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### RESEARCH ARTICLE

#### PREGNANCY OUTCOME IN SHORT CERVIX: PROGESTERONE VS CERVICAL ENCLERCLAGE.

\*Nikita Gandotra<sup>1</sup> and Vandana Nimbargi<sup>2</sup>.

1. Resident, Department of Obstetrics and Gynaecology, BharatiVidyapeeth Deemed University Medical College, Pune, Maharashtra, India.
2. Professor, Department of Obstetrics and Gynaecology, BharatiVidyapeeth Deemed University Medical College, Pune, Maharashtra, India.

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Cervical Enclerclage, Pre-term Birth,  
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#### Abstract

**Introduction:** Preterm birth (PTB), defined as birth before 37 weeks of gestation, is the leading cause of perinatal morbidity and mortality. A sonographic short cervix has emerged as a powerful predictor of preterm birth. The present study was conducted to compare the outcome of pregnancy with short cervix with natural micronized progesterone and cervical cerclage.

**Materials & Methods:** A Prospective Comparative study was conducted in the Department of Obstetrics and Gynaecology of a Tertiary Care Hospital and Medical college. A total of 50 cases of short cervix were included in the study. Out of 50 cases, 25 cases each were divided in two groups by simple random sampling: **Group A:** Given natural micronized progesterone; and **Group B:** Underwent cerclage procedure. Detailed history, ANC check-up, USG and appropriate investigations were carried out for each subject. The cases were followed thereafter in antenatal clinic till delivery and pregnancy outcome was noted.

**Results:** The mean maternal age was 22.44 years in progesterone group and 22.64 years in cerclage group ( $p=0.514$ ). The outcome of pregnancy with natural micronised progesterone reflected 36% births between 28-32 weeks of gestation, 28% after completion of 37 weeks and only 16% before 28 weeks of gestation whereas outcome with cerclage 36% between 28-32 weeks, 44% after completion of 37 weeks and 8% before 28 weeks ( $p=0.56$ ). The difference in secondary outcome measures (PPROM, LSCS rate) and neonatal outcome (mean birth weight, APGAR, duration of NICU admission, respiratory distress, development of IVH, NEC and neonatal sepsis) in cerclage and progesterone group was also statistically non-significant ( $p>0.05$ ).

**Conclusion:** Natural micronized progesterone is as effective as cervical cerclage in prevention of premature labour in women with short cervix. Use of natural micronized progesterone is more preferable in clinical practice because it is non-invasive technique, easy to administer and the patients do not suffer from surgical and anaesthesia procedure related adverse effects. It is also not associated with any hospital stay and is very economical.

**Corresponding Author:- Nikita Gandotra.**

Address:- Resident, Department of Obstetrics and Gynaecology, BharatiVidyapeeth Deemed University Medical College, Pune, Maharashtra, India.

**Introduction:-**

Preterm birth, defined by the World Health Organization (WHO) as birth prior to 37 completed weeks (259 days) after the first day of the last menstrual period preceding the pregnancy,<sup>1</sup> is a major global public health problem.<sup>2</sup> Approximately 15 million neonates are born premature worldwide yearly, implying a rate of 1 out of 10 neonates and nearly 1 million children die each year due to complications of preterm birth.<sup>3</sup> In developed countries the preterm birth rate is about 8% of all the pregnancies.<sup>3</sup> Among the 10 countries with greatest number of preterm births India has the highest number. Preterm births accounted for 75.3% of all perinatal mortality with mortality risk of 82.6 per 1000 births.<sup>4,5</sup>

A sonographic short cervix has emerged as a powerful predictor of preterm birth. It is unlikely that this condition is due to a single cause, and a multiple causation model of a sonographic short cervix has been proposed (e.g. a short cervix is syndromic in nature). Such model would have biological, diagnostic, prognostic and therapeutic implications. Indeed, patients may have a short cervix after DES exposure in utero, a cervical conization, a LEEP procedure, intrauterine infection/inflammation, a decline in progesterone action, and the challenging condition clinically referred to as idiopathic cervical insufficiency<sup>6</sup>.

Progesterone is considered a key hormone for pregnancy maintenance, and a decline of progesterone action is implicated in the onset of parturition. If such a decline occurs in the midtrimester, cervical shortening may occur, and this would predispose to preterm delivery.<sup>7-14</sup> Various randomized clinical trials and data meta-analysis showed that vaginal progesterone decreases the rate of preterm delivery and neonatal morbidity/mortality in women with a sonographic short cervix<sup>15-17</sup>.

Cervical encerclage has also been widely used as a surgical method to prevent recurrent mid-trimester pregnancy loss in women at risk. Elective cerclage placement may benefit some women with proven cervical insufficiency. Although highly contentious, more recent data suggest that cervical encerclage may reduce the risk of preterm delivery in that subgroup of asymptomatic singleton pregnancies with both shortening on TVS and a history of spontaneous preterm birth<sup>18</sup>.

The Present study aimed at comparing the effects of micronized natural progesterone and cervical encerclage in pregnancy with short cervix.

