

Comparative study between cervical cerclage and vaginal progesterone for the prevention of preterm birth in women with a history of preterm birth and a sonographic short cervix: A randomized trial

Mohamed AbdElzاهر¹, Mohamed Ali¹ and Mohamed Bedewi²

¹ Department of Obstetrics and Gynecology (Al-Azhar University, Cairo, Egypt),

² Department of Diagnostic Imaging (Salman Bin Abdulaziz University Al-Kharj-KSA)

drmohamednada@yahoo.com

Abstract: Objective: This randomized controlled trial aimed to compare cervical cerclage and vaginal progesterone for the prevention of preterm birth with a sonographic short cervix in the mid-trimester, singleton gestation and previous preterm birth. **Study design:** Women with high-risk factors for preterm birth (history of previous preterm labour/ second trimester loss [>16 weeks or <37 weeks gestation], short cervical length (<25 mm) on ultrasound at 16 to 24 weeks gestation, and Previous prophylactic cervical cerclage) were screened through TVU (Transvaginal Ultrasound) of cervix every two weeks between 14 – 24 weeks. The eligible women with sonographic short cervix <25 mm in the mid trimester, singleton gestation and previous spontaneous PTB <37 weeks of gestation were randomized either to cervical cerclage group (McDonald cerclage) or vaginal progesterone group (200mg vaginal progesterone suppository to be inserted at night. Treatment was continued until either delivery, 37 weeks of gestation or development of premature rupture of membranes. Primary outcome measure was PTB <34 weeks gestation. **Result:** One hundred women were assigned randomly. Both interventions were associated with a statistically significant reduction in the risk of preterm birth <34 weeks of gestation ($p=0.001$). Comparing using cervical cerclage and vaginal progesterone, showed that no statistical significant difference in reducing preterm birth or adverse perinatal outcomes. **Conclusion:** It was concluded that the vaginal progesterone is effective as cervical cerclage in prevention premature labor but its use is preferable in clinical because it's non-invasive technique and less cost. These results should be confirmed by large sample trial.

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1.Introduction

Preterm birth refers to a delivery that occurs before 37 weeks of gestation. Preterm birth is the leading direct cause of neonatal death (death in the first 28 days of life). It is responsible for 27 percent of neonatal deaths worldwide, comprising over one million deaths annually [1-5].

Few countries provide reliable national preterm birth prevalence data. Worldwide, the preterm birth rate is estimated to be about 11 percent (range 5 percent [parts of Europe] to 18 percent [parts of Africa]), and about 15 million children are born preterm each year (range 12 to 18 million) [2,6]. Of these preterm births, 84 percent occurred at 32 to 36 weeks, 10 percent occurred at 28 to <32 weeks, and 5 percent occurred at <28 weeks. Efforts to delay delivery in women presenting with acute preterm labor have been largely unsuccessful. For this reason, much attention has focused on preventative strategies.

A sonographic short cervix is a powerful predictor of preterm delivery [7,8], yet implementation of a screening program of all pregnant women requires the availability of a clinical intervention able to prevent preterm delivery and improve neonatal

outcome [9]. Strategies that have been considered include progesterone administration [10], cervical cerclage [11-13] and insertion of a pessary [14].

There is good evidence that progesterone supplementation reduces the rate of spontaneous singleton preterm birth in women who have had a previous spontaneous preterm singleton birth and in women with a short cervix on ultrasound examination in the current pregnancy. Among women with prior preterm birth and a singleton pregnancy, progesterone treatment decreases the risk of preterm birth by one-third (OR 0.66, 95% CI 0.53-0.82; four randomized trials), corresponding to an absolute reduction in risk of preterm birth between 0 and 26 percent across studies [15]. The risk of neonatal death is halved (OR 0.52, 95% CI 0.25-0.96). Among women with short cervical length, progesterone treatment leads to an absolute reduction in risk of preterm birth between 8.8 and 15.2 percent [15].

