A Randomized Controlled Trial to Evaluate the Effect of Vaginal Progesterone on the Incidence of Spontaneous Early Preterm Delivery in Asymptomatic Women Found At Routine Mid-Trimester Screening to Have a Short Cervix

¹Priyankar Kanrar, ²Debdut Banerjee, ³Chaitali Karmakar, ⁴Dr. Arunima Chaudhuri, ⁵Deepteemayee Sahoo, ⁶Sisir Kumar Biswas

¹MS G &O RMO cum Clinical Tutor, G &O BMCH Burdwan Medical College and Hospital, West Bengal, India.

²MS G&O, Assistant Professor G&O, Burdwan Medical College and Hospital, West Bengal, India.

³MS G&O, RMO cum Clinical Tutor, G&O College of Medicine and Sagore Dutta Hospital, Kamarhati, West Bengal, India.

⁴Associate Professor Department of Physiology, Rampurhat Government Medical College and Hospital, West Bengal, India.

⁵MS trainee resident, G &O Burdwan Medical College and Hospital, West Bengal, India. ⁶MS trainee resident G &O, Burdwan Medical College and Hospital, West Bengal, India. *Corresponding Author: Debdut Banerjee,

ABSTRACT:

Background: Aims: To evaluate the effect of vaginal progesterone on the incidence of spontaneous early preterm delivery in asymptomatic women found at routine mid-trimester screening to have a short cervix. **Materials and methods:** This prospective randomized single blinded interventional study was conducted in a time span of one year in a medical college of West Bengal after taking Institutional ethical clearance and informed consent of the subjects.

137 mothers, having cervical length of \leq 2.5cm and who fulfilled the exclusion and inclusion criteria, were found to be eligible for inclusion in the study. They were randomized into study and control group. Mothers in the study group received 200 mg of natural micronized progesterone vaginally from 20-24 wks of gestation up to 33 weeks 6 days or until start of spontaneous labour pain, whichever is earlier. Mothers in the control group received multivitamin capsules vaginally for the same duration. Data on pregnancy outcome were obtained from the hospital records. The obstetrical records of all patients delivering before 37 weeks were examined to determine whether the delivery was medically indicated or spontaneous. Spontaneous deliveries included those with spontaneous onset of labor. Pregnancy outcomes were compared in these groups. SPSS version 16 was used to analyze the data.

Results: There was no difference in the basic characteristics between the two groups i.e. age, parity, income, BMI and previous preterm delivery and in gestational age and cervical length. Most of the patients had cervical length between > 20mm to \leq 25mm in two groups, 79% in progesterone group and 68% in placebo group. 3 patients in progesterone group had cervical length \leq 15mm and 1 patient in placebo group had cervical length \leq 15mm.On analysis, no statistical difference was noted and both groups were comparable. It was found that 26% patients in progesterone groups had preterm birth < 37 weeks period of gestation and 54% patients in placebo groups.

Conclusion: Vaginal administration of progesterone in cases of short cervix (< 2.5 cm) can prevent preterm birth \leq 34 weeks by at least 16.9 % and 27.6 % before <37 weeks. Therefore, in a documented case of short cervix progesterone administration is justified to avoid / minimize the preterm labor before 34 weeks and its associated sequalae.

Keywords: Cervical length, pre-term labor, progesterone.

INTRODUCTION

According to the World Health Organization, 3 million newborns die each year due to complications related to pregnancy and childbirth¹ and preterm birth is a leading cause of neonatal and infant mortality as well as short and long-term disability.¹ The infant mortality rate (IMR) per 1,000 live births for infants born at less than 32 weeks of gestation was 180.9, nearly 70 times the rate for infants born between 37 and 41 weeks of gestation.²A recent systematic review has estimated that 12.9 million births, i.e. 9.6% of all births world wide

I.

were preterm³ Rates for preterm birth range between 6% and 12% in developed countries and are generally higher in developing countries.^{3, 4}Nearly 24% children born prematurely across the globe in 2010 were from India.¹

Although all births before 37 weeks of gestation are defined as preterm, most damage and death occurs in infants delivered before 34 weeks.^{5, 6} The lower the gestational age at delivery, the greater the need for expensive interventions and support to improve the infant's chances of survival. About 40% of all preterm births occur before 34 weeks and 20% before 32 weeks.^{3, 4}

