

Role of Progesterone for the Prevention of Preterm Labour

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ABSTRACT

Objective: To access the benefits of progesterone administration for the prevention of preterm birth in women and their infants.

Study design: Randomized controlled trial

Place & duration of study: The study was conducted in the department of Obstetrics & Gynaecology Unit-I, at Bahawal Victoria Hospital, Bahawalpur from 01-11-2011 to 31-12-2011.

Material & methods: We conducted a double-blind, placebo-controlled trial. A total of 60 women with the history of previous spontaneous preterm birth were included in the study. Women were enrolled at Antenatal outdoor department of Bahawal Victoria Hospital, Bahawalpur at 16 to 20 weeks of gestation and randomly assigned to receive either weekly injections of 250mg of 17P(progesterone) or weekly injections of an inert oil placebo; injections were continued until delivery or to 36 weeks of gestation. The primary outcome was preterm delivery before 37 weeks of gestation & fetal outcome.

Results: Base-line characteristics of the women in the progesterone group and the placebo group were similar. Treatment with 17 Progesterone significantly reduced the risk of delivery at less than 37 weeks of gestation with incidence 11(36.6%) in the progesterone group vs. 83.3 % (25 patients) in the placebo group. Infants of women treated with progesterone also had improved outcome as compare to the placebo group but the difference was not statistically significant.

Conclusion: For women with a history of spontaneous preterm birth, progesterone was associated with a significant reduction in preterm birth before 37 weeks& improve fetal outcome.

Key words: Progesterone, preterm delivery, fetal outcome

INTRODUCTION

Preterm delivery — that is, delivery before 37 completed weeks of gestation — is the major determinant of infant mortality in developing countries¹. It is very common in Pakistan and is the factor most responsible for the relatively high infant mortality in our country. The rate of preterm delivery has increased progressively from 9 percent to 12 percent over the past two decades².

A number of factors have been identified that are linked to a higher risk of a preterm birth: age at the upper and lower end of the reproductive years (<18 & >35 years), reduced pregnancy interval, malnutrition, low BMI, multiple pregnancies, infections, previous history of second trimester miscarriages & previous preterm deliveries. Women with the past history of preterm births are at higher risk for a recurrence at a rate of 15–80% depending on number of previous events and their timing³.

Despite many trials of reduced uterine activity, tocolytic therapy, antibiotic therapy, and other strategies for prevention, no effective and reproducible method of preventing preterm delivery has been demonstrated⁴. Almost 50 years ago,

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Csapoet al⁵ promoted the progesterone that high progesterone levels prevent uterine contractions and low levels facilitate such contractions. This is one reason for the use of progesterone therapy in early pregnancy and the use of RU486, a progesterone antagonist, to induce abortions. Recently several studies on the use of progesterone to prevent preterm labour have been published, not all trials reported positive results^{6,7}. The suggested actions of progesterone on the pregnant myometrium include relaxation of myometrial smooth muscle, blocking of the action of oxytocin, and inhibition of the formation of gap junctions. There is evidence that local changes in the progesterone level or the ratio of progesterone to estrogen in the placenta, decidua, or fetal membranes may be important in the initiation of labor in humans. In addition, administration of progesterone antagonists in women at term results in an increased rate of spontaneous labor.

As the women who have had a preterm delivery are at especially high risk for preterm delivery in a subsequent pregnancy, we therefore conducted study to test the effectiveness of 17P as compared with placebo in the prevention of recurrent preterm delivery in this group of women. The purpose of this paper is to evaluate the information in these studies and outline the current role for the use of progesterone for this indication.

MATERIAL & METHODS

We conducted a double-blind, placebo-controlled study including pregnant women with a documented history of previous spontaneous preterm delivery. The duration of study was one year from January 2011 to December 2011.

Medical records of 60 women presenting for prenatal care at the antenatal outdoor department of Bahawal Victoria hospital were screened for eligibility to participate in the study, criteria for eligibility included a history of previous spontaneous preterm delivery and a current pregnancy between 16 weeks and 20 weeks of gestation. Reasons for exclusion were multifetal gestation, known fetal anomaly, current or planned cervical cerclage. An ultrasonographic examination was required between 14 weeks and 20 of gestation to confirm the duration of gestation and to identify any major fetal anomalies. The duration of gestation at the time of randomization was determined on the basis of the last menstrual period and the results of ultrasonography.

A total of 60 Women were enrolled at Antenatal out door department of Bahawal Victoria hospital Bahawalpur at 16 to 20 weeks of gestation.

A proforma was used to collect data from patients after taking verbal consent, patients were fully informed about the side effects of drug. Patients were divided into two groups A and B keeping in mind their age, parity and gestational age so as to make two comparable groups.

They were randomly assigned to receive either weekly injections of 250 mg of 17P or weekly injections of an inert oil placebo, injections were continued until delivery or to 36 weeks of gestation, whichever was earlier. The primary outcome was preterm delivery before 37 weeks of gestation.