A Cochrane review of cerclage for preterm birth prevention in singleton pregnancy reported a less marked, but statistically significant, reduction in preterm birth when cerclage was compared with no treatment [16]. In a meta-analysis of randomized trials

of women with singleton gestation and prior spontaneous preterm birth and short cervical length <25 mm before 24 weeks, treatment with ultrasound-indicated cerclage significantly lowered total neonatal morbidity and mortality (15.6 versus 24.8 percent without cerclage; RR 0.64, 95% CI 0.45-0.91), presumably because cerclage significantly reduced the frequency of preterm birth (delivery <35 weeks RR 0.70, 95% CI 0.55-0.89; 28.4 percent versus 41.3 percent in women without cerclage) [17]. In another meta-analysis of randomized trials of women with singleton gestations and prior preterm birth managed either by (1) cervical length screening with cerclage for short cervical length or (2) history-indicated cerclage, patients with ultrasound-indicated versus history-indicated cerclage had similar rates of preterm birth before 37 weeks (31 versus 32 percent, RR 0.97, 95% CI 0.73-1.29), preterm birth before 34 weeks (17 versus 23 percent, RR 0.76, 95% CI 0.48-1.20), and perinatal mortality (5 versus 3 percent, RR 1.77, 95% CI 0.58-5.35), and only 42 percent developed a short cervical length and received cerclage [18].

This randomized controlled trial aimed to compare cervical cerclage and vaginal progesterone for the prevention of preterm birth with a sonographic short cervix in the mid-trimester, singleton gestation and previous preterm birth.

2. Material And Methods

This is a prospective randomized study was conducted between April 2011 to June 2013 at Obstetrics and Gynecology Department, (Salman bin Abdulaziz University Hospital, Al-Kharj, KSA and Bab El sharia Hospital Al Azhar University Cairo Egypt). A written consent form was signed by every pregnant women enrolled in this study after a detailed information were given. The study was approved by the Ethical Committee of this hospital. Inclusion criteria are; (high-risk for preterm labor with one of the following criteria) 1-history of previous preterm labour/ second trimester loss (≥ 16 weeks or <37 weeks gestation), 2-singleton pregnancy with short cervical length (≤ 25 mm) on ultrasound at 16+0 to 24+0 weeks gestation, 3-Previous prophylactic cervical cerclage. Meanwhile, the exclusion criteria are as follows; 1-multiple pregnancy, 2-fetal anomalies either structural or chromosomal, 3- suspected or proven ruptures of the fetal membranes at the of time recruitment, 4-known uterine malformation.

Gestational age was calculated on basis of the last menstrual period with regular cycles or the first trimester ultrasound. At the first antenatal visit, the patients were routinely screened and treated for Neisseria Gonorrhoea and Chlamydia Trachomatis. Symptomatic Bacterial Vaginosis was also treated

with specific antibiotics and repeated cultures were performed to confirm the efficacy of treatment.

Women who have high-risk factors for PTB were screened through TVU (Transvaginal Ultrasound) of cervix every two weeks between 14 – 24 weeks. Cervical length measurements were performed by experienced sonographers using standard techniques. The patient's bladder was emptied prior to visualization of cervix, minimum pressure necessary was used to obtain a clear image of cervical canal in mid-sagittal plane.

The eligible women with sonographic short cervix <25mm in the mid trimester, singleton gestation and previous spontaneous PTB <37 weeks of gestation were randomized either to cervical cerclage group or vaginal progesterone group. Randomization was performed using a list of computer-generated random numbers and participants were assigned to their groups using sealed envelopes.

The surgical techniques of McDonald was used to perform in cervical cerclage group. Mersilene (5mm) was the preferred suture. All women assigned to cerclage group was given a single dose of intravenous Erythromycin, 500mg intraoperatively. The cerclage was removed at 37th week of gestation unless spontaneous onset of labor or rupture of membranes began. On the other hand, women assigned to vaginal progesterone group received, 200mg vaginal progesterone suppository (Uterogestan, 200mg capsule) to be inserted at night. Treatment was continued until either delivery, 37 weeks of gestation or development of premature rupture of membranes.

All women in the study were advice to reduce physical activity for the remaining days of their pregnancy. They were given prophylactic steroids (two doses of Dexamethasone, 12mg intramuscularly, 12h apart) for fetal lung maturation at 28 weeks of pregnancy.

Primary outcome measure was PTB <34 weeks gestation. Secondary outcome includes: PTB at <37 weeks, <35 weeks, and <28 weeks. Neonatal outcomes includes neonatal mortality, NICU (Neonatal Intensive Care Unit) admission, days in the Neonatal Intensive Care Unit and composite morbidity (any respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis or sepsis.)

