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PROGESTERONE SUPPLEMENTATION FOR PREVENTION OF PRETERM LABOR

Gynaecology

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ABSTRACT

Introduction: Preterm birth is currently the most important problem in maternal-child health in the developing countries. . Progesterone supplementation for the prevention of preterm labour has been advocated.

Objectives: To evaluate the effect of vaginal progesterone in the prolongation of duration of pregnancy in women at high risk of developing preterm labor.

Material and methods: This is a prospective case-control study carried out in a private maternity nursing home on100 patients , 50 cases and 50 controls. Women with history and clinical findings suggestive of risk of preterm labor, were given daily vaginal progesterone 400 mg from 16 weeks and discontinued at 36 weeks of gestation. In both groups rate of preterm labor and neonatal outcome was determined. Results: The incidence of preterm labor in progesterone group was 17.8% and in control group 36%, p value is <0.05. Conclusion: Administration of progesterone in women at high-risk of developing preterm labor reduces the incidence of preterm labor, neonatal mortality and morbidity and increases baby weight <2.5 kg.

KEYWORDS

Preterm labor, Progesterone, Preterm birth, Prevention.

Introduction:

Preterm birth is a major complication of pregnancy associated with perinatal mortality and morbidity. Although the ability of obstetric care providers to identify women at high risk for preterm birth has improved due in large part to the introduction of transvaginal cervical length measurements and cervicovaginal fetal fibronectin testing, efforts to prevent preterm birth have been largely unsuccessful. Preterm (premature) birth refers to any delivery occurring prior to 37 weeks (259 days) of gestation. Preterm labor is defined by World Health Organization as contraction of sufficient strength and frequency to effect progressive effacement of cervix between 20-37 weeks. Worldwide incidence of preterm labor is 6-10% (1). Approximately25% to 30% of preterm deliveries are to spontaneous unexplained preterm labor (2,3). Progesterone supplementation for the prevention of preterm labour has been advocated in this group. Vidaeff et al promoted the progesterone see-saw theory, according to it high progesterone levels prevent uterine contractions and low levels facilitate such contractions (4).

Aims and objectives:

To compare the effect of vaginal progesterone vis a vis placebo in the prevention of preterm labor, among women at increased risk of spontaneous preterm labor. To assess the efficacy of Progesterone in its use for tocolysis.

Material and methods:

High-risk patients seen in outpatient department and admitted in emergency in a private maternity nursing home from January 2015 to March 2016 were recruited in the study. One hundred pregnant women in the age group 20-35 years having history of preterm labor, prophylactic cervical cerclage, uterine malformation or having any other risk factor for spontaneous preterm labour and those with threatened premature labour on the basis of clinical history and evaluation by ultrasonography were included in the study. Women with multiple pregnancy, fetal anomalies, premature rupture of membrane, established preterm labor were not included. Fifty antenatal women were given 400 mg micronized sustained-release progesterone every daily , while another 50 antenatal women were given a placebo. Daily micronized sustained-release vaginal progesterone 200 mg 12-hourly was started at 16 weeks and discontinued at 36 weeks gestation or early if the woman progressed into established preterm labour.

Results and discussion:

A number of risk factors for preterm birth have been identified.Several scoring systems have been developed based on the epidemiologic risk factors ,daily habits , past history of preterm delivery in an attempt to predict women at risk for preterm birth. Unfortunately, reliance on risk factor-based screening protocols alone will fail to identify over 50% of pregnancies that deliver preterm and the majority of women who screen positive will ultimately deliver at term (2,5) The single greatest risk factor for preterm birth is a history of a prior unexplained spontaneous preterm delivery. Table 1shows the profile of women selected in this study considering these factors.

Table 1. Distribution of Women According to Profile

Patient profile	Group A (progesterone)	Group B (placebo)
Mean age (years)	28.6 years	27.6 years
Gravida 2	24 (48%)	22 (44%)
Gravida >3	26 (52%)	28 (56%)
Socioeconomic status	Class III - 20 (40%) Class IV - 30 (60%)	Class III - 28 (44%) Class IV - 22 (56%)
Preterm deliveries		
<2	16 (32%)	24 (48%)
=2	24 (48%)	18 (36%)
>2	10 (20%)	8 (16%)

The incidence of preterm labor was 54.9% in placebo group and 36.3% in progesterone-treated group in the study by Sibai et al (6) In the study by Fonseca et al (7) it was 28.5% and 13.8%, respectively, while it was 35.9% and 26.2% in the study by Meis et al (11). The incidence of preterm labor was 36% in placebo and 17.8% in progesterone group in this study ($p < 0.05$) (Table 2).

