Vaginal progesterone to prevent spontaneous preterm birth

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Abstract: Introduction: Preterm birth is the leading cause of peri-natal morbidity and mortality worldwide and contributes to 70% of neonatal morbidity and approximately half of long term neuro-developmental disabilities. Spontaneous preterm labor and delivery is considered to be one of "the great obstetrical syndromes" a term that emphasizes that obstetrical disorder with a similar phenotype is caused by multiple etiologies. One of the mechanisms of disease is the untimely decline in progesterone action. The detection of a short cervix in the mid-trimester is a powerful risk factor for preterm delivery. Vaginal progesterone can reduce the rate of preterm delivery and the rate of neonatal morbidity. **Aim:** to prove if progesterone therapy during pregnancy can reduce spontaneous preterm labor and neonatal morbidity (admission to the neonatal intensive care unit, respiratory distress syndrome, need for mechanical ventilation, etc.). **Methods:** A case control study was conducted that include women attending obstetric outpatient clinic. These women were singleton gestation with sonographic short cervix < 25mm at 12 – 14 weeks. A total of 90 pregnant women have been equally divided into three groups: **group (A):** given daily vaginal progesterone (400mg), **group (B):** had done cervical cercalage McDonald operation at 12 -14 weeks and **group (C):** had done cervical cercalage McDonald operation at 12 -14 weeks then receiving daily vaginal progesterone (400mg). **Results:** Vaginal progesterone and prophylactic cervical cercalge operation reduce the recurrence of preterm labor. **Conclusion:** With daily vaginal progesterone from 12 – 14 weeks gestation till 34 weeks is more superior as this method was associated better gestation age at time of delivery and reduce rate of neonatal morbidity.
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1. Introduction

Preterm birth is the leading cause of peri-natal morbidity and mortality worldwide and contributes to70% of neonatal morbidity and approximately half of long termneuro-developmental disabilities **(Roberto et al., 2012).** A recent systematic review has estimated that 12.9 million births or 9.6% of all births worldwide, were preterm, of which approximately 11.9 million (92.3%) were in Africa, Asia, Latin American and Caribbean **(Beck et al., 2010).** Spontaneous preterm labor and delivery is considered to be one of "the great obstetrical syndromes" a term that emphasizes that obstetrical disorder with a similar phenotype is caused by multiple pathologic processes, have a long subclinical phase and may result from complex gene-environment interactions **(Di Renzo, 2009).**

Progesterone is considered a key hormone for pregnancy maintenance and a decline action of progesterone is implicated in the onset of parturition. If such a decline occurs in the mid trimester, cervical shortening may occur, this would predispose to preterm delivery **(Parimi et al., 2008). Romero et al., 2013** concluded that progesterone treatment is only one solution for prevention of preterm birth before 34 weeks of gestation.

Aim of the Work

The aim of the current study is to prove if progesterone therapy during pregnancy can reduce spontaneous preterm labor thus, neonatal morbidity, neonatal mortality, respiratory distress syndrome, low birth weight and reduce admission to neonatal intensive care unit and use of mechanical ventilation.

2. Patients and Methods

A case control study was conducted that include women attending obstetric outpatient clinic at Al-Zahraa hospital and also at the Boulak El-Dakror general hospital. These women were singleton gestation with sonographic short cervix < 25mm at 12 – 14 weeks. 90 pregnant women were involved in this study. This study started in April 2015 to April 2017.

Inclusion criteria:

- Singleton gestation with sonographic short cervix <25mm at 12 – 14 weeks.
- Intact membrane.
- At 12- 14 weeks gestational age.
- Age ranged from 18- 40 years old.
- Average body mass index 20-25.

- Women are getting pregnancy spontaneously.
- No history of scarred uterus (previous CS or myomectomy).
- No medical disease as diabetes, hypertension or thyroid disease.
- Non smokers nor alcoholic women.
- No history of ablative or excisional procedures of the cervix.

Exclusion criteria:

- Premature rupture of membrane (PROM) during follow up.
- Multiple pregnancies.
- Previous uterine scar.
- Medical disorder as (Diabetes or Hypertension).
- Thyroid disease (hypo or hyperthyroidism).
- Congenital anomalies in the fetus discovered during the follow up.
- Women are getting pregnancy by induction of ovulation or by ART.
- Placenta previa diagnosed during the follow up.
- Accidental hemorrhage happens during the follow up.
- IUFD.
- Gestational DM diagnosed during the follow up.
- Diagnosis of pre-eclampsia (increase BP or albumin in urine).

