

**Original article:**

## **Pregnancy Outcome following Cervical cerclage , use of Progesterone or Nifedipine as tocolytic agent for prevention of preterm labour**

**Bangal V.B.<sup>1</sup>,Chalasanani Shravani <sup>2</sup> , Gavhane Satyajit P.<sup>3</sup>, Aher Kunal H.<sup>4</sup>,Bhavsar Dhruval .K<sup>5</sup> , Verma Priyanka R <sup>6</sup>**

<sup>1</sup> MD, DNB Professor and Head, Dept. of Obstetrics and Gynaecology

<sup>2</sup> Postgraduate Student (MS) Dept. of Obstetrics and Gynaecology

<sup>3</sup> DNB (Obstetrics and Gynaecology) Assistant Professor, Dept. of Obstetrics and Gynaecology

<sup>4</sup> MS (Obstetrics and Gynaecology) Senior Resident, Dept. of Obstetrics and Gynaecology

<sup>5</sup> Postgraduate Student (MS) Dept. of Obstetrics and Gynaecology

<sup>6</sup> Postgraduate Student (MS) Dept. of Obstetrics and Gynaecology Rural Medical College of Pravara Institute of Medical Sciences (Deemed University) Loni, Maharashtra, India

Corresponding author: Dr.Vidyadhar B. Bangal

---

### **ABSTRACT**

**Background:** Despite significant advances in perinatal medicine and establishment of feto-maternal units, preterm birth still remains the leading cause of perinatal mortality and neonatal morbidity. The incidence of preterm labour in India is 11-14%. The main objective of the study was to observe the comparative outcome of pregnancy in women with singleton pregnancy with previous history of preterm birth and sonographic short cervix with the use of either prophylactic tocolysis, vaginal progesterone and cerclage.

**Methodology:** A prospective cross sectional observational study was carried out from September 2013 to September 2015. A total of 150 cases were selected and were divided into three groups of 50 cases each, one under Tocolysis on the basis of threatened preterm (GROUP 1), one under Vaginal progesterone on the basis of previous preterm or second trimester loss(GROUP 2) and one under cervical encirclage on the basis of cervical shortening(GROUP 3).

**Results:** All women were multiparous and had history of preterm birth. Success in prevention of preterm labour was noted in patients having bishops score less than 4 and least success rate was noted with bishops more than 7.83. Seventy six percent women who underwent cervical cerclage with cervical length less than 25mm could reach 37weeks. Cervical dilatation of 1 cm and less had maximum success rate of 89 % and 86%, when compared in all three groups. The overall successful live births were 76.66%. Overall perinatal mortality rate was 22%. Average NICU and Hospital stay in babies delivered before 34weeks was 8.6 and 27.6 days respectively and after 34weeks was 3.7 and 6.2 days respectively.

**Conclusion:** Cerclage, vaginal progesterone pessary appear to have similar effectiveness as management strategies in women with singleton pregnancy, previous spontaneous preterm birth and short cervix.

**Key words :** Tocolysis, progesterone therapy, cervical encirclage, preterm labour, Perinatal morbidity and mortality.

---

### **INTRODUCTION**

Preterm labor refers to the onset of uterine contractions of sufficient strength and frequency to effect progressive dilatation and effacement of

cervix between 20 and 37 weeks of gestation. Preterm labor complicates 5-10% of pregnancies and is a leading cause of neonatal morbidity and mortality worldwide. It is a major public health

problem in terms of loss of life, long-term disability (cerebral palsy, blindness, deafness, chronic lung disease) and health care costs both in the developing and the developed world.<sup>1</sup> Various maternal demographic, behavioral, and clinical characteristics have been associated with PTB including maternal race/ethnicity, maternal age at either extreme, cigarette smoking, low pre-pregnancy weight, psychosocial stress, previous PTB, and maternal intrauterine infections <sup>2</sup>. Various treatment modalities used for prevention or arrest of preterm labour are tocolytic agents like beta mimetics, Calcium channel blockers, Progesteron , Atociban ,Ritodrine and cervical cerclage in selected cases. Although tocolytics have not been shown to improve neonatal outcomes, they can delay preterm delivery long enough for antenatal corticosteroids to be administered or for the mother to be transported to a tertiary care facility.<sup>3</sup> In premature neonates, antenatal corticosteroids reduce morbidity and mortality.<sup>4</sup> Tocolytic therapy may therefore have an important role in improving outcomes from preterm delivery. Each tocolytic has a unique mechanism of action, side effects, and degree of complexity to administer.<sup>5</sup> A previous history of preterm labor is the strongest risk marker. It has been estimated that the incidence of preterm labor in subsequent pregnancies after one preterm birth rises to 14.3% and after two preterm births to 28% <sup>6</sup>. Other risk markers include multiple pregnancy <sup>7</sup>, cigarette smoking, cervical incompetence or uterine anomalies, uterine over-distension (polyhydraminos, macrosomia, fibroids), previous cervical surgery<sup>8</sup>, using smokeless tobacco <sup>9</sup>, bleeding in early pregnancy <sup>10</sup>, bacterial vaginosis, poor socioeconomic or educational status, and young or advanced maternal age. Pre-conceptional multivitamin treatment was inversely associated

