

ROLE OF VAGINAL PROGESTERONE IN THE PREVENTION OF PRETERM DELIVERY

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ABSTRACT

Background: Preterm Birth is the main cause of perinatal morbidity and Mortality. Progesterone has been used for preventing Preterm Labor and is being advocated for it. Its use in women presenting with Preterm labor pains has diverse results. The administration of Progesterone has been shown to lower not only the number of the episodes of preterm Uterine contractions, but it also decreases the incidence of preterm delivery in the high-risk women for Preterm delivery.

Objective: To compare the frequency of Spontaneous Preterm Birth, in the woman having a prior history of one spontaneous Preterm Delivery, who are treated by 100mg of vaginal progesterone pessary daily versus controls.

Methods: A Randomized controlled trial was carried out at the Obstetrics & Gynaecology Department of Lahore General Hospital (a tertiary care hospital) of 6 months duration from 1-09-2018 To 28-02-2019. Two groups of Patients were made. Patients in Group-A were instructed to use a vaginal pessary containing 100mg natural progesterone daily before going to sleep every night, starting from the time of enrollment to 36 weeks of pregnancy or until occurrence of preterm labor or premature rupture of membranes. Patients in Group-B did not receive progesterone pessary and acted as control. All the patient were followed up until the delivery.

Results: In Group A and in Group B mean age of the women was 27.71±3.31 and 27.81±3.57 years. There were total 60(30%) neonates who were delivered premature. In Group-A, the frequency of preterm delivery was 21%(21/100), while in Group-B it was 39%. The frequency of the Preterm delivery was quite significantly less in the women who were on progesterone as compared to the women who were not given progesterone. i.e. (p-value=0.005)

Conclusion: It is thus concluded that vaginal progesterone resulted in Significant reduction of the Preterm delivery rate in the women with a prior history of 1 spontaneous Preterm birth i.e. 21% in treatment group A vs. 39% in non-treatment group B.

KEY WORDS: Spontaneous preterm delivery, Spontaneous Preterm birth, Vaginal progesterone

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INTRODUCTION:

The Preterm birth has been defined as the delivery of a baby before 37 weeks of gestation have been completed. This is a major cause of the neonatal & infant mortality and short term & long-term disabilities. Preterm birth Rate are 6% - 12% in the developed world and are much higher in the developing countries.¹ It is

seen that about 40% of the Preterm births are occurring before 34 weeks are completed and those occurring at less than 32 weeks are 20%. So, this contributes to almost more than 50% in the Perinatal Morbidity and Mortality.²⁻⁴ Every one in five of these children have some mental retardation. Everyone in three of these children have vision impairment. About half of these Preterm children have cerebral Palsy. Others are at increased risk for cardiovascular Diseases (like infarction, hypertension and stroke) and also diabetes in later life.⁵

Many factors are known to have a high risk for Preterm birth. They include age (less than 18 & more than 35 years), short inter pregnancy interval, poor nutrition, less than normal BMI, Multiple Pregnancies,

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infections, a history of 2nd trimester miscarriage and prior preterm Birth. Those women in which there is a history of preterm Births have a high risk of recurrence i.e. 15-80% depending on the duration and number of previous preterm Birth.

Progesterone is known to play a role for the continuation of the pregnancy. It keeps the uterus relaxed. Antenatally given progesterone whatever of its dose and the route decrease the risk of giving birth to a low birth weight baby before term. Evidence shows that the local change in the level of progesterone and the progesterone and estrogen ratios in the placenta, Decidua or the fetal Membranes are important in starting labor in the human beings.³

Vaginal Progesterone gel is a bio-adhesive vaginal gel which contains micronized progesterone in an emulsion system. Physically micronized progesterone is white colour soft gel. Each of the applicator provides 1.125g of Micronized Progesterone that contains 90mg of progesterone in a base. Side effects with vaginal progesterone are few like nausea, bloating and vaginal soreness. The vaginal root also results in a high local concentration in uterus however the blood level is less. In 2003 American college of obstetrician and gynecologists recommend progesterone use in a women with a previous spontaneous Preterm birth if it is a singleton pregnancy. It is also recommended to use in women with an accidently discovered short length cervix (<15mm). But there are still controversies regarding its ideal formulation, route, dose and the long term safety issue. So this encourages further studies.⁶

The rationale to conduct this study was to determine how effectively vaginal progesterone pessary (100mg) can prevent the recurrence of preterm birth in our population as most of the studies which are conducted are from developed countries showing variable results and insufficient data is available in developing countries. Using the results of an indigenous study, an evidence-based guidelines can be made and Progesterone use can be encouraged for the prevention of Labor occurring before term.

