International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Mohapatra K et al. Int J Reprod Contracept Obstet Gynecol. 2015 Dec;4(6):1793-1797
www.ijrcog.org

pISSN 2320-1770 | eISSN 2320-1789

DOI: http://dx.doi.org/10.18203/2320-1770.ijrcog20151250

Research Article

Role of vaginal progesterone in reducing the rate of preterm labour in women with a sonographic short cervix

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Received: 08 November 2015
Accepted: 23 November 2015

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ABSTRACT

Background: Preterm labour is responsible for not only neonatal morbidity and mortality but also has long term consequences .Till now there is no effective method of prevention. Progesterone has shown promising result. But ideal candidate, ideal route and when to start the treatment are still in dilemma. The present study was undertaken to know the role of progesterone on pregnant women with sonographically short cervix.
Methods: This prospective case control study was started on 100 pregnant women with sonographic short cervix (≤2.5 cm) and between 19 – 29 weeks of gestation. 60 women, some with history of midtrimester abortion or preterm labour and some without this history were treated as cases and were given vaginal progesterone pessary 200 mg once daily till rupture of membrane or onset of labour or up to 36 weeks of gestation whichever is earlier. 40 women without any history of midtrimester abortion or preterm labour were treated as control and followed up.
Results: Among the cases 18.3%, delivered preterm and 81.7% were term deliveries. Respective proportions among control were 40% and 60% respectively. 26 among the cases and all women of control group did not have history of preterm labour and mid trimester abortion. In the case group 26.9% and in the control group 40% had preterm deliveries. Though the proportion of labour was lower among the cases it is not statistically significant ($p = 0.276$). There is mean prolongation of gestational age by 8.4± 1.29 weeks in case group in present pregnancy compared the previous one in cases with history of preterm labour and midtrimester abortion which was statistically significant .When neonatal complication are compared there is no significant difference between the two groups.
Conclusions: Vaginal progesterone started from midtrimester in pregnant ladies with short cervix with previous history of midtrimester abortion or preterm labour is effective in reducing the rate of preterm birth.

Keywords: Preterm labour, Progesterone, Short cervix

INTRODUCTION

Preterm birth defined as child birth occurring at less than 37 weeks. It is a major determinant of neonatal mortality and morbidity and has long term adverse consequences.[1,2] Of all early neonatal deaths that are not related to congenital malformation, 28% are due to preterm labour.[3] Morbidities like cerebral palsy, sensory deficits, learning disabilities and respiratory illnesses extend to later life resulting in enormous physical, psychological and economic costs.[4,5] About 9.6% of all birth around the world are preterm (2005) i.e. about 12.9 millions. Africa and Asia contributes to 85% of it.[6] Preterm labour is multifactorial in origin hence called 'Preterm Parturition Syndrome' and efforts to prevent it is largely unsuccessful. Recent date suggests that progesterone may be important in maintaining uterine quiescence by limiting the production of prostaglandins and inhibiting the expression of contraction associated protein genes within the myometrium.[7-9] ACOG recommends progesterone supplementation to be restricted to women with singleton pregnancy and a previous history of

spontaneous preterm birth.[10] At present there is little information available regarding the optimal dose of progesterone , mode of administration ,gestational age to start therapy or duration of therapy. There is evidence that pregnant women with cervical shortening may also benefit although this indication is not yet approved by FDA.

METHODS

This is a prospective interventional case control study conducted on 100 subjects in the department of O & G, S.C.B. Medical College, Cuttack, Odisha, India.

Inclusion criteria are singleton pregnancy with gestational age between 19 and 29 weeks and asymptomatic with transvaginal sonographic cervical length between 10-25 mm. Pregnant women with planned circlage, acute cervical dilation , vaginal bleeding, progesterone allergy, uterine malformation known or suspected clinical chorioamnionitis were excluded from the study. A detailed history especially obstetric history regarding mid trimester abortion or preterm labour was taken and physical examination was done. Cervical length was measured by TVS in empty bladder.

100 candidates with short cervix (≤25 mm) were taken for the study. 60 women with short cervix were selected as cases and treated with micronized vaginal progesterone 200mg once daily till 36 weeks, rupture of membrane or onset of labour whichever is earlier .In this group some women had prior history of spontaneous preterm labour or mid trimester abortion. Other 40 women without any history of spontaneous preterm labour or mid trimester abortion were followed up till delivery. Primary outcome of this study was preterm birth before 37 weeks. The key secondary outcomes were neonatal morbidities.