with both early and late preterm birth <sup>11</sup>. There is now evidence to support an association between severe periodontal disease and spontaneous preterm labor <sup>12</sup>. Short interval between pregnancies (less than 12 months) has been found to increase the risk of recurrent preterm birth <sup>13</sup>. Recently, domestic violence, especially injury due to physical abuse, was found to be significantly associated with both preterm birth and low birth weight <sup>14</sup>.The main objective of the study was to observe the comparative outcome of pregnancy in women with singleton pregnancy with recurrent history of preterm birth and sonographic short cervix with the use of either prophylactic tocolysis , vaginal progesterone and cerclage.

#### **MATERIAL AND METHODS**

A prospective observational study of 50 cases in each study group with history of previous preterm were treated by Tocolysis (GROUP 1), Vaginal/oral progesteron (GROUP 2) and cervical cerclage (GROUP 3).Tocolytic index is considered for all applicable cases. Every group is compared with general recurrence of preterm birth without treatment and from other studies. Women with The patients with previous H/O preterm delivery, multigravida with accidentally or clinically detected short cervix which is confirmed by Sonography and multigravida patients with history of second trimester abortion were included in different study groups. All primigravid patients ,patients having complications of pregnancy like pre eclampsia, eclampsia and patients with pregnancy induced hypertension , patients with medical conditions like Heart disease, Diabetes, Jaundice, bleeding disorders, patients with PV bleeding with conditions like placenta praevia, abruptio placenta ,patients under pre-existing intervention for preterm labour , pregnancy with multiple gestation. pregnancy with

advance labour, previous L.S.C.S or any uterine surgery, previous operative procedure on cervix, pregnant women with major fetal congenital anomalies incompatible with life detected by USG, intrauterine fetal demise were excluded from study. A Prospective study for a period of 24 months was carried out. Detailed history taking general physical examination, systemic examination, obstetrical examination, baseline and special investigation were carried out. Maternal age, Gestational age were noted. According to occupation patients were divided into three groups i.e heavy, moderate and sedentary workers. Heavy workers included job like farmers and labourers, moderate workers included jobs like servants, teachers, lab technicians and accountants, whereas sedentary workers included jobs like housewives. Indication for intervention, Bishop Score at admission, type of delivery, duration of postponement of pregnancy in weeks by different interventions, APGAR score of baby, Maternal and fetal complications were noted. Obstetrical outcome was recorded in terms of: gestational age at the time of delivery, mode of delivery - vaginal, assisted vaginal delivery / caesarean delivery. Details of perinatal outcome, complications if any, fetal outcome were recorded in form of Apgar score at birth, Fetal Weight, NICU admission. The study was approved by the ethical committee. Informed consent was taken from patients before starting induction. Gestational age was evaluated by last menstrual period and ultrasound. Ultrasound was done for assessing gestational age, liquor volume, maturity and fetal well being. Fetal condition was assessed by NST tracings. Bishop score was noted at the time of admission. Samples were collected for baseline laboratory tests. Relevant information in proforma was recorded. Tocolysis in threatened preterm labour was

