Vol. 15, No. 4
ORIGINAL PAPER

GYNAECOLOGY

MEDICAL CHANNEL
OCTOBER - DECEMBER 2009

PROGESTERONE THERAPY FOR PREVENTION OF PRETERM LABOUR

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ABSTRACT

OBJECTIVE: *To assess the effectiveness of 17 hydroxy progesterone in prevention of preterm labour in women with history of previous preterm labour and with threatened preterm labour in this pregnancy.*
DESIGN: *case control clinical trial.*
PLACE AND DURATION: *Private obstetric clinics, Lyari General Hospital and Hamdard University Hospital January 2006 till August 2009.*
PATIENTS AND METHODS: *The Study was done on women with singleton live pregnancy with history of previous preterm delivery or with threatened preterm labour in this pregnancy. 5o patients were selected and given weekly injection of hydro xy progesterone starting from 14-20 weeks of pregnancy and continued for 36weeks or till delivery. This group was compared with a control group of 36 patients having similar history but not receiving any treatment. Pregnancy outcomes were recorded on a proforma.*
RESULTS: *86 women were enrolled in the study 50 women in progesterone group and 36 in control group. The women in two groups were similar in term of age and parity. Mean gestational age at delivery was 36.4 in progesterone group and 34.3 in control group P = 0.004. Live birth rate was 94% in progesterone group as compared to 77.8% in control group. Perinatal mortality was significantly low in progesterone group P < 0.05. mean birth weight of babies was 2.66kg in progesterone group and 2.21kg in control goup with significant reduction in NICU admission in Progesterone group. P < 0.05. patient compliance and treatment acceptability was good with progesterone depot injections.*
CONCLUSION: *Preterm birth is a major complication of pregnancy associated with perinatal mortality and morbidity. Progesterone therapy can be advocated for prevention of preterm labour in high risk group. There are no proven teratogenic effects on baby and patient compliance in terms of fianancial and treatment acceptability is good.*

KEY WORDS: Progesterone Preterm Labour.

INTRODUCTION:

Preterm delivery that is delivery before 37 completed weeks of gestation is a major complication of pregnancy associated with perinatal mortality and morbidity. Preterm birth occurs in 7-12% of all deliveries but accounts for over 85% of perinatal morbidity and mortality[1, 2]. Although all births before 37 weeks of gestation are defined as preterm, most damage and death occurs in infants delivered before 34 weeks[3]. Survival rates are increased with improvement in neonatal care but high costs required for managing preterm infants remain a big economic burden. The consequences of prematurity have led to attempts to improve outcome by predicting, preventing and treating preterm labour. Despite many trials of reduced physical activity,tocolytic therapy, antibiotic therapy and other strategies for prevention, no effective and reproducible method of preventing preterm delivery has been demonstrated [4].

Progestational agents may prevent preterm labour. Progesterone has many cellular functions which maintain pregnancy, withdrawal is a pre-requisite of labour. 17 hydroxy progestone suppresses myometrial activity, the mechanism by which it does, remain unclear.A study on mouse model suggested that progestational agents can inhibit the rate of lipopoly saccharide inflammation induced preterm birth[5] ,The maternal fetal medicine unit networks conducted a rando mized controlled trial that evaluated the ability of 17 alpha hydroxy progesterone caproate to decrease preterm bith in high risk women [6,7]. Progesterone was administered in the second trimester before signs and symptoms of preterm labour. The

trial demonstrated a significant reduction in preterm birth rate. Based on several other trials the use of 17 alpha hydroxy progesterone for patients with previous preterm birth is advocated by American college of obstetrics and gynaecology[8].Recent surveys suggests that progesterone therapy is used for clinical situations for which it has not been studied like shortened cervix, early second trimester loss and active preterm labour [9,10].

This study was conducted in order to assess the effectiveness of 17 hydroxy progesterone in prevention of preterm labour in women with history of previous preterm labour and with threatened preterm labour in this pregnancy.

