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RESEARCH ARTICLE

VAGINAL PROGESTERONE IN RISK REDUCTION OF PRETERM BIRTH IN WOMEN WITH SHORT CERVIX IN MID TRIMESTER OF PREGNANCY

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Abstract

Background: Preterm labour is a major health challenge in obstetrics. Many risk factors being identified, the most common one is short cervical length, can be diagnosed by transvaginal ultrasound scan after 13 weeks of pregnancy. Vaginal progesterone is the most bioavailable form of progesterone that have effect on uterine and cervix. Progesterone is found to inhibit the production of proinflammatory cytokines and prostaglandins within the uterus and to inhibit myometrial contractility

Aim: To evaluate the efficacy of vaginal progesterone administration for preventing preterm birth and decrease perinatal morbidity and mortality in asymptomatic women with a singleton gestation and a mid-trimester sonographic cervical length (CL) ≤ 25 mm.

Materials And Methods: This is a prospective study of asymptomatic women with a singleton pregnancy and a sonographic short cervix (<25mm) at 19 + 0 to 23 + 6 weeks of gestation. Women were allocated randomly to receive vaginal progesterone or placebo daily starting from 19 + 0 to 23 + 6 weeks until 36 + 6 weeks, rupture of membranes or delivery, whichever occurred first. Randomization sequence was stratified by centre and history of a previous preterm birth. The primary endpoint was preterm birth before 33 weeks of gestation. Analysis was by intention to treat.

Results: Out of 100 patients for whom study was done, 20 lost to followup and remaining divided into two groups: 40 Singleton pregnant women with CL<25mm between 19 + 0 to 23 + 6 weeks of gestation with no sign and symptoms were given daily vaginal progesterone for up to 36 + 6 weeks, rupture of membranes or delivery, whichever occurred first. The dose is 200 mg once daily and a group of 40 women with cervical length of <25 mm between 19 + 0 to 23 + 6 weeks of pregnancy were given no treatment, Maximum distribution belongs to age of 19-24 years followed by 30-34 years. Most of women in this study have no history of preterm labour. In those who received vaginal progesterone 5 women had history of previous preterm labour and five women in no treatment group. It was found that there was statistically significant reduction in preterm labour in women with short cervix <2.5cm with 200mg vaginal progesterone.

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Conclusions: This updated systematic review and meta-analysis reaffirms that vaginal progesterone reduces the risk of preterm birth and neonatal morbidity and mortality in women with a singleton gestation and a mid-trimester CL ≤ 25 mm, without any deleterious effects on neurodevelopmental outcome. Clinicians should continue to perform universal transvaginal CL screening at 19 + 0 to 23 + 6 weeks of gestation in women with a singleton gestation and to offer vaginal progesterone to those with a CL ≤ 25 mm.

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Introduction:-

Preterm birth is the leading cause of perinatal morbidity and mortality and its prevention is an important health care priority. Despite many risk factors being identified for women destined to deliver preterm, short cervical length detected on transvaginal ultrasound is the most plausible, practical and sensitive risk factor for prediction of spontaneous preterm birth. The definition of short cervix is ≤2.5 cm in the mid-trimester of pregnancy, though risk of spontaneous preterm birth (sPTB) increases as the cervical length decreases. Vaginal progesterone, a naturally occurring steroid hormone, is the most bioavailable form of progesterone for uterine and cervical effects with the fewest side effects. Multiple prospective studies have consistently shown its benefits in decreasing sPTB rate in women with asymptomatic midtrimester short cervix. The safety for mother and fetus, and tolerability of vaginal progesterone is also well established. Vaginal progesterone is a minimally invasive intervention that is not painful and is very safe, with reasonable cost where the benefits (even if argued to be small) clearly outweigh the risks. Thusthere should be little hesitation for implementation of universal transvaginal cervical length screening and preventive vaginal progesterone treatment for women with short cervix.

Material And Methods:-

Study Design

This prospective study is conducted in Department of Obstetrics and Gynaecology in Chalmeda Anand Rao Institute of Medical Sciences, Karimnagar. The study period was18 months from April 2021 to October 2022

Inclusion criteria:

All the woman with singleton pregnancies who presented between 19+0 to 23+6 weeks of gestational age diagnosed with short cervix (≤2.5 cm) and intact membranes were included.

Exclusion criteria:

1) planned cerclage; 2) acute cervical dilation; 3) allergic reaction to progesterone; 4) current or recent progestogen treatment within the previous 4 weeks; 5) chronic medical conditions that would interfere with study participation or evaluation of the treatment 6) major fetal anomaly or known chromosomal abnormality; 7) uterine anatomic malformation 8) vaginal bleeding; or 9) known or suspected clinical chorioamnionitis.