**Material & Methods:-****Type of Study & Study Area:-**

A Prospective Comparative study was conducted in the Department of Obstetrics and Gynaecology of a Tertiary Care Hospital and Medical college. The study was conducted over a period of two years from August 2014 to August 2016. A written informed consent was obtained for this study from all subjects after obtaining approval of the ethical committee.

**Inclusion Criteria:-**

1. Gestational age between 18-28 weeks.
2. Singleton pregnancy.
3. Clinically short cervix 1.5-3 cm or sonographically short cervix or any sign suggestive of incompetent cervix.
4. Previous preterm delivery
5. Previous history of os tightening

**Exclusion Criteria:-**

1. Congenital anomaly
2. Multi fetal pregnancy
3. Extremely short cervix (<1.5cm)
4. Leaking per vaginally
5. Any major medical disorder (severe heart disease, severe pre-eclampsia, uncontrolled diabetes mellitus and patients in renal failure).
6. Placenta previa, intrauterine infection or inflammation

## 7. Non consented patients

### Sample Size:-

A total of 50 cases of short cervix were included in the study. Out of 50 cases, 25 cases each were divided in two groups by simple random sampling:

**Group A:** Given natural micronized progesterone (200mg bd /300 mg SR per vaginally capsules of micronized progesterone); and

**Group B:** Underwent cerclage procedure.

### Methodology:-

Study patients at the time of recruitment were subjected to:

1. Detailed clinical history
2. Clinical examination
3. Per abdomen examination
4. Per speculum examination
5. Per vaginal examination
6. Routine ANC profile
7. Ultrasonography

The cases were followed thereafter in antenatal clinic till delivery and outcome was noted. The primary outcome measures were preterm birth <32 weeks of gestation and composite perinatal morbidity and mortality (defined as the occurrence of any of the following events: respiratory distress syndrome, grade III/IV intraventricular haemorrhage, necrotizing enterocolitis, neonatal sepsis, bronchopulmonary dysplasia, or perinatal death).

Secondary outcome measures included preterm birth at <37, 34-37, and <28 weeks of gestation, respiratory distress syndrome, necrotizing enterocolitis, grade III/IV intraventricular hemorrhage, neonatal sepsis, bronchopulmonary dysplasia, perinatal mortality, a composite neonatal morbidity outcome (defined as the occurrence of any of the above mentioned neonatal morbidities), birth weight <1500 g and <2500 g, and admission to the neonatal intensive care unit (NICU).

### Data Analysis:-

Data was analyzed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA) using appropriate statistical tests.

### Results:-

The mean maternal age was 22.44 years in progesterone group and 22.64 years in cerclage group (p=0.514). Maximum number of women, 28% of progesterone group and 44% of cerclage group, were noted between 18-20 weeks gestation while 20% of progesterone and 44% of cerclage were between 20-22 weeks (p=). Maximum number of women (44%) of progesterone group had cervical length of 1.5-2 cm whereas 44% of cerclage group had cervical length of 2.1-2.5cm (Table 1). The outcome of pregnancy with natural micronised progesterone reflected 36% births between 28-32 weeks of gestation, 28% after completion of 37 weeks and only 16% before 28 weeks of gestation whereas outcome with cerclage 36% between 28-32 weeks, 44% after completion of 37 weeks and 8% before 28 weeks (p=0.56; Table 2). The difference in secondary outcome measures (PPROM, LSCS rate) in both the group were also statistically non-significant (p=1.0; Table 3). Our study also compared neonatal outcome (mean birth weight, APGAR, duration of NICU admission, respiratory distress, development of IVH, NEC and neonatal sepsis) in cerclage and progesterone group. No statistically significant difference was observed between the groups regarding neonatal parameters (p>0.05; Table 4).

### Discussion:-

The first randomized clinical trial to examine the effects of vaginal progesterone on the prevention of preterm birth in women with a short cervix was reported by da Fonseca et al.<sup>19</sup> The primary outcome of the trial was the frequency of spontaneous preterm delivery at <34 weeks of gestation. Patients allocated to receive vaginal progesterone had a lower rate of preterm delivery (<34 weeks) than those in the placebo group [19.2% (24/125) vs. 34.4% (43/125)]. In another trial, termed as "PREGNANT" trial<sup>20</sup>, It was estimated that 14 women with a cervical length between 10–20mm would need to be treated with vaginal progesterone to prevent one case of preterm birth before 33 weeks of

gestation. In addition, there was a significant decrease in the rate of preterm delivery <35 and <28 weeks of gestation. Since then, various trials and meta-analysis have shown the efficacy of vaginal progesterone to prevent preterm birth in cases with short cervix<sup>21-29</sup>.

