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ORIGINAL ARTICLE

Efficacy of adjunctive use of vaginal progesterone after cervical cerclage for prevention of 2nd trimester miscarriage due to preterm labour.

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ABSTRACT… Objective: To assesses the effectiveness of adjunctive vaginal progesterone following cervical cerclage in preventing second-trimester miscarriages as a result of preterm labor (PTL). **Study Design:** Randomized Control Trial. **Setting:** Lady Wallington Hospital, King Edward Medical University, Lahore. **Period:** July to Dec, 2024. **Methods:** The trial group (vaginal progesterone + cervical cerclage) and the control group (cervical cerclage only) were randomized to two equal groups. In order to mitigate bias, double-blinding was implemented. The principal result was the absence of preterm labor during the pregnancy. The chi-square test was employed to analyze the data, with a p-value of less than 0.05 being considered significant. **Results:** At the time of cerclage application, the mean gestational age was 14.22 ± 3.85 weeks, and the mean maternal age was 29.83 ± 3.96 years. The trial group demonstrated a considerably higher efficacy (90%) than the control group (26.7%), with a p-value of less than 0.001. In comparison to the later application (16 ± 3.89 weeks, p=0.002), the efficacy of cervical cerclage was higher when applied at an earlier gestational age (12.94 ± 3.36 weeks). The trial group had a substantially higher gestational age at delivery (35.7 ± 1.72 weeks) than the control group (34.3 ± 2.65 weeks, p=0.003). The outcomes were influenced by parity (p=0.008), while there was no significant association between maternal age and previous cerclage history. **Conclusion:** Adjunctive vaginal progesterone significantly improves outcomes in preventing PTL when combined with cervical cerclage, particularly when applied earlier in pregnancy. Further large-scale, multi-center studies are recommended to confirm these findings and guide clinical practice.

Key words: Cervical Cerclage, Efficacy, Preterm Labor, Second-Trimester Miscarriage, Vaginal Progesterone.

INTRODUCTION

The primary cause of infant mortality worldwide is preterm labor (PTL). It suggests that a child will be born prior to the completion of 37 weeks. Preterm labor was reported to be responsible for the deaths of approximately two-thirds of all neonates in the United States during their first year of life in 2001.[1] Prematurity is currently the second most common cause of mortality among infants under the age of five and the most common cause of death during the first month of life. The morbidity rate in fetuses prior to 32 weeks of gestation is 70 times greater than that in term neonates. Fetal distress, birth asphyxia, and premature delivery are the consequences of preterm labor, which can result in cerebral deformity and blindness in the child. In patients with a cervix smaller than 25 mm and a history of preterm birth (PTB), there are two interventions that can decrease the rate of PTL: cervical cerclage or vaginal progesterone administration.[2,3]

Women who have a history of spontaneous preterm birth and a cervical length of less than 25 mm are at a significantly higher risk of experiencing another preterm delivery. In such cases, cervical cerclage, reinforce it and prevent premature dilation, has been shown to be beneficial. This intervention helps in prolonging pregnancy and reducing the risk of preterm birth, which in turn improves neonatal outcomes by decreasing the likelihood of complications associated with prematurity. Additionally, the use of intramuscular progestin therapy, administered weekly, has

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been demonstrated to be effective in reducing the incidence of preterm birth in women with a prior history of spontaneous preterm delivery. Progestins help maintain uterine quiescence by promoting the relaxation of the myometrium, reducing inflammatory responses, and enhancing cervical integrity, thereby contributing to the prolongation of pregnancy. These combined approaches play a crucial role in preventing recurrent preterm births and improving perinatal outcomes.[4,5]

The prevalence of neonatal morbidities can be reduced by the timely diagnosis of preterm labor, the administration of corticosteroids to the mother, and interventions to prevent or delay preterm labor. The precise cause of preterm labor is not yet fully comprehended; however, it is preferable to prevent preterm labor and preserve the embryo within the uterus. The diagnosis of preterm labor is made on the basis of effacement and regular, excruciating uterine contractions.[6] The subsequent objective of treating preterm labor is to allocate an adequate amount of time for the optimal performance of the surgery, the mother's well-being, and the provision of all necessary instruments for the preterm infant's care.[7]

Preterm labor leading to second-trimester miscarriage remains a critical concern in obstetric care, often resulting in severe neonatal complications or fetal demise. In clinical practice, cervical cerclage is a widely used intervention to reinforce cervical integrity and prevent premature dilation; however, the role of adjunctive progesterone therapy in further reducing the risk of preterm birth needs to be thoroughly investigated, particularly in our local patient population. Limited local data is available on the effectiveness of combining vaginal progesterone with cervical cerclage, making it essential to explore its potential benefits in preventing preterm labor and improving perinatal outcomes. Globally, the reported efficacy of adjunctive progesterone therapy has been variable, with some studies demonstrating significant benefits while others showing inconsistent results. If proven effective, this intervention could be integrated into routine obstetric care protocols, offering a more comprehensive approach to managing high-risk pregnancies and improving neonatal survival rates. The findings from this study could also contribute to the development of standardized guidelines, ensuring that women at risk of preterm birth receive optimal and evidence-based care.

