DOI: https://doi.org/10.53350/pjmhs2023173304

ORIGINAL ARTICLE

Progesterone: A Hope to Prevent Preterm Births & Reduce Perinatal Mortality

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ABSTRACT

Objectives: To assess and compare the maintenance of tocolysis in preterm labor by using vaginal and intramuscular progesterone.

Study design: Randomized controlled trial.

Settings and study duration: Department of Obstetrics & Gynecology, Civil Hospital, Bahawalpur between 12th March 2019 and 11th September 2019

Materials & Methods: A total of 96 women ranging from 18 and 40 years of age presented with threatened preterm labour, at gestational age between 28 to 36 weeks were included. Out of total, Patients having multiple pregnancy, preterm premature rupture of membrane, medical disorders, IUGR and APH were excluded .All patients were given acute tocolytic therapy with oral nifedipine. Then they were divided in 2 groups. In the Group A, vaginal progesterone (Cyclogest 200mg) was given daily while in group B patients, a single intramuscular injection(IM) of 250 mg of 17-alpha-hydroxyprogesterone caproate (17 OHP) was given weekly. All patients in both groups were evaluated upto the delivery and efficacy was documented**.**

Results: The mean age was 29.34 ± .4.92 years. The gestational age was from 28 to 36 weeks with mean age of 30.91 ± 1.44 weeks. Efficacy (no preterm birth) was seen in 42 (87.50%) in group A (vaginal progesterone) and 34 (70.83%) in group B (intramuscular progesterone) with p-value of 0.044.

Conclusion: The verdict of the study is that for preventing preterm birth the efficacy of vaginal progesterone is better than intramuscular.

Keywords: vaginal progesterone, preterm birth, perinatal mortality, preterm labour, hydroxyprogesterone, tocolytic maintenance.

INTRODUCTION

Preterm labor, as defined as WHO, is labor starting after viability but prior to 37 weeks(259 days) of pregnancy.[1] Despite considerable research, preterm birth represents between 5 to 10% of deliveries in developed nations, with 8% (UK). Most occur 28 weeks and later, but 0.6% are extremely preterm (22-28 weeks).[2]

The etiology of preterm labor remains elusive. Multiple hypotheses have been proposed for labor onset, encompassing 1) untimely decidual activation 2) oxytocin induction, and 3) progesterone withdrawal.[3] Premature decidual activation, which may be impacted by elements like the fetal-decidual paracrine system, intrauterine bleeding, or a hidden upper genital tract infection, is the most likely explanation.[3,4] Preterm birth rates are elevated in developing nations compared to developed ones, making its prevention a critical public health objective.[7]

Currently, various medications can halt uterine contractions during established uterine activity, often providing up to 7 days of effectiveness. This window allows for corticosteroid administration to enhance lung maturity and in-utero transferal to facilities having neonatal (ICU). Maintenance tocolysis is crucial to prevent recurring preterm labor and birth. Progestins, employed for over 50 years, have demonstrated exceptional efficacy in preventing preterm delivery.[11]

There are numerous progestin-based medications on the market right now.[12] Progesterone contributes to the natural progression of pregnancy to full-term by inhibiting the oxytocin effect of prostaglandin F2α and α-adrenergic stimulation in the myometrium at adequate concentrations, thereby enhancing the α-adrenergic tocolytic response.[13] In a study by El Hameed focusing on women with shortened cervixes, vaginal progesterone demonstrated superior efficacy compared to intramuscular progesterone, with success rates of 90.91% and 71.10% respectively.[14]

Given the absence of local randomized clinical trials comparing vaginal and intramuscular progesterone for preterm labor prevention, this study aims to determine the most efficacious administration route. The results will inform clinical practice, potentially reducing preterm births and associated perinatal mortality and morbidity in fetuses.

MATERIALS AND METHODS

This was a Randomized controlled trial conducted at Department of Obstetrics & Gynecology, Civil Hospital, Bahawalpur. The study duration was 6 months from 12th March 2019 to 11th September 2019.

Total 96 patients having age ranging from18-40 years, singleton pregnancy, intact membranes, parity ranging from 1-4, The gestational age between week 28-36, assessed via LMP were hence included. The following women were excluded: multiple pregnancies, antepartum hemorrhage, with a history of diabetes mellitus(DM), pre-eclampsia and cardiovascular disease, severe intra-uterine growth retardation (IUGR), short cervix <25mm, cervix >2cm dilated, preterm premature rupture of membrane (PPROM), & contraindications to progesterone/ allergy to progesterone.