Statistical analysis was performed by SPSS-16 software. Descriptive analysis like mean, SD has been carried out for comparison of mean levels of different parameters under study. Comparison of mean of characteristics between case and control has been undertaken by independent sample –t – test. Test of association of categorical variables with case and control has been studied with the help of chi-square Test.

RESULTS

One hundred pregnant women participated in the study. However there is no significant difference in age, gestational age at first presentation and cervical length in case and control group. Prior history of spontaneous preterm labour, midtrimester abortion was there in 34 (56.7%) pregnant women in case group. No pregnant women of control group had such history. Mean duration of treatment in case group was 10.3 weeks.

Table 1: Demographic characteristics of women.

characteristics	Case (n = 60)	Control (n = 60)	Independent sample 't' test	'p'
Mean age	25.5± 2.825*	24.35± 1.703*	2.308	0.63
Obstetric history H/O preterm birth and midtrimester abortion	34 (56.7%)	0		0.06
Gestational age at first presentation	25.1 ± 2.1*	24.3 ± 1.6*	1.927	0.05
Cervical length	2.282 ± 0.116*	2.270 ± 0.097*	0.527	0.60
Duration of treatment	10.3±3.1	-		-

Values are expressed in Mean ± SD

Table 2: Proportion of Preterm birth by subject Groups.

Gestational age at delivery	Case		Control		Total		Chi-Square and 'p' value
	No.	%	No.	%	No.	%	
Preterm	11	18.3	16	40	27	27	$\chi^2 = 5.716$ 'p' = 0.017
Term	49	81.7	24	60	73	73	
Total	60	100	40	100	100	100	

Table 2 shows that among the cases 18.3% delivered preterm and 81.7% were terms and the respective proportion among control was 40% and 60%.The chi-square test of independence revealed higher association with term birth among cases (p = 0.0170).

Table 3 shows that the relative risk of preterm among cases was 0.607 while that among the control was 1.802. This implied lower relative risk of preterm birth among the cases is seen.

Table 3: Risk estimate for preterm in case and control.

Risk Estimate of Preterm/Term	Value	95% Confidence Interval	
n = 100		Lower	Upper
For cohort Group = Case	0.607	0.375	0.983
For cohort Group = Control	1.802	1.146	2.835

Table 4 shows that there is a mean prolongation of gestational age by 8.4± 1.290 weeks in case group in present pregnancy compared to the previous one which was found to be statistically significant.

Table 5 shows that 66 subjects, 26 among the cases and 40 among the controls did not have history of preterm labour or midtrimester abortion. In the case group 26.9% and in the control group 40% had preterm delivery. Though the proportion of preterm labour was lower among the cases it is not statistically significant (p = 0.276)

Table 4: Comparison of GA at delivery with GA at previous delivery or abortion.

Gestational age in weeks	Paired Samples Statistics (n =34)		
	Mean	Std. Deviation	'P'
GA at delivery in present pregnancy	37.13	1.697	p= 0.00
GA at previous delivery or abortion	28.73	6.828	
Mean difference ± S.E. in weeks	8.4±1.290		

S.E.- Standard Error

Table 5: Preterm birth among women with no h/o preterm birth or midtrimester abortion by groups.

Gestational age at delivery	Case		Control		Total		Chi-Square and 'p' value
	No.	%	No.	%	No.	%	
Preterm	7	26.90	16	40.00	23	34.80	χ^2 = 1.187 'p' = 0.276
Term	19	73.10	24	60.00	43	65.20	
Total	26	100.00	40	100.00	66	100.00	

While comparing the neonatal complication like RDS, LBW, VLBW, no complication was seen in 75% and 60% in case and control group respectively. There is no statistically significant difference in complications among the case and control group.

Table 6 shows that percentage of term delivery has increased with the increase in cervical length both among cases and controls.

Table 6: Comparison of GA at delivery with cervical length.

Cervix Length (Cm.)	Gestational Age	Group				Total	
		Case		Control			
		Number	%	Number	%	Number	%
2 - 2.25	Term	17	73.9	6	42.9	23	62.2
	Preterm	6	26.1	8	57.1	14	37.8
	Total	23	100	14	100	37	100
>2.25 - 2.5	Term	32	86.5	18	69.2	50	79.4
	Preterm	5	13.5	8	30.8	13	20.6
	Total	37	100	26	100	63	100
Total	Term	49	81.7	24	60	73	73
	Preterm	11	18.3	16	40	27	27
	Total	60	100	40	100	100	100

Table 7: Neonatal complications by group.

