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ORIGINAL ARTICLE

RANDOMISED CONTROL STUDY OF USE OF PROGESTERONE V/S PLACEBO FOR MANAGEMENT OF SYMPTOMATIC PLACENTA PREVIA BEFORE 34 WEEKS OF GESTATION IN A TERTIARY CARE CENTRE

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ABSTRACT: INTRODUCTION: APH complicates 3-5% of pregnancies and is a leading cause of perinatal and maternal mortality worldwide. Progesterone is essential in maintenance of pregnancy and helps in prolongation of pregnancy. Different trials have been done to show the efficacy and safety of progesterone in prevention of preterm birth but study related to use in expectant management of symptomatic placenta previa is very limited. **AIMS AND OBJECTIVE:** The objective of our study is to determine the effectiveness of intramascular 17 alpha hydroxy progesterone Caproate therapies vs. placebo in conservative management of patient with symptomatic placenta previa before 34 weeks of gestation. **MATERIALS AND METHODS:** It is a randomized control study with 100 pregnant women attending Obstetric deptt. at Nilratan Sircar Medical College and Hospital, Kolkata with symptomatic placenta previa having episode of warning haemorrhage before 34 weeks of gestation and fulfilling inclusion criteria were enrolled for the study in a two year period from January 2013 to December 2014. Statistical analysis was performed using student t-test and chai-square test where appropriate. **RESULTS AND ANALYSIS:** In our study prolongation of pregnancy in progesterone receiving group is statistically significant (p-value<0.001), significant difference were also found in gestational age at delivery (p value of 0.0288), birth-weight (p-value of 0.0470). **CONCLUSION:** In this study use of 17 alpha hydroxy progesterone in expectant management of symptomatic placenta previa tends to be beneficial than placebo.
KEYWORDS: Placenta previa, Progesterone, Pregnancy.

INTRODUCTION: Antepartum hemorrhage (APH) is defined as bleeding from or in to the genital tract, occurring from 24+0 weeks of pregnancy and prior to the birth of the baby.[1]APH complicates 3–5% of pregnancies and is a leading cause of perinatal and maternal mortality worldwide.[1]Placenta previa is associated with a maternal mortality rate of approximately 0.03% and perinatal mortality of 8.1% in the developed world and much more in developing countries.[2,3] A significant degree of uterine contractility has been observed in association with symptomatic placenta previa and a large percentage of women who have placenta previa associated with hemorrhage will experience subclinical uterine contractions before the onset of overt vaginal bleeding as per literatures.[4-6]

Recent study show varieties of tocolytic agents are being advocated for management of symptomatic placenta previa.[7] Progesterone is essential for maintenance of pregnancy and helps in prolongation of pregnancy.[8] 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 unknown until very recently. 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[9]
2. It is a potent inhibitor of formation gap junctions between myometrial cells[10]
3. Local changes in progesterone or Estrogen/Progesterone ratio.[11]
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.[12] Different trials have been done to show the efficacy and safety of progesterone in prevention of recurrent preterm birth since 1960.[13-15] Study related to use of progesterone in expectant management of symptomatic placenta is very limited.[16,17]

AIMS AND OBJECTIVES: The objective of our study is to determine the effectiveness of intramuscular 17α hydroxy progesterone caproate therapy versus placebo in conservative management of patients with symptomatic placenta previa before 34 weeks of gestation.

Primary outcome measure was prolongation of pregnancy and secondary outcome measures were maternal outcomes i.e. number of episodes of bleeding, number of blood transfusion required, birth weight of babies.

INCLUSION CRITERIA:

- Placenta previa is diagnosed when the lowest placental edge is located within 5 cm of the internal os on ultrasonography.
- Placenta previa symptomatic with at least one episode of bleeding.
- Estimated gestational age within 28 to 34 weeks.
- Maternal age > 18 yrs.
- Singleton pregnancy.

EXCLUSION CRITERIA:

- Premature rupture of membranes.
- Severe bleeding requiring an immediate termination of pregnancy.
- Abnormal fetal heart rates requiring an immediate termination of pregnancy.
- Intrauterine fetal death.
- Pre-eclampsia, chorioamnionitis, liver disease, severe chronic renal disease, heart disease, diabetes.
- Abruptio placentae.
- Haemodynamically unstable.