METHODS

The research was conducted in the procedure chamber of the gynecology department at Lady Willingdon Hospital in Lahore after approval from ethical institutional review board (461/RC/KEMU/13-07-23). Subjects who satisfied the operational definitions and inclusion criteria were admitted to the study after providing written informed consent in this randomized controlled trial.

The study enrolled pregnant women between the ages of 20 and 35 who were in their first trimester, specifically between 12 and 14 weeks of gestation, and carrying a singleton pregnancy. Inclusion criteria required that participants had one or more risk factors associated with cervical insufficiency or preterm birth. These factors included a documented history of second-trimester pregnancy loss characterized by painless cervical dilatation, which is indicative of cervical incompetence. Additionally, women who had previously undergone cervical cerclage placement due to cervical insufficiency in the second trimester, as determined by sonographic evidence of cervical shortening to less than 2.5 cm, were included. The study also encompassed women with a prior history of spontaneous preterm labor in a previous pregnancy, further identifying those at high risk for recurrent preterm birth.

Women in the control group will endure cervical cerclage, but they will not receive vaginal progesterone pessaries. A woman who is less than 37 weeks pregnant and has regular uterine contractions (6 or more contractions in 1 hour) and is over 14 weeks pregnant is diagnosed with preterm labor. Any instance of preterm labor that transpired during the trial was regarded as a failure. Second trimester miscarriage was the term used to

describe the termination of pregnancy as a result of preterm labor during the second trimester. The efficacy of this trial was assessed in terms of the percentage of women who will maintain a viable pregnancy for at least 34 weeks. Any instance of preterm labor that transpired during the trial was regarded as a failure. The technique employed was non-probability consecutive sampling.

The WHO sample size calculator was used to determine the sample size of 60, with 30 in each group. The percentage of patients attaining a positive outcome in the Treatment group was 95%, and in the Control group, it was 71%. The confidence level was 80%, and the absolute precision was 5%.

All patients' information, including their age, parity, history of prior PTL, and gestational age at the commencement of the trial (as determined by a reliable LMP), was recorded. The treatment administered to the other group was concealed from the control group. Patients were monitored until delivery or the conclusion of their pregnancy, and those who exceeded 34 weeks of gestation were documented.

All subjects will undergo a vaginal examination with a sterile speculum following induction. In order to guarantee membrane integrity, the fern test was implemented. Urinalysis will assist in the identification of any indications of urinary infection. In the event that an infection was detected during the urine culture test, subjects were subsequently excluded. Exclusion criteria included a history of anti-phospholipid syndrome, chronic hypertension, diabetes mellitus, uterine fibroids, threatened abortion, and severe anemia (haemoglobin less than 7 mg/dl) in women. Patients with polyhydramnios, IUGR (reported by consultant radiologist on obstetrical ultrasonography), cervical dilatation ≥3 cm, and indications of infection in urinalysis.

Using McDonald's suture, cervical cerclage was performed and randomly assigned to either the T-treatment or the C-control group. Women in the Treatment group were advised to take 200 mg of vaginal progesterone pessaries daily until 34 weeks of gestation following cervical cerclage. Women in the Control group were advised to undergo cervical cerclage but were not provided with vaginal progesterone pessaries and were frequently monitored. Any instance of preterm labor that transpired during the trial was regarded as a failure.

After data analysis using the SPSS-23, frequency and percentage of qualitative variables, such as efficacy and previous history of cerclage, were determined. The mean ±SD was calculated for the quantitative variables, including age and gestational age at the start of the trial and at delivery. Stratification was employed to control the impact of effect modifiers such as age, parity, gestational age, and general body health on the outcome. The chi square test was used to determine the significance of these modifiers ($p<0.05$).

RESULTS

A total of 60 expectant women who were chosen for the study and random sampling technique with double blinding was employed to evenly distribute them into two groups of 30 in order to eliminate selection bias. The control group and the trial group were the two categories. The mean gestational age in weeks was 14.22 ± 3.85 weeks, and the mean maternal age of the selected expectant women was 29.83 ± 3.96 years.