All the patients will be submitted to the following steps:

- Informed consent was taken from each patient.
- Full history.
- Each patient was submitted for height and weight measurement for estimation of the BMI, general examination, and abdominal examination.
- Obstetric ultrasound is done for checking the number of the fetuses, viability, gestational age, placental location and cervical length at 12 -14 weeks using LOGIQ V5 ultrasound.

-Trans-vaginal ultrasound is only technique which can be reliable to measure cervical length.

Investigation:

- CBC was done.
- -Fasting blood sugar done routinely at every antenatal visit.
- -Complete urine analysis every 2 weeks starting at 24 weeks.
- -Documentation of receiving tocolytic drugs or not / and time of delivery.

We selected90 patients were randomly allocated equally to three groups:

Group A: (30 patients):

In this group we had given them daily vaginal progesterone (400mg) starting from 12-14 Weeks gestational age and till 36 Weeks or delivery.

Group B: (30 patients):

In this group we had done cervical cerclage McDonald operation at 12-14 weeks.

Group C: (30 patients):

In this group we had done cervical cerclage McDonald operation at 12-14 weeks then receiving daily vaginal progesterone (400mg).

Follow up:

The patients were followed up with the regular antenatal care schedules and were asked to report any symptoms of preterm lobour or preterm rupture of membranes. A pelvic ultra-sound scan was done at 32 weeks of gestational to assess the condition of the cervix. The treatment was continued until completed 37 weeks of gestation or delivery if it took place before that date.

Statistical Methods

Data were analyzed using SPSS© Statistics version 17 (SPSS© Corp., Armonk, NY, USA).

Normality of numerical data distribution was examined using the Shapiro-Wilk test. Normally distributed numerical variables were presented as mean and SD and intergroup differences were compared using the unpaired t test (for two-group comparison) or one-way analysis of variance (ANOVA) (for multiple-group comparison). The Tukey-Kramer post hoc test was applied when ANOVA revealed a statistically significant difference among the groups.

Categorical variables were presented as number and percentage and intergroup differences were compared using Fisher's exact test (for nominal data) or the chi-squared test for trend (for ordinal data).

Multivariable binary logistic regression analysis was used to examine the independent effect of vaginal progesterone or cervical cercalge on the occurrence of PTL as adjusted for the effect of possible confounding factors.

Receiver-operating characteristic (ROC) curve analysis was used to examine the overall predictive value of the regression model. The area under the ROC curve (AUC) is interpreted as follows:

Area under ROC curve (AUC)	Diagnostic / predictive value
.9 – 1.0	Excellent
.8 –.89	Good
.7 –.79	Fair
.6 –.69	Poor
<.6	Fail

P-value <0.05 was considered statistically significant.
P-value >0.05 was considered statistically not significant.
P-value <0.001 was considered statistically highly significant.

3. Results

Table1. Demographic characteristics of the three study groups:

Variable	Vaginal progesterone (n=30)	Cervical cerclage (n=30)	Vaginal progesterone + Cervical cerclage (n=30)	F / X^2	Df	p-value
Age (years)	27.4 ± 6.1	25.8 ± 4.7	27.5 ± 5.8	0.850	2 & 87	.431¶
Parity				1.013	1	.314§
P0	8 (26.7%)	7 (23.3%)	8 (26.7%)			
P1	9 (31.1%)	11 (36.7%)	10 (33.3%)			
P2	7 (22.2%)	6 (20.0%)	6 (20.0%)			
P3	3 (10.0%)	4 (13.3%)	4 (13.3%)			
P4 or higher	3 (10.0%)	2 (6.7%)	2 (6.7%)			

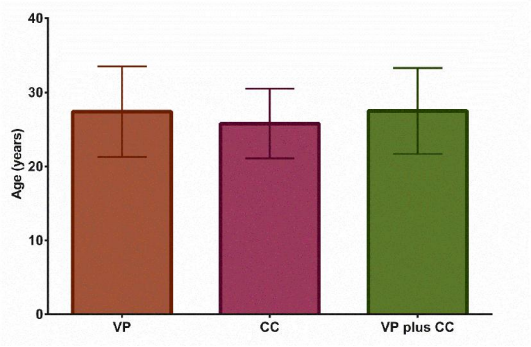

Figure (1). Mean age in the three study groups.