Table 2. Incidence of Preterm Labor in Progesterone treated Group vs Placebo

Study done by	Progesterone treated group	Placebo group
Sibai et al	36.3%	54.9%
Fonseca et al	13.8%	28.5%
Meis et al	26.2%	35.9%
Johnson et al	12.8%	40.9%
Present study ($p \leq 0.05$)	17.8%	36%

In the study by Meis et al (8) babies with birth weight <2.5 kg were 27% in progesterone-treated group and 41% in control group with relative risk (0.66), confidence interval (CI) 0.51-0.87. In our study, babies with birth weight <2.5 kg were 28% in progesterone treated group and 54% in control group .It was found that labor was postponed by 2-4 weeks in 88% of cases. In the study done by Johnson et al (9) and Da Fonseca et al (10) delivery of cases occurred at 38.6 weeks and 35.2 weeks, respectively while that of controls, occurred at 37 weeks and 36

weeks, respectively. Da Fonseca and co investigators randomly assigned 142 women at high-risk for preterm delivery (based on at least one previous spontaneous preterm birth, prophylactic cervical cerclage, or uterine malformation) to daily supplementation with progesterone vaginal suppositories (100 mg) or placebo from 24 through 34 weeks of gestation. Women randomized to progesterone prophylaxis had a significantly reduced risk of recurrent preterm birth at all gestational ages studied: < 37 weeks (14% vs 29% in the placebo group; P < .05), and < 34 weeks (3% vs 19%; P < .05). In this study, delivery of cases was delayed up to 38 weeks and of controls up to 34.5 weeks (Table 3).

Table 3. Mean Gestational Age in Progesterone Group vs Placebo Group

Study done by	Cases (weeks)	Controls (weeks)
Johnson et al	38.6	35.2
Da Fonseca et al	37	36
Present study	38	34.5

In the study by Meis et al (8) babies with birth weight <2.5 kg were 27% in progesterone-treated group and 41% in control group with relative risk (0.66), confidence interval (CI) 0.51-0.87. In our study, babies with birth weight <2.5 kg were 28% in progesterone treated group and 54% in control group .It was found that labor was postponed by 2-4 weeks in 88% of cases. In the study done by Johnson et al (9) and Da Fonseca et al (10) delivery of cases occurred at 38.6 weeks and 35.2 weeks, respectively while that of controls, occurred at 37 weeks and 36 weeks, respectively. Da Fonseca and co investigators randomly assigned 142 women at high-risk for preterm delivery (based on at least one previous spontaneous preterm birth, prophylactic cervical cerclage, or uterine malformation) to daily supplementation with progesterone vaginal suppositories (100 mg) or placebo from 24 through 34 weeks of gestation. Women randomized to progesterone prophylaxis had a significantly reduced risk of recurrent preterm birth at all gestational ages studied: < 37 weeks (14% vs 29% in the placebo group; P < .05), and < 34 weeks (3% vs 19%; P < .05). In this study, delivery of cases was delayed up to 38 weeks and of controls up to 34.5 weeks (Table 3).

TableIn the study of Meis et al (11) infants treated with progesterone had significantly lower rate of necrotizing enterocolitis, intraventricular hemorrhage and need for supplemental oxygen. Dodd et al (12) found that infants with intraventricular hemorrhage were very less in progesterone treated group. Meis and co investigators randomly assigned 459 patients with a documented history of a prior spontaneous preterm delivery to Progesterone or placebo beginning at 16 to 20 weeks of gestation and continuing until 36 weeks. Women randomized to prophylaxis had a significantly reduced risk of recurrent preterm birth at all gestational ages studied: < 37 weeks (36% vs 55% in the placebo group). Moreover, infants born to mothers treated with Progesterone had less perinatal morbidity and significantly reduced rates of necrotizing enterocolitis, intraventricular hemorrhage, and need for supplemental oxygen. In our study, it was found that number of days of neonatal intensive care unit stay was significantly reduced in infant delivered to progesterone treated group.

Conclusion

There are no consistent data that any intervention, including hydration, antibiotics, or tocolytic therapy, can delay delivery in women for longer than 24 to 48 hours once they have presented in preterm labor. For this reason, much attention has focused on preventive strategies. Recent data suggest that progesterone may be important in maintaining uterine quiescence in the latter half of pregnancy by limiting the production of stimulatory prostaglandins and inhibiting the expression of contraction- associated protein genes (ion channels, oxytocin and prostaglandin receptors, and gap junctions) within the myometrium (13). Several areas of controversy like dose, route of administration, economic analyses, still exist regarding the use of progesterone supplementation to prevent preterm birth. However preterm birth complicates one in eight deliveries and remains a major cause of perinatal morbidity and mortalityand It is now clear that in the weeks preceding labor, the onset of labor both at term and preterm is associated with a functional withdrawal of progesterone activity at the level of the uterus. It is data such as these that provide the rationale behind the use of progesterone supplementation to prevent preterm labor and birth. Appropriate candidates should be counseled about the potential benefits of progesterone supplementation from 16 to 20 weeks up to 37 weeks of gestation to prevent preterm birth in any subsequent pregnancy. Although supplemental progesterone does appear to be effective in preventing preterm birth in some high-risk women, it should not be seen as a panacea. The results of this study has shown promising result in reducing the incidence of preterm birth and low-birth weight babies

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