth weight and perinatal outcome.
- To study the maternal complications.

MATERIALS AND METHODS

The present prospective study entitled *"Prophylactic use of micronized progesterone in prevention of preterm labour "*, has been conducted in the Department of Obstetrics & Gynaecology at Kamlaraja Hospital, Gajra Raja Medical College, Gwalior for a period of 1 year from September 2014 to October 2015.

Study Period

1 year (September 2014 to October 2015).

Study Group

Study group consisted of 200 outdoor & indore cases, of which 175 were enrolled for the study, as 25 cases were lost to follow-up. The enrolled 175 cases received intramuscular micronized progesterone 200 micron biweekly from the time they were recruited in the study till 34 weeks of gestation.

Inclusion Criteria

- Singleton pregnancy with at least previous one spontaneous preterm delivery.
- Present pregnancy between 18–28 weeks period of gestation.
- Willing for follow-up.

Exclusion Criteria

- Multi-fetal gestation.
- Known fetal anomaly.
- Cases with documented cervical incompetence and case's found with cervical length less than 2.5 cm on USG at any time during the study period.
- PPROM
- Iatrogenic preterm delivery
- Non-compliant cases
- Cases with previous pregnancy, where the cause of preterm labour was PPROM, multiple gestation and/or congenital anomaly were also excluded from the present study

175 women with singleton pregnancy between 18 to 28 weeks period of gestation with history of at least one previous preterm vaginal delivery were included in this study. Cases willing for follow-up were included in the study. A written voluntary informed consent was taken from all the cases after counseling and explaining the study protocol including risks, alternative therapies and available options.

OBSERVATION

This study was conducted in the Department of Obstetrics and Gynecology, Kamla Raja Hospital, Gwalior. The cases were studied for a period of 1 year from September 2014 to October 2015.

175 cases that were enrolled in the study were given Injectable micronized progesterone 200 micron twice weekly from the day they were recruited till 33/34 weeks of gestation.

As many factors place a case in high risk for preterm apart from a history of previous preterm labour, so at the time of recruitment various characteristics were also studied.

DISCUSSION

Table-1: Characteristics of various studies which are compared

Characteristics	Present study	Meis [10]	Da Fonascea[9]	Rai. P [13]
Type of study	Prospective study	Double blinded RCT	Double blinded RCT	Double blinded RCT
Sample size	175	463	142	150
Progesterone route and dose	Intramuscular micronized progesterone 200mg Biweekly	Intramuscular injections of 17-OHPC,250 mg Weekly	Vaginal micronized progesterone 100mg daily	Oral micronized progesterone 100 mg BD
Inclusion criteria	Previous spontaneous preterm delivery	Previous spontaneous preterm delivery	Previous preterm labour, prophylactic cerclage or uterine malformation*	Previous spontaneous preterm delivery
Initiation /ending	18-28 wks/34 wks	16-20 wks/37wks	24 wks/34 wks	18-24 wks/36 wks

Age

In the present study, the mean age of the cases in the study was 25.21±3.155 years with the range 18 - 31 years. Eight cases were of 18 years of age. Papeirnik [5] has shown that extremes of age are high risk factors of preterm labour. The study established that women <21 and those >36 years are at an increased risk of preterm labour. Meis PJ [10] and Rai P [13] also included women with a mean age of 26±5.6 and 26.5±5.4 in study and control groups respectively which is comparable to the cases in the present study.

Previous obstetric history

A history of previous preterm labour increases the likelyhood of preterm deliveries in subsequent pregnancies. Fedrick J [4], Bakketeig L S [6] and Keirse MJNC [7] showed that in case with a history of previous preterm labour there was a 17-40% increased risk of preterm labour in subsequent pregnancy. This risk doubles to 70-80% with two or more previous preterm labours.