Preterm birth is the leading cause of perinatal morbidity and mortality worldwide.¹For surviving infants, the health implications of immaturityare significant, particularly in relation to respiratory distress syndrome⁷, and subsequent risk of developing chronic lung disease⁸, and other long-term neuro developmental disabilities including cerebral palsy.⁹Neurodevelopmental disabilities can range from major disabilities such as cerebral palsy, mental retardation, and sensory impairments to more subtle disorders, including language and learning problems, attention deficit hyperactivity disorder, and behavioral and social-emotional difficulties, cognitive deficits, academic underachieving, grade failures and increased need for remedial assistance. Preterm infants are also at increased risk for growth and health problems, such as asthma or reactive airway disease, with associated increased emotional, physical, and monetary costs to families and society.

Two-thirds of preterm births in the United States are spontaneous (sPTB) and account for half of infant hospitalization costs and a quarter of pediatric costs.^{5, 6}In 2005, over \$26.2 billion was spent in the United States on prematurity-related medical problems. It would make sense that decrease in incidence of prematurity would benefit the mother, the child, the family, and society in general with decreased morbidity, mortality, and societal long-term burden as well as cost savings. As an example, CIGNA HealthCare reported a \$6000 per pregnancy cost savings with good maternity care resulting in slight decrease in prematurity.^{10, 11}

Focus has now shifted towards primary and secondary prevention and to identify multiple risk factors for preterm births. Two of the most important predictors of preterm delivery are prior obstetrical history and cervical effacement measured as shortened cervical length (sCL) by ultra sound. The definition of short cervix has varied in various studies, but most commonly accepted is ≤ 2.5 cm in the midtrimester (20 - 24weeks) of pregnancy, though risk of spontaneous preterm birth (sPTB) increases as the cervical length decreases.¹²

In a well-designed double blinded, multi-centric observational study of women with prior preterm birth at less than 32 weeks, serial measurements of cervical length by transvaginal Ultrasonography had a good predictor of preterm birth. With this method, using a cervical length cut off of 25 mm, sensitivity, specificity and PPV of an abnormal test were 69%, 80%, and 55% respectively. Accuracy of transvaginal Ultrasonography depends on gestational age. Thus in women with clinical risk factor of preterm birth, the PPV for preterm birth of a cervical length less than 25mm at 14 to 18 weeks are 70% whereas it drops to 40% when the short cervix is found between 18 and 20 weeks¹².

Progesterone is believed to play an important role in continuation of pregnancy and keeping the uterus in a relaxed state. Antenatal administration of progesterone, irrespective of route and dose, appears to reduce the risk of preterm birth. Randomized trials have shown that progesterone administration in women who previously delivered prematurely reduces the risk of recurrent premature delivery.¹³A study¹⁴ showed that administration of vaginal progesterone gel to women with a short cervix (10-20 mm) was associated with a substantial reduction in the rate of preterm delivery <33 weeks (primary end point),<35 weeks and <28 weeks of gestation. Cochrane review¹⁵analyzed the benefits and harms of progesterone for the prevention of preterm birth for women considered at risk of preterm delivery. The American College of Obstetrics and Gynecology recommends that the use of antenatal progesterone to prevent preterm birth should be restricted to women with a documented history of prior spontaneous preterm delivery at less than 37 weeks or to women incidentally (i.e. without routine screening) found to have a short cervix (less than 15 mm).

In a population of 2107 women studied, low risk population without recognized risk factors, the incidence of preterm birth before 35 weeks' gestation when cervical length was < 25 mm measured at 24 weeks' gestation, has been reported as 3%.¹⁶There is insufficient evidence to recommend routine TVS for cervical length assessment in women with no risk factors.¹⁷However during routine maternal and fetal USG scan CL can be measured.

Regarding conservative management, there is no evidence to show that insertion of an ultrasound indicated cerclage in woman diagnosed as a short cervix reduce their risk of preterm birth and also no evidence that bed rest or hospitalization improves pregnancy outcome. But 3centres Collaboration recommend offering vaginal progesterone 90-200mg to women shown to have a cervix < 20mm at 18-22 weeks 'gestation. On average, this would be expected to halve their risk of preterm birth.^{18,19}

We designed a randomized controlled trial to evaluate the effect of vaginal progesterone on the incidence of spontaneous early preterm delivery in asymptomatic women found at routine mid-trimester screening to have a short cervix (≤ 25 mm).

