Original Research Article

Efficacy of intramuscular progesterone in prevention of preterm birth in patients with history of preterm birth

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ABSTRACT

Background: Preterm birth is associated with many adverse outcomes and is defined as birth of a baby before 37 weeks of gestation. Around 15 million babies born preterm around the world with survival rates at different gestational like less 23 week, 23 weeks, 24 weeks and 25 weeks are 0%, 15%, 55% and 80% respectively. Progesterone has shown to reduce the incidence of preterm birth. Objective of the study was to find out frequency of preterm birth in patients (with previous history of preterm birth) treated with intramuscular progesterone.
Methods: It was randomized controlled trial conducted in the department of Obstetrics and Gynecology, Unit-I, Sir Ganga Ram Hospital Lahore, Pakistan conducted from October 2017 to April 2018. It included 530 pregnant women with history of at least 1 previous preterm delivery presenting in antenatal clinic between 16-20 weeks of gestation. The lottery method was employed to segregate patients in two groups. Patients received intramuscular progesterone injection proluton depot 250 mg intramuscular weekly from 16-20 weeks till 37 weeks and other group received placebo drug.
Results: Mean age was 27.52±4.57 years while the mean gestational age was 17.39±1.38 weeks. The mean gestational age at delivery was significantly higher among intramuscular group (36.14±2.23 versus 35.07±2.97 weeks; p=0.000). The frequency of preterm delivery was significantly lower in intramuscular group (24.9% versus 39.6%; p=0.000) as compared to placebo group.
Conclusions: Frequency of preterm delivery was significantly lower in patients treated with intramuscular progesterone (24.9% versus 39.6%; p=0.000) irrespective of patients age, parity, BMI and number of previous preterm deliveries.

Keywords: Efficacy, Intramuscular progesterone, Preterm delivery, Prevention

INTRODUCTION

Preterm birth is associated with many adverse outcomes and is defined as birth of a baby before 37 weeks of gestation. Around 15 million babies born preterm around the world with survival rates at different gestational like less 23 week, 23 weeks, 24 weeks and 25 weeks are 0%, 15%, 55% and 80% respectively. If we look at worldwide rates of preterm deliveries, it is around 15% in Europe, 18% in Africa, 12% in America. Problems faced by babies born preterm are as follow: cerebral palsy, growth retardation, respiratory distress syndrome, intra ventricular hemorrhage, necrotizing enterocolitis, retinopathy of prematurity. The cost of management of preterm deliveries and babies is very high but unfortunately outcomes are not so good. So the focus is on prevention of preterm deliveries. Risk factors for preterm deliveries are maternal age, genetic

predisposition, Afiro-American lineage, short cervical length, twin pregnancy, infectious diseases, smoking, uterine anomaly, previous curettage or cervical coning.[1-8]

Many drugs are used to prevent preterm deliveries which include tocolytics, antibiotics and steroids. The role of progesterone in prevention of preterm deliveries was first identified in 1954. Many studies have been conducted to assess the role of progesterone in prevention of preterm labor and results of the studies are encouraging. Though the exact mechanism have not yet known. It is suggested that it antagonizes the effect of estrogen on myometrium, accelerate decay of oxytocin and reduce inflammation by reducing production of prostaglandins. American Congress of Obstetricians and Gynecologists (ACOG) has recommended use of progesterone in women with history of preterm delivery, premature rupture of membranes and those with short cervix. Studies have shown that progesterone have no role in preventing preterm deliveries in patients with twin pregnancies, so here it is not recommended.[2,5-9]

So the aim of the current study was to determine the frequency of preterm birth in patients treated with oral versus intramuscular progesterone in patients having history of previous preterm birth in our population. So that maternal and fetal morbidity and mortality can be reduced. This will also help reducing the cost and stress faced by both doctors and family. Also to compare present study statistics with local and international data.

METHODS

It was a randomized controlled trial conducted in the Gynecology outdoor department of the Sir Ganga ram Hospital Lahore, Pakistan from 5 October 2017 to 4 April 2018 to know the efficacy of intramuscular progesterone injection in preventing preterm birth in women with history of preterm birth, Ethical permission was taken from the institutional review board and consent was taken from patients. Data was collected on a specifically designed questionnaire.