MATERIALS & METHODS: It is a randomized control study with 100 pregnant women attending NRSMCH obstetrics emergency with symptomatic placenta previa that is having episode of warning hemorrhage before 34 weeks of gestation and fulfilling the inclusion criteria were enrolled for the study in 2 year period. Maternal general examination done, temperature, pulse, blood pressure etc were noted. Gestational age was confirmed clinically and by USG of early weeks of gestation.

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Per abdominal examination regarding uterine activity, tone and tenderness, liquor volume, fundal height and presentation, FHS pattern were thoroughly noted. Active vaginal bleeding was excluded by inspection of the soaked pads and amount of blood clots. Type of placenta previa was determined by ultrasound. All patients initially received steroid prophylaxis, then, patients are randomly assigned having 50 pregnant mothers in each group to receive either intramuscular 17α hydroxyl progesterone caproate 500 mg twice weekly or placebo until 37 weeks of gestation or till delivery whichever is earlier.

RESULTS AND DISCUSSION:

	Group receiving im progesterone (n=50)	**Group receiving placebo (n=50)**	**Statistical analysis P value**
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	
Type of placenta previa Central Partial Marginal Low lying	 9 13 18 10	 5 15 16 14	 P value 0.1824 $X^2$4.860
Hb %	9.37±2.21	10.02±1.97	Pvalue 0.1238

Table 1

	Group receiving im progesterone (n=50)	**Group receiving placebo (n=50)**	**Statistical analysis P value**
Mean gestational age at delivery (days)±sd	236.82±8.589719	232.7±9.92883	P value 0.0288 Statistically significant
Mean latency (days)±sd	7.02±3.755214	3.08±2.70178	P value <0.001 Statistically very significant
Birth weight (mean±sd)	2.094±0.299258	1.95±0.3312	P value 0.0470 statistically significant
Recurrent bleeding	32	39	P value 0.1861
Blood transfusion required	5	4	
Nicu admission	16	23	P value 0.5681
Neonatal death	9	13	

Table 2

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In our study there is no significant difference between IM progesterone group and placebo group regarding baseline characteristics like maternal age, parity, gestational age at admission, type of placenta previa, Hb % on admission. Study showed that prolongation of pregnancy in progesterone receiving group is statistically significant (p value <0.001), significant difference were also found in gestational age at delivery (p value 0.0288), birth weight (p value 0.0470). Recurrent episode of bleeding was not significant (p value> 0.05) in both groups. There was no significant difference regarding NICU admission and neonatal death in study and control groups.

A. Sharma, V. Suri, I. Gupta conducted study[7] PGIMER, Chandigarh with use of ritordine hydrochloride as tocolytic in symptomatic placenta previa showed significant prolongation of pregnancy (25.33 vs. 14.47 days, P-0.05) and difference in birth weight (2270 g vs.1950 g, P-0.05). There was no observed statistical difference between the two groups with regard to number of episodes of haemorrhage after admission, total amount of blood loss during stay in hospital, number of blood transfusions and maternal complications due to tocolysis in the study group. Metanalysis by[16] Bose DA, Assel BG, Hill JB, Chauhan SP sice 1995to 2009 showed results of the one RCT indicated that pregnancy is prolonged for more than 7 days with continued tocolytics (OR 3.10, 95% CI 1.38 to 6.96) but combined results of two retrospective studies did not confirm the prolongation (OR 1.19, 95% CI 0.63 to 2.28).

Richard E and Besinger et al [17] in 1995 found that tocolytic intervention in cases of symptomatic preterm previa associated with clinically significant prolongation of pregnancy i.e admission to delivery (39.2 vs 26.9 days, p < 0.02) and increased birth weight (2520 vs 2124 gm, p < 0.03). Tocolytic therapy in these cases does not appear to have an impact on frequency or severity of recurrent vaginal bleeding. Saju et al also used tocolytic agents effectively in placenta previa.[18]Towers et al study for evaluating the use of tocolytic agents in preterm patients with third-trimester bleeding showed it is safe and not appear to be any increased morbidity or mortality in a controlled tertiary setting.[19]

CONCLUSION: In this study use of 17α OH progesterone in expectant management of symptomatic placenta previa tends to be beneficial than placebo. But there are limited studies in this field. So the prospective randomized clinical trials with large number of patients are required to further explore the effectiveness of progesterone in the symptomatic placenta previa.

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