Table 1 shows demographic characteristics (include mean age (years) and parity) in the three study groups. Mean age in group **(A)** (27.4), group **(B)** (25.8) and (27.5) in group **(C)**. No significant difference between the 3 groups in age (years) or parity.

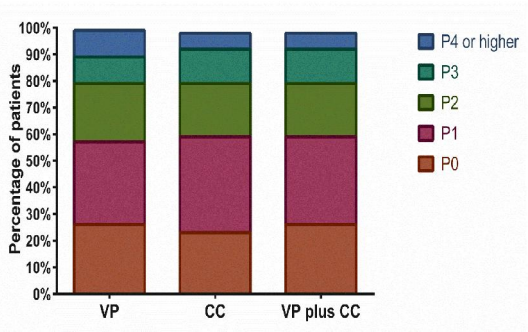

Figure (2). Parity in the three study groups.

Table2. Mode of delivery in the three study groups:

Variable	Vaginal progesterone (n=30)	Cervical cerclage (n=30)	Vaginal progesterone + Cervical cerclage (n=30)	p-value¶
Mode of delivery				.774
SVD	17 (56.7%)	14 (46.7%)	14 (46.7%)	
CS	13 (43.3%)	16 (53.3%)	16 (53.3%)	

Table 2 shows mode of delivery in the three study groups as group (A) showing 56.7% delivered by spontaneous normal vaginal delivery and 13% by CS, group (B) 46.7% delivered by SVD and 53.3% delivered by CS and group (C) 46.7% delivered by SVD and 53.3% delivered by CS. No significant difference between the three groups.

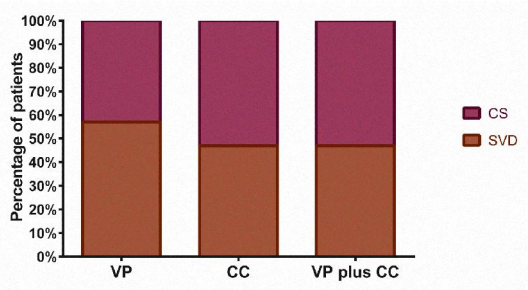

Figure (3). Mode of delivery in the three study groups.

Table3. Gestational age at delivery and incidence of spontaneous preterm (<36weeks) labor in the three study groups:

Variable	Vaginal progesterone (n=30)	Cervical cerclage (n=30)	Vaginal progesterone + Cervical cerclage (n=30)	F (df=2 & 87)	p-value
Gestational age at delivery (weeks)	37.1 ±.7	35.5 ± 1.3	36.2 ± 02.1	8.686	<.001¶
Spontaneouss preterm labor (<36 weeks)	4 (13.3.0%)	23 (76.7%)	12 (40.0%)		<.001§

Table 3 shows that 13.3%% had Spontaneous preterm labor in group (A), 76.7% in group (B) and 40.0% in group (C). P value =0.001 which is highly significant in group (A) which receiving daily vaginal progesterone.

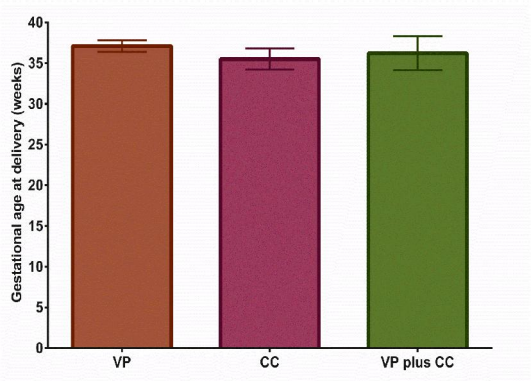

Figure (4). Mean gestational age at delivery in the three study groups.

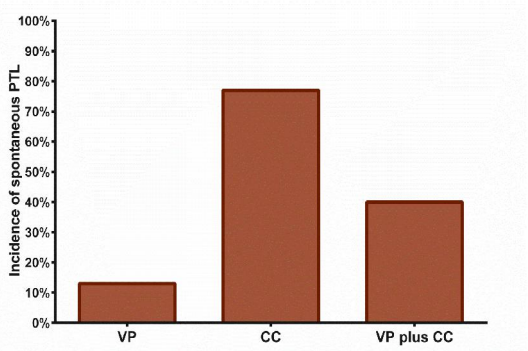

Figure (5). Incidence of spontaneous PTL in the three study groups.

