Original Article

Clinical Outcome of Arabin Cervical Pessary in Women at Risk of Preterm Birth in Indian Scenario

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Background : Preterm birth complications are the leading cause of neonatal morbidity and mortality. This study was designed to ascertain the role of Arabin cervical pessaries in the management of women at risk of spontaneous preterm birth.

Methods : It was a Randomized Controlled Trial, on pregnant women with 12-24 weeks of pregnancy with either history of >2 spontaneous preterm birth or cervical length <25 mm with or without a history of spontaneous preterm birth. Women were randomly assigned to Arabin cervical pessary group (50) or the progesterone group (46). The primary outcome was the preterm birth rate at <37 weeks and <34 weeks. Secondary outcomes were any maternal side effects along with the neonatal outcome.

Results : The preterm birth rate <34 weeks gestation was less frequent, 8/50(16%) in the pessary group *versus* 16/46 (34.78%) in the progesterone group, with a relative risk of 0.46, the p-value of 0.042. Preterm birth rate <37 weeks in pessary group was 41/50 (82%) *versus* 41/46 (89.13%) in progesterone group, relative risk 0.92, p-value 0.32. In the pessary group, there was a significant reduction in further threatened preterm labour 38% *versus* 60.87% in the progesterone group (p=0.025) which subsequently reduces the use of tocolytics.

Conclusion : The study shows that cervical pessary can be considered an affordable, safe and reliable option for reducing the rate of early spontaneous preterm birth in singleton pregnancies in women at risk of spontaneous preterm birth.

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Preterm birth and complications associated with prematurity contribute maximally to neonatal mortality. The global rate of preterm birth is quite variable, it ranges from 5% to 18% among various countries[1]. India is leading among the top fifteen nations contributing to two-thirds of the world's preterm babies. More than 80% of premature births occur between 32 to 37 weeks of gestation. The management cost of premature babies is massive which further enhances if the birth weight is less than 1000 grams[2]. Approximately 40-45% of premature babies are born because of spontaneous preterm labour which is more than iatrogenic early induction of labour whether for an obstetrical or medical reason[1]. So early prediction and effective management strategy of spontaneous preterm labour will play a vital role in bringing down the rate of preterm birth and cutting back its economic load.

Editor's Comment :

- Arabin cervical pessary is a safe and economical alternative to natural micronized progesterone for the management of threatened preterm labour.
- Arabin cervical pessary can be used as convenient, one time treatment and has shown encouraging results in terms of prolongation of gestational age.

Despite robust research to develop an effective screening tool for early prediction of preterm labour, we are still dependent on short cervical length on transvaginal sonography before 28 weeks of gestation. The gradual decrease in cervical length and the presence of funneling further increase the risk of preterm labour. In women, at high risk of preterm labour either on cervical assessment or history alone cervical cerclage is the treatment of choice for a long time. For placement of cervical cerclage, women require hospital admission, operation theatre and general anesthesia with conflicting results in success. Various formulations of progesterone are also used in different doses and routes like vaginal, oral and intramuscular for the management of preterm labour. Various studies have quoted that more exposure to progesterone during

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pregnancy can act as a triggering factor for some chronic conditions in fetuses that may appear later in adult life. A higher level of maternal progesterone will elevate the fetal progesterone levels, which adversely affect the progesterone target cells in the fetal pituitary, testis of a male fetus and developing fetal reproductive system[3].

Cervical cerclage and progesterone have some pros and cons. So, there is a need and space for the introduction of a novel approach in form of Arabin cervical pessary which appears effective and safer than cervical cerclage and progesterone. This study aims to assure the efficacy and safety of Arabin cervical pessary in the prevention of preterm birth in the Indian population.

Materials and Methods

This study was conducted in the Department of Obstetrics and Gynaecology. The study was executed as a randomized controlled trial with allocation concealment. The purposive sampling method was used to recruit study participants from November, 2019 to June, 2021 who had consulted inpatient and Outpatient Departments. We enrolled pregnant women, having 12 to 24 weeks of pregnancy with a past history of spontaneous preterm birth, second-trimester abortions, traumatic obstetrics delivery, multiple dilatation and curettage, antepartum hemorrhage, multifetal gestation and polyhydramnios.

The recruited participants were called for an initial TVS assessment of cervical length and then reassessed every two weeks for any cervical changes. Screening of infections from the lower genitourinary tract was done by vaginal swab culture, endocervical culture, and urine culture in all the recruited participants.