Cervical cerclage was introduced in 1955 by V. N. Shirodkar, Professor of Midwifery and Gynecology at the Grand Medical College in Bombay, India.<sup>30</sup> The procedure was developed in response to his observation that “some women abort repeatedly between the fourth and seventh months, and no amount of rest and treatment with hormones seemed to help them in retaining the product of conception.” Despite the 50 years that have elapsed since the introduction of cerclage as a procedure, there is conflicting evidence about its efficacy for standard indications (i.e. prophylactic) or for some patients with a sonographic short cervix. Several randomized clinical trials have been conducted to date which have yielded mixed results<sup>31-38</sup>. A meta-analysis of randomized clinical trials of patients with a prior history of preterm birth and a short cervical length (<25mm) suggests that cervical cerclage is effective in reducing the rate of preterm birth and perinatal morbidity/mortality.<sup>158</sup> A different meta-analysis has suggested that women with a prior spontaneous preterm birth and singleton gestation may be monitored safely with transvaginal sonographic cervical length measurements<sup>39</sup>.

In present study, we observed that both vaginal progesterone and cerclage in patients with a short cervix was associated with a significant reduction in the risk of preterm birth. The key finding is that both are equally effective for the prevention of preterm birth and adverse perinatal outcomes.

Very few studies has directly compared cervical cerclage and vaginal progesterone for the prevention of preterm birth in women with a sonographic short cervix. Most previous randomized trials allocated to receive vaginal progesterone versus placebo /no treatment, or cerclage versus no cerclage for the prevention of preterm birth.

Keeler et al.<sup>40</sup> compared between patients with short cervix on transvaginal ultrasound between 16 and 24 weeks' gestation treated with McDonald cerclage and those treated with weekly intramuscular injections of 17 alphahydroxyprogesterone caproate. Spontaneous Pre-term Birth (PTB) prior to 35 weeks' gestation occurred in 16/42 (38.1%) of the cerclage group and in 16/37 (43.2%) of the 17OHP-C group (relative risk, 1.14 95% CI, 0.67, 97 1.93). A post hoc analysis of patients with a prior PTB showed no difference in spontaneous PTB <35 weeks between groups. Conde-Agudelo and co-investigators performed an indirect comparison of vaginal progesterone versus cerclage, using placebo/no cerclage as the common comparator. Four studies evaluating vaginal progesterone versus placebo (158 patients) and five evaluating cerclage versus no cerclage (504 patients) were included. 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<sup>41</sup>.

The strength of this study is that it is first study in this region to compare directly between vaginal progesterone and cervical cerclage. All previous studies compare either vaginal progesterone with placebo or cervical cerclage with placebo or conducted an indirect comparison. Our study compares two methods directly to be more practical and to avoid the hidden bias such as selection bias which affect indirect comparing.

**Table 1:-** Distribution of subjects based on baseline characteristics

Characteristic (n=50)	Progesterone group (n=25)	Cerclage group (n=25)	p- value
Maternal age (in years)	22.44± 1.91	22.64± 1.99	0.719
Parity	0.48±0.65	0.36± 0.63	0.514
Gestational age at start of treatment (weeks)	23.2±3.26	22.08±3.13	0.222
Cervical length (mm)	21.92±3.48	22.08±2.98	0.862

**Table 2:-** Distribution of subjects based on Primary Pregnancy Outcome

Pregnancy Outcome	Group		p- value
	Progesterone group (n=25)	Cerclage group (n=25)	
< 28 weeks	4 (16%)	2 (8%)	0.56
28-32 weeks	9 (36%)	9 (36%)	
33-37 weeks	5 (20%)	3 (12%)	
> 37 weeks	7 (28%)	11 (44%)	
Total	25 (100%)	25 (100%)	

**Table 3:-** Distribution of subjects based on Secondary Pregnancy Outcome

Pregnancy Outcome	Group		p- value
	Progesterone group (n=25)	Cerclage group (n=25)	
PPROM	1 (4%)	2 (8%)	1.0
LSCS	2 (8%)	1 (4%)	1.0

**Table 4:-** Distribution of subjects based on Neonatal Outcome

Outcome	Group		p- value
	Progesterone group (n=25)	Cerclage group (n=25)	
Birth weight (g)	2.1±0.18	2.1± 0.19	0.19
APGAR Score	9±0.91	9.4± 0.70	0.09
Days in NICU per admission	15.83±1.01	11±0.92	0.14
NICU admission	6 (24%)	3 (12%)	0.46
Intraventricular hemorrhage	1 (4%)	1 (4%)	1.00
Respiratory Distress	3 (12%)	2	0.67
Necrotizing Enterocolitis	1 (4%)	1 (4%)	1.00
Neonatal sepsis	1 (4%)	1 (4%)	1.00
Bronchopulmonary dysplasia	0	0	NA
Perinatal death	0	0	NA

**Conclusion:-**

The observations made in present study suggests that natural micronized progesterone is as effective as cervical cerclage in prevention of premature labour in a women with singleton pregnancy with short cervix. Use of natural micronized progesterone is more preferable in clinical practice because it is non-invasive technique, easy to administer and the patients do not suffer from surgical and anaesthesia procedure related adverse effects such as pain, headache, vomiting and other complications. It is also not associated with any hospital stay and is very economical. Using vaginal progesterone saves time for patients as well as doctors.

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**Conflict Of Interest:-**

None declared

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