PATIENTS AND METHODS:-

The sudy was conducted at private obstetric clinics of Mamji Hospital and Imam Clinic and at Lyari General Hospital and Hamdard University Hospital from january 2006 august 2009. women coming for antenatal care and booking with singleton live pregnancy between 14 weeks and 20 weeks with a history of spontaneous preterm delivery in a previous pregnancy or signs and symptoms of threatened preterm labour in this pregnancy were included in the study. Patients with complains of lower abdominal pain and / or heaviness, irritable uterus and with recurrent urinary and genital infections were taken as those with treatened preterm labour. The exclusion criteria were fetal anomalies, multiple gestation, cervical cerclage due to short or incompetent cervix, painful regular uterine contractions, history of ruptured membranes, hypertension or diabetes requiring medication or a seizure disorder. A delailed obstetrical history was taken and estimated date of delivery was calculated. Gestational age was determined from menstrual history and from early first trimenter scan. An ultrasound was perfomed between 14-20 weeks to reconfirm gestational age and to exclude fetal anomalies and a short incompetant cervix. Women eligible for trial were given intra muscular (intragluteal) injection of hydroxy progesterone coproate 250mg every week. The injections contined until 36 weeks of gestation or delivery which ever occurred first. The patients received routine antenatal care and with more frequent antenatal visits considering the known level of risk of preterm delivery.

After delivery the antenatal, delivery, newborn and post partum records were reveiwed. Birth weight of infant and neonatal course as well as maternal complications were recorded. Babies were followed till discharge home from hospital or in NICU untill discharge. Preterm delivery was defined as delivery of less than 37 completed weeks of gestation.

The primary outcome was preterm delivery before 37 weeks of pregnancy. The secondary outcome measures were birth weight, still birth or neonatal death and fetal complications (RDS, NICU admissions, ventilatory support, photo therapy (jaundice) and sepsts) and maternal compliance and acceptance to treatment.

The results of the trial group were compared with a similar group of high risk women for preterm labour fulfilling the eligibility criteria. Their records were retrospectively reveiwed. The women in control group did

RESULTS:

TABLE I.

CHARACTERISTICS OF WOMEN UNDERGOING TRIAL.

	PROGESTERONE GROUP	**CONTROL GROUP**
TOTAL NO. OF PATIENTS.	50	36
AGE (YEARS)	30.02 ± 4.27	29.03 ± 4.21
PARITY	2.62 ± 1.79	2.86 ± 1.10
BODY WEIGHT (KG)	67.78 ± 8.62	72.75 ± 10.5
PREVIOUS PRETERM DELIVERIES	28 (56%)	16 (44.4%)

TABLE II.

PREGNANCY OUTCOMES

MATERNAL	**PROGESTERONE GROUP N = 50**	**CONTROL GROUP**	**P VALUE**
Gestational age at delivery (weeks) mode of delivery	36.14 ± 2.63	34.33 ± 2.61	0.004
SVD	38 (76.0%)	27 (75%)	0.365
LSCS	12 (24%)	9 (25%)	0.571
Characteristics of Labour			
Induced	8 (16%)	8 (22.2%)	0.541
Spontaneous	26 (52%)	18 (50%)	0.541
Prom	12 (24%)	8 (15.7%)	0.001
Chorioamnionits	1 (2%)	2 (5.6%)	0.000
Fetal			
Alive	47 (94%)	28 (77.8%)	0.001
Still born	1 (2%)	3 (8.3%)	0.000
Neonatal death	1 (2%)	4 (11.1%)	0.000
Birth weight	2.66 kg ± 0.455	2.219 ± 0.65	0.003
Congenital anomalies	0	0	0
NICU admission	3 (6%)	18 (50%)	0.000
Oxygen therapy	3 (6%)	15 (41.7%)	0.000
Ventilatory support	0 (0%)	6 (16.7%)	0.000
RDS	2 (4%)	8 (22.2%)	0.001
Neonatal jaundice	8 (16%)	6 (16.7%)	0.541
Sepsis	8 (16%)	6 (16.7%)	0.54

not received any other medication during pregnancy except routine antenatal care, rest and general measures.

