Original Article

DOI: 10.17354/ijss/2015/395

Evaluation of the Effect of Progesterone and Placebo in Parturient of Symptomatic Placenta Previa: A Prospective Randomized Control Study

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Abstract

Background: Antepartum hemorrhage and placenta previa effects majority of pregnant women endangering their life both maternal and fetal. Symptomatic placenta previa are being treated with tocolytic agents. Progesterone is the most common used drug for the preservation of pregnancy and aids in the extension of pregnancy.

Materials and Methods: A 80 patients were randomly assigned to two groups using computer-generated randomization. Group A (40 patients) received a placebo twice a week and Group P (40 patients) received injection 17α-hydroxyprogesterone caproate (500 mg, IM). Various complications related to mother and fetus were compared in both the groups.

Result: Significant difference was seen in the elongation of pregnancy, gestational age at the time of delivery and birth weight of the fetus.

Conclusion: In the present study, 17α OH progesterone use in the hopeful management of symptomatic placenta previa inclines to be valuable than placebo, thus reducing the maternal and fetal complications.

Key words: Placebo, Placenta previa, Pregnancy, Progesterone

INTRODUCTION

Antepartum hemorrhage (APH), also called as pre-partum hemorrhage, is genital bleeding in pregnancy from 24th week gestational age to the delivery of the baby. 3-5% of pregnancies worldwide are affected by APH, resulting in perinatal and maternal mortality. APH is found to be usually associated with placenta previa.[1]

The placenta previa is defined as obstetric difficulty in which the placenta is implanted partially or solely in the lower uterine segment. Maternal mortality and perinatal mortality rate of roughly 0.03% and 8.1%, respectively, are found in the developed world. This percentage is more in developing countries like India.[2] Large percentage of women according to literature experience uterine contractility before the beginning of unconcealed vaginal bleeding.[3]

The current study shows that symptomatic placenta previa are being treated with tocolytic agents.[4] The progesterone is necessary for the preservation of pregnancy and aids in the extension of pregnancy. The progesterone, also known as pregn-4-ene-3, 20-dione is an endogenous steroid and involved in the menstrual cycle, pregnancy, and embryogenesis of humans. It is included in a steroid hormones group called as progestogens. The progesterone is also a key metabolic intermediate in the making of other endogenous steroids such as the sex hormones and the corticosteroids. They show a vital part in brain function as a neurosteroid.[5] Reduction of the rate of long-term morbidity requires delayed delivery which facilitates the maturity of vital organs. Though the thorough mechanism of action is not known but proposed mechanisms were:

Access this article online

IJSS

www.ijss-sn.com

Month of Submission : 07-2015
Month of Peer Review : 08-2015
Month of Acceptance : 08-2015
Month of Publishing : 09-2015

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(a) It acts principally through creating uterine inertness and upholds cervical length. It has immunosuppressive activity and stops consequence of oxytocin on myometrium. (b) It is a powerful inhibitor of gap junctions between myometrial cells. (c) Local fluctuations in progesterone or estrogen or progesterone ratio. (d) Suppression of calcium-calmodulin-myosin light chain kinase system, decreasing calcium flux and shifting the resting potential of smooth muscle are the root of progesterone action.[6]

This condition is also linked with decreased fetal birth weight. It should be reflected as a medical emergency, and medical consideration should be pursued immediately, as if it is left untreated it can lead to death of the mother, fetus, or both.[7,8] The aim of the present study is to define the usefulness of intramuscular 17α-hydroxyprogesterone caproate therapy versus placebo in the conventional treatment of patients with symptomatic placenta previa before 34 weeks of gestation. Various parameters like a prolongation of pregnancy and maternal results, i.e. the number of occurrences of bleeding, number of blood transfusion required, birth weight of babies, etc., and were noted to resolve the effect of progesterone.