Data registration and Statistical analysis:

The results were tabulated and statistically analyzed using a computer program SPSS 15 (statistic a package for social science). The sample mean (X), standard deviation (SD), and standard error of the mean as well as the range were obtained for numerical variables. For non-numerical variables, the frequency, distribution and percentage were calculated. The student's (t) test was used to test the significance of the

difference between 2 independent means. The Chi square test (X^2) was used to test whether the distribution of a certain phenomenon among two or more groups was equal or not. The probability (P) value was calculated and a P -value < 0.05 was considered statistically significant

3.Results

Out of 117 patients who were eligible in our stud, seventeen patients were refused to participate in the study. One hundred patients were randomized to either cervical cerclage group (50 pt.) and vaginal progesterone group (50 pt.), three patients among cervical cerclage group lost the follow up and two patients among vaginal progesterone group. The flow chart of the patients included in the study is shown in (Figure I).

There were no significant difference in base line characteristics between the studied groups (Table I). Specifically, previous cervical operation (including cervical cerclage), and previous obstetric history (including preterm births). The women with history of preterm birth before 34 weeks was reported in 35 patients (74.5%) in cervical cerclage group study and 33 patients (68.8%) in vaginal progesterone group ($P=0.5$). there were no statistically significant difference between gestational age and cervical length at start of treatment.

The rate of primary outcome spontaneous birth before 34 weeks of gestation was 10 patients (21.2%) in cervical cerclage group and 13 patients (27.1%) in the vaginal progesterone group ($p=0.392$) no significant difference between two groups (Table II) but incidence of spontaneous preterm labor before 34 weeks marked decrease in both groups if compared with women with history of preterm labor before 34 weeks ($p=0.001$) (Table 1).

The average gestational age at the time of delivery was 36.3 ± 3 weeks in cervical cerclage group and 35.7 ± 2.9 weeks in vaginal progesterone group ($P=0.392$). There was also no statistically significant difference in gestational age at delivery when analyzed for the both groups <37 weeks, <35 weeks and <28 weeks of gestation (Table II), however two women (4.3%) delivered at <28 weeks of gestation in cervical cerclage group compared with one woman (2.1%) in vaginal progesterone group ($p =0.545$). Although there were no significant differences in the route of delivery, more on women with cervical cerclage rather than vaginal progesterone group who delivered by cesarean section [10 (21.3%) vs. 5 (10.4%)], respectively ($p =0.147$) (Table 2).

There were no statistically significant difference between the two group regarding neonatal outcome (Table 3).

