Integrating cervical length measurement into routine antenatal screening and only emergency cerclage when indicated

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Summary

Purpose: To integrate cervical length measurement into antenatal screening and apply emergency cerclage when indicated to prevent spontaneous deliveries at < 34 weeks of gestation. *Methods:* Cervical length measurements of 400 pregnant volunteers were obtained at gestational weeks 12-14, 18-20 and 28-32. Whenever a cervical measurement < 30 mm was observed, vaginal cultures and bacterial vaginosis were investigated, and weekly cervical length measurements were performed thereafter. Emergency cerclage was performed whenever complete cervical effacement and ≥ 3 cm cervical dilatation were observed before 32 completed weeks of gestation. We adopted and tested a strategy of only emergency cerclage application when clinically indicated after ultrasound screening and microbial monitoring of short cervices. Patients were given cyclooxygenase-inhibitors, progesterone, and antibiotics in the postoperative period. *Results:* Spontaneous preterm births at < 34 weeks of gestation occurred in 15 women (3.8%). We performed five emergency cerclages according to the presented screening strategy between 20-28 weeks of gestation all of which reached > 34 weeks. We successfully postponed 62.5% (5/8) of deliveries before 32 completed weeks and 33.3% (5/15) of deliveries before 34 completed weeks. *Conclusion:* Routine cervical length measurement combined with serial transvaginal sonograms and vaginal microbial monitoring of the short cervices will avoid unnecessary prophylactic cerclages while increasing the success of emergency cerclages performed upon solid clinical findings.

Key words: Preterm birth; Cervical insufficiency; Cervical length measurement; Cervical cerclage; Bacterial vaginosis

Introduction

Preterm birth before 37 weeks of gestation is the leading cause of neonatal morbidity and mortality. One of the risk factors for preterm birth is cervical insufficiency. The traditional obstetric dogma considered cervical insufficiency as a dichotomous variable. Recently newer models have proposed cervical competence as a continuum and insufficiency may result from loss of connective tissue due to operations, congenital disorders of the uterus and cervix, infection/colonization, local or systemic hormonal effects, inflammatory processes or genetic predisposition [1, 2].

During the last decade, transvaginal ultrasound (TVS) screening of the cervix has been used to predict preterm deliveries [3-5]. Different studies used cervical length screening at 11-14 weeks of gestation, 18-22 weeks of gestation, and 24-28 weeks of gestation and calculated variable sensitivities for cervical length cut-off values of 15 mm, 25 mm, and 30 mm [3, 4, 6-8].

As the prevalence of preterm birth is low, cervical length screening would generate either a false-positive rate or a low sensitivity [9]. This has constituted the main pitfall of intervention studies using prophylactic or emergency cerclage placement depending on the results of cervical length screening, because cerclage application may result in unintended complications like preterm labor, premature rupture of the membranes, chorioamnionitis or abruption. Not surprisingly inconclusive or conflicting results have been reported from studies conducted on different pregnant populations with variable screening strategies, cerclage techniques, and follow-up methods after cerclage placement [5, 7, 8, 10-12].

To overcome the low sensitivity and positive predictive value (PPV) of cervical length screening, several other variables have been used including cervical funneling, degree of cervical funneling > 25%, cervical dilatation > 5 mm, visible fetal membranes, and number of prior preterm births [4, 5, 12-14]. Despite these efforts, the ideal selection criteria remain to be determined.

Increasing data points out the importance of microbial invasion of the amniotic cavity by microbial flora of the lower genital tract and discriminates short cervices as a predisposing factor for this invasion [1, 15].

In our study, we aimed to test whether integrating cervical length measurement into antenatal screening can help identify patients at risk for preterm delivery. We also used this data to test an evidence-based algorithm including microbial screening and ultrasound follow-up for the management of short cervices and evaluation of the outcome of emergent cerclage placement when indicated.

Materials and Methods

This prospective follow-up study was performed on patients who underwent an ultrasonographic examination between 12-14 weeks of gestation in an obstetric unit of a tertiary center at Kocaeli University School of Medicine, Kocaeli, Turkey between June 2003 and April 2005. The local ethics committee approved the study. The study population consisted of 400 consecutive pregnant women who gave written consent.

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In our study, our primary outcome measure was to test whether integrating cervical length measurement to antenatal screening would help identify patients at risk for preterm delivery. Our secondary outcome measure was to assess ultrasound (US) follow-up for the management of short cervices and evaluation of the outcome of emergent cerclage placement only when indicated.

Criteria for enrollment included all patients who underwent US examination between 12-14 weeks of gestation. Gestational age was determined by the last menstrual period and/or by first trimester US if the patient was unsure of the date of her last menstrual period. Exclusion criteria included pregnancies complicated by multiple gestations, induced abortions due to fetal anomaly or women who had their first antenatal visit after 14 weeks of gestation.