Inclusion Criteria :

- All asymptomatic pregnant women of 12-24 weeks of gestation with a history of >2 spontaneous preterm birth
- All pregnant women of 12-24 weeks of pregnancy with or without a history of one spontaneous preterm birth with cervical length <25 mm

Exclusion Criteria :

- Active preterm labour
- Clinical evidence of chorioamnionitis
- Vaginal bleeding
- Preterm premature rupture of membranes
- Evidence of fetal compromise or fetal death
- Lethal fetal malformation
- Multiple gestations
- Silicon allergy

Material :

Arabin Cervical Pessary (Fig 1) is a soft, flexible, perforated and dome shape made up of silicon. Its inner diameter is to be fitted as high as possible around the cervix and its outer diameter is to hold the pessary against the vaginal wall to support the pelvic floor. Arabin cervical pessary rectifies the cervicovaginal angle by rotating the cervix to approach the posterior vaginal wall. It is available in three sizes small, medium, and large. The commonly used ones are small and medium sizes; small should be preferred for a singleton pregnancy, thin-built and short-statured women whilst medium and large should be offered to taller women and edematous cervix respectively.

Group Distribution :

Participants who had signed the informed written consent were randomly assigned into two groups by using the simple randomization sealed envelope method. All the sealed opaque envelopes having assigned group cards were numbered sequentially along with the signatures on the back of envelopes, prepared by persons not involved in the trial. Once a patient has consented to enter for trial, the envelope was assigned and opened by trained medical personnel independent of the trial.

Group 1 — was prescribed with insertion of Arabin cervical pessary and post-procedural TVS to ensure correct placement of Pessary.

Group 2 — was prescribed oral natural micronized progesterone Sustained Release (SR) 200 mg BD.

A preliminary examination to evaluate the cervical length, with a special note on the presence or absence of funneling through TVS was done. Judicious screening of any form of genitourinary infection was done by performing vaginal swabs, endocervical swabs, and urine cultures. Treatment of infections with specific antimicrobial drugs was completed before insertion of pessary.

Insertion :

The patient was laid in the dorsal lithotomy position and the shoulder support with a pillow. The gel-covered

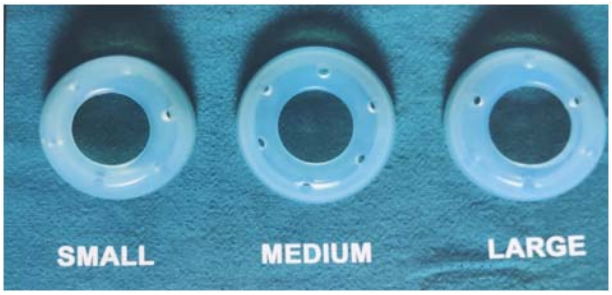

Fig 1 — Arabin Cervical Pessary

pessary was folded with the smaller diameter directed upwards so that the pessary can be placed toward the top of the posterior fornix. While inserting the pessary it remains folded until the upper vaginal fornix is approached, then slide as high as possible with the smaller diameter surrounding the cervix. The correctly placed pessary was not perceived by the patient and to ensure this we asked the patient to stand up and walk a few steps. If the patient complained of any pain or uneasiness, the size and placement were reassessed. A post-insertion TVS was done in every patient to ascertain the correct placement of the pessary.

Removal :

The pessary was removed at 37 weeks of gestation. Pessary removal before 37 weeks was considered in patients with active preterm labour not responding to tocolysis, in case of severe vaginal bleeding, premature rupture of membranes, or suspect of chorioamnionitis.

Primary Outcome :

Prolongation of gestational age in terms of delivery >37 weeks, 34-37 weeks, 34-28 weeks, and <28 weeks

Secondary Outcome :

- Subsequent threatened preterm labour episodes and use of tocolytics (Tablet Nifedipine 20 mg twice daily)
- Premature rupture of membranes (PROM)
- Complications such as expulsion, infection, discharge, and bleeding
- Neonatal outcomes in terms of neonatal infections (sepsis), necrotizing enterocolitis, respiratory distress syndrome, hyperbilirubinemia and neonatal death

Statistical Analysis :

The data are communicated as percentages, mean with Standard Deviation (SD). Mean ± Standard Deviation was calculated for all quantitative data. Categorical variables were displayed by using frequency measures. The Chi-square test was used for group comparison. Mean, standard deviation, p-value, and Relative- Risk were calculated. The p-value <0.05 is the measure of significance. The SPSS 22.0 version (Chicago, Inc, USA) Window software was used for statistical analysis.

Results

The study flow is depicted in Fig 2. We recruited 404 eligible pregnant women during the study period for primary assessment out of which 102 women had declined to participate in the trial due to personal constraints, 196 women had not fulfilled the inclusion criteria and 8 women were diagnosed as placenta previa. A total of 98 women had consented to participate in the trial after satisfying the inclusion criteria. Two patients did not complete the study protocol from the progesterone group. So, in the final analysis, we have 50 patients in the pessary group and 46 patients in the progesterone group.