II. MATERIALS AND METHODS:

Study Area:

This prospective randomized single blinded interventional study was conducted in a time span of one yearin a medical college of West Bengal after taking Institutional ethical clearance and informed consent of the subjects.

The study was conducted on the antenatal patients attending the outpatients department and offered informed consent to undergo a TVS at 20 - 24 weeks of gestation during their routine anomaly scan. Gestational age was calculated using Naegle's formula and confirmed by Ultrasonography.

Inclusion Criteria:

1. Singleton pregnancy

Exclusion Criteria:

During entry in the study

- 1. Multifetal gestation
- 2. Patient refusal to participation
- 3. Gestation more than 24 weeks at the USG diagnosis of short cervix
- 4. Progesterone use in the current pregnancy (ongoing or past)
- 5. Presence of a cervical cerclage
- 6. Presence of a low lying placenta
- 7. Presence of major fetal anomalies

During conduction of study

1. Preterm prelabour rupture of the membranes (PPROM)

137 mothers, having cervical length of \leq 2.5cm and who fulfilled the exclusion and inclusion criteria, werefound to be eligible for inclusion in the study. They were randomized into study and control group. Mothers in the study group received 200 mg of natural micronized progesterone vaginally from 20-24 wks of gestation up to 33 weeks 6 days or until start of spontaneous labour pain, whichever is earlier. Mothers in the control group received multivitamin capsules vaginally for the same duration.

Data Collection Technique and Tool:

- The cervical length was measured by the sonography machine of the make GE logic Q7 Pro/GE logic Q5 using 4.5 MHz probe.
- Natural micronized progesterone capsule.
- Multivitamin capsule (Placebo).
- All the data that were gathered were compiled in a tabulated manner and was analyzed using statistical software (SPSS version 16) as per the nature of the data.
- We used amber coloured, emptied, washed and dried "Betadine" bottles as a container for progesterone and placebo(identical appearing multivitamin capsule) &lebeled asstudy and control respectively.
- Both natural micronized progesterone and multivitamin capsule are soft gelatin capsule and identical looking. The drug and placebo were free supplied by companies, which had no involvement in study interpretation.
- Cases were given natural micronized progesterone 200 mg vaginally at bedtime from 20-24 weeks to 33 weeks 6 days of gestation or until start of spontaneous labour pain, whichever was earlier.Controls were given placebo (multivitamins) capsules vaginally.
- The pregnant mothers during their routine follow up visits were asked about symptoms related to administration of progesterone, like sleepiness, fatigue, headache and vaginal irritation. Any history of painful uterine contraction and vaginal discharge were also asked for. A detailed examination of the maternal pulse, blood pressure, weight, height, tone of uterus, fetal movement and fetal heart rate were also recorded.

• Data on pregnancy outcome were obtained from the hospital records. The obstetrical records of all patients delivering before 37 weeks were examined to determine whether the delivery was medically indicated or spontaneous. Spontaneous deliveries included those with spontaneous onset of labor.

Parameters taken:

Maternal:

- 1. Name
- 2. Age
- 3. Hospital Registration no:
- 4. Income/month
- 5. LMP& EDD
- 6. Obstetric Score
- 7. BMI
- 8. Weeks of gestation at randomization
- 9. Cervical length (mm) at the time of randomization
- 10. Period of gestation at delivery
- 11. Mode of delivery

Perinatal

- 1) Gestational age at delivery
- 2) Birth weight
- 3) Composite adverse outcome
- i) Intraventricular hemorrhage
- ii) Respiratory distress syndrome
- iii) Retinopathy of prematurity
- iv) Necrotizing enterocolitis
- v) Others
- 4) Composite therapy related outcome
- i) Admission to a neonatal intensive care unit
- ii) Ventilation
- iii) Phototherapy
- iv) Treatment for proven or suspected sepsis
- v) Blood transfusion
- vi) Others
- 5) Neonatal death

METHOD OF STUDY: Patient enrollment:



Follow up:

a. Patients were followed up throughout whole antenatal period.

b. At the time of randomization, the patients were informed that symptoms related to the administration of progesterone could include sleepiness, fatigue, headaches and vaginal irritation, but that these symptoms are common in pregnancy.