Ultrasonographic examinations were performed with a 6.5 MHz transvaginal transducer (Siemens Medical Systems, Inc). A single specialist performed the measurements in order to eliminate the possibility for interobserver variability in measurement technique. The specialist was blinded to the woman's previous cervical length records. After the patient emptied her bladder, she was placed in the lithotomy position. TVS measurements of the cervix were made with a standard technique, as previously described by Iams *et al.* [6]. The internal cervical os was identified by a sagittal plane view, and the calipers were placed at the furthest points between the internal and external cervical os. When funneling was present, the distance over which endocervical walls were juxtaposed was measured. Three measurements were recorded for each and the shortest measurements were used.

According to the trial protocol, cervical length was measured first at 12-14 weeks corresponding to routine first trimester nuchal translucency screening, second at 18-20 weeks corresponding to triple test and abnormality screening and lastly at 28-32 weeks of gestation. Spontaneous deliveries and cerclage placements until 36 completed gestational weeks formed Group 1, iatrogenic inductions of labor for maternal and fetal indications until 36 completed gestational weeks formed Group 2, and term deliveries at ≥ 37 weeks formed Group 3.

Whenever a cervical length measurement < 30 mm was observed, weekly cervical length measurements were performed thereafter. Patients with a cervical length < 30 mm were scheduled for vaginal examination three to five days following TVS examination. All vaginal samples obtained were inoculated into a selective Todd-Hewitt broth with 8 μg/ml gentamicin plus 15 μg/ml nalidixic acid and transported immediately to microbiology laboratory. After 18 to 24 hours of incubation selective broth medium was subcultured onto 5% sheep blood agar. All plated media were incubated overnight at 35°C in 5% carbon dioxide. After 24 hours both beta-hemolytic and non-hemolytic colonies resembling Group B hemolytic streptococcus were evaluated according to morphology and the presence of hemolysis. Facultative gram-positive coccus that grows on blood agar, small, gray-white flat colonies, and beta-hemolysis characteristics were used to select colonies for identification. Presumptive identification of GBS includes Gram's stain, a negative catalase test and the Christie-Atkins-Munch-Peterson test with synergistic hemolysis. All negative subculture plates were reincubated for an additional 18-24 hours and reexamined.

Patients were also screened for bacterial vaginosis. A polyester swab taken from the junction of the upper third and lower two-thirds of the lateral vaginal wall was rolled on a glass slide. The slides were Gram stained and interpreted according to the criteria of Nugent *et al.* [16]. Bacterial vaginosis was diagnosed if the Gram stain score was 7 to 10. Patients with bacterial vaginosis were treated with ornidazole 500 mg/5 days and povidone iodine 0.2 g/7 days. Control vaginal samples were obtained a week after completion of therapy and repeated whenever necessary.

Whenever a cervical length ≤ 15 mm was observed on TVS, a speculum examination was performed for vaginal cultures, bacterial vaginosis screening and presence of visible membranes [14]. Patients were offered "emergency" cerclage placement in the presence of a fully effaced cervix and a dilatation ≥ 3 cm with visible protrusion of intact fetal membranes at or below the external cervical os. We assumed full effacement and 3 cm cervical dilatation as an irreversible end-point of forthcoming delivery due to the following evidence: i) only 21% of instantly diagnosed women with advanced cervical dilatation remained undelivered after one week despite tocolysis between 24-35 gestational weeks [17], ii) < 15 mm cervical length at midtrimester refers to the 1st percentile of all population-based large studies and carried a 50% delivery rate before 32 completed weeks irrespective of dilatation [4, 6, 7] iii) our cut-off point is a follow-up finding which indicated a progression rather than a single screening reflecting an indicator of forthcoming preterm delivery [3, 18].

All cerclage procedures were of the McDonald type with Mersilene tape (Ethicon, Summerville, NJ) used as sutures placed a minimum of 3 cm above the most distal part of the cervix, together with two no. 2.0 polyglactin sutures (Vicryl, Ethicon) placed circularly 1-2 cm above the most distal part of the external cervical os closing the cervix tightly. None of the patients in the cerclage group had any evidence of chorioamnionitis such as fever > 38°C, uterine tenderness, fetal tachycardia, marked leukocytosis (> 15,000x10^6/l) or elevated C-reactive protein (> 15 mg/l). Results were available at the time of cerclage. All patients with cerclages received sulbactam and ampicillin (3 g/day for 7 days), and metronidazole (0.5% for a day). Women who were allocated to emergency cerclage were given indomethacine (300 mg/day for 3 days) and progesterone (300 mg/day for 10 days). Indomethacine was given because of its inhibitory effect on prostaglandins (prostaglandins are upregulated in inflammation via interleukin-1 and cause uterine contractions in the myometrium and fetal membranes) [19]. Progesterone treatment was prescribed to cerclage cases as it was found to decrease recurrent preterm delivery and suppress genes necessary for uterine contractility [20].