Study Procedure

All of the drug required throughout the treatment interval for a randomized woman was included in drug kits to be assigned to each patient at each study visit in order to prevent dispensing errors. Prior to dispensing the assigned treatment, medical and obstetric history and physical examination data were collected from each participant. Treatment was to be initiated between 19 + 0 and 23 + 6 weeks' gestational age. Women self-administered the study drug once daily.

Study participants were instructed to return to the study centre every 2 weeks. During each visit, subjects were interviewed to determine the occurrence of adverse events, use of concomitant medications and compliance with study drug. Women were asked to return unused study drug from the previous 2 weeks, and determination of compliance was based on the amount of study drug not used.

Study drug was continued until 36 + 6 weeks' gestational age, rupture of membranes or delivery, whichever occurred first. The progesterone and placebo tablets were identical in appearance. Both the active drug and the placebo were supplied in boxes of 14 applicators and were labelled with a unique kit number. Subjects received a 2-

week supply at randomization and at each subsequent visit. They also received a 1-week emergency supply kit at the time of randomization and were resupplied during the treatment period if additional applicators were required before attending the next visit.

Ethical Issues

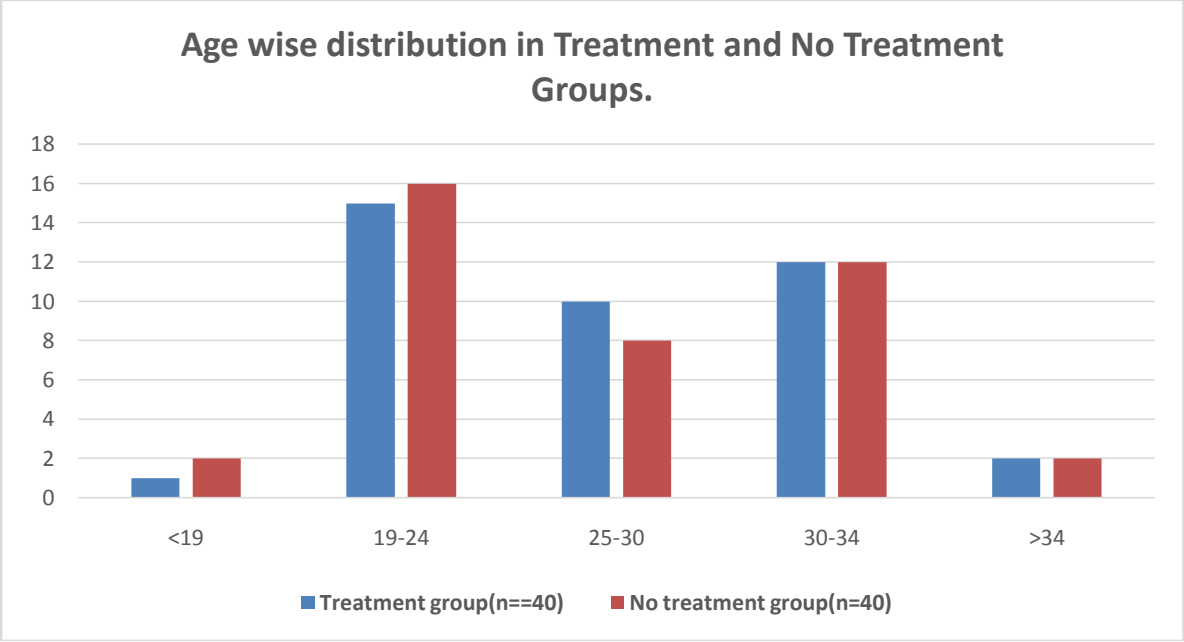
Informed consent was taken verbally from all women, the study was approved by ethics committee CAIMS, Karimnagar. These findings were recorded on astandardised proforma.

Results:-

In this randomized controlled study 100 women were enrolled in the research, 20 lost to followup and remaining divided into two groups: 40 Singleton pregnant women with CL < 25 mm between 19 + 0 to 23 + 6 weeks of gestation with no sign and symptoms were given daily vaginal progesterone 200 mg up to 36+6 weeks, rupture of membranes or delivery whichever occurred firstand a group of 40 women with cervical length of<25 mm between19 + 0 to 23 + 6 weeks of pregnancy were given placebo. Maximum distribution belongs to age of 19-24 years followed by 30-34 years, no significant difference between those rural and urban area and both belong to medium socioeconomic level, main group of women were nulliparous. Most of women in this study have no history of preterm labour. In those who received vaginal progesterone 5 women had history of previous preterm labour and five women in no treatment group.