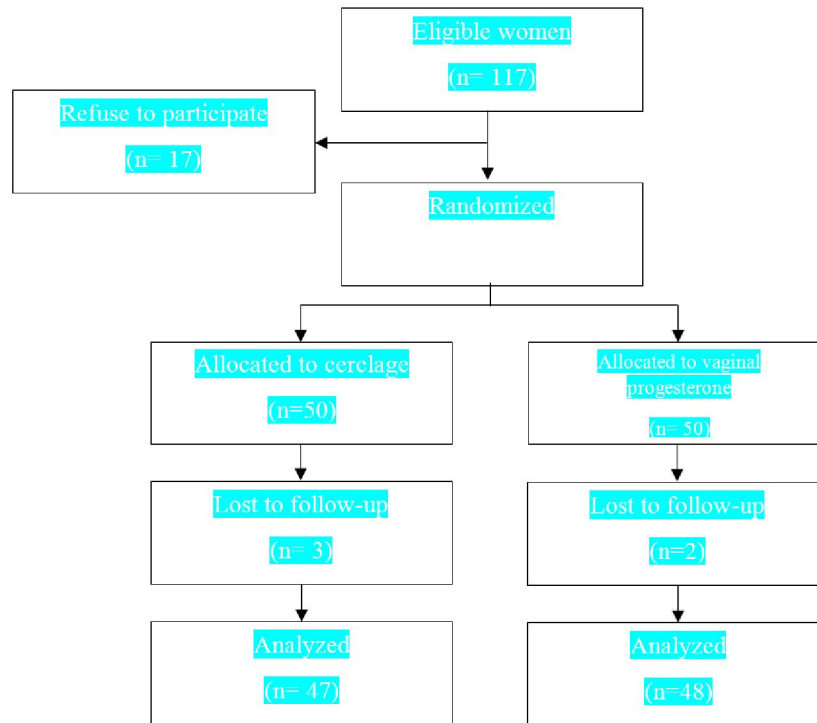


Figure I. Flowchart of the patient included in this study

Table 1: **Baseline Characteristics of Participants in both Groups**

Characteristic	Cerclage group (n=47)	Vaginal Progesterone group (n=48)	P value
Maternal age (in years)	23.7±3.2	24.1±3.7	0.576
Parity	2.8 ± 1.5	3.4 ± 2.2	0.08
BMI (Body Mass Index)	31.7±3.04	32.3±4.3	0.457
Smoker	6 (12.8%)	5 (10.4%)	0.720
Previous PTB <34 weeks	35 (74.5%)	33(68.8%)	0.537
Previous cerclage	4 (8.5%)	3 (6.3%)	0.673
Previous cervical surgery (n%)	7 (14.9%)	9 (18.8%)	0.616
GA at randomization (week)	21 ± 1.4	20.9 ± 0.8	0.376
Cervical length (mm) when treatment start	23.2 ± 1.2	23.5 ± 0.7	0.144

Table 2: **Obstetric Outcome**

Outcome	Cerclage group (n=47)	Vaginal Progesterone group(n=48)	P-value
Gestational delivery (in weeks)	36.3 ± 3	35.7 ± 2.9	0.392
Primary outcome			0.509
Preterm birth <34	10(21.2%)	13 (27.1%)	
Secondary outcomes			
Preterm birth <37	17 (36.2%)	19 (39.6%)	0.732
Preterm birth <35	14 (29.8%)	16(33.3%)	0.710
Preterm birth <28	2 (4.3%)	1 (2.1%)	0.545
PPROM (n)	5 (10.6%)	7 (14.6%)	0.563
Caesarean Delivery	10 (21.3%)	5 (10.4%)	0.147

PPROM: Preterm Premature Rupture of Membranes

Table 3: **Neonatal Outcome**

Outcome	Cerclage group (n= 47)	Vaginal Progesterone group (n=48)	P-value
Birth weight (g)	288.7 ± 810	3071± 594	0.211
NICU admission (n%)	13 (27.7%)	11 (22.9%)	0.595
Days in NICU per admission	53.1 ± 29.8	42.1 ± 21.1	0.314
Intraventricular hemorrhage	1 (2.1%)	0	0.310
Respiratory Distress	5 (10.6%)	6 (12.5%)	0.777
Necrotizing Enterocolitis	0	1(2.1%)	0.320
Perinatal death (n%)	5 (10.6%)	5 (10.4%)	0.972

NICU: Neonatal Intensive Care Unit

4. Discussion

The key finding is thatcervical cerclage and vaginal progesterone are equally effective for the prevention of preterm birth and adverse perinatal outcomes in patients with a short cervix in midtrimester, singleton gestation, and history of spontaneous preterm birth, but no show statistically significant differences between cervical cerclage and vaginal progesterone in reducing preterm birth or adverse perinatal outcomes.

No randomized controlled trial has directly comparedcervical cerclage and vaginal progesterone for the prevention of preterm birth in women with a

sonographic short cervix in the midtrimester, singleton gestation, and previous spontaneous preterm birth. All previous randomized trials allocated to receive vaginal progesterone versus placebo/no treatment, or cerclage versus no cerclage for the prevention of preterm birth.

da Fonseca and co-investigators randomly assigned 142 women at high-risk for preterm delivery (based on at least one previous spontaneous singleton preterm birth, prophylactic cervical cerclage, or uterine malformation) to daily supplementation with progesterone vaginal suppositories (100 mg) or placebo from 24 through 34 weeks of gestation [19].

Active prophylaxis significantly reduced the risk of delivery at all gestational ages studied: <37 weeks (14 versus 29 percent in the placebo group), <34 weeks (3 versus 19 percent in the placebo group). By monitoring all patients with an external tocodynamometer once a week for 60 minutes, the investigators were also able to demonstrate a significant difference in the frequency of spontaneous uterine contractions between the two groups, suggesting that progesterone supplementation may exert its effect by maintaining uterine quiescence in the latter half of pregnancy.

In an RCT[20] evaluating just the 46 singleton gestations with prior SPTB < 35 weeks and short TVU CL < 28 mm at 18-22 weeks, vaginal progesterone 90-mg gel daily started at 18-23 weeks until 37 weeks was associated with significant decreases in the rates of both PTB < 32 weeks and neonatal intensive care unit admission compared to placebo [24]. In 71 singleton gestations with prior PTB, vaginal progesterone 100-mg suppositories daily between 24-34 weeks was associated with significant reduction in incidences of PTB < 37 weeks (24% vs 50%; odds ratio [OR], 3.11; 95% CI, 1.13– 8.53) and <34 weeks (5.4% vs 26.5%; OR, 6.30; 95% CI, 1.25–31.70) compared to placebo [26]. In a meta-analysis, including 169 singleton gestations with prior PTB and TVU CL < 25 mm mostly <25 weeks, vaginal progesterone was associated with a significant reduction in PTB < 33 weeks (RR, 0.54; 95% CI, 0.30–0.98) and in composite neonatal morbidity and mortality (RR, 0.41; 95% CI, 0.17–0.98) [23].