The frequency of the parity of the women selected for the research is illustrated in Figure-1. The data indicated that 5 individuals (8.33%) were single-parity, 24 individuals (40%) were para 2, 20 individuals (30.33%) were para 3, and 11 individuals (18.33%) were para 4 at the time of the investigation. The previous history of cervical cerclage application was demonstrated by 22 individuals (36.7%).

The efficacy of the control and trial groups was assessed in accordance with the operational definition of "No episode of preterm labor" during the current pregnancy. According to the data analysis, the trial group exhibited efficacy in 27 cases (90%), while the control group exhibited efficacy in only 8 cases (26.7%). The results were

highly significant, as evidenced by the p value of <0.001 on the chi-square test.

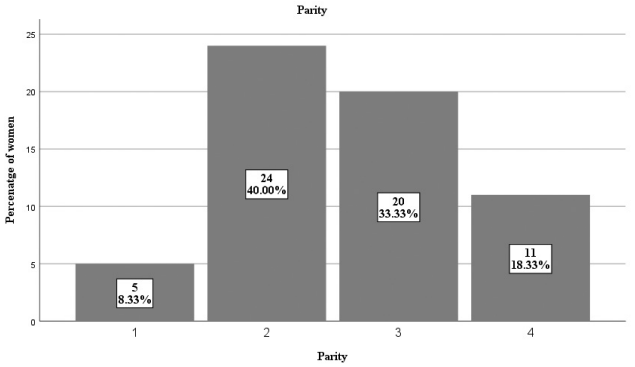

Figure-1. Bar chart showing parity of selected pregnant ladies.

Groups	Efficacy Shown Y/N		P-Value
	Yes	No	
Trial Group	27(90%)	3(10%)	<0.001
Control Group	8(26.7%)	22(73.3%)	
Parity (1)	5(100%)	0(0%)	0.008
Parity (2)	8(33.3%)	16(66.7%)	
Parity (3)	14(70%)	6(30%)	
Parity (4)	8(72.7%)	3(27.3%)	
Previous History of Cervical cerclage	13(59.1%)	9(40.9%)	0.928
No Previous History of Cervical cerclage	22(57.9%)	16(42.1%)	

Table-I. Comparison of trail group with control group and other variables with patients who showed efficacy.

The analysis of various factors influencing the efficacy of cervical cerclage revealed significant associations. Parity was found to impact the success rate, with higher parity associated with a decreased likelihood of efficacy in both the control and trial groups, as indicated by the chi-square test (p=0.008). However, a previous history of cervical cerclage did not show any significant correlation with treatment success.

The timing of cervical cerclage application played a crucial role in its effectiveness. Cerclage performed at an earlier gestational age (mean 12.94 ± 3.36 weeks) demonstrated a significantly higher success rate compared to procedures done later (mean 16 ± 3.89 weeks, p=0.002). Additionally, gestational age at delivery was also a key determinant of efficacy. Women in the trial group had a significantly longer gestation at delivery (mean 35.7 ± 1.72 weeks) compared to those in the control group (mean 34.3 ± 2.65 weeks, p=0.003), reinforcing the benefits of adjunctive progesterone. However, maternal age did not exhibit a significant association with treatment efficacy.

Variable	Efficacy (Yes/No)	Mean ± SD	Mean Difference	P-Value
Gestational age (weeks)	Yes	12.94±3.36	3.05	0.002
	No	16±3.89		
Gestational age at delivery (weeks)	Yes	35.7±1.72	1.43	0.003
	No	34.3±2.65		
Maternal Age (years)	Yes	29.40±3.38	1.04	0.320
	No	30.44±4.67		

Table-II. Showing the details of the outcome variable with respect to various effect modifiers

DISCUSSION

We are investigating individuals who have received cervical cerclage to ascertain the necessity of progestin in preventing premature labor. The therapy group exhibited a notable enhancement in infant morbidity indicators.[8] Numerous controlled trials have been conducted on vaginal progesterone therapy, and reported reductions in the incidence of preterm birth and neonatal fatalities in women with a short cervix and a history of preterm delivery.[9] The incidence of PTB in women at risk can be reduced by intramuscular progesterone therapy with cerclage, as determined by another meta-analysis. However, the benefits of vaginal pessaries were inconsistent.[10]

This study illustrates the effectiveness of vaginal progesterone as an adjunctive treatment

following cervical cerclage in the prevention of second-trimester miscarriages caused by preterm labor (PTL). A total of 60 expectant women were enrolled and randomly assigned to the trial and control groups. Based on the results, the trial group (vaginal progesterone) demonstrated a considerably higher efficacy (90%) than the control group (26.7%), with a highly significant p-value (<0.001). The efficacy of cervical cerclage was significantly influenced by the gestational age at the time of application. Success rates were higher when the cerclage was applied earlier (mean gestational age of 12.94 ± 3.36 weeks) (p=0.002). Furthermore, there was a significant correlation between higher outcomes and a prolonged gestational age at delivery (mean of 35.7 ± 1.72 weeks) (p=0.003). Efficacy was also discovered to be influenced by parity, as the success rate was reduced as the number of parities increased (p=0.008). Nevertheless, there was no significant correlation between efficacy and maternal age or prior history of cervical cerclage.