Table-2: Comparison of baseline characteristics of cases at recruitment in various studies

		Meis *et al*.[10]	da Fonesecea *et al*. [9]	Pushpanjali Rai *et al*. [13]	Present study
Age in year	Study	26.0 ± 5.6	26.8	26.07 ± 3.2	25.214±3.10
	Control	26.5 ± 5.4	27.8	25.72 ± 3.42	-
	P value	NS	NS	0.53	-
No. of previous abortion	Study	-	-	0.70 ± 0.89	1.5±0.809
	Control	-	-	0.66 ± 0.76	-
	P value	-	-	0.75	-
No. of previous preterm labour	Study	1.4 ± 0.7	-	1.21 ± 0.83	2±0.599
	Control	1.6 ± 0.9	-	1.31 ± 0.82	-
	P value	0.007	-	0.27	-
Mean POG at recruitment	Study	18.4 ± 1.4	25.2	20.69 ± 2.83	22.5±1.599
	Control	18.4 ± 1.4	26.5	20.73 ± 1.78	-
	P value	1.000	NS	0.92	-

The present study included those antenatal cases that had at least one previous spontaneous preterm vaginal delivery which in itself places them in a high-risk category. Subsequent studies to prove the effect of progesterone in prevention of preterm labour by Meis P J [10], da Fonascae EB [9] and Rai P [13] also had inclusion criteria of previous spontaneous preterm vaginal delivery.

The mean number of previous preterm labours amongst the recruited cases in the above mentioned studies ranged from 1.2-1.4. In the present study the mean number of previous preterm deliveries was 2±0.599 with range of 1 to 3. The results were comparable with other studies. Similarly, number of previous abortions amongst the recruited cases was 1.5±0.809, which was comparable with other studies.

Gestational age at delivery

Various randomized controlled trials and meta-analysis conducted using progestins have shown significant reduction in preterm labour [9, 10]. Keirse MJNC [7] term labour in the treatment versus placebo groups (OR 0.05; 95% CI, 0.30–0.85). Similar findings were noted in a recent meta-analysis by Sanchez-Ramos I [18] using 17-OHPC (PTL in the treatment group 26% vs 35.9% in placebo [OR 0.45; 95% CI, 0.25–0.80]). The only study, by da Fonseca EB [9], to use natural progesterone via the vaginal route showed that the incidence of PTL was 13.8% in the treatment group compared to 28.5% in the placebo group ($P = 0.03$). The results of the present study using injectable micronized progesterone are in agreement with previous studies of intramuscular progestins and vaginal micronized progesterone as the incidence of PTL was %, in view of a smaller sample size in the present study, it does reflect positively on the ability of micronized progesterone to prevent preterm labour.

Table-3: Comparison of various trials for preterm delivery

Gestational age at delivery		Meis PJ [10]	Da Fonescea EB [9]	Rai P [13]	Present study
< 32 weeks	Study	35 (11.4)	-	2.7%	0
	Control	30 (19.6%)	-	24.3%	-
	P value	0.02	-	Significant	-
< 34 weeks	Study	30.7	2.8%	29.7%	0.5%
	Control	20.6	18.4%	45.0%	-
	P value	0.02	0.002	Significant	-
< 37 weeks	Study	36.3%	13.8%	39.2%	32.1%
	Control	54.9%	28.5	59.2%	-
	P value	0.001	0.03	0.002	-

Results from a randomized controlled trial conducted by Meis P J [10] showed that treatment with 17-OHPC reduced the risk of delivery before 34 weeks of gestation (20.6% vs 30.7%, RR 0.67; 95% CI, 0.48–0.93) and 32 weeks of gestation (11.4% vs 19.6%, RR 0.58; 95% CI, 0.32–0.91). Similarly, the frequency of preterm delivery before 34 weeks was 2.6% in the treatment group compared with 18.6% in the placebo group in the study by Da Fonseca EB [9]. Rai P [13], showed that the number of women who had preterm delivery was lower in the oral micronized progesterone group when compared with that of the control group (29 vs. 44 women, $P = 0.002$). Further analysis showed that the OMP had a protective role in preventing PTL between 28 weeks and 31 weeks plus 6 days (RR 0.20; 95% CI, 0.05–0.73;). In the present study, none of the cases delivered before 32 weeks. 1 (0.5%) of the case delivered before 34 weeks. On stopping the drug at 34 weeks 56/175 (32.1%) of the cases delivered before 37 weeks. There was higher percentage of term deliveries

in the study suggesting that injectable micronized progesterone does have a beneficial role in prolonging pregnancy in these women who are at a higher risk of preterm delivery. Rai P [13] analyzed that the mean gestational age at delivery was higher in the OMP group (36.1 Vs 34.0 weeks, p<0.001). In the present study we also found same results with the injectable form.

