Original Article

Efficacy of 17 Alpha Hydroxy Progesterone in Prevention of Preterm Labour in High Risk Patients

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Abstract

Objective: To determine the efficacy of 17 α OH progesterone in prevention of preterm labour in high risk patients.

Study Design: Randomized control trial.

Place and Duration of Study: Department of Obstetric and gynecology, Fatima Memorial Hospital, Lahore during January 2008 to December 2010.

Patients and Methods: Two hundreds women fulfilling inclusion criteria were recruited in study and were divided into two groups (treated and non-treated). The 17 α OH progesterone injections were started from 20 weeks and on ward on weekly basis until 36 weeks of gestation or delivery whichever occurred first. The primary end point was preterm birth, defined as birth occurring before 37 weeks of gestation. Other outcomes were frequency of episodes of uterine contractions, episodes of preterm labour and response to treatment with beta – mimetics.

Results: The treatment with 17 α OH progesterone helped to prolong pregnancy to full term in 66% as compared to those non treated 11%. There was 4.17 (2.65 – 6.60) time higher RR in non-treated group as compared to treated group for preterm delivery between 35 – 37 weeks. Similarly the RR was 4.94 (2.61-8.58) and 6.33 (2.95 – 13.60) in non-treated group as compare to treated group of preterm deliveries between 32 – 35 weeks and < 32 weeks respectively.

Conclusion: Women with previous preterm births when treated with 17 α OH progesterone showed significant reduction in spontaneous early preterm delivery.

Keywords: 17 α OH progesterone, preterm delivery, previous preterm deliveries.

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Introduction

Preterm delivery is defined as delivery before 37 completed weeks of gestation and is the major determinant of infant mortality and morbidity in both developed and developing countries.[1] The rate of preterm delivery in the United States has increased progressively from 9% to 12% over the past two decades.[2] Similarly in Canada the prevalence has increased from 6.3% of live births in 1981 – 83 to 6.6% in 1991 and 7.6% in 2000,[3,4] although a large proportion of this increase in due to multiple pregnancies. Despite many trials of

reduced activity, tocolytic therapy, antibiotic therapy and other strategies for prevention, no effective and reproducible method of preventing preterm delivery has been achieved.[4]

Hence various studies have been done to determine the risk factors involved in preterm delivery and the results have been analyzed.[5] Preterm delivery is more common among blacks, poor, single, under weight, cigarette smoker, women with multiple pregnancies and with uterine anomalies. Another important factor is history of previous preterm deliveries. Population data suggests that women who have had a pervious preterm birth are more likely to give preterm birth in a subsequent pregnancy with up to a third of women giving birth prior to 37 weeks.[5-7] Some authors estimated the rate of recurrent preterm birth to be 22.5%, which represents a two and a half fold increase in risk of preterm birth, when compared to those have not had a previous spontaneous preterm birth.[8]

It is well documented that preterm delivery is a major determinant of neonatal morbidity and mortality, and also on the gestational age of preterm delivery. The prevalence of poor neonatal outcome is 77%, 35% and 12% when delivered preterm between 24 – 27, 28 – 32 and 32 – 34 weeks respectively.[9] Factors responsible for poor outcome include respiratory distress syndrome (RDS), branchopulmonary dysplasia, intraventricular haemorrhage (IVH), periventricular leucomalacia, necrotizing enterocolitis and sepsis. There are very few interventions that improve the outcome of preterm labour like the use of antenatal corticosteroids to prevent RDS, IVH, periventricular leucomalacia.[10] Most studies on tocolysis with the exception of one recent paper on nitroglycerin, had very limited clinical use,[11] whereas other trials using reduced activity, antibiotic therapy showed no effectiveness. Physiological measures (the monitoring of uterine contractions), anatomical measures (the ultrasonographic measurement of cervical length), and biochemical measures (the assessment of fetal fibronectin in cervicovaginal secretions) are also poorly predictive of the risk of preterm delivery.