OBJECTIVE

To determine the frequency of spontaneous preterm delivery in those women with a prior history of one spontaneous Preterm birth, who are treated with 100mg of vaginal progesterone pessary daily versus controls.

METHODS

A randomized Controlled trial was carried out at the Obstetrics & Gynaecology department of Lahore General Hospital (a tertiary care hospital) of 6 months duration from 1-09-2018 To 28-02-2019 using Nonprobability, purposive sampling method.

Permission was sought from the ethical committee of Lahore General Hospital. This randomized controlled trial was carried out at the Obstetrics & Gynaecology Department of Lahore General Hospital (a tertiary care hospital) for 6 months of duration from 1-09-2018 To 28-02-2019. A total of 200 patients were included using the nonprobability, purposive sampling method. Patients attending the prenatal clinic, 25 – 35 years old, with a single pregnancy between 24 and 34 weeks with a history of 1 spontaneous preterm birth with Parity \leq 5 were included in this study. The patients with fetal demise or anomaly (on USG) or advanced Labour (>3cm) or bulging membrane or ruptured on speculum examination and with current or planned cervical cerclage treatment were excluded. Patients with maternal pathologies in which preterm termination of pregnancy is required or contraindication to progesterone treatment were also not included.

A random number list was created by the computer and patients were assigned either 'Group-A or Group-B' according to this list. Patients in Group-A were instructed to use a vaginal pessary containing 100mg natural progesterone daily before going to sleep every night, starting from the time of enrollment to 36 weeks of pregnancy or until the occurrence of Preterm labor or premature rupture of the membranes. Patients in Group-B did not receive progesterone pessary and acted as the control. The gestational period was determined from the last normal menstrual period. A detailed anomaly scan was done to rule out fetal malformations before each enrollment. Prenatal care of the patients was done according to standard departmental protocols. All the patients were followed up until delivery. Management of patients who had Preterm labor was left to the discretion of the attending obstetrician. Data entry and analysis were carried out using SPSS v.17. The p-value was considered significant if <0.05.

RESULTS:

The Mean age of women in group:A and Group:B, was 27.71 \pm 3.31 and 27.81 \pm 3.57 years respectively. The minimum age in both groups was 20 while maximum age was 35 in both groups. (Table-1)

In Group A there were 55 primiparous and 45 multiparous while in Group B there were 56 primiparous and 44 were multiparous. (Table-2)

In Group A: progesterone was given at an average gestational age of 26.36 \pm 4.16-week. (Table-3)

In the Group A, the mean gestational age at delivery, was 31.50 \pm 2.84 weeks while in Group: B the mean gestational Age at time of delivery, was 30.76 \pm 2.49 week respectively. (Table4)

In Group A, preterm delivery was 21% (21/100) while in Group B it was 39%. The frequency of preterm

delivery was Significantly less in the women ,treated with progesterone as compared to those women who were not given progesterone. The difference is statistically Significant with the P-value of 0.005. (Table-5)

TABLE-1: Descriptive statistics for age distribution in treatment groups

	GroupA Progesterone	GroupB Control	Total
<i>N</i>	100	100	200
<i>Mean</i>	27.71	27.81	27.76
<i>SD</i>	3.31	3.57	3.43
<i>Minimum</i>	20	20	20
<i>Maximum</i>	35	35	35

TABLE-2: Parity status of women in treatment groups

	Group-A (Progesterone)	Group-B (Control)	Total
<i>Primiparous</i>	55(55%)	56(56%)	111
<i>Multiparous</i>	45(45%)	44(44%)	89
<i>Total</i>	100	100	200