Mode of delivery

In the present study, it was observed that there was a 58/175 (33.1%) cesarean rate amongst the cases in the study. Most of the indications for cesarean in the cases were for obstetrical indications like breech, fetal distress, precious pregnancy, cephalopelvic disproportion and meconium stained liquor. 117/175(66.9%) cases delivered vaginally.

Meis P J [10] in his study showed no difference in the cesarean rate in both the study and control groups (25.2% Vs 25%).

Neonatal outcome

The use of progesterone as discussed above does have an effect in prolonging pregnancy in cases who are at a high risk of preterm delivery as a result the prematurity rate is decreased thus improving the neonatal outcomes with respect to mean age at delivery APGAR score.

Among 21 NICU admission 10(47.6%) developed infant pathological jaundice, 7(33.3%) developed birth asphyxia, 3(14.2%) developed infant respiratory distress syndrome and 1(4.9%) developed septicemia.
Of these there were 5 neonatal deaths

Maternal side effects

There are many studies to establish the role of progesterone in prevention of preterm labor but the side effects of the drug have not been studied or noted. In the present study dizziness 30/77(38.9%), vague abdominal pain 26/77 (33.7%), nausea vomiting 21/77(27.4%) were seen. In the study by Rai P [13] cases in oral micronized progesterone group had acne (n=2), esophageal reflux (n=2), and somnolence (n=1), while cases in the control group experienced acne (n=1), somnolence (n=1), headache (n=1), and depression (n=4).

SUMMARY

- Single center prospective study was conducted in "Department of Obstetrics & Gynecology , Kamla Raja Hospital, G.R. Medical college , Gwalior" to assess the role of injectable micronized progesterone in the prevention of preterm labor and its safety. 175 cases with history of at least one previous spontaneous preterm vaginal delivery were recruited.
- Cases in the study were given Injectable micronized progesterone intramuscularly biweekly. Therapy was started from the day of recruitment (18 - 28 wks POG) and was given up to 34 weeks period of gestation.
- Case profile: Mean age was 25.21±3, 77.2% (135 out of 175) of the cases were from low socioeconomic status, 69.1 %(121 out of 175) were uneducated.
- The number of previous abortions in the study was 1.5 ± 0.809 and the number of previous preterm labour was 1.5±0.599.
- Mean POG at the time of recruitment was 2 ± 1.599.
- In this study twenty six cases required tocolysis 26 out of 175 (14.8%)
- In this study 57 out of 175(32.5%) of the cases required antenatal corticosteroids.
- None of the case in this study delivered before 32 weeks. 1 out of 175(0.5%) cases delivered before 34 weeks. 56 out of 175 (32.1%) of the cases delivered between 34 to 36+6 weeks. Overall 57 out of 175 (32.6%) of the cases delivered before 37 weeks.
- Mean period of gestational at delivery was 40.5±1.76 weeks.
- 58 out of 175 (33.2%) cases underwent caesarean section. caesarean sections were because of obstetrical indications like breech 14 out of 58(24.3%), fetal distress 17 out of 58 (29.3) , precious pregnancy 16 out of 58(27.5%) & CPD 11 out of 58(18.9%)
- Among 21 NICU admission 10 (47.6 %) developed Infant pathological jaundice, 7 (33.3%) developed birth asphyxia, 3 (14.2%) developed Infant respiratory distress syndrome & 1 (4.9%) developed septicemia.
- Side effects such as Dizziness 30 out of 77(38.9%), vague abdominal pain 26 out of 77 (33.7%), nausea vomiting 21 out of 77(27.4%) were seen.