achieved with Tab. Nifedipine sustain release, given orally twice daily since detection of signs of premature labour and till cessation of contractions. Observations were made to assess again the success of tocolysis. (GROUP 1) The patients who had history of preterm labour were started with micronized progesterone 200 microgram twice daily since second trimester. Progesterone was given in oral and vaginal route and effects were studied. (GROUP 2) Cervical cerclage was done in Patients with history of preterm birth and Ultrasound diagnosed short cervical length (<25mm or 25mm) are observed with their outcome in terms of preterm delivery or timely delivery. Cervical encirclage was done in vaginally under all aseptic precaution in OT and prolene no 1 suture material is used. (GROUP 3). Patient's were labeled as unsuccessful intervention, when did not sustain pregnancy till or after 48hrs of tocolysis administration. Cervical cerclage procedure was said to be unsuccessful, when patients went in spontaneous preterm labor with progressive uterine activity, progressed cervical ripening (Bishops compared in labor) and when cervical stitch required premature removal before 34 completed weeks. Progesterone was administered as empirical treatment in patients with a previous history of preterm labour, hence treatment failure was considered, when if patient went in labor without lung maturity. All patients were advised to take regular medication and report for scheduled antenatal visit. They were asked to report in case of development of any additional symptoms. All women were advised to come for stitch removal and delivery at hospital. Statistical analysis was done by Asus computer using graph pad in stat version 3.1.

## RESULTS-

Highest percentage (40.6%) of patients were from age group 21 – 25 years. Most of the patients were involved in heavy work (46%). Maximum incidence of preterm labour was observed at gestational age of 28 – 32 wks. Maximum success rate in prevention of preterm labour was in gestational of 28 – 32wks ( 42.6%) . Maximum number of cases had Bishops score <4 at the time of admission and tocolysis was most effective, when Bishops score was <4 and was least effective when bishops score is > 7. **(Graph 1)**

In 35 cases out of 150 patients (23.33%) preterm labour could not be arrested. In remaining 115 patients (76.66%) pregnancy could be prolonged for variable periods. Out of 150 cases 21.4% cases underwent LSCS and 78.6% had preterm vaginal delivery. Twenty six percent babies developed respiratory distress, birth asphyxia in 12% and neonatal septicaemia in 19.3%. Side effects of the drug was dose related and in none of the cases it was not necessary to discontinue iv infusion and oral treatment. Seventy six percent cases responded to cerclage when performed with cervical length less than 25mm. **(Table 1)** Preterm labour could be arrested when cervical dilatation was 1 cm and less at admission. There were 76.66% live births in the present study. The perinatal mortality rate was 22%. **(Graph 2)** Average NICU and Hospital stay in babies delivered before 34weeks was 8.6 and 27.6 days respectively and after 34weeks was 3.7 and 6.2 days respectively. **(Graph 3)**

## DISCUSSION

Astin et al <sup>15</sup> published a report on four studies evaluating vaginal progesterone versus placebo (158 patients) and five evaluating cerclage versus no cerclage (504 patients). Both interventions were associated with a statistically significant reduction in the risk of preterm birth <32 weeks of gestation

and composite perinatal morbidity and mortality compared with placebo/no cerclage. Adjusted indirect meta-analyses did not show statistically significant differences between vaginal progesterone and cerclage in reducing preterm birth or adverse perinatal outcomes. Based on state-of-the-art methodology for indirect comparisons, either vaginal progesterone or cerclage are equally efficacious in the prevention of preterm birth in women with a sonographic short cervix in the midtrimester, singleton gestation, and previous preterm birth.

## Applied Physiology & Anatomy Digest

Now indexed in

Google scholar &  
Index Copernicus

Medworld asia

Hassan et al<sup>16</sup> conducted a multicenter, randomized, double-blind, placebo-controlled trial that enrolled asymptomatic women with a singleton pregnancy and a sonographic short cervix (10-20 mm) at 19 + 0 to 23 + 6 weeks of gestation. Women were allocated randomly to receive vaginal progesterone gel or placebo daily starting from 20 to 23 + 6 weeks until 36 + 6 weeks, rupture of membranes or delivery, whichever occurred first. Randomization sequence was stratified by center and history of a previous preterm birth. The primary endpoint was preterm birth before 33 weeks of gestation. Of 465 women randomized, seven were lost to follow-up and 458 (vaginal progesterone gel, n=235; placebo, n=223) were included in the analysis. Women allocated to receive vaginal progesterone had a lower rate of preterm birth before 33 weeks than did those allocated to placebo (8.9% (n=21) vs 16.1% (n=36); relative risk (RR), 0.55; 95% CI, 0.33-0.92; P=0.02). The administration of vaginal progesterone gel to women with a sonographic short cervix in the mid-trimester is associated with a 45% reduction in the rate of preterm birth before 33 weeks of gestation and with improved neonatal outcome.

