Research Article

Role of progesterone in prevention of preterm labor among women with a short cervix

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Abstract

Introduction: Asymptomatic women found at midgestation to have a short cervix are at increased risk for spontaneous early preterm delivery. Progesterone has an essential role in maintaining pregnancy, primarily through establishing uterine quiescence. **Methods:** This was a prospective randomized, single-blind, placebo-controlled study for a period of three years**.** 248 antenatal women with a ultrasonographic measurement of short cervix (10-20mm) at 20-22 weeks of gestation, were recruited for the study. The randomization allocation was 1: 1 (vaginal progesterone capsule: placebo). Subjects were instructed to introduce one capsule into her vagina at bedtime from 24 to 36 weeks gestation. The primary outcome measure was spontaneous delivery before 34 completed weeks of gestation. **Results:** Out of the 8900 women who underwent sonographic measurement of cervical length between 20 to 22 weeks of gestation, 2.84% (253) were reported to have a cervical length of 10–20 mm. 248 women were included in the analysis set (progesterone capsule, n = 125; placebo, n = 123). Patients of progesterone group had a significantly lower rate of preterm birth before 34 weeks of gestation compared to placebo group (20.8% Vs 36.5%; P = 0.006) and significantly higher rate of deliveries after 37 weeks of gestation in progesterone group compared to placebo group (60% vs 43%; P= 0.008). Neonates of progesterone group women had a significantly lower frequency of RDS than placebo group (7.2% vs 14.6%; P = 0.04). **Conclusion:** Routine assessment of the risk of preterm birth with cervical ultrasound along with vaginal progesterone for women with a short cervix is cost-effective. In women with a short cervix, treatment with progesterone reduces the rate of spontaneous early preterm delivery.

Keywords: Preterm labor, progesterone, transvaginal ultrasonography, cervix.

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INTRODUCTION

Preterm labor still remains as a challenge in practice of obstetric care. The incidence of preterm birth is variably reported between 5% and 11% of all births[1,2] and its prevention continues to remain elusive, with many reports indicating an increase in the prevalence of preterm birth over recent years.[3,4,5] Improvements in neonatal care have led to higher rates of survival among very premature infants, but a major effect on the associated mortality and morbidity will be achieved only by better identification of women at high risk for preterm delivery and by development of an effective intervention to prevent this complication. Asymptomatic women found at midgestation to have a short cervix are at greatly increased risk for spontaneous early preterm delivery.[6] Measuring the cervical length is a readily learned skill for obstetrical sonographers. Progesterone has an essential role in maintaining pregnancy, primarily through establishing uterine quiescence[7,8] This is achieved through suppression of the calcium-calmodulin-myosin light chain kinase system, reducing calcium flux and altering the resting potential of smooth muscle[9]. With this background we designed our study to evaluate the role of progesterone in prevention of preterm labor among women with a short cervix.

MATERIAL AND METHODS

This was a prospective randomized, single-blind, placebo-controlled study for a period of three years from December 2010 to November 2013. The study was approved by the Ethics Committee of College of Medicine and JNM Hospital, Kalyani**.** A total of 248