Both the groups were comparable in terms of demographic characteristics as shown in Table 1. In the pessary group, the mean age was 29.14 years, and 28.54 years in the progesterone group. The mean BMI in the pessary group was 23.76±3.62 and in the progesterone group was 23.85±3.69. In the pessary group, the mean gestational age at the time of enrollment was 23.70±3.62 weeks and in the progesterone, the group was 23.70±3.69 weeks. Most of our study participants did not have a past history of preterm birth in any of the groups. In the pessary group, the mean cervical length was 1.49 cm and in the progesterone group, it was 1.33 cm. Funneling was

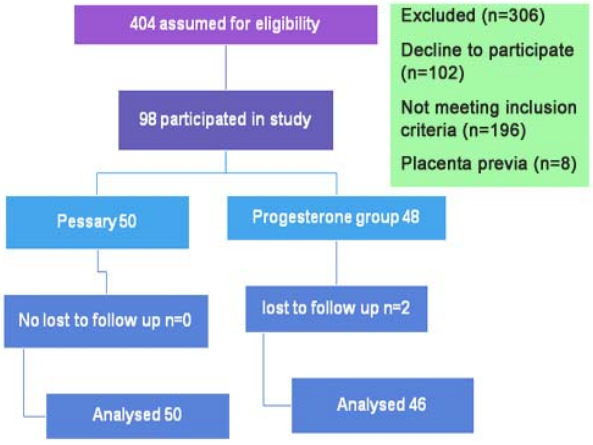

Fig 2 — Flowchart showing the distribution of patients in study groups

Table 1 — *Demographic profile of patients*

	Pessary group (N=50)	Progesterone group (N=46)	P value	Chi-square value
Age (Years±SD)	29.14±2.76	28.54±2.75	0.482	1.45
BMI	23.76±3.62	23.85± 3.69	0.536	2.178
Gestational age at enrollment	23.70±3.62	23.70± 3.69	0.839	0.840
H/O previous preterm birth :				
No PTB	36%(18)	47.83%(22)		
1 PTB	28%(14)	23.91%(11)	0.68	1.487
2 PTB	26%(13)	21.74%(10)		
≥3 PTB	10%(05)	06.52%(03)		
Cervical length at enrollment (cm)	1.49± 0.48	1.33±0.48	0.485	1.44
Funneling at enrollment on TVS	76%(38)	65.22%(30)	0.245	1.348
Sludge at enrollment on TVS	4%(02)	2.17%(01)	0.607	0.263

noted in 38(76%) patients at the time of enrollment in the pessary group and 30 (65.22%) patients in the progesterone group.

Various morbidities during the course of pregnancy in the study period were described in Table 2. Subsequent threatened labour episodes were present in 4(8%) cases in the pessary group while it was reported by 12(26.09%) patients in the progesterone group. The statistical difference is significant (p=0.017) in both groups in terms of the occurrence of subsequent threatened labour episodes. In the pessary group 19 (38%) patients and the progesterone group 28(60.87%) patients, needed tocolytic therapy in the form of tablet nifedipine 20 mg two times a day and the difference was statistically significant with the p-value 0.025. Bleeding episodes were reported by 2(4%) patients in the pessary group and 2(4.35%) patients in the progesterone group. Premature rupture of membranes was found in 2(4%) patients in the pessary group and it was found in 6(13.04%) patients in the progesterone group. Vaginal discharge was reported by all the patients of the pessary group 50(100%) and 18(39.13%) patients in the progesterone group. We have to remove pessary in 7 (14%) patients on medical grounds and 11(22%)patients needed repositioning of pessary without its removal. The mean duration of hospital stay due to various morbidities was 3.2 days in the pessary group and 4.5 days in the progesterone group.

Table 2 — *Maternal morbidities in the antenatal period*

	Pessary group (N=50)	Progesterone group (N=46)	P value	Chi-square value
Subsequent threatened preterm labour episodes	8%(04)	26.09%(12)	0.017	5.64
Tocolytic therapy in form of Tab-Nifedipine 20mg bd	38%(19)	60.87%(28)	0.025	5.01
Corticosteroid treatment for fetal lung maturation	94%(47)	84.78%(39)	0.139	2.181
Bleeding in pregnancy	4%(02)	4.35%(02)	0.932	0.007
Premature rupture of membranes :	4%(02)	13.04%(06)	0.109	2.565
30-32 weeks	00%	66.67%		
32-35 weeks	04%	33.33%		
Side effects :				
- Vaginal discharge	100%(50)	39.13%(18)		
- Pessary repositioning without removal	22%(11)	-		
- Pessary removal(medical indication)	14%(07)	-		
Maternal hospital stay (mean)	3.2 days	4.5 days		