Dr. Agustin Conde-Agudelo et al. found that vaginal progesterone significantly reduced the risk of preterm delivery, neonatal morbidity/mortality, and NICU admission compared to placebo. It also lowered the risk of preterm birth and low birth weight compared to no cerclage. Indirect meta-analysis showed no significant difference between cerclage and vaginal progesterone in preventing preterm birth or adverse perinatal outcomes. Vaginal progesterone and cerclage demonstrate equivalent efficacy in avoiding preterm delivery and improving perinatal outcomes in women with a singleton pregnancy, a midtrimester sonographically identified short cervix, and a history of spontaneous premature birth. The chosen therapy will depend on the cost-effectiveness of treatments, adverse effects, and the preferences of the patient or clinician.[11]

A study found that the non-progesterone group had a higher incidence of spontaneous abortion (P=0.016), while the progesterone group had greater mean gestational age and birth weight. However, the progesterone group had more preterm births, low Apgar scores, and NICU admissions. Vaginal progesterone after McDonald cerclage reduced second-trimester abortion and improved perinatal outcomes in singleton pregnancies.[12]

In a study, earlier delivery was noted in patients with cerclage and vaginal progesterone, as demonstrated by a significant difference in the avoidance of preterm birth before 35 weeks gestational age between the groups (p = 0.035). The cerclage group (29%) and the cerclage plus 17-OHPC group (34%) had similar rates of preterm birth before 35 weeks (p = 0.533). The odds ratio for the risk of preterm birth before 35 weeks among women with cerclage and vaginal progesterone, compared to all other patients, was 5.21 (95% CI: 1.3-21.2). Comparable protection of preterm birth was attained when cerclage was administered together intramuscular progesterone, in contrast to cerclage alone. The correlation between cerclage, vaginal progesterone, and elevated risks of preterm birth may stem from the characteristics of the group rather than the therapies under investigation.[13]

Combined therapy with vaginal progesterone and cervical cerclage significantly lowers the risk of preterm birth compared to either intervention alone. A meta-analysis demonstrated a reduced risk of preterm birth before 37 weeks with combined therapy compared to cerclage alone (RR 0.51) or progesterone alone (RR 0.75).[14] Similarly, a cohort study found that dual therapy was associated with a lower risk of delivery before 28 weeks compared to cerclage alone (13% vs. 34%, crude RR 0.38).[15]

Studies consistently report no significant increase in adverse maternal or neonatal outcomes with dual therapy compared to monotherapy. Given its effectiveness in reducing preterm birth, preventing second-trimester miscarriage, and improving neonatal outcomes, combined therapy is a valuable approach, especially in high-risk pregnancies.[16] The findings support the integration of vaginal progesterone into clinical practice for high-risk pregnancies requiring cervical cerclage. This combined approach can reduce preterm birth rates, decrease neonatal

morbidity, and enhance perinatal survival. Future large-scale, multi-center trials are necessary to validate these results and establish standardized protocols, ultimately improving maternal and neonatal care.

CONCLUSION

These findings suggest that vaginal progesterone as an adjunct to cervical cerclage significantly improves outcomes in preventing preterm labor and second-trimester miscarriage. Early application of cervical cerclage appears critical to achieving better results. Further research with larger sample sizes may help validate these findings and refine clinical guidelines.

LIMITATIONS

This study has several limitations that may affect the generalizability of its findings. The small sample size and single-center design limit the applicability of results to broader populations. Additionally, the short follow-up period excludes the assessment of long-term maternal and neonatal outcomes. Potential confounders, such as socioeconomic status and comorbidities, were not analyzed, which could have influenced the results. Compliance with vaginal progesterone was not monitored, making it difficult to determine its true effectiveness in real-world settings. Furthermore, the exclusion of high-risk groups, such as multiple pregnancies, restricts the study's applicability to a more diverse patient population.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Iqra Aftab:** Data collection, analysis, paper writing.
2	**Javaria Gulzar:** Data collection, paper writing.
3	**Sadiya Butt:** Discussion writing and review of manuscript.
4	**Mafia Akbar:** Data entry and review of manuscript.
5	**Mariam Riaz:** Data analysis, manuscript writing.
6	**Ayesha Malik:** Review of manuscript.