Dodd JM<sup>17</sup> conducted a study to assess the benefits and harms of progesterone for the prevention of preterm birth for women considered to be at increased risk of preterm birth and their infants. Authors searched the Cochrane Pregnancy and Childbirth Group's Trials Register (14 January 2013) and reviewed the reference list of all articles. Randomised controlled trials, in which progesterone was given for preventing preterm birth. Thirty-six randomised controlled trials (8523 women and 12,515 infants) were included. Progesterone was associated with a statistically significant reduction in the risk of perinatal

mortality (six studies; 1453 women; risk ratio (RR) 0.50, 95% confidence interval (CI) 0.33 to 0.75), preterm birth less than 34 weeks (five studies; 602 women; average RR 0.31, 95% CI 0.14 to 0.69), infant birthweight less than 2500 g (four studies; 692 infants; RR 0.58, 95% CI 0.42 to 0.79), use of assisted ventilation (three studies; 633 women; RR 0.40, 95% CI 0.18 to 0.90), necrotising enterocolitis (three studies; 1170 women; RR 0.30, 95% CI 0.10 to 0.89), neonatal death (six studies; 1453 women; RR 0.45, 95% CI 0.27 to 0.76), admission to neonatal intensive care unit (three studies; 389 women; RR 0.24, 95% CI 0.14 to 0.40), preterm birth less than 37 weeks (10 studies; 1750 women; average RR 0.55, 95% CI 0.42 to 0.74) and a statistically significant increase in pregnancy prolongation in weeks (one study; 148 women; mean difference (MD) 4.47, 95% CI 2.15 to 6.79). Authors concluded that the use of progesterone was associated with benefits in infant health following administration in women considered to be at increased risk of preterm birth due either to a prior preterm birth or where a short cervix has been identified on ultrasound examination. However, there was limited information available relating to longer-term infant and childhood outcomes, the assessment of which remains a priority.

Flenady et al<sup>18</sup> conducted a study to assess the effects on maternal, fetal and neonatal outcomes of calcium channel blockers (CCB), administered as a tocolytic agent, to women in preterm labour.

All published and unpublished randomised trials in which CCBs were used for tocolysis for women in labour between 20 and 36 completed weeks' gestation. Calcium channel blockers (mainly nifedipine) for women in preterm labour have benefits over placebo or no treatment in terms of postponement of birth thus, theoretically,

allowing time for administration of antenatal corticosteroids and transfer to higher level care. Calcium channel blockers were shown to have benefits over betamimetics with respect to prolongation of pregnancy, serious neonatal morbidity, and maternal adverse effects. Tejada et al<sup>19</sup> conducted a multicentre, randomised, double-blind, placebo-controlled trial to evaluate the effectiveness of 200 mg of daily vaginal natural progesterone to prevent preterm birth in women with preterm labour. A total of 385 women with preterm labour (24<sup>0/7</sup> to 33<sup>6/7</sup> weeks of gestation) treated with acute tocolysis. Participants were randomly allocated to either 200 mg daily of self-administered vaginal progesterone or placebo within 48 hours of starting acute tocolysis. Primary outcome was delivery before 37 weeks of gestation. Secondary outcomes were delivery before 32 and 34 weeks, adverse effects, duration of tocolysis, re-admissions for preterm labour, length of hospital stay, and neonatal morbidity and mortality. The study was ended prematurely based on results of the intermediate analysis. Preterm birth occurred in 42.5% of women in the progesterone group versus 35.5% in the placebo group (relative risk [RR] 1.2; 95% confidence interval [95% CI] 0.93–1.5). Delivery at <32 and <34 weeks did not differ between the two groups (12.9 versus 9.7%; [RR 1.3; 95% CI 0.7–2.5] and 19.7 versus 12.9% [RR 1.5; 95% CI 0.9–2.4], respectively). The duration of tocolysis, hospitalisation, and recurrence of preterm labour were comparable between groups. Neonatal morbidity occurred in 44 (22.8%) cases on progesterone versus 35 (18.8%) cases on placebo (RR: 1.2; 95% CI 0.82–1.8), whereas there were 4 (2%) neonatal deaths in each study group. Study concluded that there is no evidence that the daily administration of 200 mg vaginal progesterone decreases preterm birth or improves

