Comparison of the frequency of preterm births in patients treated with oral versus intramuscular progesterone with history of previous preterm birth

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ABSTRACT

Background: Globally, it has proven that preterm birth is associated with perinatal mortality to the extent of >75%, and >50% of perinatal and long term morbidity. 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. The aim was to find out frequency of preterm birth in patients treated with oral versus intramuscular progesterone.

Methods: Randomized controlled trial conducted in the department of obstetrics and gynecology, Sir Ganga Ram hospital Lahore, Pakistan conducted from 5 October 2017 to 4 April 2018. This study involved 530 pregnant women with history of at least 1 previous preterm delivery presenting in antenatal clinic between 16-20 weeks of gestation. Group I received oral progesterone 10 mg tablet duphaston BD from 20 weeks till 37 weeks. Group II received intramuscular progesterone injection proluton depot 250 mg IM weekly from 16-20 weeks till 37 weeks.

Results: The mean age of the patients was 27.52±4.57 years while the mean gestational age was 17.39±1.38 weeks. 47.5% of the patient were para 2 followed by para 3 (32.3%) and para 1 (20.2%). 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 oral group.

Conclusions: Frequency of preterm delivery was significantly lower in patients treated with intramuscular progesterone (24.9% versus 39.6%; p=0.000) as compared to oral progesterone.

Keywords: Preterm delivery, Oral progesterone, Intramuscular progesterone

INTRODUCTION

Preterm birth (PTB) has an incidence of 11% worldwide and one of the common complications of pregnancy. PTB is associated with perinatal mortality to the extent of >75% and >50% of perinatal and long-term morbidity.1-3 More than 15 million babies have PTB annually and over 1 million babies suffer life threatening complications of PTB.4

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.\textsuperscript{5} Pakistan contribution of perinatal death by prematurity is 15.8%.\textsuperscript{6}

Most effective of PTB in prediction by risk rate and its prevention. Different studies have been conducted to establish the role of progesterone for prevention of PTB and now American congress of obstetrics and gynecologist (ACOG) and society for maternal-fetal medicine (SMFM) also recommend use of progesterone in prevention of PTB.\textsuperscript{7,8}

Progesterone causes uterine quiescence by reducing the gap junction formation. It decreases prostaglandin production that leads to cervical stromal degradation reduction and change ascending inflammation barrier of cervix.\textsuperscript{9}

The action of inhibiting the cervical ripening and preventing PTB depends on progesterone proper route and vehicle. Progesterone is available in natural as well as synthetic forms for vaginal, oral and intramuscular uses. Its preferable route is still a highly active area of research.

Oral progesterone are easy to take but are less effective because of first pass hepatic metabolism leading o variable plasma levels, it is usually non-compliant by the patients due to its side effects like headache, nausea, vomiting and sleepiness on oral intake.\textsuperscript{10} While intramuscular progesterone, 17 α-hydroxyl progesterone is a synthetic derivative of hydroxyl progesterone (natural progesterone) and is exact duplicate of progesterone produced in placenta and corpus luteum. So it is highly absorbable and provided high and more sustained plasma levels (half-life is 7.8 days) so used as 250 mg/weekly.\textsuperscript{11,12} In other trials its higher doses or shorter intervals was used but non proved the efficacy.\textsuperscript{13-16} It is also cost effective and low dose is required. Applying pressure after the injection also minimizes the risk of swelling and bruising. So both the routes have their own pros and cons.

A study was done in India in which 23 of 46 women treated with 17 α-hydroxyl progesterone (intramuscular) delivered pre-term (50%) when compared to a control group.\textsuperscript{17} Various studies also prove role of oral progesterone in reducing the risk of PTB for example PTB occurred in 29 out of 47 (39.2%) using oral progesterone versus a controlled group 44 PTBs out of 74 (59.5%).\textsuperscript{18} In order to compare the effectiveness between two routes of progesterone, Maher et al concluded that daily vaginal progesterone administration is associated with lower rates of PTBs as compared to intramuscular weekly progesterone administration after a randomized trial of 502 singleton pregnant women.\textsuperscript{19-22}

A recent systematic view and meta-analysis showed that women who received vaginal progesterone had significantly lower rates of PTB and NICU admissions compared with women who received 17 α-OHPC. There are various studies available which prove role of oral and intramuscular progesterone in the prevention of PTB independently or in combination with control groups but there is no comparative data available between these two up till now. So this study will be first of its kind to help to choose a better route. It will be a beneficial intervention for our low resource community by decreasing the PTB and its sequels.