530 women fulfilling the inclusion criteria [maternal age between 18-35 years, gestational age between 16-20 weeks (according to LMP)], Singleton pregnancy on ultrasound, Previous history of one or more preterm births, Intact amniotic membranes (no history of leaking) were taken into this study from OPD. Detailed history was obtained. Confounding variables were controlled by strict exclusion criteria (preterm rupture of membranes, chorioamnionitis on history (leaking, fever), clinical examination and laboratory intra uterine growth retardation, anomalous fetus on ultrasound, oligohydramnios on ultrasound and clinically, Medical complication (gestational diabetes, pregnancy induced hypertension BP >140/90 mmHg), urinary tract infection on history of burning micturition, dysuria, frequency and urgency of urine).

The lottery method was used to segregate the Patients into two groups. Group-I received placebo drug from 20 weeks till 37 weeks. Drug compliant charts in form of pill taking form were given to group-I participants to regulate timely intake of drug. Compliance was checked by calculating total number of tablets taken. Group-II patients received intramuscular progesterone injection proluton depot (17-α hydroxyl progesterone) 250 mg intramuscularly weekly from 16-20 weeks till 37 weeks. Patients compliance was maintained by entering the date and time of injection on their antenatal cards. Patients follow up was done on outdoor basis weekly to regulate their routine antenatal checkup. All the patients entering active preterm labor were identified and were managed according to standard protocol. Frequency of preterm birth was recorded. All the information was recorded using a specially designed proforma and under supervision of an expert obstetrician. Statistical analysis was done by using SPSS 21. Numerical variables; age, and gestational age at the time of delivery have been presented by mean±SD. Frequency has been calculated for parity. Data was stratified for age, parity, number of previous preterm births and BMI to address effect modifiers. Post-stratification chi-square test was used taking p value ≤0.05 as statistically significant.

RESULTS

The age of the patients ranged from 18 years to 35 years with a mean of 27.52±4.57 years. The gestational age of the patients ranged from 16 weeks to 20 weeks with a mean of 17.39±1.38 weeks. 47.5% of the patients were para 2 followed by para 3 (32.3%) and para 1 (20.2%). Rest of the baseline characteristics are shown in the table below.

Table 1: Baseline characteristics of intramuscular injection group.

Characteristics	Intramuscular progesterone
Number	265
Age (years)	27.64±4.59
Gestational age (weeks)	17.40±1.39
Parity	
Primiparous	53 (20.0%)
Para 2	127 (47.9%)
Para 3	85 (32.1%)
BMI (Kg/m²)	28.06±3.32
Previous preterm births	1.23±0.42
1	205 (77.4%)
2	60 (22.6%)
Gestational age at delivery (weeks)	36.14±2.23

These patients were randomly allocated into two treatment groups. When compared both the groups were comparable in terms of all parameters as shown in Table 2.

The frequency of preterm delivery was significantly lower in intramuscular group with p value =0.000. This difference was seen across all age, parity, number of previous preterm deliveries and BMI groups. These findings have been summarized in Table 3.

Table 2: Baseline characteristics of study groups.

Characteristics	Placebo (n=265)	Intramuscular progesterone (n=265)	P value
Age (years)	27.40±4.56	27.64±4.59	0.556
Gestational age (weeks)	17.37±1.37	17.40±1.39	0.777
Parity			
Primiparas	54 (20.3%)	53 (20.0%)	
Para 2	125 (47.2%)	127 (47.9%)	0.985
Para 3	86 (32.5%)	85 (32.1%)	
BMI (Kg/m^2)	28.14±3.57	28.06±3.32	0.795
Previous preterm births	1.17±0.38	1.23±0.42	0.129
1	219 (82.6%)	205 (77.4%)	0.128
2	46 (17.4%)	60 (22.6%)	
Gestational age at delivery (weeks)	35.07±2.97	36.14±2.23	0.000*

Table 3: Comparison of frequency of preterm delivery between study groups.