Owen and co-investigators a total of 1014 women underwent transvaginal ultrasonographic screening between 16 and 22 6/7 weeks' gestation. If the cervical length was at least 30 mm; scan frequency was every 2 weeks and increased to weekly when the cervical length was 25 to 29 mm. Those women whose cervical length shortened to less than 25 mm were randomly assigned to undergo McDonald cerclage or no cerclage. The primary outcome was the rate of preterm birth before 35 weeks' Gestation. Three hundred eighteen women (30%) developed cervical length shortening, and 302 consented to randomization. The rate of preterm birth in the no cerclage group was 42% versus 32% in the cerclage group (OR, 0.67; 95% CI, 0.42–1.07; $P = .09$). Survival analysis also demonstrated an improvement in overall pregnancy prolongation in the cerclage group ($P = .053$). In planned secondary analyses, birth before 37 weeks ($P = .01$), previable birth (at < 24 weeks; $P = .03$), and perinatal mortality ($P = .046$) were less common in the cerclage group [12].

Berghella and colleagues [17] sought to estimate whether cerclage prevented preterm birth and

perinatal mortality and morbidity in selected high-risk women, women with a prior spontaneous preterm birth, a singleton gestation, and a shortened cervical length. This meta-analysis included the same 4 trials as that discussed previously, but also included the multicenter, randomized trial of cerclage for preterm birth prevention [12]. Cerclage was found to significantly reduce preterm birth before 37, 32, 28, and 24 weeks of gestation. Although a composite outcome of either perinatal mortality or morbidity was also significantly reduced in the cerclage group (16%) versus the no cerclage group (25%; RR, 0.64; 95% CI, 0.45–0.91), preventing specific neonatal morbidities, alone or as a neonatal composite morbidity, has yet to be statistically demonstrated. [21,22]. Thus, the chief benefit of ultrasound-indicated cerclage for shortened cervical length in women with prior spontaneous preterm birth seems to be from preventing periviable births [21].

In our study both intervention were associated with a statistically significant reduction in the risk of preterm birth < 34 weeks of gestation if compared with women with history of preterm labor before 34 weeks ($p = 0.001$), this agree with all previous randomized trials allocated to receive vaginal progesterone versus placebo/no treatment, or cerclage versus no cerclage for the prevention of preterm birth [17,19-22].

Conde-Agudelo and co-investigators were 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[25], this agree with our study.

Comparing using cervical cerclage and vaginal progesterone, showed that no statistical significant difference. But using vaginal progesterone has many advantages. Firstly, it is non-invasive technique with easy administration. Secondly, the patients do not suffer from surgical procedure adverse such as anesthesia, pain and complication. Thirdly, using vaginal progesterone saves time for patients and doctors. Lastly, its cost is lesser than cervical cerclage. From above mentioned reasons, it is clear that using vaginal progesterone is superior in management of premature labor.

The strength of this study is that it is first study was conducted to compare directly between vaginal progesterone and cervical cerclage. All previous studies compare either vaginal progesterone with placebo or cervical cerclage with placebo. Recently, a systematic review was done to compare between vaginal progesterone and cervical cerclage and the results demonstrate that there is no statistical difference between both methods. Despite this results agrees with our result but it is indirect comparing. Our research prefer to compare two methods directly to be more practical and to avoid the hidden bias such as selection bias which affect indirect comparing.

Conclusion and recommendation

It was concluded that the vaginal progesterone is effective as cervical cerclage in prevention of premature labor but its use is preferable in clinical because it's non-invasive technique and less cost.

The limitation of this study is small sample size so it is recommend to conduct another study with large sample size. Hopefully our findings will stimulate other groups to publish their results of large cohorts with clearly agreed-upon, and reproducible, protocols and complete follow-up that will complement the data presented here. We also hope that international collaborations will be set up to test these treatments in adequately powered randomized trials, involving both low-risk and high-risk women.

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