TABLE-3: Gestational age at which drug was given in treatment group- a

	Group-A (Progesterone)
<i>N</i>	100
<i>Mean</i>	26.36
<i>SD</i>	4.16
<i>Minimum</i>	12
<i>Maximum</i>	33

TABLE-4: Gestational Age at time of delivery in Treatment Group

	Group-A (Progesterone)	Group-B (Control)	Total
<i>n</i>	100	100	200
<i>Mean</i>	31.50	30.76	31.13
<i>SD</i>	2.84	2.49	2.69
<i>Minimum</i>	24	24	24
<i>Maximum</i>	34	34	36

TABLE-5: Frequency of spontaneous preterm delivery in treatment groups

	GroupA (Progesterone)	Group- B(Control)	Total
<i>Preterm Yes</i>	21(21%)	39(39%)	60
<i>Birth No</i>	79(79%)	61(61%)	140
<i>Total</i>	100	100	200

Chi-Square Test=7.71 p-value=0.005

DISCUSSION

The major cause of perinatal Mortality /Morbidity is Preterm delivery. Globally this is the main cause of neonatal death . Preterm birth is held responsible for the almost 80% of Neonatal deaths and almost 50% of the long term Morbidity of the surviving infant^{2,7}. There are many known intervention that can prevent or treat Preterm Births, but none of them have appeared to be effective. Recent evidences showed that progesterone support are proved to be helpful by recent evidence in preventing Preterm birth⁸. Many trials have been conducted using progesterone preparations for preventing of preterm birth.

In this study it was observed that women who were on progesterone therapy, among them premature delivery was seen in 21% and women who were in control group, among them frequency of preterm delivery was 39%.

Cetingozet al. reported a difference in preterm labor between the placebo(57.2%) and the progesteron group (40%). More women were delivered before 37 weeks in placebo group i.e: 57.2%, than the progesterone group i.e: 40%⁹. Results of this study are consistent with the results of our study confirming the beneficial effect of progesterone for the prevention of Preterm Birth.

In a randomized placebo controlled trial of da Fonseca et al., a significant reduction in preterm delivery was seen¹⁰.

A Randomized, double blind, Placebo controlled trial Daily treatment with 90 mg Progesterone Vaginal Gel did not decrease the frequency of early Preterm Birth¹¹.

On the other hand, a local study from Pakistan has reported that progesterone was associated with a decrease in Preterm birth before 37 weeks i.e. 36.6% (11 patients) in the Progesterone- group Vs 83.3 % (25 patients) in the Placebo- group¹².

A similar study from Egypt was done on the efficacy of progesterone when given intra muscularly for prevention of Preterm Labor. In the progesterone Group, 8 while 13 in control out of the 25 women were delivered before term (32%)¹³.

Some Meta analysis and systemic reviews of randomized Controlled trials have also shown that women receiving progesterone had somewhat, lower rate of Preterm Delivery¹⁴⁻¹⁶

Recent researches have suggested that progesterone may possibly be important in keeping the uterus quiet in the last half of pregnancy . It limits the stimulatory prostaglandins production and also inhibits the Contraction Associated Protein Genes Expression in myometrium^{17,18}.

It is evident that, though the levels of Progesterone in the circulation of mother in the preceding weeks of labor do not show a significant change, but the onset of labour at or before term, is associated with a functionally progesterone activity withdrawal from the uterus¹⁷.

Keeping in the mind the above discussion and results of this study, it was evident and confirmed that progesterone is effective for prevention of the Preterm Delivery in women at risk.

CONCLUSION

It is concluded that the use of vaginal progesterone has shown reduction significantly of preterm delivery rate in those women who had a prior history of 1 spontaneous preterm Birth i.e. 21% in treatment group A vs. 39% in non-treatment group B. So clearly, there is some strong evidence, that there is some benefit of giving progesterone, to a pregnant women who had a history of Preterm labor.

ETHICAL APPROVAL

The study was approved by the Ethical Review Committee of Postgraduate Medical Institute, Ameer ud Din Medical College, Lahore, Pakistan.

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AUTHORS' CONTRIBUTION:

MI: Collection of patient's data
MAFZ: Supervision of research
AS: Data collection, manuscript writing
ST: Supervision, manuscript writing
NY: Literature research
KQ: Statistical and Data analysis