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antenatal women with a transvaginal ultrasonographic measurement of short cervix (cervical length 10-20mm) at 20 to 22 weeks of gestation, were recruited for the study in College of Medicine and JNM Hospital. Inclusion criteria were 1) singleton gestation 2) gestational age between 24 weeks-34 weeks 3) transvaginal sonographic cervical length 10-20mm; and 4) asymptomatic, i.e. without signs or symptoms of preterm labor. Exclusion criteria included 1) planned circlage 2) acute cervical dilation 3) History of allergic reaction to progesterone 4) current or recent progestogen treatment within the previous 4 weeks 5) chronic medical conditions that would interfere with study participation or evaluation of the treatment (e.g. seizures, psychiatric disorders, uncontrolled chronic hypertension, congestive heart failure, chronic renal failure, uncontrolled diabetes mellitus with end-organ dysfunction, active thrombophlebitis or a thromboembolic disorder, active liver dysfunction , known or suspected malignancy of the breast or genital organs) 6) major fetal anomaly or known chromosomal abnormality 7) uterine anatomic malformation 8) vaginal bleeding or 9) known or suspected clinical chorioamnionitis. Participants were provided written informed consent form for study prior to participation in the trial. The randomization allocation was 1: 1 (vaginal progesterone capsule: placebo). Subjects were instructed to introduce one capsule (200mg) into her vagina every night before going to sleep from 24 to 36 weeks gestation and were asked to return to our study center every 2 weeks. During each visit, subjects were interviewed to determine the occurrence of adverse events, use of concomitant medications and compliance with study drug. The obstetrical records of all patients delivering before 34 weeks were examined to determine whether the delivery is medically indicated or spontaneous. Patients who developed preterm labor during the study were treated according to the standard practice of this institution. The primary outcome measure was spontaneous delivery before 34 completed weeks (238 days) of gestation. The secondary outcome measures were birth weight, fetal or neonatal death, major adverse outcomes before discharge from the hospital (intraventricular hemorrhage, respiratory distress syndrome, retinopathy of prematurity, or necrotizing entercolitis), and need for neonatal special care (admission to a neonatal intensive care unit, ventilation, phototherapy, treatment for proven or suspected sepsis, or blood transfusion).Parameters of evaluation were spontaneous delivery before 34 completed weeks of gestation, adverse effects of progesterone, fetal or neonatal death and major adverse neonatal outcomes before discharge from the hospital (intraventricular hemorrhage, respiratory distress syndrome, or necrotizing entercolitis) and need for neonatal special care.

RESULTS

Of the 8900 women who underwent sonographic measurement of cervical length between 19 + 0and 23 + 6 weeks of gestation, 2.84% (253) were reported to have a cervical length of 10–20 mm. 250 women agreed to participate and were randomized (vaginal progesterone capsule, n = 125; placebo n = 125) , of whom 2 were lost to follow-up. Thus, 248 women were included in the analysis set (vaginal progesterone capsule, n = 125; placebo, n = 123). The trial ended on the delivery date of the last delivered participant. Baseline maternal characteristics were similar between the placebo and the vaginal progesterone groups (Table 1). Of the 248 women, 8.87% (n = 22) had a history of a previous preterm birth between 20 and 35 weeks of gestation.

Table 1: Characteristics of study groups

Characteristics	Progesterone group	Placebo group	P value
Age (years)Average	23.128	23.138	0.98
Standard Deviation	3.553	3.495	
BMI*Average	23.056	22.85	0.5
Standard Deviation	2.643	2.89	
Obstetric history Primipara	85 (68%)	86 (69.9%)	0.78
No previous preterm birth	28 (22.4%)	27 (21.9%)	0.96
H/O previous preterm birth	12 (9.6%)	10 (8.13%)	0.26
Cervical length (millimeter) Average	14.312	14.42	0.75
Standard Deviation	2.579	2.755	
Gestational age at 1st dose Average	159.168	160.22	0.01
Standard Deviation	3.743	3.345	

*BMI (Body Mass Index) - Weight in kilogram/height in metre^2.

Patients allocated to receive vaginal progesterone capsule had a significantly lower rate of preterm birth before 34 weeks of gestation compared with those allocated to placebo (20.8% (n = 26) vs. 36.5% (n = 45); P = 0.006). There was also significantly higher rate of deliveries after 37 weeks of gestation in progesterone capsule group compared to placebo group (60% (n=75) vs. 43% (n=53); P= 0.008). In terms of infant outcome, neonates born to women allocated to receive vaginal progesterone had a significantly lower frequency of RDS than did those born

to women allocated to receive placebo (7.2% (n = 9) vs. 14.6% (n = 18); P = 0.04). The other neonatal outcomes are listed in Table 2. Besides RDS, there was significantly lower rate of infants born less than 1.5 kg in progesterone group compared to placebo group (8% (n=10) vs. 20.3% (n=15); P= 0.007) as seen in Table 2.