CONCLUSION

It is concluded from the present study that by using micronized progesterone in mothers with previous spontaneous preterm birth and bad obstetrics history we can reduce the incidence of preterm birth and prolong the period of gestation till term thus alleviating mental trauma to mother and reduces maternal morbidity. There is definitely improvement in birth weight and good neonatal outcome thus reducing perinatal morbidity and mortality due to preterm birth complications like RDS, Necrotising enterocolitis, Intraventricular hemorrhage.

REFERENCES

1. Martin JA. Hamilton BE. Ventura SE, Menacker F and MM Park. Births: final data for 2000. Natl Vital Stat Rep. 2002; 50(5):1–101.

2. Goldenberg RL, Culhane JF, Iams JM, Romero R. Epidemiology and causes of preterm labour. Lancet. 2008; 371:75–84.
3. Moster D, Lie RT, Markestad T. Long-term medical and social consequences of preterm labour. N Engl J Med 2008; 359:262–73.
4. Fedrick J, Anderson ABM. Factors associated with spontaneous preterm labour. Br J Obstet Gynaecol 1976; 83:342-50.
5. Papeirnik E. Prediction of Preterm baby. Clin Obstet Gynaecol: 1984; 11(2):315-36.
6. Bakketeig LS, Hoffman HJ, Harley EE. The tendency to repeat gestational age and birth weight in successive births. Am J Obstet Gynecol. 1979;135:1086-103.
7. Keirse MJNC, Rush RW, Anderson ABM, Turnbull AC. Risk of preterm delivery in cases with previous preterm delivery and/or abortion. Br J Obstet Gynecol. 1978;85(2):81-5.
8. Keirse MJNC. Progesterone administration in pregnancy may prevent pre-term delivery. Br J Obstet Gynecol. 1990; 97:149-54.
9. Da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M. Prophylactic administration of progsesterone by vaginal suppository to reduce the incidence of spontaneous preterm labour in women at increased risk: a randomized placebo-controlled double-blind study. Am J Obstet Gynecol. 2003; 188:419-24.
10. Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, Spong CY, Hauth JC, Miodovnik M, Varner MW, Leveno KJ. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. New England Journal of Medicine. 2003 Jun 12;348(24):2379-85.
11. Mackenzie R, Walker M, Armson A, Hannah ME. Progesterone for the prevention of preterm labour among women at increased risk:a systematic review and meta-analysis of randomized controlled trials, Am J Obstet Gynecol.2006;194:1234–42.
12. Coomarasamy A, Thangaratinam S, Gee H, Khan KS. Progesterone for the prevention of preterm labour:a critical evaluation of evidence, Eur J Obstet Gynecol Reprod Biol. 2006;129:111–118.
13. Rai P, Rajaram S, Goel N, Ayalur Gopalakrishnan RA, Agarwal R, Mehta S. Oral micronized progesterone for prevention of preterm labour. Int J Obstet Gynecol. 2009; 104:42-3.
14. Majhi P, Bagga R, Kalra J, Sharma M. Intravaginal use of natural micronized progesterone to prevent pre-term birth: A randomized trial in India. J Obstet Gynaecol. 2009 Aug;29(6):493-8.
15. Cetingoz E, Cam C, Sakalli M, Karateke A, Celik C, Sancak A. Progesterone effects on preterm labour in high-risk pregnancies: a randomized placebo-controlled trial. Arch Gynecol Obstet. 2011 Mar;283(3):423-9.
16. Glover MM, McKenna DS, Downing CM, Smith DB, Croom CS, Sonek JD. A randomized trial of micronized progesterone for the prevention of recurrent preterm birth. American journal of perinatology. 2011 May;28(05):377-81.
17. Hassan SS, Romero R, Vidyadhari D, Fusey S, Baxter JK, Khandelwal M, Vijayaraghavan J, Trivedi Y, Soma-Pillay P, Sambarey P, Dayal A. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. Ultrasound in Obstetrics & Gynecology. 2011 Jul 1;38(1):18-31.
18. Sanchez-Ramos L, Kaunitz AM, Delke I. Progestational agents to prevent preterm birth: a meta-analysis of randomized controlled trials. Obstetrics & Gynecology. 2005 Feb 1;105(2):273-9.