Age	Treatment group(n==40)	No treatment group(n=40)
<19	1(2.5%)	2(5%)
19-24	15(37.5%)	16(40%)
25-30	10(25%)	8(20%)
30-34	12(30%)	12(30%)
>34	2(5%)	2(5%)

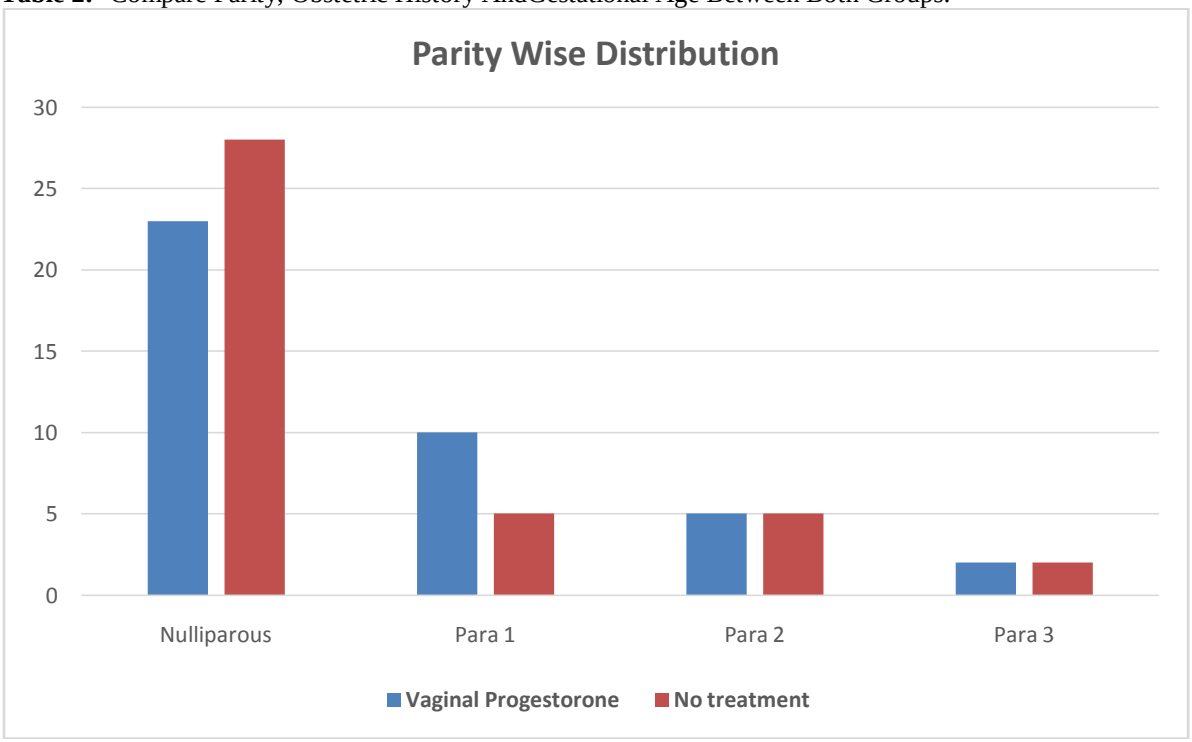
Table 1;- Age wise distribution in treatment group and No treatment group.



Obstetrics History	Vaginal Progesterone	No Treatment	P Value
Parity			
Nulliparous	23	28	0.29
Para 1	10	5	
Para 2	5	5	
Para 3	2	2	

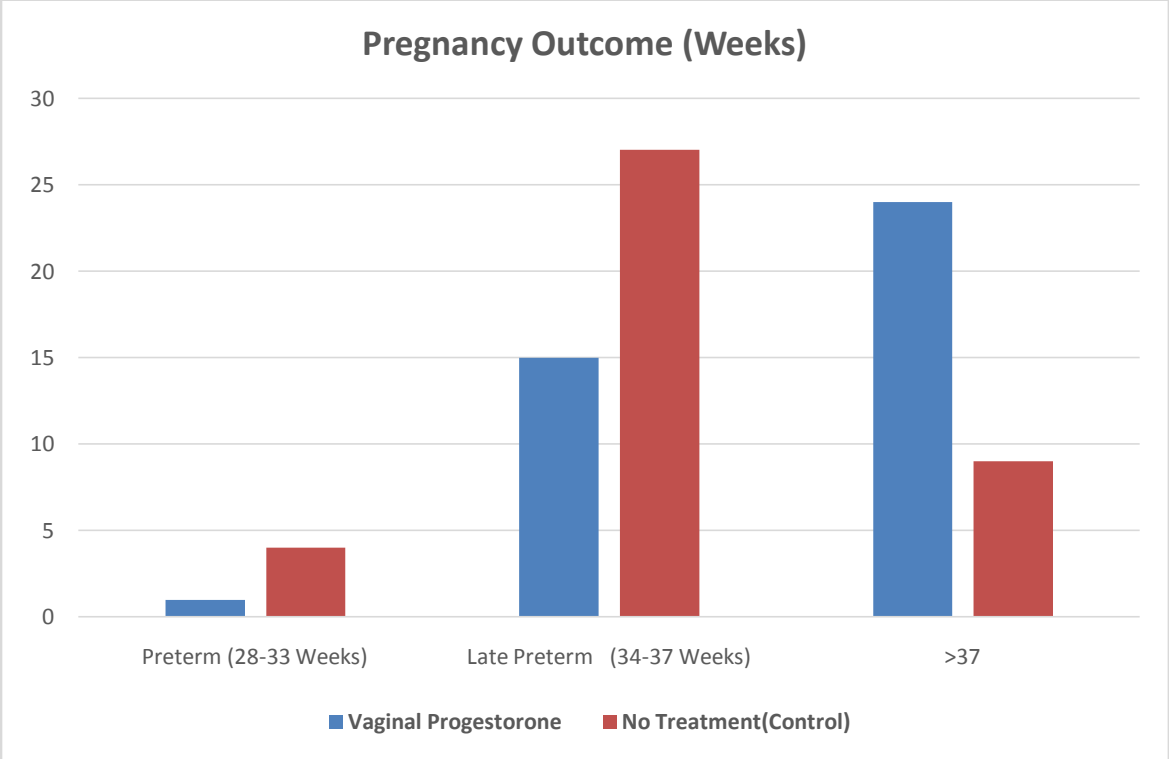
Previous Preterm Labor			
None	35	35	0.42
One	3	4	
Two	2	1	
Gestational Age			
19+0 to 21+6 Weeks	37	25	<0.001
22+0 to 23+6 Weeks	3	15	
Mean ± Sd	24.3±0.5	25.1±1.0	<0.001*