Characteristics	Placebo (n=265)	Intramuscular progesterone (n=265)	P value
Preterm delivery	105 (39.6%)	66 (24.9%)	0.000*
Age groups (in years)			
18-23	30/72 (41.7%)	13/54 (24.1%)	0.039*
24-29	41/104 (39.4%)	34/130 (26.2%)	0.031*
30-35	34/89 (38.2%)	19/81 (23.5%)	0.038*
Parity			
Primiparas	22/54 (40.7%)	12/53 (22.6%)	0.044*
Para 2	50/125 (40.0%)	34/127 (26.8%)	0.026*
Para 3	33/86 (38.4%)	20/85 (23.5%)	0.036*
BMI (Kg/m^2)			
20-25	27/67 (40.3%)	16/66 (24.2%)	0.048*
25-30	45/116 (38.8%)	32/126 (25.4%)	0.025*
30-35	33/82 (40.2%)	18/73 (24.7%)	0.039*
Previous preterm births			
1	86/219 (39.3%)	52/205 (25.4%)	0.002*
2	19/46 (41.3%)	14/60 (23.3%)	0.048*

DISCUSSION

Preterm birth is associated with over 75% of all perinatal mortality and more than 50% of perinatal and long term morbidity.[10] A recent systemic review has estimated that 9.6% of all the births were preterm, of which approximately 92.3% were in Asia, Africa, Latin America and Caribbean.[11] Pakistan contribution of perinatal death by prematurity is 15.8%.[12]

Different studies have been conducted to establish the role of progesterone for prevention of preterm birth. Oral progesterone are easy to take but are less effective because of first pass hepatic metabolism leading to variable plasma levels while intramuscular progesterone carries the risk of swelling and bruising at injection site.[13]

The mean age of the patients was 27.52±4.57 years. A similar mean age in patients with previous preterm delivery has been reported previously by Glover et al in 2011 (27.2±4.9 years), Hameed et al in 2012 (27.8±6.55 years), and Berghella et al in 2010 (26.3±4.5 years) among American, Egyptian and British populations respectively.[14-16] Choudhary et al in 2014 (24.11±2.386 years), Rai et al in 2009 (26.07±3.24 years) reported similar mean age among Indian such patients.[13,17]

The mean gestational age was 17.39±1.38 weeks in the present study. Results of current study match with those of Glover et al who observed a mean gestational age of 17.0±2.4 weeks previously in 2011.[14] A relatively higher mean gestational age was observed by Berghella et al in 2010 (19.6±2.0 weeks) and Rai et al in 2009 (20.69±2.83 weeks).[13,16]

The mean BMI of the patients was 28.10±3.44 kg/m². A similar mean BMI of 26.1±6.9 kg/m² and 27.3±7.5 kg/m² was previously observed by Grobman et al in 2012 and Glover et al in 2011 respectively among American such patients.[14,18]

The mean gestational age at delivery was significantly higher among intramuscular group (36.14±2.23 versus 35.07±2.97 weeks; p=0.000). A similar significant difference was reported by Hameed et al in intramuscular progesterone (36.3±2.4 versus 34.2±2.6 weeks; p=0.002) versus placebo.[15] Choudhary et al in 2014 also observed similar difference in oral progesterone (36.79±2.64 versus 35.90±2.00 weeks; p=0.076) versus placebo but the difference was statistically insignificant.[17] Grobman et al in 2012 observed similar insignificant difference in intramuscular progesterone (37.6±3.9 versus 37.4±4.3 weeks; p=0.93) versus placebo.[18]

The frequency of preterm delivery was significantly lower in intramuscular group (24.9% versus 39.6%; p=0.000) as compared to placebo group. This difference was seen across all age, parity, number of previous preterm deliveries and BMI groups. Our results match with those of Grobman et al in 2012 (25.1%) and Hameed et al in 2012 (21.4%) who reported similar frequency of preterm delivery with intramuscular progesterone.[15,18]

CONCLUSION

So it can be concluded from that frequency of preterm delivery is significantly lower in patients treated with intramuscular progesterone irrespective of patient's age, parity, BMI and number of previous preterm deliveries. Though it is shown by studies that progesterone by any route is ineffective in reducing preterm delivery in multiple pregnancy. In singleton pregnancy it has shown benefit and it is due to contraction inhibition and reducing inflammation and with no short term side effects.

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