Complications	Group				Chi-Square and 'p' value
	Case		Control		
	No	%	No	%	
No Complication	45	75	24	60	χ^2 = 9.292 'p' = 0.026
RDS	5	8.3	0	0	
LBW / VLBW	7	11.7	10	25	
RDS & LBW	3	5	6	15	
Total	60	100	40	100	

DISCUSSION

Preterm birth is the leading cause of morbidity and mortality worldwide and prevention is an important healthcare priority. Preterm parturition is caused by multiple etiologies. One of the mechanism of the disease is the ultimate decline in progesterone action, which can present as a clinically silent sonographic short cervix in the midtrimester abortion.[11] The basis for this hypothesis is that the administration of progesterone receptor antagonist (Mifepristone) to pregnant women lead to cervical priming (which includes shortening of cervix).[12-14] For these reasons it has been proposed that a progesterone deficiency can be corrected by the administration of this hormone in close anatomic proximity to the cervix thereby preventing preterm labour.

One hundred asymptomatic women with singleton pregnancy with a TVS cervix length (≤25 mm) were included in the study after taking consent. The case groups were given vaginal progesterone and control group were only followed up.

Mean age in the case and control group were 25.5 ± 2.827 years and 24.35 ±1.703 years respectively. This is in accordance to the study by Gamze et al whose mean maternal age was 25.38 ± 4.54 years.[15] Mean cervical length in our study was 2.282 ±0.116 cm and 2.270 ± 0.977 cm in the case and control group respectively which was corroborating with the study by Romero et al.[16] But in the PREGNANT trial a sonographic short cervix was taken as 10-20 mm.[17]

Mean gestational age of enrollment among cases was 25.1 ± 2.1 weeks and among controls 24.3 ± 1.6 weeks but in PREGNANT trial asymptomatic women were enrolled at 19-23 weeks of gestation, this is because patients present to us at a later gestational age.

Mean duration of treatment for cases in our study was 10 ± 3.1 weeks .but the study conducted by da Fonseca et al women with a short cervix (≤15 mm) were treated from 24 to 34 weeks.[19]

Table 2 shows that in our study 18.3% were preterm and 81.7% were term among the cases and the respective proportion among control was 40% and 60%. The study conducted by da Fonseca et al showed the similar results. But in PREGNANT trial patient had a lower rate of preterm birth before 34 weeks than those allocated to placebo (8.9% vs 16.1%) which is much lower than the present study. This may be because their primary endpoint of preterm birth is 34 weeks and they had used 90mg of progesterone gel instead of pessaries.

Table 4 shows that in our study in the case group, among cases with history of preterm birth or midtrimester abortion gestational age (GA) at delivery (n= 34) has a mean of 37.13 ± 1.697 weeks and GA at previous preterm delivery or abortion had a mean of 28.73 ± 6.828 weeks with a mean prolongation of GA by 8.4 ± 1.290 weeks which was found to be statistically significant. In an individual patient metaanalysis women treated with vaginal progesterone had a significant reduction in the rate of preterm birth < 33 weeks (RR: 0.58; 95% CI: 0.42 – 0.80).

Table 5 shows that Twenty six among the cases and 40 among the controls with short cervix did not have history of preterm labour; but the preterm delivery was 26.9% and 40% in cases and controls respectively. But chi-square test did not reveal any significant association (p =0.276) of prevention of preterm labour in a case of short cervix without prior history of preterm labour or midtrimester abortion. But in the trial conducted by da Fonseca et al, patients allocated to receive vaginal progesterone had a lower rate of preterm labour (19.2% Vs 34.4%). It may be due to late enrollment or small sample size in our study.

Table 6 shows that in our study in the cervix length 2-2.24cm, term delivery was 73.9% and 42.9% among cases and control respectively. In the cervix length group 2.25 - 2.5 cm term delivery among cases was 86.5% and 69.2% among the controls. In the study conducted by Timor Tritsch et al the mean cervical length was shorter in cases delivery before 37 weeks than in those delivery at term (16.9 mm Vs 31.9 mm).[18] The percentage of term delivery has increased with the increase in cervical length both among cases and controls in both the studies.

Table 7 shows that neonatal complications were not different in both the groups in our study, where as in PREGNANT trial neonates born to mothers to receive vaginal progesterone gel had a significantly lower frequency of RDS than the placebo group (3% vs 7.6%).

CONCLUSIONS

Progesterone supplementation prevents preterm birth only in one third of cases in ideal circumstances. A better understanding of the molecular mechanism by which progesterone acts to maintain myometrial quiescence and prevent uterine contractions and cervical changes will allow obstetric care provider to develop more effective interventions.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Mohapatra K, Ghosh S, Dash R, Sahoo B. Role of vaginal progesterone in reducing the rate of preterm labour in women with a sonographic short cervixInt J Reprod Contracept Obstet Gynecol 2015;4:1793-7.