

PREVENTION OF RECURRENT PRETERM DELIVERY BY 17 ALPHA HYDROXYL PROGESTERONE CAPROATE

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ABSTRACT

Introduction: Preterm delivery occurs before 37 completed weeks of gestation and it is the major determinant of infant mortality in developed countries. Preterm delivery is the factor most responsible for the relatively high infant mortality in our country. 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 demonstrated. One treatment that showed promise in small trials was prophylactic treatment with pro-gestational compounds. The purpose of this work is to determine the effectiveness of 17 alpha hydroxyl progesterone in prevention of preterm delivery in women who had a previous preterm birth. It was a descriptive case study and was conducted in the department of Obstetrics and Gynaecology Fatima Memorial Hospital, Lahore for a period of twelve months from January 2011 to December 2011. A total of 135 cases were received by non-probability purposive sampling technique.

Results: In this study majority of the patients i.e. 46.67% (n = 63) were between 26 – 30 years, 24.44% (n = 33) were found between 22 – 25 years, whereas 28.89% (n = 39) were found between 31 – 35 years, mean age was found to be 28.24 + 3.83. Most of the patients i.e. 69.62% (n = 94) were found between 21 – 24 weeks and 30.37% (n = 41) were found between 16 – 20 weeks. Data regarding number of previous preterm deliveries showed that majority of the patients i.e. 39.25% (n = 53) were found only 1 previous preterm delivery, 27.49% (n = 29) with 3 and > 3 previous preterm births were found only in 11.86% (n = 16). Prolongation of pregnancy beyond 36 weeks of gestation is described where 68.15% (n = 92) are shown to be delivered beyond 36 weeks and only 31.85% (n = 43) could not deliver beyond 36 weeks of gestation.

INTRODUCTION

Preterm birth is delivery before 37 weeks of gestation. It occurs in 1 of 8 pregnancies.¹ Preterm labour and delivery are major causes of perinatal mortality and morbidity especially in developing countries and a significant proportion of survivors i.e. 10 – 15% have residual disabilities.² A meta analysis shows the overall perinatal mortality in preterm group was 368 / 1000 which fell with advancing gestational age from being 66% at 28 – 31 weeks and 38% at 32 – 33 weeks to 20% at 34 – 36 weeks.³ Despite many trial of reduced activity, tocolytic therapy, antibiotic therapy and other strategies for prevention, no effective and reducible method of preventing preterm delivery has been demonstrated. Progesterone has been widely used in an attempt to prevent threatened miscarriage, recurrent miscarriage and preterm labour.⁴ A meta analysis⁵ found 17 alpha hydroxy progesterone caproate, a natural metabolite of progesterone showed, in composite, a significant reduction in rate of preterm delivery. Randomised controlled trial showed significantly reduced risk of preterm delivery at gestational age less than 37 weeks in a group treated with 17 – OHP caproate then with placebo, i.e. 42% versus 63% respectively.¹ Extensive experience

with progesterone has shown it not to be teratogen.⁶ In Meis trial 17 – OHP – is associated with less desirable side effect prolife than natural progesterone, and statistically non-significant increase in miscarriages (0.9%) still birth (0.5%) with its use.⁷ The actions of progesterone on pregnant myometrium include relaxation of myometrial smooth muscle, blocking of the action of oxytocin and inhibition of the formation of gap junction.¹ Treatment with progesterone is emerging as standard of care for prevention of preterm delivery in woman who previously had such a history. Treatment with 7 α – OHP is also cost effective as estimated (in a medical center Cleveland, OH USA) decline of USD 3800 per women and expected lifetime medical cost of treated infants are estimated to decline by USD 15,900.⁸ Women who had a previous preterm delivery are especially at high risk for preterm delivery in a subsequent pregnancy. In a developing country like ours there is dire need to find out the treatment to control recurrent preterm births, thus prolong the pregnancy and reduce perinatal morbidity and mortality associated with it and reduce the cost of neonatal intensive care required in such children. The aim of the study was to evaluate the use of 17 α – OH progesterone in

prevention of preterm delivery in a woman who had a previous preterm birth.