c. At each follow-up visit, we asked the patients whether they had noted an increase in severity or frequency of these symptoms and whether they had any new symptoms since the beginning of treatment.

d. Adherence was checked by counting the capsules at these visits.

e. Patients were admitted in our Institution as needed and were managed accordingly.

f. Pregnancy outcomes were compared in these groups. Two groups were managed in antenatal period as per our hospital protocol. During intrapartum period, mode of onset of labour, mode of delivery, gestational age at birth, birth weight, NICU admission and in post natal period any composite adverse outcome, need for any composite therapy, neonatal death have been calculated & compared in these two groups. SPSS version 16 was used to analyze the data.

III. **RESULTS**:

137 women who were considered eligible (having a cervical length of ≤ 25 mm and who fulfilled inclusion and exclusion criteria) for the study only 114 women (53 in the progesterone group 50 in placebo group) completed the study protocol successfully and so were considered for analysis of the observations. There was no difference in the basic characteristics between the two groups i.e. age, parity, income, BMI and previous preterm delivery and in gestational age and cervical length. Most of the patients had cervical length between > 20mm to ≤ 25 mm in two groups, 79% in progesterone group and 68% in placebo group. 3 patients in progesterone group had cervical length ≤ 15 mm and 1 patient in placebo group had cervical length ≤ 15 mm.On analysis, no statistical difference was noted and both groups were comparable.

Table 1 shows incidence of preterm birth < 37 weeks among two groups. It was found that 26% patients in progesterone groups had preterm birth < 37 weeks period of gestation and 54% patients in placebo groups had preterm birth < 37 weeks period of gestation with relative risk 0.489 and P value 0.004. The result was statistically highly significant.

Table – 1: Comparison of preterm birth < 37 wks between Progester	one group and Placebo group.
---	------------------------------

Progesterone group no (%)	Placebo group no (%)	Relative risk (RR)	95% CI	P value
14(26)	27(54)	0.489168	0.29 , 0.82	0.004**

P-value <0.05 (*significant) P-value <0.01 (**highly significant)

There were 14 cases of preterm birth < 37 weeks in progesterone group and 27 cases in the placebo group. So, vaginal administration of progesterone in cases of documented short cervix can reduce spontaneous preterm birth by 27.6 %. In our study we also found that vaginal administration of progesterone in cases of documented short cervix can reduce spontaneous preterm birth \leq 34 wks by at least 16.9 % (15.1% vs 32%). We also found that 7 patients in progesterone group and 11 patients in placebo groups with cervical length >1.5 to \leq 2 cm suffered from preterm labour and among mothers with cervical length > 2 to 2.5 cm, 4 in progesterone groups and 15 in placebo groups had preterm labour, that result was significant. 4 mothers had preterm labour with cervical length \leq 1.5 cm and 3 of them in progesterone group. That result may be due to less no of patients enrolled in our study or may be another reasons behind it. Our study failed to establish any straight forward relationship between cervical length \leq 1.5cm at 20-24 weeks and prediction of preterm labour before 34 weeks. There was statistically significant difference between the two groups (favouring progesterone treatment) as regards to admission in NICU (P value – 0.024) and treatment for sepsis (P value – 0.017).

Table 2 shows incidence of preterm birth \leq 34weeks among two groups. It was found that 15.1% patients in progesterone groups had preterm birth \leq 34 weeks period of gestation and 32% patients in placebo groups had preterm birth \leq 34 weeks period of gestation with relative risk 0.47 and P value 0.043. The result was statistically significant.

Table – 2:Comparison	of	preterm birth < 34 wks	between	Progesterone grou	ip and Placebo	group
	~-		Nee nee in		p and - meeso	8- ° ~ P

Progesterone group no (%)	Placebo group no (%)	Relative risk (RR)	95% CI	P value
8(15.1)	16(32)	0.471698	0.22 , 1	0.043*

P-value <0.05 (*significant)

P-value <0.01 (**highly significant)

Table 3 shows Distribution of Preterm Births in Progesterone and Placebo groups. Most of preterm birth occurred in moderate to late preterm group, 18.9% in progesterone group and 40% in placebo group (P value 0.016) which was statistically significant.