Table 2:- Compare Parity, Obstetric History AndGestational Age Between Both Groups.



Pregnancyoutcome (Weeks)	**Vaginal Progestorone**	**No Treatment(Control)**	**P Value**
Preterm (28-33 Weeks)	1(2.5%)	4(10%)	0.17
Late Preterm (34-37 Weeks)	15(37.5%)	27(67.5%)	
>37 weeks	24(60%)	9(22.5%)	
Mean ±Sd	37.5±2.2	34.0±2.7	0.06
Median	38	35	0.052

Table 3:- Shows Gestational Age At Delivery For Both Groups.



Discussion:-

Our findings suggest that the percentage of preterm birth among women attending our hospital is about 7-10%.Among 80 delivered in study period, study confirmed that preterm birth in group that received vaginal progesterone were less than those who received no treatment, and this difference was statistically significant, this findings defeated by Meena Khandelwal., et al. study that conducted in Cooper University Hospital in USA in 2012. Short cervical length belonged majorly to younger age group in our study this finding agreed with Heath., et al. study conducted in fetal medicine in Harris Birthright Research Centre. King's College Hospital Medical School, London, UK, shows that maternal age (35) years are associated with a risk of short cervix.

The percentage of preterm birth in women receiving vaginal progesterone was less than no treatment group.37.5% of women using vaginal Progestorone delivered between (34-37 weeks) and only 2.5% of this group delivered preterm between 28 -33 weeks and most of them (60%) of this group delivered after 37 weeks. Mean ± 2.2, and about those women with no treatment group, 67.5% delivered between 34 weeks and 10% delivered before 33 weeks and only 22.5% delivered after 37 weeks. Mean± SD, 34± 2.7 and Odds ratio 0.45%. Vaginal progesterone does not have effect on the risk of preterm labour <32 weeks in patients with cervical length <22mm and previous history of preterm birth regarding the dose of 200mg this agreed with Danish., et al. at 2011 in the Department of Obstetrics and Gynaecology, Medical University of Vienna, in Austria.

Vaginal progesterone of 200 mg daily up to 36+6 weeks, rupture of membranes or delivery whichever occurred first appeared to have favourable effect on pregnant women with short cervix <25mm. Our study showed there is significant decrease in preterm labour (27.5%) compared to placebo group. It is agreed with the study that done by Romero R., et al., showed a 40% reduction in the rate of preterm birth before 37 weeks of gestation with administration of vaginal progesterone to women with a sonographic short cervix in the mid-trimester. Also Hassan., et al. in USA in 2016, showed by updated systematic reviewed and meta-analysis confirmed that the risk of preterm birth and neonatal morbidity and mortality reduced with the use of vaginal progesterone in a singleton pregnancy with short cervix at mid-trimester CL ≤ 25 mm. Conde-Agudelo, et al. at 2013 USA, adjusted indirect metaanalyses, either vaginal progesterone or cerclage are both useful in the prevention of preterm birth in women with ultrasound short cervix in the mid trimester in singleton pregnancy, and previous preterm birth.

Conclusion:-

The use of vaginal progesterone in mid-trimester of pregnancy between 19 + 0 to 23 + 6 weeks of gestation may benefit in women with a short cervical length <25mm in mid-trimester of pregnancy with no history of preterm birth or with previous history of preterm birth.

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