**METHODS**

This was a randomized control trial, after approval from hospital’s ethical review committee, 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) from 5 October 2017 to 4 April 2018 were taken into this study from OPD. Informed consent from the patients was obtained for taking part in the study and using their data in research. Detailed history was obtained. Confounding variables were controlled by strict exclusion criteria (PROM, chorioamnionitis on history (leaking, fever), clinical examination and labs IUGR, anomalous fetus on ultrasound, 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 oral progesterone 10 mg tablet duphaston (dydrogesterone) BD from 20 weeks till 37 weeks. Group II received intramuscular progesterone injection prolution depot (17-α hydroxyl progesterone) 250 mg IM weekly from 16-20 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 tablet taken. Group II 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 fellow of CPSP. The SPSS version 21 was used to analyse the data. Numerical variables like age and gestational age at the time of delivery have been presented by mean±SD. Frequency has been calculated for parity. Data has been stratified for age, parity, no. of previous preterm births and BMI to address effect modifiers. Post-stratification Chi-square test has been applied 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%). The BMI of the patients ranged from 21.73 kg/m\(^2\) to 34.60 kg/m\(^2\) with a mean of 28.10±3.44 kg/m\(^2\). The number of previous preterm births ranged from 1 to 2 with a mean of 1.20±.40. 80% of patients had 1 previous preterm delivery while 20% patients had 2 previous preterm deliveries. These findings have been summarized in Table 1.

These patients were randomly allocated into two treatment groups. When compared both the groups were comparable in terms of mean age (p=0.556), mean gestational age (p=0.777), mean BMI (p=0.795), parity (p=0.985) and previous preterm deliveries distribution (p=0.128). However, 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) as compared to oral group as shown in Table 2.

The frequency of preterm delivery was significantly lower in intramuscular group (24.9% versus 39.6%; p=0.000) as compared to oral group. 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 1: Baseline characteristics of study population.**

| Characteristics                  | n=530          |
|----------------------------------|---------------|
| Age (in years)                   | 27.52±4.57    |
| Gestational age (in weeks)       | 17.39±1.38    |
| **Parity**                       |               |
| Primiparous (%)                  | 107 (20.2)    |
| Para 2 (%)                       | 252 (47.5)    |
| Para 3 (%)                       | 171 (32.3)    |
| BMI (kg/m\(^2\))                 | 28.10±3.44    |
| Previous preterm births          | 1.20±.40      |
| 1 (%)                            | 424 (80.0)    |
| 2 (%)                            | 106 (20.0)    |
| Gestational age at delivery (in weeks) | 35.61±2.68 |

**Table 2: Baseline characteristics of study groups.**

| Characteristics                  | Oral progesterone | Intramuscular progesterone |
|----------------------------------|-------------------|---------------------------|
| N                                | n=265             | n=265                     |
| Age (in years)                   | 27.40±4.56        | 27.64±4.59                |
| Gestational age (in weeks)       | 17.37±1.37        | 17.40±1.39                |
| **Parity**                       |                   |                           |
| Primiparous (%)                  | 54 (20.3)         | 53 (20.0)                 |
| Para 2 (%)                       | 125 (47.2)        | 127 (47.9)                |
| Para 3 (%)                       | 86 (32.5)         | 85 (32.1)                 |
| BMI (kg/m\(^2\))                 | 28.14±3.57        | 28.06±3.32                |
| Previous preterm births          | 1.17±.38          | 1.23±.42                  |
| 1 (%)                            | 219 (82.6)        | 205 (77.4)                |
| 2 (%)                            | 46 (17.4)         | 60 (22.6)                 |
| Gestational age at delivery (in weeks) | 35.07±2.97       | 36.14±2.23                |

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

| Characteristics                  | Oral progesterone (%) | Intramuscular progesterone (%) | P value |
|----------------------------------|-----------------------|--------------------------------|---------|
| N                                | n=265                 | n=265                          |         |
| 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*  |

Continued.
**DISCUSSION**

Preterm birth is associated with perinatal mortality to the extent of >75% and ≥50% of perinatal and long-term morbidity.1,3 More than 15 million babies have preterm birth annually and over 1 million babies suffer life threatening complications of preterm birth.4

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.3 Pakistan contribution of perinatal death by prematurity is 15.8%.6

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.17 There are various studies available which prove role of oral and intramuscular progesterone in the prevention of preterm birth independently or in combination with control groups but there was no comparative data available.