Table – 5. Distribution of Treterin Birthshi Trogesterone and Tracebo groups.								
	Progesterone group no (%)	Placebo group no (%)	Relative risk (RR)	95% CI	P value			
extremely preterm (<28 weeks)	0 (0.0)	1 (2)	0.00	NA	0.312			
Very preterm (28 to <32 weeks)	4 (7.5)	6 (12)	0.63	0.19 , 2.1	0.447			
moderate to late preterm (32 to <37 weeks)	10 (18.9)	20(40)	0.47	0.25 , 0.91	0.016*			

Table – 3: Distribution of Preterm Birthsin Progesterone and Placebo groups.

P-value <0.05 (*significant)

P-value <0.01 (**highly significant)

Table 4 shows that, among $CL \le 15$ mm ,incidence of extremely preterm birth 1 in placebo group but 2 very preterm birth occurred in progesterone group with P value was 0.014, statistically significant and 1 moderate to late preterm birth occurred in progesterone group. Among CL > 15mm to ≤ 20 mm, incidence of very preterm birth 3 in placebo groups and 1 in progesterone groups and incidence of moderate to late preterm birth 8 in placebo groups and 6 in progesterone groups. All results were statistically non significant. It was found that among CL > 20mm to ≤ 25 mm incidence of very preterm birth 3 in placebo groups and 1 in progesterone groups. All results were statistically non significant. It was found that among CL > 20mm to ≤ 25 mm incidence of very preterm birth 3 in placebo groups and 1 in progesterone groups. We found statistically highly significant result with P value 0.002 in case of moderate to late preterm birth.

Table- 4: shows relation between Cervical length at randomization and preterm birth

Preterm birth	Cervical 15mm	length ≤	P value Cervical length > 15mm to ≤ 20mm		P value	ical length >PCervical lenn to ≤ 20 mmvalue20mmto ≤ 25 mmto ≤ 25 mm		ength >	P value
	Progest erone groups	Placeb o groups		Progeste rone groups	Placebo groups		Progesteron e groups	Placebo groups	
extremely preterm (<28 weeks)	0	1	NA	0	0	NA	0	0	NA
Very preterm (28 to <32 weeks)	2	0	0.014*	1	3	0.631	1	3	0.233
moderatetolatepreterm(32to<37weeks)	1	0	0.221	6	8	0.279	3	12	0.002**

P-value <0.05 (*significant)

P-value <0.01 (**highly significant)

Mean birth weight in progesterone group was 2414.87gm and in placebo group was 2191.08 gm with P value 0.053, non-significant. Reports showed that 47 % baby in progesterone group and 54 % baby in placebo group had birth weight between 1500gm to \leq 2500gm.Regarding birth weight <1500gm, it was found that 3 in progesterone group and 7 in placebo group. We found 47 % baby in progesterone group and 32% baby in placebo group had normal birth weight i.e.>2500gm.The distribution as a whole was equally distributed among groups. Table 5 shows distribution of composite adverse outcomes in progesterone group 4% and in placebo group 20% with relative risk 0.188 and P value 0.01.Result was statistically highly significant. In a case of respiratory distress syndrome incidence were 15% in progesterone group and 16% in placebo group with P value 0.899.We found one patient in progesterone group and five in placebo group had retinopathy of prematurity, result was statistically non-significant and in case of necrotizing enterocolitis, result found that incidence were 8% in progesterone group and 16% in placebo group had retinopathy of significant.

Table – 5: Distribution of	f Composite adverse out	comes in Progesterone a	and Placebo groups.

Composite adverse outcomes	Progesterone group no (%)	Placebo group no (%)	Relative risk (RR)	95% CI	P value
Intraventricular haemorrhage(IVH)	2(4)	10(20)	0.188679	0.04 , 0.82	0.010*
Respiratory distress syndrome (RDS)	8(15)	8(16)	0.943396	0.38 , 2.32	0.899
Retinopathy of prematurity (ROP)	1(2)	5(10)	0.188679	0.02, 1.56	0.079
Necrotizing enterocolitis (NEC)	4(8)	8(16)	0.471698	0.15 , 1.47	0.181

P-value <0.05 (*significant)

P-value <0.01 (**highly significant)

IV. DISCUSSION

It is obvious from our study that in women with a short cervix, the daily vaginal administration of 200 mg of progesterone from 20-24 to 33 weeks 6 days of gestation significantly reduces the rate of spontaneous preterm delivery. There was no significant reduction in perinatal mortality. However, the trial was not designed with sufficient power to address these end points.