Table4. Fetal Birth weight and incidence of Low (<2500 g) birth weight in the three study groups:

Variable	Vaginal progesterone (n=30)	Cervical cerclage (n=30)	Vaginal progesterone + Cervical cerclage (n=30)	F (df=2 & 87)	p-value
Birth weight (g)	2927 ±299	2233 ± 439	2530 ± 299‡§	17.548	<.001¶
Low (<2500 g) birth weight	1 (3.30%)	21 (70.0%)	12 (40.0%)		<.001§

Table 4 shows fetal birth weight and incidence of low birth weight less than 2500g as (3.3%), (70.0%) and (40.0%) in the three groups respectively. P value =0.001 which is highly significant in group (A).

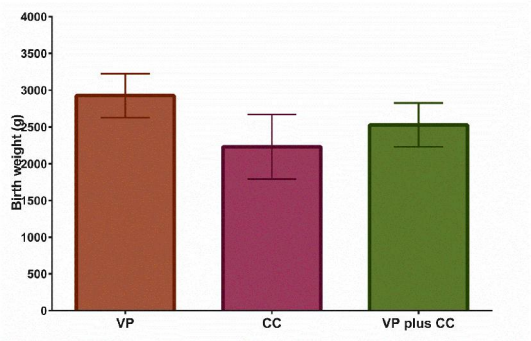

Figure (6). Mean birth weight in the three study groups.

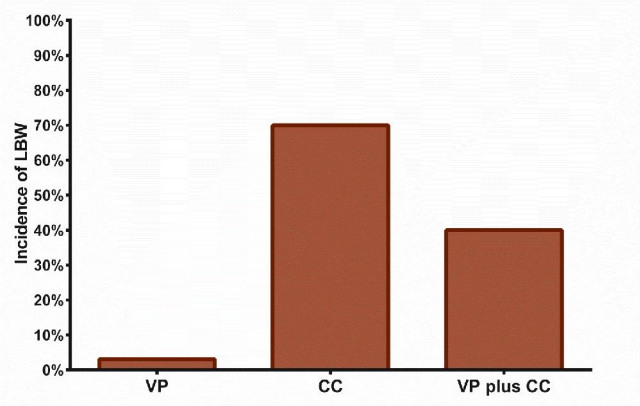

Figure (7). Incidence of LBW in the three study groups.

Table5. Apgar score and incidence of Low (<7) Apgar score in the three study groups:

Variable	Vaginal progesterone (n=30)	Cervical cerclage (n=30)	Vaginal progesterone + Cervical cerclage (n=30)	F (df=2 & 87)	p-value
Apgar score	7.8 ± 1.0†	5.3 ± 2.1	6.6 ± 2.2‡	13.445	<.001¶
Low (<7) Apgar score	2 (6.7%)	18 (60.0%)	9(30.0%)		<.001§

Table 5 Apgar score and incidence of low (<7) Apgar score in the three study groups as (6.7%), (60.0%) and (30.0%) respectively. Which is more better Apgar score in group (A).

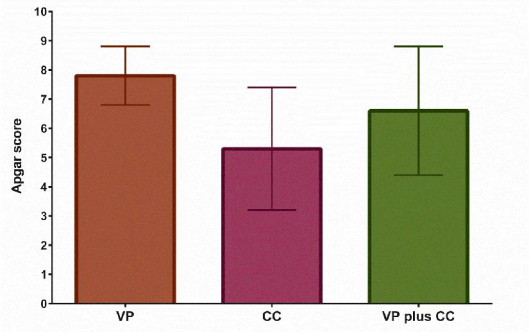

Figure (8). Mean Apgar score in the three study groups.

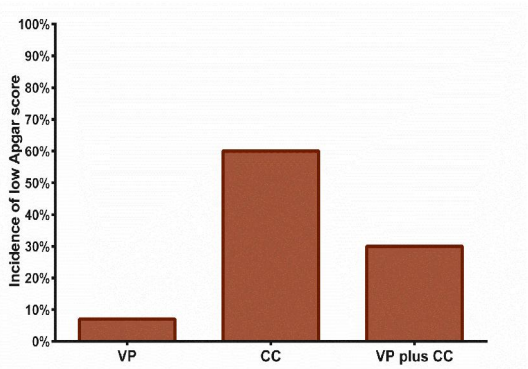

Figure (9). Incidence of low Apgar score in the three study groups.