MATERIAL AND METHODS

Settings

This study was conducted at the Department of Obstetrics and Gynaecology, Fatima Memorial Hospital, Lahore for a duration of 12 months from Jan – Dec, 2011 and 135 patients were included in the study. It was a descriptive study.

Sample Selection

Inclusion Criteria

- Age 22 – 35 years.
- Singleton pregnancy of any parity (on ultrasound).
- History of preterm birth in previous pregnancy (determined by history or medical record if available).
- Current pregnancy 16 to 24 weeks of gestation by dating scan.

Exclusion Criteria

- Multiple pregnancy (on ultrasound).
- Fetal or uterine structural abnormality (on ultrasound).
- PROM (clinical assessment).
- Contra-indication to tocolysis i.e. distress, chorioamnionitis, pre-eclampsia (clinically assessed).
- Diagnosed cases of maternal disease including diabetes, hypertension, cancer or liver disease requiring medical treatment.

Data Collection Procedure

A total of 135 cases having a previous history of preterm labour, fulfilling the inclusion criteria were identified from OPD. They were informed, consent was taken for administration of injection and using their data in research, confidentiality of identity was ensured. The demographic information such as name, age and address were recorded. Group was offered intramuscular injection of 17α – OHP 250 mg till 36 weeks or delivery. Patient was categorised as non-complied if there is more than 10 days gap between the two injections. In addition to weekly visit for study injection women received routine perinatal care with their obstetrician i.e. 3 – 4 weeks in first and second trimester and every 2 weeks from 28 weeks to 36 weeks and weekly thereafter. If patients go into preterm delivery, she was managed by her obstetrician according to standard protocols that might necessitate admission and even tocolysis. In these cases, the administration of injections continued on weekly basis till 36 weeks of gestation or delivery which ever occur first.

Pregnancy outcome measure was included the prolongation of pregnancy beyond 36 weeks (yes or

no) were recorded. All this information was recorded in a pre-designed proforma. Effect modifiers like number of previous preterm deliveries and gestational age at start of treatment was studied through stratification.

RESULTS

A total of 135 patients fulfilling inclusion / exclusion criteria were studied to determine the effectiveness of 17α – OH progesterone in prevention of preterm delivery who had a previous preterm birth. The data was collected by specially designed proforma and then analysed through SPSS version 10.

While studying the distribution of cases by age it was found that majority of the patients i.e. 46.67% (n = 63) were between 26 – 30 years, 24.44% (n = 33) were found between 22 – 25 years while 28.89% (n = 39) were found between 31 – 35 years, mean age was found to 28.24 ± 3.83 (Table 1).

Gestational age at the start of treatment was calculated and presented in Table 2, most of the patients i.e. 69.62% (n = 94) were found between

Table 1: Age Distribution in n = 135.

Age in Years	No. of Patients (n)	%
21 – 25	11	7.33
26 – 30	97	64.67
31 – 35	42	28
Total	150	100
Mean and S.D	29.03 ± 7.96	

Table 2: Gestational age at the start of treatment.

Gestational Age (in Weeks)	No. of Patients	%
16 – 20	41	30.37
21 – 24	94	69.62
Total	135	100

Table 3: No. of previous pre-term deliveries.

No. of Previous Preterm Deliveries	No. of Patients	%
1	53	39.25
2	37	27.40
3	29	21.49
> 3	16	11.86
Total	135	100

21 – 24 weeks and 30.37% (n = 41) were found between 16 – 20 weeks.

Data regarding number of previous preterm deliveries showed that majority of the patients 39.25% (n = 53) had only 1 previous pre-term delivery, 27.40% (n = 37) with 2, 21.49% (n = 29) with 3 and > 3 previous pre-term births were found only in 11.86% Table 3.

In Table 4, prolongation of pregnancy beyond 36 weeks of gestation is described where 68.15% (n = 92) are shown to be delivered beyond 36 weeks and only 31.85% (n = 43) could not deliver beyond 36 weeks of gestation.

Table 4: Prolongation of pregnancy beyond 36 weeks.