Both the study by Fonseca EB et al²⁰ and the currenttrial used a similar approach to identify the patientsat risk, namely, screening with transvaginal sonographyto diagnose a short cervix. Differences between thetrials are that our study excluded twin gestations, which have not been shown to benefit from the prophylactic administration of progesteroneor 17alpha-hydroxyprogesterone caproate. The cervical length for inclusion into the study by Fonseca et al⁴³ was 10–20 mm. We extended the upper limit of cervical length to 25 mm to explorewhether vaginal progesterone would have a beneficial effect beyond 20 mm and therefore expand its therapeuticrange. The treatment protocol in our study called forinitiation of vaginal progesterone as early as 20 weeks of gestation, continuing until 33 + 6 weeks, while Fonseca et al⁴³ began at 24 weeks and stopped at 34 weeks (it is possible that earlier treatment may confer more beneficial effects).

In our studythe distribution of age among the Progesterone group was from 19 years to 35 years of age with a mean of 25.92 years. In Place bogroup the age distribution was from 20 years to 33 years of age with a mean of 26.14 years with a P value 0.791 both groups were comparable. Distribution of Progesterone and Placebo Group in different age groups< 30 yrs, 30 yrs to ≤ 35 yrs was also comparable. This finding is in accordance with the study performed in Eduardo B. et al.²⁰

In our study the distribution of mean BMI among the Progesterone group was 23.74 kg/m² and among the Placebo group was 23.64 kg/m², statistically not significant. and distribution body mass index $\leq 25,>25$ to $\leq 30,>30$ kg/m² among Progesterone group was 6%,72%,21%,2% and in Placebo group was 0%,84%,14%,2% respectively , also statistically not significant, corresponding with the study performed in Eduardo B. et al.²⁰

According to our study, the distribution of parity, Nullipara, P_1 , P_2 among Progesterone group were 77.4%, 20.8%, 1.9% and among Placebo group were 60%, 38%, 2%, comparable in both groups.

In present study distribution of parous with h/o one previous preterm birthin Progesterone group was 5.66% and in Placebo group was 8%, statistically not significant(P value 0.638).

In our study we found that all mothers, parous with h/o one previous preterm birth in both group delivered prematurely, but the study done by Mercer BM et al²¹showed that only about 10% of spontaneous early preterm births occur in women with this history.

The discordance may be due to limited number of cases in our study and also we did not perform repeat measurement of cervical length every 2 weeks which was done in a case of very high risk womenincluding those with a previous second-trimester loss or very early spontaneous PTBwith short cervix, to find that any need for cerclage or not, as performed in Berghella V et al.¹²

In our study, we measured cervical length between 20 to 24 weeks POG with mean 160.75 days in Progesterone group and 159.86 days in Placebo group, with mean cervical length measured in Progesterone group 2.3 cm and in Placebo 2.32 cm.

In our study we found that 4 patients among 2508 antenatal mother i.e. 0.1595% had cervical length ≤ 15 mm,not comparable to study done by Fonseca EB et al.²⁰ Where1%-2% of the general population of women carrying an uncomplicated singleton gestation developa cervical length ≤ 15 mm before 24 weeks. This disparity due to less no of patients enrolled in our study.

In this study all of 4 patients delivered preterm baby, which don't match with study done by Eduardo B et al.²⁰In that study 30.9% among cervical length \leq 15 mmdelivered preterm.

In this study Cervical length at randomization in Progesterone and Placebo groups ≤ 15 mm, >

15mm to \leq 20mm, > 20mm to \leq 25mm were 6%,15%,79% and 2%,30%,68% respectively.

Our study showed that, spontaneous birth before 37 weeks of gestation was 26% in the progesterone group and 54% in the placebo group (relative risk, 0.489; 95% confidence interval [CI] 0.29 to 0.82). This result was statistically highly significant, P was 0.004. This finding is in accordance with the study performed inDodd et al.¹⁵

In our study, we found that spontaneous birth before 34 weeks of gestation was 8 (15.1%) in progesterone group and 16 (32%) in the placebo group (relative risk 0.471698, 95% confidence interval [CI] 0.22 to 1) ,which was statistically significant, P was 0.043, Fonseca EB et al^{20} and Dodd et al^{15} had shown similar results.