Hospitalization was maintained and the women were restricted to bed rest for 48 hours. They were discharged from the hospital within 10-15 days of cerclage operation. Daily US follow-up of amniotic fluid level and vaginal speculum examination for amniotic fluid flow were performed until the patients were discharged from the hospital. Irregular uterine contractions were observed in one of the five cerclage patients which disappeared with the addition of nifedipine (60 mg/day for 7 days). Transient oligohydramnios developed in four of five cerclage patients following indomethacine treatment but all recovered within two weeks of follow-up. Patients underwent TVS weekly after discharge and bed rest was advised until delivery. Cerclages were removed at the 35th week of gestation due to high magnitude of uterine contractions and bleeding from the cerclage side in one case and electively at 37 weeks of gestation in the remaining four cases.

The statistical analysis of the data was performed using the Statistical Package for Social Sciences for Windows (SPSS, Chicago, IL, USA). Our hospital is a reference center for a population of about two million people. The rate of preterm deliveries of patients that are followed up in our center from the beginning of their pregnancies was 11.5% during the year preceding our study. This rate is twice the 5.6% rate found in a population-based study in our country [21]. This is due to our

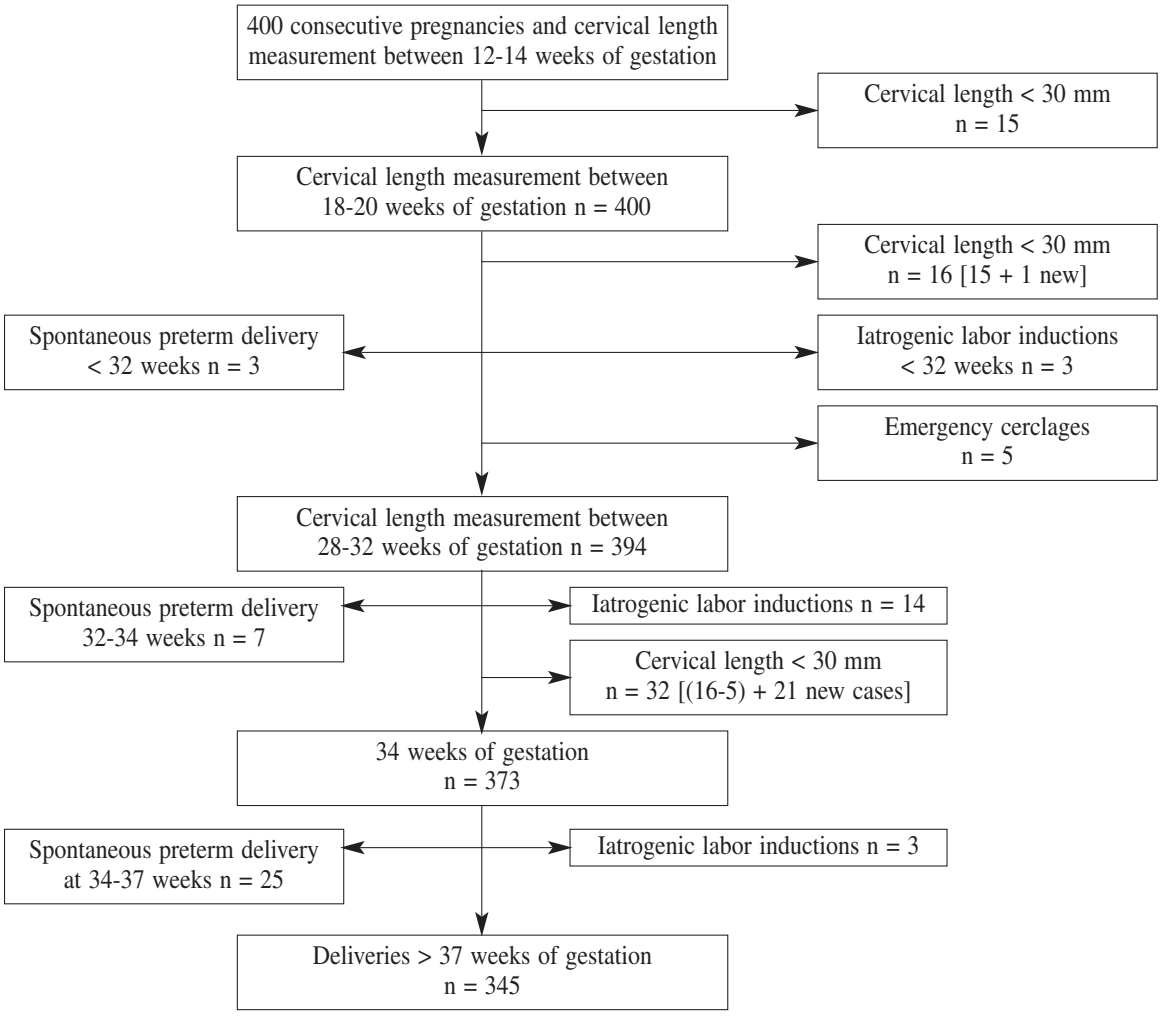

Figure 1. — Flow-chart of the study.

patient population which is mainly formed from high-risk women and women with previously poor maternal and fetal outcomes. Using the 11.5% rate, the number of patients that will represent our population with a 3% error at $\alpha = 0.05$ was calculated to be 393. Accordingly we recruited 400 consecutive women who consented to the study protocol in order to compensate any lost to follow-up or protocol deviations.

Results were reported as mean ± standard deviation and percentages. Differences between the groups were assessed using the chi-square test for categorical data. To detect the differences of continuous variables between the groups, analysis of variance (ANOVA) and Tukey tests were used. For all comparisons $p < 0.05$ was considered statistically significant.

Results

From June 2003 to April 2005, a total of 400 women were recruited in the follow-up. The algorithm of the study is presented in Figure 1.