Table 3 gives the details of the pregnancy outcome in terms of the gestational age of delivery. After pessary insertion,a maximum number of patients that are 33(66%) successfully carry their pregnancy up to 34-37 weeks of gestation and in the progesterone group the maximum number of patients delivered at 34-37 weeks of gestation that are 25(54.35%). Two patients (4%) underwent spontaneous delivery before 28 weeks of gestation in the pessary group and in the progesterone group 2(4.35%) patients delivered spontaneously before the completion of 28 weeks. In the pessary group, 6(12%) patients spontaneously delivered between the gestational age of 28-34 weeks and in the progesterone group, 14(30.43%) patients delivered spontaneously at this gestational age. In the pessary group, 9(18%) patients successfully continued their pregnancy beyond 37 weeks of gestation and 5(10.87%) attain that milestone in the progesterone group. In the pessary group mean gestational age of delivery was 35.08 weeks and in the progesterone group it was 33.76 weeks. In the progesterone group, the preterm birth rate at <34 weeks was significantly more (p=0.042) but no significant difference was detected in both groups in terms of spontaneous preterm birth rate at <37 weeks of gestation (RR=0.92; p=0.32 at 95%CI).

The distribution of cases according to fetal/neonatal outcomes was elaborated in Table 4. Neonatal death in the pessary group was seen in 2(4%) babies and the progesterone group, it was in 3(6.52%) babies (p-0.58). Necrotizing enterocolitis was diagnosed in 3(6%) babies in the pessary group and in the progesterone group, it was in 4(8.70%) babies (p=0.614). Respiratory distress syndrome was observed in 10(20%) babies in the pessary group and the progesterone group was observed in 14(30.43%) babies (p=0.243). Treatment of sepsis was given in 6(12%) babies in the pessary group and it was needed in 7(15.22%) babies of the progesterone group (p=0.646). In the pessary group, hyperbilirubinemia was seen in 7(14%) babies, and in the progesterone group, it was seen in 10 babies (p=0.326). Statistical differencewas not significant in

Table 3 — *Pregnancy outcomes in terms of delivery*

	Pessary group (N=50)	Progesterone group (N=46)	P value	Chi-square value
Pregnancy outcomes - Delivery				
<28 weeks	4%(02)	4.35%(02)	0.152	5.288
28-34 weeks	12%(06)	30.43%(14)		
34-37 weeks	66%(33)	54.35%(25)		
>37 weeks	18%(09)	10.87%(05)		
Main outcomes of pregnancy				
Delivery <34 weeks	16%(08)	34.78%(16)	0.832	RR 0.97
Delivery<37 weeks	82%(41)	89.13%(41)		(0.76-1.24)
Mean GA at delivery(weeks)	35.08	33.76		

Table 4 — *Distribution of cases according to fetal/ neonatal outcomes*

Fetal/Neonatal level	No of cases in the pessary group (N=50)	%	No of cases the progesterone group (N=46)	%	RR	P value
Fetal death	00	00	00	00	00	00
Neonatal death	02	04%	03	6.52%	0.61	0.58
Morbidity						
Necrotizing enterocolitis	03	6%	04	8.70%	0.69(0.16-2.9)	0.614
Respiratory distress syndrome	10	20%	14	30.43%	0.65(0.32-1.33)	0.243
Treatment of sepsis	06	12%	07	15.22%	0.79(0.28-2.17)	0.646
Hyperbilirubinemia	07	14%	10	21.74%	0.64(0.26-1.55)	0.326

any of the groups in terms of neonatal outcomes.

Discussion

With the completion of this trial, we can figure out that a significant number of patients who were managed with Arabin cervical pessary were able to carry their pregnancy beyond 34 weeks of gestation as compared with patients treated with progesterone. The spontaneous preterm delivery rate at <34 weeks was significantly higher in the progesterone-treated patients (RR=0.04; p=0.042 at 95%CI). We can speculate that Arabin cervical pessary is helpful in prolongation of gestation and thus decreasing the rate of early prematurity. In the literature search, we found the study performed by Le Dang Khoa, *et al* observed that spontaneous preterm delivery at <34 weeks of gestation had occurred in 24(16%) patients in the pessary treated arm versus 33(22%) in the patients managed with progesterone (RR=0.73,95%CI= 0.46-1.18, p-0.24)[4]. However, the overall perinatal outcome was not significantly different.Rodolfo C Pacagnella, *et al* conducted a study using vaginal progesterone and cervical pessary in combination and observed that even with the use of combination therapy prolongation of gestational >37 weeks and the neonatal outcome were not significantly improved over with the sole use of vaginal progesterone. They also inferred that the spontaneous preterm birth rate <34 weeks was significantly low and this finding was more prominently observed in the group of primiparous women presented with cervical length <25mm (RR=0.59,95%CI 0.37-0.94; p-0.02)[5].