There was one case of extremely preterm birth i.e. <28 weeks in placebo group and number of very preterm birth (28 to < 32 weeks) in progesterone group was 4 (7.5%), in the placebo group was 6 (12%) (relative risk 0.63, 95% confidence interval [CI] 0.19 to 2.1, not statistically significant, P was 0.447. But regarding moderate to late preterm(32 to <37 weeks) there was statistically significant difference found in two groups P value 0.016.

Among cervical length>15mm to ≤ 20 mm there was no statistical significant difference found in two groups in case of very preterm birth and moderate to late preterm birth with P value0.631 and 0.279 respectively.

In case of cervical length>20 mm to ≤ 25 mm there was no statistical significant difference found in two groups in very preterm birth with P value 0.233 and but regarding moderate to late preterm birth there was 12 cases in placebo group and 3 cases in progesterone group with P value 0.002, so difference was statistically highly significant.

In our study regarding neonatal death one case was found in progesterone group and three cases in placebo group with relative risk 0.314465,95% CI 0.03, 2.92 and P value 0.280. This result is corresponding to the study done by Eduardo B et al⁴³ but not similar to other RCT by Hassan SS et al.¹⁴

In our study no statistically significant difference was found among two groups in case of mean birth weight and distribution of birth weight, comparable to the results of the study done by Eduardo B. et al.²⁰

In present study, regarding composite adverse outcome (Respiratory distress syndrome, Retinopathy of prematurity, Necrotizing enterocolitis) there were no statistically significant difference found among two group also similar to study done by Eduardo B. et al.²⁰

But RCT done by Hassan et al¹⁴shows progesterone was also effective on better neonatal outcomes such as respiratory distress syndrome (3.0% vs. 7.6%, P = 0.03) also supported by study done by Replens Columbia Laboratories.

In our study there was statistically significant difference present among two groups in Intraventricular hemorrhage outcome,4% in progesterone group,20% in placebo group, with relative risk 0.188679 ,95%CI (0.04, 0.82) and P value 0.010. This result is not similar to study done by Eduardo B et al²⁰ but study done by Hassan SS et al¹⁴, Romero R et al²² showed improvement of composite neonatal adverse outcome.

In our study there was no statistically significant difference between two groups regarding maternal side effects which is similar to study done by Eduardo B. et al²⁰, Romero R et al.²²

In this study we found statistically significant difference in case of NICU admission in two groups with relative risk 0.58 ,95% CI(0.36 - 0.95) and P value 0.024. This is similar to study done by DeFranco EA et al.²³In that study result found lower NICU admissions (15.8 vs 51.9%, P = 0.01) in progesterone group.

We also found that no significant difference between two groups regarding composite adverse outcomes like ventilation, phototherapy, blood transfusion concordant with Eduardo B et al.²⁰But regarding treatment for sepsis we found statistically significant difference between two groups with P value 0.017.

V. CONCLUSION

Vaginal administration of progesterone in cases of short cervix (< 2.5 cm) can prevent preterm birth \leq 34 weeks by at least 16.9 % and 27.6 % before <37 weeks. Therefore, in a documented case of short cervix progesterone administration is justified to avoid / minimize the preterm labor before 34 weeks and its associated sequalae. In our study, uncertainty remains about the optimal dosage and the exact gestational age at which progesterone therapy needs to be commenced. Therefore, for universal cervical length screening of all women with singleton

Gestation at midtrimester, and offering prophylactic treatment with vaginal progesterone in those with short cervix further studies needed.