The collected data was entered in SPSS version 10 for analysis. Frequencies were determined. Tables were formed, percentages were calculated to know the statistical significance between two groups. Chi square test was applied to compare the outcome.

RESULTS

Base-line characteristics of the women in the progesterone group and in the placebo group were similar. The age of women were between 24 & 35 years between the two groups & the median was 29 in group A & 28 in group B. The range of BMI was between 20 & 35 & the median was 22 in group A & 23 in group B. 20 women in group A & 19 in group B had history of one preterm delivery. The history of 2 or more than 2 preterm deliveries was positive in 10 patients in group A & 11 in group B. The mean period of gestational age at the start of study was 17 weeks in group A & 16.5 in group B & It varies between 16-

20weeks. The main outcome of the study was occurrence of preterm labour. The incidence of preterm labour was found to be 11(36.6%) in progesterone (Group A) & 25(83.3%) in placebo group B. Delivery at less than 35 weeks of gestation, the incidence was 6(20%) in group A & 9(30%) in group B and delivery at less than 32 weeks of gestation 4(13.33%) versus 7(23.33%) respectively. The second outcome was fetal outcome. Two perinatal deaths occurred in group A & five in group B & 22% newborn in progesterone group & 30% in placebo group needed admission in intensive neonatal care.

Table -1: Characteristics of study participants

Characteristics	Group-A	Group-B
Median age	29	28
Age range	24-34	24-35
BMI median	22	23
BMI range	20-35	20-35
One preterm delivery	20	10
More than 2 preterm deliveries	10	11
Mean period of gestation at randomization	17	16.5
Range of period of gestation at randomization	16-20 weeks	16-20 weeks

Table-2: Maternal & fetal outcome

Maternal outcome	Group-A	Group-B	P value
Delivery at<37 weeks	11 (36.7%)	25(83.3%)	<0.001
Fetal outcome			
Perinatal death	2 (6.7%)	5 (16.7%)	0.228
Birth weight <2500	5 (16.7%)	6 (20%)	0.739
Need for intensive neonatal care	7 (23.3%)	9 (30%)	0.559

DISCUSSION

Prematurity is the leading cause of neonatal death and handicap⁸. Although all births before 37 weeks of gestation are defined as preterm, most damage and deaths occurs in infants delivered before 34 weeks⁹. Improvements in neonatal care have led to higher rates of survival among very premature infants, but a major effect on the associated mortality and morbidity will be achieved only by better identification of women at high risk for preterm delivery and by development of an effective intervention to prevent this complication.

A study showed the results comparable with our data, the treatment with 17Progesterone on a weekly basis, beginning at 16 to 20 weeks of gestation and continued to delivery or 36 weeks of gestation, significantly reduced the rate of preterm delivery before 37 weeks, 35 weeks, and 32 weeks of gestation among women at high risk for preterm

delivery^{10,11}. The rates of several complications of prematurity were correspondingly decreased among the infants of women assigned to this therapy.

The women enrolled in this study had high rates of preterm delivery, 83.3% of the women who received the placebo injections delivering before 37 weeks of gestation. This high rate of preterm delivery is most likely related to the history of previous preterm deliveries. The earlier in a pregnancy a preterm delivery occurs, the greater the chance of preterm delivery in a subsequent pregnancy¹² and one third of the women enrolled had more than one previous preterm delivery. Therefore, the women in this study had particularly high risk. They were also strongly motivated, and compliance was excellent.

Preterm delivery has multiple causes. Some evidence suggests that the causes of early preterm delivery differ from those of later preterm delivery, with earlier preterm deliveries more often being related to infection. Whereas 17P would not be expected to affect an infectious process, in this study, it provided potent protection against early as well as later preterm delivery. The mechanisms of action of 17P in prolonging gestation are not entirely known. We chose to use 17P because of reports of its effectiveness in some previous trials^{10,11}. Recently several studies on the use of progesterone to prevent preterm labour have been published. In contrast to our results one meta-analysis found no evidence of effectiveness of progestational compounds in the prevention of preterm delivery or the prevention of recurrent miscarriage¹². Another meta-analysis, restricted to trials of 17 alpha-hydroxyprogesterone caproate (17PA), a natural metabolite of progesterone, showed, a significant reduction in the rate of preterm delivery¹³. We therefore chose this pharmacologic agent as the active drug for our study.

However, a recently reported trial in which progesterone suppositories were used suggested that this route of administration may be a reliable alternative. The risk of preterm delivery was lower among participants in that study than among the women in our study. The entry criteria included a history of delivery before 37 weeks of gestation. The women in the placebo group in that trial had a rate of preterm delivery of 53.3% as compared with 36.3% in the progesterone group. These results lend support to the concept of prophylactic use of progesterone to prevent preterm delivery.

Treatment with 17P also resulted in improved neonatal outcomes. It was found that 17P appeared to

be safe, there was no increase in the rate of congenital anomalies in the progesterone group.

CONCLUSIONS

For women with a history of spontaneous preterm birth, progesterone was associated with a significant reduction in preterm birth before 37 weeks & improve fetal outcome.

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