Table 2: Outcome according to study group

Outcome	Progesterone group	Placebo group	P value
Primary outcome <34 weeks	26 (20.8%)	45 (36.5%)	0.006
Secondary outcome <28 weeks	7 (5.6%)	15 (12.1%)	0.069
>37 weeks	75 (60%)	53 (43%)	0.008
Infant birth weight<2.5 kg	30 (24%)	44 (35.7%)	0.04
<1.5 kg	10 (8%)	25 (20.3%)	0.007
Respiratory Distress Syndrome (RDS)	9 (7.2%)	18 (14.6%)	0.045
Neonatal sepsis	3 (2.4%)	5 (4.06%0	0.356
Necrotizing enterocolitis	0	1	0.3173
Intraventricular Haemorrhage	1 (10.8%)	3 (2.4%)	0.113
Perinatal death	0	1	0.3173

There was no case of congenital anomaly in either group. There were no major adverse events or side effects in either group. Regarding labor and delivery data, there were no meaningful differences in method of delivery.

DISCUSSION

The prevention of preterm birth is a major healthcare priority. The American College of Obstetricians and Gynecologists Committee on Obstetric Practice recommends that women who have had a previous preterm delivery should be considered for treatment with progesterone in a subsequent pregnancy but notes that the ideal formulation, optimal route of delivery, and long-term safety of progesterone remain unknown.[10] Epidemiologic and animal studies have found no significant relationship between clinically administered progestational drugs and congenital malformations.[11] The results of our randomized study demonstrate that in women with a short cervix, the daily vaginal administration of 200 mg of progesterone from 24 to 34 weeks of gestation significantly reduces the rate of spontaneous preterm delivery. The primary result of our study is similar to that reported by Fonseca *et al*.[12], who found that vaginal progesterone (200 mg vaginal capsules) administered to women with a cervical length ≤15 mm at a median gestational age of 23 weeks reduced the rate of spontaneous preterm (<34 weeks) delivery by 44%.In another similar multicentric trial by S S Hassan *et al*, there was a 45% reduction in the rate of preterm delivery before 33 weeks with 38% reduction in the rate of preterm birth <35 weeks, a 50% reduction at <28 weeks, and a 53% reduction in the rate of birth weight <1500 g on vaginal use of progesterone in women with short cervix (≤2cm). In addition, the reduction in preterm birth observed in that trial translated into the improvement of clinically important neonatal outcomes such as RDS and three composite perinatal mortality/neonatal morbidity scores.[13] We used 200 mg of progesterone, in contrast to the 100-mg dose used in a randomized trial of women with a history of preterm birth.[14] This high dose was chosen in several studies because patients with a very short cervix are particularly high risk for preterm delivery.[15,16] S. S. Hasan *et al* also used 200 mg of progesterone vaginally in their study.[13] Our study excluded twin gestations, which have not been shown to benefit from the prophylactic administration of progesterone[17] or 17 alpha-hydroxyprogesterone caproate[18,19]. The cervical length for entry into our study was 10–20 mm. Patients with a cervical length of 10 mm or less has a higher rate of intra-amniotic infection/inflammation[20] and are less likely to benefit from progesterone administration than are patients with a longer cervix. Use of progesterone in patients with cervical length up to 20 mm was found to have a beneficial effect in preventing preterm labor.[13] Sonographic cervical length is the most powerful predictor for preterm birth in the index pregnancy and is more informative than is a history of previous preterm birth.[21,22] Selecting patients for prophylactic administration of progestogens based only on a history of a previous preterm birth[23,14,24] would have limited effect on the prevention of preterm delivery worldwide, because most women who deliver preterm neonates do not have this history. Moreover, such strategy cannot be implemented in nulliparous women; therefore, universal risk assessment (primigravidae and parous women) is possible with transvaginal cervical ultrasound.[13] Romero R *et al* concluded in their article that routine assessment of the risk of preterm birth with cervical ultrasound coupled with vaginal progesterone for women with a short cervix is cost-effective, and the implementation of such a policy is urgently needed. Vaginal progesterone is as effective as cervical circlage in reducing the rate of preterm delivery in women with a singleton gestation, history of preterm birth, and a short cervix (<25 mm).[25]

CONCLUSION

Preterm birth is a significant problem in obstetric care, affecting women with considerable health hazards for infants leading to economic burden on their family. Routine assessment of the risk of preterm birth with cervical ultrasound along with vaginal progesterone for women with a short cervix is cost-effective. In women with a short cervix, treatment with progesterone reduces the rate of spontaneous early preterm delivery.

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