REFERENCES

- [1]. Maternal mortality in 2005: estimates developed by WHO, UNICEF, UNFPA, and The World Bank. Geneva: World Health Organization; 2007
- [2]. Mathews TJ, Curtin SC, MacDorman MF. Infant mortality statistics from the 1998 period linked with birth/infant death data set. Natl Vital Stat Rep 2000; 48(12):1-25.
- [3]. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth, The Lancet, 2008:371(9606);75-84.
- [4]. Lang C, iams J. Goals and strategies for prevention of preterm birth: an obstetric perspective.Pediatric clinics of North America 2009;56:537-563.
- [5]. Marlow N, Wolke D, Bracewell MA, Samara M. Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med 2005;352: 9-19.
- [6]. Veen S, Ens-Dokkum MH, Schreuder AM, Verloove-Vanhorick SP, Brand R, Ruys JH. Impairments, disabilities, and handicaps of very preterm and very-lowbirthweight infants at five years of age: the Collaborative Project on Preterm and Small for Gestational Age Infants (POPS) in the Netherlands. Lancet 1991;338:33-6
- [7]. Daya S. Efficacy of progesterone support for pregnancy in women with recurrent miscarriage. A metaanalysis of controlled trials. Br J Obstet Gynaecol 1989; 96: 275–280.
- [8]. Keirse MJ. Progestogen administration in pregnancy may prevent preterm delivery. Br J Obstet Gynaecol 1990; 97: 149–154..
- [9]. Goldstein P, Berrier J, Rosen S, Sacks HS, Chalmers TC. A meta-analysis of randomized control trials of progestational agents in pregnancy.Br J ObstetGynaecol 1989; 96: 265–274.
- [10]. National Research Council. Preterm birth: causes, consequences, and prevention. In: Behrman RE, Butler AS, editors. Committeeon Understanding Premature Birth Assuring Healthy Outcomes. Washington, DC: The National Academies Press; 2007.
- [11]. March of Dimes Foundation. Medical costs for one premature baby could cover a dozen healthy births. March 17, 2009.
- [12]. Berghella V, Tolosa JE, Kuhlman K, et al. Cervical ultrasonography compared to manual examination as a predictor of preterm delivery. Am J Obstet Gynecol. 1997;177:723–730
- [13]. American College of Obstetricians and Gynecologists. Use of progesterone to reduce preterm birth. Committee Opinion No. 419. Washington, DC: American College of Obstetricians and Gynecologists; 2008.
- [14]. S.S.Hassan, R.Romeo, D.Vidyadhari et al. : ultrasound Obset. Gynecol 2011;38:18-31.
- [15]. Dodd JM, Flenady V, Cincotta R, Crowther CA. Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. Cochrane Database of Systematic Reviews 2006;Issue 1. Art. No.: CD004947; (last updated on 31 December 2008).
- [16]. Iams JD,Goldenberg RL,Mercer BM. The preterm birth prediction study:can low risk women destined for spontaneous preterm birth be identified?American journal of Obst & Gynae 2001; 184(4):652-655.
- [17]. Berghella V,Baxter JK,Hendrix NW.Cervical assessment by ultrasound for preventing preterm delivery.Cochrene Database of Systematic Reviews 2009,ISSUE 3.Art. No:CD007235.DOI:10,1002/14651858.CD007235.pub2.
- [18]. da Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH. Progesterone and the risk of preterm birth among women with a short cervix. N Engl JMed 2007; 357: 462–469.

- [19]. Berghella V, Odibo AO, To MS, Rust O, Althuisius SM. "Cerclage for short cervix on ultrasonography; meta-analysis of trials using individual patient data". Obstetrics & Gynecology 2005;106 (1): 181–189.
- [20]. Fonseca EB, Celik E, Parra M, Singh M, Nikolaides KH, Fetal Medicine Foundation Second Trimester Screening Group. "Progesterone and the risk of preterm birth among women with a short cervix". New England Journal of Medicine 2007; 357 (5): 462–469..
- [21]. Goldenberg RL, Iams JD, Mercer BM, et al. "The preterm prediction study: the value of new vs standard risk factors in predicting early and all spontaneous preterm births. NICHD MFMU Network". American Journal of Public Health 1998;88 (2): 233–238.
- [22]. Romero R. Prevention of spontaneous preterm birth: the role of sonographic cervical length in identifying patients who may benefit from progesterone treatment. Ultrasound Obstet Gynecol. 2007;30: 675–686.
- [23]. DeFranco EA, O'Brien JM, Adair CD, Lewis DF, Hall DR, Fusey Set al. Vaginal progesterone is associated with a decrease in risk for early preterm birth and improved neonatal outcome in women with a short cervix: a secondary analysis from randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol 2007; 30: 697 705.

*Corresponding author: Debdut Banerjee, MS G&O, Assistant Professor G&O, Burdwan Medical College and Hospital, West Bengal, India.