MATERIALS AND METHODS

After obtaining Institutional Ethical approval 80 pregnant females of maternal age more than 18 years, singleton pregnancy, gestational age of the third trimester were recruited in our Department of Obstetrics and Gynecology with placental previa where placenta on ultrasonographic investigation was located around 5 cm of internal os or symptomatic (minimum one episode of bleeding) placenta previa were enrolled for our study. We excluded the patients with twin pregnancy, premature rupture of membranes, abnormal fetal heart rate (FHR) or severe maternal bleeding advocating early termination of pregnancy, intra-uterine death, abruption placentae, pre-eclampsia, chorioamnionitis, and patients suffering from severe renal or liver or heart disease.

After proper history taking, the examination was performed including the vital parameters were noted. The gestational age of both the groups were correlated both by clinical examination and by using ultrasonography. A skilled gynecologist executed the per-abdominal examination and assessed the parturient's uterine tone, activity, tenderness, fundal height, liquor amount, FHS pattern, and fetal presentation. The type of presentation of placenta was diagnosed using ultrasonography.

The patients were randomly assigned to two groups using computer-generated randomization. Group A (40 patients) received a placebo twice a week, and Group P (40 patients) received Inj. 17α-hydroxy progesterone caproate (500 mg, IM). In the both study groups, the assigned drug or placebo as per study protocol were continued until the delivery of the baby or 37 weeks of gestation.

Both the groups received steroid prophylaxis before being enrolled in the study. The amount of bleeding and the neonatal outcome were observed in both the study groups.

Statistical Analysis

All the parametric data was analyzed using Student's *t*-test and non-parametric data using Chi-square or Fisher test whichever is applicable. Data was analyzed using Statistical Package for Social Sciences version 19.0. A $P < 0.05$ was considered statistically significant.

RESULTS

Regarding baseline features such as maternal age, parity, gestational age at the time of admission, placenta previa type, and Hb% on admission showed no significant difference between IM progesterone group and placebo group (Table 1). However, the significant difference was seen in the elongation of pregnancy in progesterone

Table 1: Comparison of parameters of patients of two groups

Variable	Group A	Group P	*P* value
Age of mother (years) (mean±SD)	25.62±4.29	25.71±4.87	0.92
Parity (mean±SD)	1.19±1.21	1.24±1.22	0.85
Gestational age at admission (days) (mean±SD)	235.5±9.01	236.4±9.27	0.67
Placenta previa type			
Central	9	7	
Partial	8	4	
Marginal	14	17	
Low lying	9	11	0.69
Hb %	10.29±1.95	10.47±1.56	0.64

SD: Standard deviation, Hb: Hemoglobin

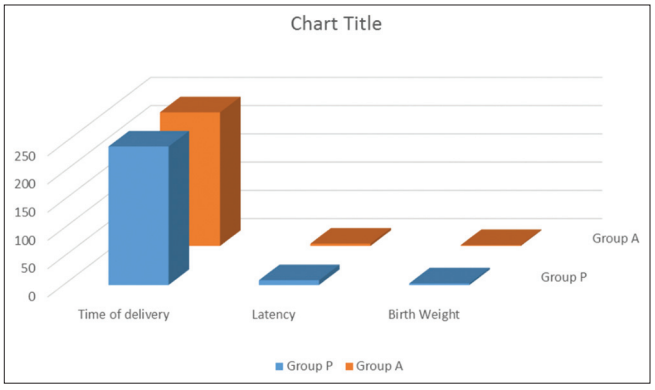

Figure 1: The parameters which showed significant differences in two groups

Table 2: Comparison of results of two groups

Variable	*n*=40		*P* value
	Group P	Group A	
Gestational age at the time of delivery (days) (mean±SD)	245.21±8.27	236.53±9.55	0.001*
Latency (days) (mean±SD)	8.49±3.65	4.01±2.41	0.001*
Birth weight (mean±SD)	2.95±0.93	1.52±0.84	0.001*
Blood transfusion required	6	8	0.77
Recurrent bleeding	31	35	0.38
NICU admission	12	19	0.16
Neonatal deaths	5	11	0.17

NICU: Neonatal intensive-care unit, SD: Standard deviation

accepting group as compared to the placebo group ($P < 0.001$). The gestational age at the time of delivery also showed a significant difference ($P < 0.001$). Maternal outcomes like episodes of bleeding and requirement of blood transfusion also showed no significant difference. Feature like the weight of a baby at the time of delivery showed a significant difference between two groups ($P < 0.001$). There was no substantial difference in NICU admission and neonatal death in control and study groups (Table 2).