Table 6. Need of NICU in the three study groups:

Variable	Vaginal progesterone (n=30)	Cervical cerclage (n=30)	Vaginal progesterone + Cervical cerclage (n=30)	p-value¶
NICU admission	1 (3.3%)	13 (43.3%)	7 (23.3%)	.001

Table 6 shows need for NICU in the three study groups as 7 in group (C), 13 in group (B) and only 1 in group (A). P value =0.001 which is highly significant in group (A).

Table 7: Neonatal death in the three study groups:

Variable	Vaginal progesterone (n=30)	Cervical cerclage (n=30)	Vaginal progesterone + Cervical cerclage (n=30)	p-value¶
Neonatal death	0 (0.0%)	3 (10.0%)	2 (6.7%)	.001

Table 7 represents incidence of neonatal death which happened in (10.0%) in group (B), (6.7%) in group (C) and zero% in group (A). P value =0.001 which is highly significant in group (A).

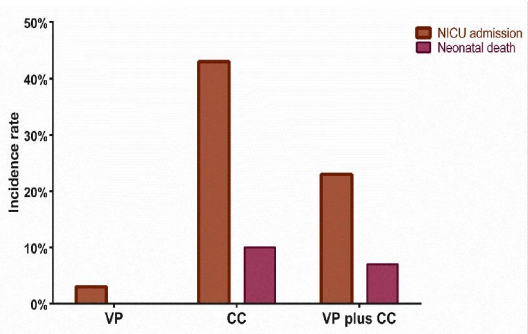

Figure (10). Incidence of NICU admission and neonatal death in the three study groups.

Table 8: Need for tocolysis between the three study groups:

Variable	Vaginal progesterone (n=30)	Cervical cerclage (n=30)	Vaginal progesterone + Cervical cerclage (n=30)	p-value¶
Need for tocolysis	7 (23.33%)	23(76.67.3%)	5 (16.67%)	.001

Table 8 shows need for tocolsis as only 5 (16.67%) pregnant women need for tocolysis after they had done both cervical cerclage and vaginal progesterone in group (C), 7 (23.33%) pregnant women need for tocolysis after receiving daily vaginal progesterone in group (A) and 23(76.67%) pregnant women in group (B) who had done only cervical cerclage.

4. Discussion

In this study there groups were selected each group individed 30 patients the mean age of the patients in **group A** = 27.4 ± 6.1versus 25.8± 4.7 in **group B** versus 27.5± 5.8 in **group** C the p value =0.431 so no significant difference between the three groups.

Regarding the gravidity and the parity between the three groups no significant difference as the P value is 0.314 and in three groups, rang of the parity was variable from primigravida to para four or more.

Regarding the mode of delivery in the three groups no significant difference as the P value.774 whether the patient had spontaneous vaginal delivery or cesaeren section.

In this study the three groups were selected groups (A) received vaginal progesterone daily (400mg) starting at 12 - 14 weeks after we assess the length of the cervix, group (B) cervical cerclage was done at 12-14 weeks and group (C) cervical cerclage was done at 12 weeks followed by daily vaginal progesterone administration. There was reduction in preterm labour less than 37 weeks in group (A) which is highly significant (P=0.001) in comparison to preterm labor in group (B) and (C).

Regarding preterm labor <36weeks, it was found that 4 patients (13.3%) had preterm labor in group A, 23 patients (76.7%) had preterm labor in group B and 12 patients (40%) in group C respectively showing highly significant difference (P=.001) between the three groups.

So the three methods of treatment cause reduction in preterm labor less than 36 weeks. Regarding the incidence of patients who delivered less than 36 weeks it was high in group B who had done cervical cerclage. Then we compare between group A (vaginal progesterone) and group C (cervical cercalage & vaginal progesterone) regarding preterm labor, vaginal progesterone is more effective than cervical cerclage in reducing the rate of preterm delivery in women with singleton gestation and short cervix< 25mm.

Regarding mode of delivery in the three study groups, group (A) is showing 56.7% delivered by spontaneous normal vaginal delivery and 13 % by CS, group (B) 46.7% delivered by SVD and 53.3% delivered by CS and group (C) 46.7% delivered by SVD and 53.3% delivered by CS. No significant difference between the three groups.

In this study we compared between the three groups regarding Apgar score and incidence of low (<7) Apgar score as 6.7%, 60.0% and 30% respectively. Which is more better Apgar score in group (A).