Goya, *et al*[6] and Saccone, *et al*[7] procured dissimilar outcomes, inferring that the Arabin cervical pessary could be more helpful in prolongation of gestational age if during antenatal care we optimally select the patients by incorporating TVS and cervical length monitoring in women at high-risk of preterm birth. Although,based on past obstetrics history, just 11% of the screened participants were at high risk of preterm birth in the study of Goya, *et al*[6] found a preterm birth rate with a relative risk of 0.24(0.13-0.43) at 34 weeks of gestation. However, the study conducted by Saccone, *et al*[7] is different in terms of participant recruitment. They screened all pregnant women with an asymptomatic singleton gestation with short cervical length on transvaginal sonography without a past history of spontaneous preterm birth. They found a significant reduction in the preterm birth rate at <34 weeks of gestation with a relative risk of 0.48(0.24-0.95). The difference in the outcomes of cervical pessary in various studies might be due to different inclusion criteria for participant recruitment. A more comprehensive analysis is required, whether the study claiming a higher preterm birth rate had recruited participants with one or more risk factors for preterm birth as compared to studies showing a low preterm birth rate like 9.4% by Hui, *et al*[8].

Le Dang Khoa, *et al*[4] concluded in their study that overall neonatal outcome was significantly better in women managed with a cervical pessary, especially in terms of Respiratory Distress Syndrome (RDS) and neonatal sepsis. Although maternal outcomes were not showing any significant difference.

A higher rate of vaginal discharge was observed in women managed with cervical pessary without any other significant morbidity. However, a large number of patients with cervical pessary complaints of vaginal discharge but none of the studies found any increase in the rate of cervicovaginal infection. Nicolaides, *et al*[9] had performed high vaginal swab culture and did not report any increase in the rate of cervicovaginal infections with the use of a cervical pessary. The largest randomized controlled trial was performed by Norman, *et al*[10] to evaluate the role of vaginal progesterone in the reduction of spontaneous preterm birth in high-risk pregnant women. This trial demonstrated that there was no significant reduction in the preterm birth rate in the vaginal progesterone group versus the placebo group and concluded the poor efficacy of vaginal progesterone in improving the perinatal outcome. Although, this study was conducted on a very diverse study population and was not sufficiently powered to infer any significant deference. Relatively there is fewer research publication on Arabin cervical pessary, with heterogeneity in outcomes, pointing toward the need for further exploration. The Arabin cervical pessary, a non-hormonal, non-invasive, acceptable and easily

demountable novel approach is creating its place in the management of pregnant women at risk of preterm birth.

Conclusion

In the global scenario, premature birth is a prominent cause of morbidities in the neonatal period as well as the leading cause of neonatal death. Premature birth also has long-term implications in form of various neurological morbidities in children. For a long time, we have solely depended on cervical cerclage and different progesterone formulations for managing preterm labour. Both of the modalities have their advantages and limitations, leaving space for the search for some safer yet effective novel mode of treatment like cervical pessary. We analyzed the effectiveness and safety profile of Arabin cervical pessary in comparison to progesterone. Pessary insertion is a non-invasive, outpatient procedure that alleviates the need for cervical stitches and any form of anesthesia. Pessary seems economical for the patient. With the use of pessary recurrence rates of threatened preterm labour episodes and hospital stays were significantly reduced which makes it more acceptable for the patients,socially as well as financially. However, we could not observe any significant reduction in the spontaneous preterm delivery rate below 37 weeks of gestation in the pessary group but a significant reduction was demonstrated in less than 34 weeks of gestation. We could not observe any prominent maternal and neonatal side effects with the use of a pessary. After analyzing the data, we can say that Arabin cervical can be opted for as a safe, reliable and cost-effective device for reducing the rate of early spontaneous preterm birth in singleton pregnancies in women at high risk of preterm birth.

In developing countries like India, which carry the major load of preterm babies, there is an urgent need for low-cost, low-technical prevention modalities that can be introduced easily by various types of community health practitioners at the periphery, to reduce the burden of preterm birth and associated neonatal morbidities. To establish the role of pessary in the management of preterm labour, large multicentric randomized trials will be needed.

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