Data was analysed using SPSS version 13. Continous variables were compared using paired t test and categorical variables were compared using chi-square test. Statistical significance was taken as $P < 0.05$.

RESULTS:-

A total of 86 women were included in the study on the basis of review of medical records from January 2006 till August 2009. Of these, 50 women were given depot porgesterone injections and the rest 36 were those who continued their pregnancy with out any pharmacological intervention. The women in two group were similar in terms of mean. Age and parity. However women in control group have a relatively higher body weight (67.78 v/s 72.75). The women in progesterone group had more previous preterm deliveries (28 (56%) v/s 16 (44.4%) than in control group. (Table I).

The mean gestational age at delivery was 36.4 ± 2.63 weeks in progesterone group as compared with 34.33 ± 2.61 weeks in control group ($P = 0.004$). There was no significant difference in mode of delivery in both the groups. Similarly both the groups had same frequency of induced or spontaneous labour. However pre labour rupture of membranes (prom) was more in progesterone group than in control group which was statistically significant (24% V/S 15.7%) ($P = 0.001$) (Table II) 94% women delivered alive babies in progesterone group as compared to 77.8% in control group ($P = 0.001$) still borns and neonatal deaths were also significantly low in progesterone group ($P < 0.05$). mean birth weight of babies in progesterone group was 2.66 kg v/s 2.21 kg in control group which is also significant ($P = 0.003$)

Significant reductions in NICU admissions, requirement of oxygen therapy and ventilatory support was found in progesterone group ($P < 0.05$) Table II. Only 2 babies had RDS in progesterone group as compared with 8 in control group ($P = 0.001$). There is no significant difference in rates of neonatal jaundice and sepsis (16% v/s 16.7%) in both groups (Table II). Overall patient compliance and treatment acceptability to progesterone injections given weekly was good.

DISCUSSION:

The results of this trial demonstrate that treatment with hydroxyl progesterone on a weekly basis beginning at 14-20 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. There was significant reduction in perinatal mortality and neonatal morbidity. Hence the consequences of prematurity were decreased among infants of women receiving progesterone therapy. Women assigned to progesterone therapy in our trial had history of previous preterm delivery a rate of around 56% but after treatment the mean gestational age of delivery was 36 weeks. Women in the control group with previous history of preterm delivery 44.4% they had a mean gestational age at delivery of around 34 weeks. Similar evidence was seen in various other studies were progesterone therapy was used in women with previous history of preterm labour, women with short cervix & women with twin pregnancy to prolong pregnancy and reduce the risk of prematurity in infants [6, 10, 11, 12,13].

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. Hydroxy progesterone caproate is unlikely to affect an infectious process but in our study it provided protection against preterm delivery in women threatened for preterm labour. The mechanisms of action of progesterone in prolonging gestation in not known. However recommended actions of progestone include relaxation of myometrial smooth muscle, blocking action of oxytocin and inhibition of formation of gap junctions[16,17].

There is a 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 ($P < .005$). 94% were born alive in progesterone group showing a good perinatal outcome.

The mean birth was 2.6kg in progesterone group as companed with 2.2kg in control group. Similar results were observed in other studies [10, 11, 12, 13].

There was s significant reduction in NICU admission, requirement of supplemental oxygen therapy and vantilatory support ($P < 0.05$) in progesterone group.[18,19]

No congenital anomaly was found in babies born to mothers receiving progestone therapy. The results are consistent with surveys of the literature that have shown no teratogenic effects from the use of hydroxyl progesterone in pregnancy.

Progesterone therapy was 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 [20].

CONCLUSION:

Preterm birth is a major complication of pregnancy associated with perinatal mortality and morbidity. Progesterone therapy can be advocated for prevention of preterm labour in high risk group. There are no proven teratogenic effects on baby and patient compliance in terms of fianancial and treatment acceptability is good.

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