Prolongation	No. of Patients	%
Yes	92	68.15
No	43	31.85
Total	135	31.85

DISCUSSION

Preterm delivery is defined as a delivery before 37 completed weeks of gestation and is a major determinant of infant mortality in developed countries.⁹ Preterm birth occurs in 7 – 12% of all deliveries and accounts for over 85% of perinatal mortality and morbidity. Although all births before 37 weeks of gestation are defined as preterm, most damage and death occurs in infants before 34 weeks. Survival rates are increased with improvement in neonatal care but high costs required for managing preterm infants remain a big economic burden, which is very difficult for the population of our country, where majority of the people cannot even meet their basic needs. In this situation pre-natal care of the patients and a burden of infant care especially premature is very difficult and many people cannot afford it and it results in neonatal mortality as well.

Despite many trials of reduced physical activity, tocolytic therapy, antibiotic therapy and other strategies for prevention and no effective and reproducible method of preventing preterm delivery has been demonstrated.¹⁰

Pro-gestational agents may prevent preterm labour. Progesterone has many cellular functions which maintain pregnancy. 17 – Hydroxy progesterone suppresses myometrial activity but the exact mechanism remains unclear. Its withdrawal is a pre-requisite for onset of labour. Prophylactic treatment with pro-gestational compounds showed promise in small trials¹¹⁻¹⁴ but not all trials showed positive results.^{15,16} One meta – analysis found no evidence of effectiveness of pro-gestational compounds in the prevention

of preterm delivery or the prevention of recurrent miscarriage.^{17,18} Another meta – analysis, restricted to trials of 17 alpha – hydroxyl progesterone (17P), a natural metabolite of progesterone, showed, in composite, a significant reduction in the rate of preterm delivery.^{18,19} We therefore choose this pharmacological agent as the active drug for our study.

The results of this study demonstrate that treatment with hydroxyl progesterone on a weekly basis beginning at 16 – 24 weeks of gestation and continued till delivery or 36 weeks of gestation, significantly reduced the rate of preterm delivery before 36 weeks of gestation among women at high risk for preterm delivery. Hence the consequences of prematurity can be decreased among infants of women receiving progesterone therapy.

Women assigned to progesterone therapy in our trial had history of previous preterm delivery but after treatment the mean gestational age of delivery was 36 weeks. Similar evidence is seen in various other studies where progesterone therapy was used in women with previous history of preterm labour, women with short cervix and women with twin pregnancy to prolong pregnancy and reduce the risk of prematurity in infants.^{15,16}

Preterm delivery has multiple causes, the causes of early preterm delivery differ from those of later preterm delivery, early preterm deliveries are more often related to infections. Hydroxyl progesterone caproate is unlikely to affect an infectious process but in our study it provided protection against preterm delivery in women with history of preterm labour. The mechanisms of action of progesterone in prolonging gestation is not known. However recommended actions of progesterone include relaxation of myometrial smooth muscle, blocking action of oxytocin and inhibition of formation of gap junctions.^{20,21}

The limitations of this descriptive case series is that we did not create a control group for more comprehensive comparison determine the difference in reduction of premature infants. However some other studies compared and found that there was significant reduction in neonatal mortality in progesterone group with only one neonatal death due to respiratory distress syndrome and only one still birth due to chorioamnionitis as compared with control group (P < 0.005). A total of 94% were born alive in progesterone group showing a good perinatal outcome. The mean birth was 2.6 kg in progesterone group as compared with 2.2 kg in control group.

Similar results are observed in other studies. There was a significant reduction in NICU admission, requirement of supplemental oxygen therapy and ventilatory support (P > 0.05) in progesterone group. No congenital anomaly was found in babies born to mothers receiving progesterone therapy.²²

The results are consistent with surveys of the literature that have shown no teratogenic effects from the use of Hydroxy progesterone in pregnancy. Progesterone therapy is associated with significant reduction in risk of preterm birth less than 36 weeks, infant birth weight of less than 2500 grams and reduction in neonatal morbidity (RDS, sepsis, NICU admission) and neonatal mortality as is also seen in many studies.

It is **concluded** that weekly injections of $17 \pm -$ OHP resulted in a substantial reduction in the rate of recurrent preterm delivery among women who were at particularly high risk for preterm delivery and reduced the likelihood of several complications in their infants.

ACKNOWLEDGEMENT

The authors are thankful to the administration of FMH College of Medicine and Dentistry, Lahore to support this study.

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