neonatal outcome in women with preterm labour. Naik G. N. et al<sup>20</sup> carried out a study to assess the effects of calcium channel blockers as maintenance therapy on preventing preterm birth after threatened preterm labour. Review included the randomised controlled trials of calcium channel blockers used as maintenance therapy to prevent preterm birth after threatened preterm labour, compared with placebo or no treatment. Authors included six trials that enrolled 794 women and their babies and all assessed nifedipine as calcium channel blocker maintenance therapy. The six trials were judged to be at a moderate risk of bias overall. No differences in the incidence of preterm birth (risk ratio (RR) 0.97; 95% confidence interval (CI) 0.87 to 1.09; five trials, 681 women), birth within 48 hours of treatment (RR 0.46; 95% CI 0.07 to 3.00; two trials, 128 women) or neonatal mortality (average RR 0.75; 95% CI 0.05 to 11.76; two trials, 133 infants) were seen when nifedipine maintenance therapy was compared with placebo or no treatment. No trials reported on longer-term follow-up of infants. Women receiving nifedipine maintenance therapy were significantly more likely to have their pregnancy prolonged (mean difference (MD) 5.35 days; 95% CI 0.49 to 10.21; four trials, 275 women); however, no differences between groups were shown for birth at less than 34 weeks' gestation, birth at less than 28 weeks' gestation, birth within seven days of treatment, or gestational age at birth. No significant differences were shown between the nifedipine and control groups for any of the secondary neonatal morbidities reported. Similarly, no significant differences were seen for the outcomes relating to the use of health services, except for in one trial, where infants whose mothers received nifedipine were significantly more likely to have a longer length of hospital stay as compared with infants born to mothers

who received a placebo (MD 14.00 days; 95% CI 4.21 to 23.79; 60 infants). Authors concluded that based on the current available evidence, maintenance treatment with a calcium channel

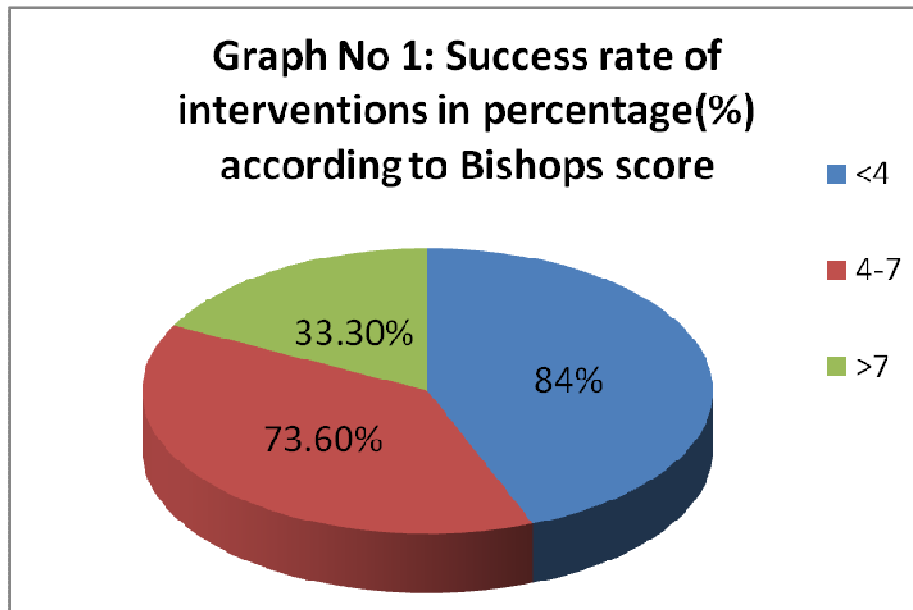
#### CONCLUSION

Preterm labour is not a disease, rather the final event of myriad of factors that can complicate pregnancy. Despite all advances to Neonatology, the most efficient way for decreasing perinatal mortality and morbidity is to keep the foetus inside the uterus as close to term as possible.. The uterus is the best incubator even in modern obstetrics. The results of the present study have shown that tocolysis, encirclage and pregesterone were effective in diminishing uterine contractions in cases of preterm labour, they could prolong the

blocker after threatened preterm labour does not prevent preterm birth or improve maternal or infant outcomes.