Our study involved 530 pregnant women with history of at least 1 previous preterm delivery presenting in antenatal clinic between 16-20 weeks of gestation. These Patients were divided into two groups using lottery method. Group I received oral progesterone 10 mg tablet duphaston (dydrogesterone) BD from 20 weeks till 37 weeks. Group II received intramuscular progesterone injection prolon uterus depot (17α hydroxy progesterone) 250 mg IM weekly from 16-20 weeks till 37 weeks. A written informed consent was obtained from every patient. The mean age of the patients was 27.5±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 (27.4±6.55 years) and Berghella et al in 2010 (26.3±4.5 years) among American, Egyptian and British populations respectively.21,25 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.18,26 Grobman et al reported much lower mean age of 22.8±5.3 years in American population in 2012.27

The mean gestational age was 17.39±1.38 weeks in the present study. Our results match with those of Glover et al who observed a mean gestational age of 17.0±2.4 weeks previously in 2011.23 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).18,25 The mean BMI of the patients was 28.10±3.44Kg/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.23,27 The number of previous preterm births ranged from 1 to 2 with a mean of 1.20±0.40. Rai et al in 2009 observed a similar mean number of previous preterm deliveries (1.21±0.53) among Indian population.18 Glover et al however observed quite higher mean number of previous preterm deliveries and reported it to be 1.5±0.9.23

When compared both the groups were comparable in terms of mean age (p=0.556), mean gestational age (p=0.777), mean BMI (p=0.795), parity (p=0.985) and previous preterm deliveries distribution (p=0.128). Thus there was no inherent bias in the study groups.

The mean gestational age at delivery was significantly higher among intramuscular group (36.1±2.23 versus 35.07±2.97 weeks; p=0.00). 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.24 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.15 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.27

| Characteristics                  | Oral progesterone (%) | Intramuscular progesterone (%) | P value |
|----------------------------------|-----------------------|--------------------------------|---------|
| **Parity**                       |                       |                                |         |
| Primiparas                       | 22/54 (40.7)          | 12/53 (22.6)                   | 0.044*  |
| Para 2                           | 50/125 (40.0)         | 34/127 (26.6)                  | 0.026*  |
| Para 3                           | 33/86 (38.4)          | 20/85 (23.5)                   | 0.036*  |
| **BMI (in kg/m²)**               |                       |                                |         |
| 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*  |

Chi-square tests; *observed difference was statistically significant.
The frequency of preterm delivery was significantly lower in intramuscular group (24.9% versus 39.6%; p=0.000) as compared to oral 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.24,27 While a similar frequency of 39.2% has been reported by Rai et al in 2009 with oral progesterone.18 Thus the frequency of preterm delivery was significantly lower in patients treated with intramuscular progesterone (24.9% versus 39.6%; p=0.000) as compared to oral progesterone irrespective of patients age, parity, BMI and number of previous preterm deliveries.

The present study is first of its kind and compares oral versus intramuscular progesterone for the first time in the treatment of preterm delivery. The results of the present study confirm that intramuscular progesterone was superior to oral form and should be prescribed in future practice. It was exact duplicate of progesterone produced in placenta and corpus luteum and was highly absorbable. Therefore it provides high and more sustained plasma levels (half-life is 7.8 days).28 It was also cost effective and low dose was required. Applying pressure after the injection can reduce the risk of swelling and bruising and can thus make it more acceptable to the patient.

Limitations

The limitations of the study were that it was a single institution study and the sample size was small.

CONCLUSION

The results of the present study confirm that intramuscular progesterone is superior to oral form and should be prescribed in future practice. It is exact duplicate of progesterone produced in placenta and corpus luteum and is highly absorbable. Therefore it provides high and more sustained plasma levels (half-life is 7.8 days). It is also cost effective and low dose is required. Applying pressure after the injection can reduce the risk of swelling and bruising and can thus make it more acceptable to the patient.

Frequency of preterm delivery was significantly lower in patients treated with intramuscular progesterone (24.9% versus 39.6%; p=0.000) as compared to oral progesterone irrespective of patients age, parity, BMI and number of previous preterm deliveries.

Recommendations

It is recommended that intramuscular progesterone can be safely use for prevention of preterm birth in means of effectiveness, cost and side effects as compared to oral progesterone.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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