In this study we compared between groups A (vaginal progesterone), group B (cervical cerclage group) and group C (cervical cerclage and vaginal progesterone) regarding need for neonatal Intensive Care Unit (ICU) after delivery, neonatal mortality and low fetal birth weight.

The fetal birth weightoutcome in group A (FBW < 2.5 kg) were (1baby) (3.3%), (21 babies) (70.0%) in group B. and (12 babies) (40.0%) in group C in which P value < 0.001 has highly significant difference in group A who is recevied daily vaginal progesterone (400mg).

Regarding the need to post-delivery neonatal ICU in group A (1 baby) (3.3%) in group (A), (13 babies) (43.33%) need post-delivery ICU in group (B) and (7) babies (23.3%) in group (C) the P value =0.001 which is highly significant in group A.

And regarding the neonatal mortality between the three groups in group A the result was zero (0.0%) in comparison to 3(10.0%) in the B group and 2 (6.7%) in group C the P value was 0.363. So we see that significance between the three groups regarding the need to the post-delivery ICU. But regarding the neonatal mortality there was no statistically significant difference between the three groups but the number in group A was zero.

Regarding need for the tocolysis, comparison between the three groups revealed the following: in group A 7 patients need tocolysis (23.33%) in comparison to 23 patients in group B (76.67%) and 5 patients in group C (16.67%), the P value =0.001 has highly significant difference in group C who had cervical cerclage and vaginal progesterone.

Alfirevic et al 2004 selected the high-risk group for early preterm delivery depending on the trans-vaginal sonographic measurement of cervical length. They undertook a multicenter randomized controlled trial to investigate whether, in women with a short cervix identified by routine trans-vaginal scanning at 12-14 weeks' gestation. Primary outcome was the frequency of delivery before 36 completed weeks of

pregnancy in the three study groups, group (A) was (13.3%), (76.7%) in group (B) and (40.0%) in group (C) with (P <.001) with significant differences in perinatal or maternal morbidity or mortality. They concluded that the insertion of a Shirodkar suture in women with a short cervix does not substantially reduce the risk of early preterm delivery.

The cerclage and prophylactic use of progesterone can reduce the risk of preterm delivery **(Fonseca et al., 2008).**

Owen et al 2009 assessed cerclage to prevent recurrent preterm birth in women with short cervix. They selected 1014women with prior spontaneous preterm birth less than 34 weeks and screened them for short cervix and randomly assigned to cerclage if cervical length was less than 25 mm. Three hundred and two were randomized; 42% of women not assigned and 32% of those assigned to cerclage delivered less than 35 weeks (P =.09). In planned analyses, birth less than 24 weeks (P =.03) and perinatal mortality (P =.046) were less frequent in the cerclage group. There was a significant interaction between cervical length and cerclage. Birth less than 35 weeks (P =.006) was reduced if the cervix less than 15 mm stratum with a null effect in the 15-24 mm stratum. So they concluded that In women with a prior spontaneous preterm birth less than 34 weeks and cervical length less than 25 mm, cerclage reduced previable birth and perinatal mortality but did not prevent birth less than 35 weeks, unless cervical length was less than 15 mm.

Berghella et al 2010 carried out A meta-analysis of trials of women with singleton gestations and second-trimester transvaginalsonographic cervical lenght< 25 mm randomized to cerclage or no cerclage. The degree of CL shortening was correlated to the efficacy of cerclage in preventing preterm birth. There was a significant reduction in preterm birth < 35 weeks in the cerclage compared with no cerclage groups in 208 singleton gestations with both a previous preterm birth and CL < 25 mm (relative risk, 0.61; 95% CI, 0.40-0.92). In these women, preterm birth < 37 weeks was significantly reduced with cerclage for CL < or = 5.9 mm, < or = 15.9 mm, 16-24.9 mm and < 25 mm. He concluded that comparison between 2 groups both having short cervix one group undergo cerclage and the other group no cerclage and the study shows that the cerclage improves the pregnancy outcome regardless the degree of cervical shortening.