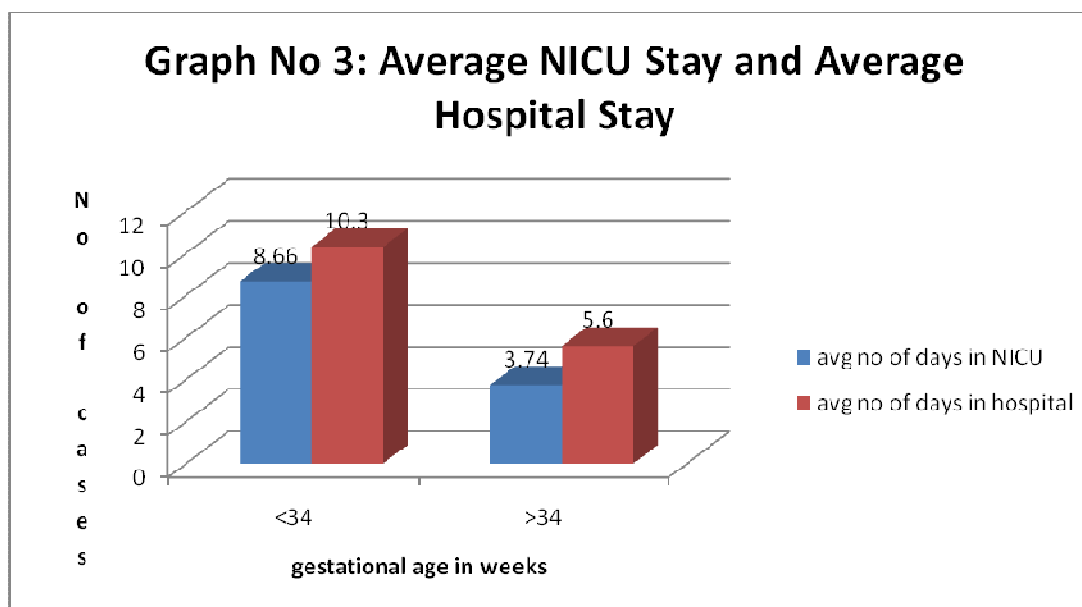
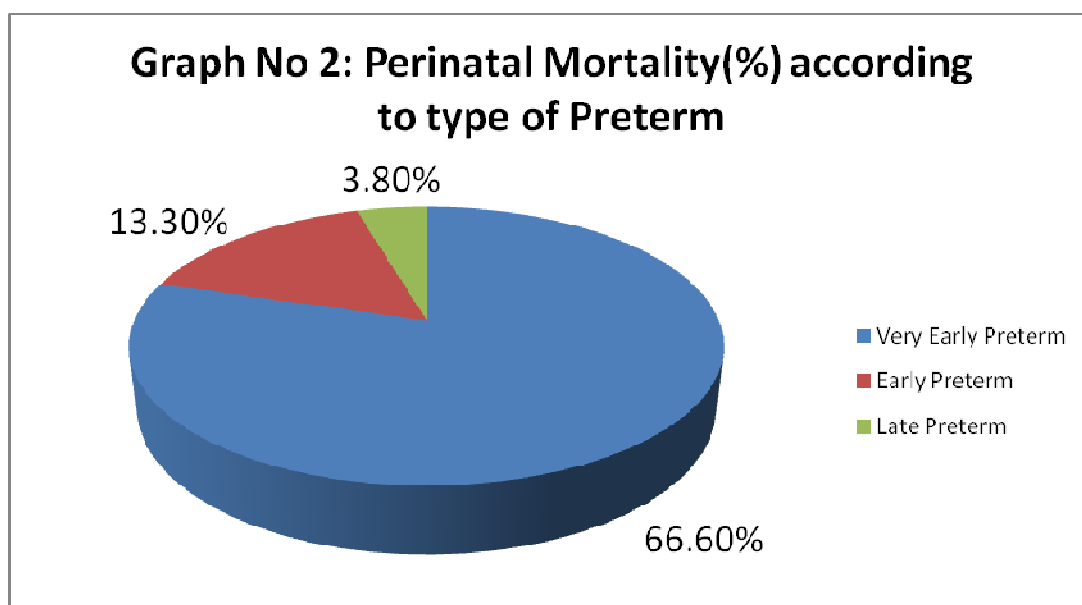
pregnancy for variable period of time. The extended period did give chance for the administration of corticosteroids to mother as preventive measure for respiratory problems in premature newborn. All three interventions , by extending the term of gestation have helped in reduction of perinatal mortality and morbidity associated prematurity. An extended study with large sample size can validate the results of the present study.