Ethical committee approved this study and from each and every patient the written and informed consent was taken.

Operational definition of Preterm labour was set as regular painful uterine contractions, > 2 contractions in 10 minutes with progressive cervicle effacement & dilatation. during 24 weeks to 37weeks of gestation. Defining criteria for arrested preterm labour was after stopping a tocolytic therapy and a 12-h contraction-free period afterwards. Efficacy of drug is defined as birth at term; 37 weeks.

At the admission time, out of all patients who had an obstetrical ultrasound evaluation confirmed estimated gestational age. All patients were given oral nifedipine 20 mg stat followed by maintenance dose as 10 mg 6hrly or 8hrly (max 60mg). All patients got antibiotic prophylaxis an oral erythromycin 500 mg twice daily for 7 days. 12mg dose of betamethasone twice was injected during the first 24hours of admission.

Random selection of patients and division into two groups A and B. Group A, vaginal progesterone (Cyclogest suppository) with each suppository (200 mg) was given daily at bed time. Group B patients, a single dose of intramuscular injection of 17-alpha-hydroxyprogesterone caproate(200mg) was given weekly, till the patient reaches term or delivers before it. Evaluation of all were done by researchers. The drug is labeled to be efficacious if there will be no preterm birth .This data including demographic features,

efficacy was documented on a proforma

Data was analyzed by using SPSS version 20.0. the Age, height,gestational age, weight and BMI were presented as mean and standard deviation. Parity, previous h/o preterm delivery and efficacy were presented as frequency and percentages. Chi-square test was used as the test of significance. P value ≤0.05 was considered as statistically significant. Effect modifiers were controlled by stratification of data in terms of age, gestational age, parity, BMI and h/o preterm birth. Post-stratification chi-square was applied to see the effect of this on efficacy and p-value ≤0.05 was taken as significant.

RESULT

Range of age between 18 to 35 years with mean age being 29.34 ± 4.92 years. The group A mean age of women was 29.10 ± 5.0. In group B was 29.46 ± 4.86 years. Most of the patients 44 (45.83%) were between 18 to 30 years of age.The Gestational age range was week 28 to 36 and mean age being 30.91 ± 1.44 weeks. The mean gestational age in group A was 30.98 ± 1.51weeks and in group B was 30.90 ± 1.39 weeks. Majority of the patients 81 (84.37%) were between 28 to 32 weeks of gestation. Mean BMI was 28.93 ± 2.63 kg/m^2. History of previous preterm birth was seen in 47% of patients in both groups.(Table 1)

Efficacy (in terms of no preterm birth) observed in 42 (87.50%) in group A (vaginal progesterone) and 34 (70.83%). B group (intramuscular progesterone) with p-value of 0.044 (Table II).

Stratification of efficacy in regards to age groups, gestational age, parity, BMI and h/o preterm birth (Table III).

Table-1: Patient's demographic profile in both groups.

		Group A (n=48)		Group B (n=48)		Total (n=96)	
		No. of patients	%age	No. of patients	%age	No. of patients	%age
Age (years)	18-30	23	47.92	21	43.75	44	45.83
	31-40	25	52.08	27	56.25	52	54.17
Gest. Age	28-32 weeks	40	83.33	41	85.42	81	84.37
	32-36 weeks	08	16.17	07	14.58	15	15.63
Parity	1-2	23	47.92	23	47.92	46	47.92
	3-4	25	52.08	25	52.08	50	52.08
BMI	≤27	14	19.17	15	31.25	29	30.21
	>27	34	70.83	33	68.75	67	69.79
H/O preterm birth	Yes	23	47.92	23	47.92	46	47.92
	No	25	52.08	25	52.08	50	52.08

Table 2: Effectiveness comparison between both Groups (n=96).

		Group A (n=48)		Group B (n=48)	
		No. of Patients	%age	No. of Patients	%age
Efficacy	Yes	42	87.50	34	70.83
	No	06	12.50	14	29.17

Significant statistical p value = 0.044.

Efficacy: prevention of preterm birth (<37weeks)

Table 3: Stratification of efficacy with respect to age groups in both groups.