About 50 years ago Csapo et al[12] promoted his see – saw theory on progesterone. According to his theory high progesterone levels prevent uterine contractions and low levels facilitate such contractions. 17 α OH progesterone is a natural metabolite of progesterone and has been widely used in attempt to prevent threatened miscarriage, recurrent miscarriage and taking advantage of Csapo et al theory, now has bee used in prevention of preterm labour. Though exact action of 17 α OH progesterone therapy in preventing preterm labour and delivery is debatable.[13-15] Meis et al reported a significant reduction in the rate of recurrent preterm birth in high-risk group of women randomly assigned to receiving 17 – hydroxyprogesterone caproate compared with the placebo group. In response to these recent reports, the American College of Obstetricians and Gynecologists issued a Committee Opinion in support of the use of 17 – hydroxyprogesterone caproate. After the release of the committee opinion statement, many obstetricians now prescribe 17 – hydroxyprogesteronecaproate for prevention of preterm delivery.

Women who have had previous preterm delivery are especially at risk of having preterm delivery in a subsequent pregnancy. The goal of our research is to determine the effectiveness of 17 α OH progesterone in prevention of preterm birth in such patients and to reduce the likelihood of several complications in infants in our setup.

Material and Methods

Two hundreds women fulfilling inclusion criteria were recruited in study and were divided into two groups (treated and non-treated). Inclusion criteria for eligibility was women with singleton pregnancy and with a history of spontaneous preterm delivery in previous pregnancies. Exclusion criteria included multifetal gestation, fetal anomalies, current or planned cervical cerclage, any medical disorder requiring early delivery or a plan to deliver else. Where as the duration of gestation at the time of randomization was determined on basis of last menstrual period and dating scan. Ultrasonography was also used to detect and rule out any major fetal anomaly.

After entering the study, 1:1 ratio was used for this assignment of women to treated or non treated group. The injections were started from 20 weeks and on ward on weekly basis until 36 weeks of gestation or delivery whichever occurred first. If the patient went in preterm labour she was managed in accordance to standard protocol that might necessitate admission, tocolysis with beta mimetics and steroids. In the treated group injections were continued on weekly basis until 36 weeks or till delivery.

The primary end point was preterm birth, defined as birth occurring before 37 weeks of gestation. Other outcomes were frequency of episodes of uterine con-

tractions, episodes of preterm labour and response to treatment with beta – mimetics.

Results

Age distribution of the patients in our study showed 45% (1 = 45) between 22 – 25 years, 33% (n = 33) were between 26 – 30 years, while only 22% (n = 22) were found between 31 – 35 years, mean age was found to 27.42 ± 3.84.

We recorded the history of previously preterm deliveries in Table 2, where majority were with previous one preterm delivery is 43%, whereas 28% had previous two preterm deliveries, and 16% had previous three preterm deliveries. There were 13 women with short cervical length.

The overall preterm birth rate in our study population was 61.5%. The treatment with 17 α OH progesterone helped to prolong pregnancy to full term in 66% as compared to those untreated, 11% with a p-value < 0.001.

There was 4.17 (2.65 – 6.60) time higher RR in non treated group as compare to treated group for preterm delivery between 35 – 37 weeks. Similarly the RR was 4.94 (2.61 – 8.58) and 6.33 (2.95 – 13.60) in non treated group as compare to treatment group of preterm deliveries between 32 – 35 weeks and < 32 weeks respectively. Significant difference was seen in terms of admission with preterm labour in both groups 69% versus 32% (treated and non-treated group) and when beta – mimetics were used to treat preterm labour it was found that delivery was delayed beyond 72 hours in treated group as compared to non treated 85% versus 36%.

Table 1: Age Distribution.

Age (In Years)	Treated (n = 100)		Non-treated (n = 100)	
	No. of Patients	%	No. of Patients	%
22 – 25	45	45	38	38
26 – 31	33	33	42	42
31 – 35	22	22	20	20
Total	100	100	100	100
Mean and S.D.	27.42 ± 3.84		28.03 ± 3.79	

Table 2: Selection criteria of patients.