Meis et al 2006 conducted a double-blind, placebo-controlled trial involving pregnant women were enrolled at 19 clinical centers at 16 to 20 weeks of gestation and randomly assigned by a central data center, in a 2:1 ratio, to receive either vaginal progesterone (400mg) or placebo; vaginal progesterone was continued until delivery or to 36 weeks of gestation. The primary outcome was preterm delivery before 37 weeks of gestation. Analysis was performed according to the intention-to-treat principle. Base-line characteristics of the 310 women in the progesterone group and the 153 women in the placebo group were similar. Treatment with vaginal progesterone significantly reduced the risk of delivery at less than 37 weeks of gestation (incidence, 36.3 percent in the progesterone group vs. 54.9 percent in the placebo group; relative risk, 0.66 [95 percent confidence interval, 0.54 to 0.81]), delivery at less than 35 weeks of gestation (incidence, 20.6 percent vs. 30.7 percent; relative risk, 0.67 [95 percent confidence interval, 0.48 to 0.93]), and delivery at less than 32 weeks of gestation (11.4 percent vs. 19.6 percent; relative risk, 0.58 [95 percent confidence interval, 0.37 to 0.91]). Infants of women treated with vaginal progesterone had significantly lower rates of necrotizing enterocolitis, intraventricular hemorrhage, and need for supplemental oxygen. **Meis et al 2006** concluded that vaginal progesterone resulted in a substantial reduction in the rate of recurrent preterm delivery among women who were at particularly high risk for preterm delivery and reduced the likelihood of several complications in their infants. Our study Support the results of **Meis et al 2006** regarding that vaginal progesterone reduce the rate of preterm labour and decrease the infant morbidity and mortality. And when vaginal progesterone compared to cerclage, progesterone was better regarding the gestational age at delivery and less need for tocolysis.

Sanchez –Ramos et al., 2009 has compared between two groups both have history of spontaneous preterm labour one group received progesterone and the other group received placebo.

The mean age in progesterone group was 25.32±4.15 vs. 25.60±3.85years in placebo group with no significant difference (P>0.05) between both groups. Gravidity in progesterone group was 3.96±1.06 vs. 4.08±0.997 in placebo group with no significant difference (P>0.05). The mean gestational age was 37.47± 1.559 in progesterone group vs. 34.71±2.49 in placebo group (P <0.05). In the progesterone group 8 of 25 women delivered before completion of 37 weeks of gestation (32%) and 17 women delivered full term (68%). In placebo group 13 of 25 women delivered before completion of 37weeks of gestation (52%) and 12 women delivered full term (48%).

Fetal birth weight in progesterone group was 2988.00±477.031 vs. 2702.00±501.140 in placebo group with significant difference (P>0.05) while an increase in the rate of fetal birth weight over 2500g that occurred in progesterone group was 20 (80%) vs. 15 (60%) in placebo group.

Three of neonates in progesterone group needed NICU for different causes and represented 12% vs. 9 and represented 36% in placebo group. Also 1 neonatal death occurred in progesterone group and represented 4% vs. 4 and represented 16% in placebo group with significant difference (P<0.05) between two groups. The results of **Sanchez-Ramos 2009** study demonstrate the positive effect of progesterone on the incidence of preterm labor. Delivery at <37 gestational weeks was reduced by 20% compared with the placebo group. Similar reductions were seen in delivery less than 34weeks.

The results of our study support **Sanchez-Ramos** study 2009 as the progesterone improve the gestational age in group A with the mean gestational age in this current study is 37.1 ± 0.7and higher in **Sanchez** study in the same group 37.47±1.559 regarding the fetal weight the mean Fetal birth weight in progesterone group was 2988.00±477.031 and the mean fetal birth weight in this current study in group A 2927 ± 299.

Keeler et al 2009 compared between patients with short cervix on trans-vaginal ultrasound between 16 and 24 weeks' gestation treated with McDonald cerclage and those treated with vaginal progesterone. From November 2003 through December 2006, asymptomatic, singleton pregnancies were screened with transvaginal ultrasound between 16-24 weeks' gestation. Patients with a cervical length (CL) < or =25 mm were offered enrollment. Patients were randomly assigned to treatment with McDonald cerclage or vaginal progesterone. The primary outcome was spontaneous preterm birth (PTB) prior to 35 weeks' gestation. Seventy-nine patients met inclusion criteria; 42 were randomly assigned to the cerclage and 37 to vaginal progesterone. Spontaneous PTB prior to 35 weeks' gestation occurred in 16/42 (38.1%) of the cerclage group and in 16/37 (43.2%) of progesterone group (relative risk, 1.14 95% CI, 0.67, 1.93). A post hoc analysis of patients with a prior PTB showed no difference in spontaneous PTB <35 weeks between groups. Our study showed that both progesterone and cervical cerclage reduce preterm labour with vaginal progesterone more superior to cervical cerclage regarding the gestational age at time of delivery. Also in this current study perinatal morbidity and mortality regard fetal birth weight less than 2500g, need for neonatal intensive care unit and neonatal death are decrease in the three groups but much less in group A. so vaginal progesterone is effective as cerclage in reducing rate of preterm delivery in women with singleton gestation and short cervix < 25mm.