		Group A (n=48)		Group B (n=48)		p-value
		Efficacy		Efficacy		
		Yes	No	Yes	No	
Age of patients (years)	18-25	19	04	15	06	0.377
	26-35	23	02	19	08	0.048
Gestational age (weeks)	28-32	35	05	28	13	0.038
	33-36	07	01	06	01	0.919
Parity	1-2	20	03	17	06	0.265
	3-4	22	03	17	08	0.088
BMI	≤27	12	02	12	03	0.684
	>27	30	04	22	11	0.034
H/O premature birth	Yes	20	03	17	06	0.265
	No	22	03	17	08	0.088

DISCUSSION

The study aimed to assess whether there were any disparities in efficacy between the use of vaginal pessary and intramuscular progesterone preparations for lowering the occurrence of preterm birth following acute tocolysis. What was found more effective was Vaginal progesterone more effective than an intramuscular preparation in reducing the number of deliveries before 34 weeks of pregnancy. Gestational age in our study was between 28 and 36 weeks with mean of age being 30.91 weeks. While majority of the patients 81 (84.37%) were between 28 to 32 weeks of gestation.

Few authors used progesterone at earlier gestation & found it effective. In Maher et al.'s study, vaginal progesterone initiated between 14-18 weeks and continued until 36 weeks resulted in fewer deliveries before 34 weeks compared to intramuscular administration (p = 0.02).[12]

At 28 and 32 weeks, 87.5% vaginal progesterone treated patients group and 70.83% intramuscular progesterone treated group showed no preterm birth (p=0.044).[9] in study of Abd El Hameed[14], revealing greater efficacy in preventing preterm labor using vaginal progesterone (90.91%) compared to intramuscular progesterone (71.10%) in women with short cervixes.[14]

A Turkish study supported our finding that combining vaginal progesterone and tocolytic treatment significantly extended pregnancies and raised birth weights in threatened preterm labor.[24]

In a local study[25], Mean patient age was 26, with parity from 1-5 and a mean gestational age of 22 weeks at presentation, 36 weeks at delivery. Vaginal progesterone group delivered at 36.67 ± 1.92 weeks, and IM group at 35.43 ± 2.62 weeks (P < 0.05). Effectiveness (delivery ≥ 37 weeks) was 47%, with 57% vaginal and 37.8% IM (P < 0.05). Vaginal progesterone showed greater efficacy after stratification (P < 0.05).[25.] This study's results align with mine, aiding in developing an SOP for our teaching unit.

Olga Pustotina et al[28] women having short cervix prevented the preterm birth by using dydrogesterone, 17OHP, oral/vaginal micronized progesterone compared to cerclage. Less effective were Dydrogesterone, 17OHP, and oral progesterone.

More research is needed for clinical use because the both vaginal and intramuscular progesterone are somewhat equally effective.

Shambhavi et al[29] The study involved 100 women who having a history of preterm birth or abortion, and they were randomly either 200mg vaginal progesterone or 250mg IM 17-OHPC until delivery or 37 weeks. The preterm birth rate before 37 weeks that all groups showed similarity, with a 20% rate in the vaginal progesterone group and 20.8% rate in the IM 17-OHPC group. Furthermore, the rates of preterm birth before 34 weeks and 28 weeks were also comparable between the two groups.

Elimian A et al[31] The recurrent preterm birth rate was reduced similarly by both drugs, according to a trial conducted on patients with history of spontaneous preterm birth, using weekly a intra muscular (IM) hydroxyprogesterone caproate (250mg) or daily vaginal progesterone (100mg).[30]

Bafghi AS et al. found intramuscular and vaginal progesterone have comparable efficacy.

Jarde et al[33] found vaginal progesterone the only effective intervention 40 trials were conducted that prevented preterm birth pregnancies that were singleton.

CONCLUSION

Conclusion is that using a corticosteroid injection to promote fetal lung maturation, some benefit can be gained from extending the pregnancy period, which will aid in reducing the mother's and fetus's morbidity and mortality perinatally. As a result, it is recommended that vaginal progesterone be used as the primary option for tocolysis maintenance to prevent preterm birth once threatened preterm labor has been stopped, as the study found it to be more effective than intramuscular progesterone. As WHO has put preterm labour for research till 2025, so our department has planned further trials on different aspects of prevention of preterm birth.

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