GRAPH 1



**TABLE NO 1: CERVICAL DILATATION TO PERCENTAGE OF SUCCESS IN ALL GROUPS**

Cervical dilatation(cm)	Total Number of cases			Unsuccessful cases	Successful Cases	Success Rate %
	Tocolysis	Cerclage	Progesteron			
00	6	5	17	4	24	86
01	27	22	21	8	62	89
02	15	13	12	10	30	75
03	2	10	0	5	07	58





**Acknowledgement:** The authors express their deep sense of gratitude to Dean, Rural Medical College, Loni , Maharashtra, India.

#### REFERENCES:

- 1-Edwin Chandraharan, Sabaratnam Arulkumaran .Recent advances in management of preterm labor. J Obstet Gynecol India 2005; 55(2): 118- 124
2. Chan RL. Biochemical markers of spontaneous preterm birth in asymptomatic women. Biomed Res Int. 2014;2014:164081. [PMC free article] [PubMed]
- 3-Haas DM, Imperiale TF, Kirkpatrick PR, Klein RW, Zollinger TW, Golichowski AM. Tocolytic therapy: a meta-analysis and decision analysis. Obstet Gynecol 2009;113:585-94.
- 4-Roberts D, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2006;(3):CD004454.
- 5-Goldenberg RL. The management of preterm labor. Obstet Gynecol 2002;100:1020-37. CrossRefPubMedWeb of Science
6. Bakketeig LS, Hoffman HJ, Harley EE. The tendency to repeat gestational age and birth weight in successive births. BMJ 1979;135:1086-103.
7. Kaltreider DF, Kohl S. Epidemiology of preterm labor. Clin Obstet Gynecol 1980;23:17-30.
8. Sadler L, Saftlas A, Wang W et al. Treatment of cervical intraepithelial neoplasia and risk of preterm delivery. JAMA 2004;291:2100-6.
9. Gupta PC, Sreevidya S. Smokeless tobacco use, birth weight and gestational age: population based prospective study of 1217 women in Mumbai, India. BMJ 2004;328(7455): 1538.
10. Yang J, Hartmann KE, Savitz DA et al. Vaginal bleeding during pregnancy and preterm birth. Am J Epidemiol 2004; 160:118-25.
11. Vahratian A, Siega-Riz AM, Savitz DA et al. Multivitamin use and the risk of preterm labour. Am J Epidemiol 2004;160:886-92.
12. Goepfert AR, Jeffcoat MK, Andrews WW et al. Periodontal disease and upper genital tract inflammation in early spontaneous preterm birth. Obstet Gynecol 2004;104:777-83.
13. Krymko H, Bashiri A, Smolin A et al. Risk factors for recurrent preterm delivery. Eur J Obstet Gynecol 2004; 113:160-3.
14. Neggers Y, Goldenberg R, Cliver S et al. Effects of domestic violence on preterm birth and low birth weight. Acta Obstet Gynecol Scand 2004;83:455-60.
- 15-Agustin CONDE-AGUDELO et al. Vaginal progesterone versus cervical cerclage for the prevention of preterm birth in women with a sonographic short cervix, singleton gestation, and previous preterm birth: a systematic review and indirect comparison meta-analysis Am J Obstet Gynecol. 2013 ; 208(1): 42.e1–42.e18.
- 16-Hassan SS<sup>1</sup> et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol. 2011 Jul;38(1):18-31. doi: 10.1002/uog.9017. Epub 2011 Jun 15.
- 17-Dodd JM Prenatal administration of progesterone for preventing preterm birth in women considered to be at

risk of preterm birth Cochrane Database Syst Rev. 2013 Jul 31;(7):CD004947. doi: 10.1002/14651858.CD004947.pub3.

18-Flenady V, Calcium channel blockers for inhibiting preterm labour and birth.. Cochrane Database Syst Rev. 2014 Jun 5;(6):CD002255. doi: 10.1002/14651858.CD002255.pub2.

19-B Martinez de Tejada et al .Prevention of preterm delivery with vaginal progesterone in women with preterm labour (4P): randomised double-blind placebo-controlled trial. Cochrane database of systematic reviews 2015; 122( 1):80-91

20- Naik Gaunekar et al Maintenance therapy with calcium channel blockers for preventing preterm birth after threatened preterm labour. Cochrane Database of Systematic Reviews. DOI:10.1002/14651858.CD004071.pub3 ,2013