Treated (n = 100)		Non-treated (n = 100)	
No. of Patients	%	No. of Patients	%
43	43	39	39
28	28	34	34
16	16	21	21
100	100	100	100
		P- value = 0.554	

Table 3: Prolongation of pregnancy beyond 37 weeks.

Prolongation of Pregnancy beyond 37 weeks	Treated (n = 100)		Non-treated (n = 100)	
	No. of Patients	%	No. of Patients	%
Yes	66	66	11	11
No	34	34	89	89
Total	100	100	100	100

Chi-square = 63.88 P-value < 0.001

Discussion

Treatment with 17 α OH progesterone on a

Table 4: Gestational age at the time of pre-term delivery.

	Non-treated		Treated	
	35 – 37 Weeks	32 – 35 Weeks	< 32 Weeks	> 37 Weeks
Non-treated	49	23	17	11
Treated	16	11	7	66

R.R	4.19	95% C.I.	1.74 – 10.08	2.65 – 6.60	2.65 – 8.58	2.95 – 13.60

weekly basis, beginning at 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.

Numerous studies have been conducted on 17 α OH progesterone showing its effectiveness in previous studies.[7,13-19] The entry criteria for our study included a history of delivery before 37 weeks of gestation. The women in the placebo group in our trial had a rate prolongation of pregnancy by 11 percent as compared with 66 percent in the progesterone group. These results lend support to the concept of prophylactic use of progesterone to prevent preterm delivery.

When comparing the results with other international studies, similar results were found. In 2008 Dodd et al[16] concluded that women who received 17 α OH progesterone were statistically significantly less likely to deliver before 37 weeks. Whereas the trial done by Dodd et al in 2008 also studied the neonatal outcome, our study has been solely focused on the efficacy of 17 α OH progesterone.

Similar results were seen by meta analyses done by Sanchez Ramos et al,[17] Mackenzie et al[18] also found reduction in preterm deliveries by 43% when17 α OH progesterone were used in high risk women in second trimester. All these meta analyses agree on prophylactic use of when17 α OH progesterone early in gestation but not earlier than 20 weeks, which has also recently been recommended by various randomized control trials.

Fonseca et al[19] included patients with shortened cervical length and administered progesterone (200 mg / day) in patients with cervical length < 1.5 cm at 22-26 wks and found RR for preterm labour of 0.56 (0.36 – 0.86). Similar study has been done by Rosue et al[20] and the results showed a RR of 1.1 (0.9 – 1.5%); Rosue et al however included twin pregnancy in his study and control groups.

Our study correlates more to the one conducted in Meis et al in 2003, where in the inclusion criteria remained previous preterm labour like our study. Four hundred and sixty three patients were included in the study and they were given 250 mg 17 OH progesterone weekly from 16 to 20 weeks to 36 weeks like our study. The results were similar in favour for use of progesterone early in gestation to prevent preterm delivery.

Based on our study results as well as other meta-analysis, we have come up with recommendations in managing women at high risk of preterm labour, which are listed as below:

Recommendations

1. Women at risk of preterm labour, should be encouraged to participate in studies after explaining the role of progesterone in preterm labour especially in our countries where neonatal facilities are not available in basic health units.
2. No adverse fetal effects are seen when used for prolonged duration. No adverse maternal effects are seen in all studies except one study where the prevalence of gestational diabetes was 12.9% when treated with 17 α OH progesterone as compared to control 4.9%.[21]
3. Women should be informed that more research is needed on formulation (17 α OH progesterone vs. progesterone), route (I/m vs. vaginal) and optimal dosage for progesterone use.
4. Further data is required to see its effectiveness in terms of reducing respiratory distress syndrome, necrotizing enterocolitis, patent ductus arteriosus, sepsis and perinatal death.

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