DISCUSSION

Some studies[9,10] have recommended that the prophylactic usage of progesterone lessens the rates of preterm birth in pregnancy. Besides these women with a single issue and with a positive history of spontaneous preterm birth, short cervix notified on ultrasound at 19-25 weeks gestation also requires the prophylactic use of progesterone. Both synthetic intramuscular 17α-hydroxyprogesterone (17-OHPC) and natural vaginal micronized preparation have been studied.[11] The FDA permitted progesterone practice in 2011 and the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine mentioned it in their 2012 treatment guidelines.[12] The use of 17-OHPC in patients with placenta previa have been recommended in injectable form and not a vagina. Whereas in women with a short cervix (<20 mm) vaginal progesterone is the desired option. So in this study, IM progesterone was used in the patients.[13]

In our study, we found a significant difference in parameters like a prolongation of pregnancy and difference in birth weight in two groups. Similar findings were observed in 2004 in which use of ritodrine hydrochloride as tocolytic in symptomatic placenta previa exhibited significant elongation of pregnancy (25.33 vs. 14.47 days, $P = 0.05$) and variance in birth weight (2270 g vs. 1950 g, $P = 0.05$). Other parameters such as number of events of hemorrhage following admission, total quantity of blood loss during visit in hospital, blood transfusions numbers, and maternal difficulties showed no difference supporting our outcomes.[14]

Similarly, another metanalysis done by Bose *et al.* from 1995 to 2009 showed that pregnancy is extended for more than 7 days with continued tocolytics (odd ratio 3.10, 95% of confidence interval [CI] 1.38-6.96).[15]

A Cochrane review published in 2013 concise the progesterone effect in women with a past history of preterm birth grounded on 11 RCTs that involved 1899 patients. The progesterone was allied with a decreased risk of preterm birth at <34 weeks (relative risk [RR] 0.31, 95% of CI 0.14-0.69) and perinatal mortality (RR 0.50, 95% of CI 0.33-0.75). Along with this decreased rates of infants, low birth weight <2500 g, neonatal death, necrotizing enterocolitis, and admission to a neonatal intensive care unit was observed.[16]

The preterm birth mechanism in multiple pregnancies is probably related to uterine distension. Some authors have advised that asymptomatic twin pregnancies may need increased doses of progesterone in order to be effective at falling preterm birth in a similar way to singleton pregnancies.[17] So, further research is required to decide the doses of progesterone in different pregnancies.

Recently, protection concerns have been upraised about the issue of use of 17-OHPC. In a study, encompassing women with triplet pregnancies, the group getting weekly injections of 250 mg 17-OHPC experienced 13 mid-trimester fetal fatalities ver. none in the placebo group ($P < 0.02$).[18] In alternative study[19] of twin pregnancies in women with a short cervix, treatment with 17-OHPC was connected with a substantial increase in the rate of preterm birth at <32 weeks (29% vs. 12%; $P = 0.007$).

CONCLUSION

In the present study, 17α OH progesterone use in the hopeful management of symptomatic placenta previa inclines to be valuable than placebo. However, there is inadequate research in this field. So, the prospective randomized clinical trials with a huge number of patients are mandatory to further search the efficiency of progesterone in the symptomatic placenta previa.

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How to cite this article: Singh P, Jain SK. Evaluation of the Effect of Progesterone and Placebo in Parturient of Symptomatic Placenta Previa: A Prospective Randomized Control Study. Int J Sci Stud 2015;3(6):69-72.

Source of Support: Nil, **Conflict of Interest:** None declared.