Groome et al 2011 has compared between two groups both have history of spontaneous preterm labour one group received vaginal progesterone and the other group received placebo.

According to**Groome et al 2011**, the mean age in progesterone group was 25.32±4.15 vs. 25.60±3.85 years in placebo group with no significant difference (P>0.05) between both groups. Gravidity in progesterone group was 3.96±1.06 vs. 4.08±0.997 in placebo group with no significant difference (P>0.05). The mean gestational age was 37.47±1.559 in progesterone group vs. 34.71±2.49 in placebo group (P<0.05). In the progesterone group 8 of 25 women delivered before completion of 37 weeks of gestation (32%) and 17 women delivered full term (68%). In placebo group 13 of 25 women delivered before completion of 37weeks of gestation (52%) and 12 women delivered full term (48%).

Fetal birth weight in progesterone group was 2988.00±477.031 vs. 2702.00±501.140 in placebo group with significant difference (P>0.05) while an increase in the rate of fetal birth weight over 2500g that occurred in progesterone group was 20 (80%) vs. 15 (60%) in placebo group.

Three of neonates in progesterone group needed NICU for different causes and represented 12% vs. 9 and represented 36% in placebo group. Also 1 neonatal death occurred in progesterone group and represented 4% vs. 4 and represented 16% in placebo group with significant difference (P<0.05) between two groups. The results of **Groom et al2011** study demonstrate the positive effect of progesterone on the incidence of preterm labor. Delivery at <37 gestational weeks was reduced by 20% compared with the placebo group. Similar reductions were seen in delivery less than 34weeks.

The results of our study support **Groom et al 2011** study as the progesterone improve the gestational age in group A with the mean gestational age in my study is 37.1 ±7 and higher in Groom et al study. Regarding the fetal weight the mean Fetal birth weight in progesterone group was 2988.00±477.031 and the mean FBW in my our study in group A (vaginal progesterone) 2927 ± 299 and the rate of fetal birth weight less than 2500g that occurred in progesterone group according to **Groom et al** study 2011 was 20 (80%) and according to our study 1(3.30%) in group A.

The results of **Groom et al., 2011** study and our study are in accord with other investigators who reported the results of a large multi-center trial of progesterone conducted by the Maternal Fetal Medicine Units Network of the National Institute of Child Health and Human Development. The study enrolled women with a documented history of a previous spontaneous preterm delivery, which occurred as a consequence of either spontaneous preterm labour or preterm premature rupture of the fetal membranes.

Condo et al 2013 had done a retrospective

indirect comparison between progesterone and cervical cerclage in prevention of preterm labour as no randomized controlled trial has compared vaginal progesterone and cervical cerclage directly for the prevention of preterm birth in women with a sonographic short cervix in the mid trimester, singleton gestation, and previous spontaneous preterm birth. **Condo et al 2013** performed an indirect comparison of vaginal progesterone versus cerclage using placebo/no cerclage as the common comparator. They taken four studies that evaluated vaginal progesterone versus placebo (158 patients) and 5 studies that evaluated cerclage versus no cerclage (504 patients) were included in women with a sonographic short cervix in the mid trimester, singleton gestation, and previous spontaneous preterm birth. Both interventions were associated with a statistically significant reduction in the risk of preterm birth at <32 weeks of gestation and composite perinatal morbidity and mortality compared with placebo/no cerclage. Adjusted indirect metanalyses did not show statistically significant differences between vaginal progesterone and cerclage in the reduction of preterm birth or adverse perinatal outcomes. Based on state-of-the-art methods 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 mid trimester, singleton gestation, and previous preterm birth. Selection of the optimal treatment needs to consider adverse events, cost and patient/clinician preferences. This study goes in contrast to this current study as this study is direct comparison between cerclage and progesterone and current study shows that progesterone is better than cerclage regarding the gestational age and less neonatal morbidity and mortality.

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