Selected maternal variables according to the groups are presented in Table 1. Maternal education, multiparity, occupational status, tobacco usage, presence of previous abortions and curettages were similar among the groups. Mean maternal age of group II was significantly higher than group III ($p = 0.01$). Previous preterm delivery was significantly more frequent in group I compared to group II and III ($p < 0.001$). On the other hand, the rate of

Table 1. — *Maternal variables according to the groups. Data are presented as mean ± SD or numbers (percentages).*

	Group I† (n = 39)	Group II (n = 20)	Group III (n = 341)	p
Maternal age (years)	28.8 ± 6	30.2 ± 5.1*	27.3 ± 4.8	0.01*
Education (years)	9.6 ± 4.2	7.4 ± 4	10 ± 3.9	0.06
Multiparity	20 (51.3)	12 (60)	176 (51.6)	0.7
No occupation	25 (64.1)	12 (60)	180 (52.8)	0.3
Tobacco use	3 (8.8)	0	20 (7.4)	0.5
Previous abortion ≥ 1	10 (25.6)	6 (30)	69 (20.2)	0.4
Previous D&C ≥ 1	4 (10.3)	4 (20)	40 (11.7)	0.5
Previous preterm delivery at 14-34 weeks ≥ 1	8 (20.5)	0	16 (4.7)	< 0.001**
Mullerian anomaly	2 (5.1)	1 (5)	3 (0.9)	0.049**
Threatened abortion in studied pregnancies	9 (23.1)	3 (15)	17 (5.0)	< 0.001**
Infertility treatment in studied pregnancies	5 (12.8)	4 (20)	9 (2.7)	< 0.001*

*Significantly higher than group 3 ($p = 0.03$), ANOVA, Tukey tests.
**Significantly different, $p < 0.05$, chi-square test.
†All patients with emergency cerclage were analyzed under this group.

Table 2. — *Flow-chart of the study until 32 completed weeks of gestation.*

Cervical length screening	Findings	Intervention	Outcome and medical treatment
400 consecutive pregnancies at 12-14 weeks of gestation	Cervix < 30 mm (n = 15)	- Culture screening and weekly ultrasound follow-up (n = 15)	- Cervical shortening progressed in three cases - Four bacterial vaginosis, one group B streptococcus, and one E.coli colonization treated
400 pregnancies at 18-20 weeks of gestation	Cervix < 30 mm (n = 16) (15 previously diagnosed cases plus one new case)	- Culture screening and weekly ultrasound follow-up (n = 16) - Three labor inductions - 5 emergency cerclages at 20, 21, 23, 24,27 weeks	- Antibiotics, progesterone and indomethacine treatment in 5 cerclage cases - One recurrent bacterial vaginosis treated - Three spontaneous deliveries < 32 completed weeks
394 consecutive pregnancies at 28-32 weeks of gestation	Cervix < 30 mm (n = 32) (16 previously diagnosed cases minus four cerclage cases plus 20 new cases)	- Culture screening and weekly ultrasound follow-up (n = 32)	- Four bacterial vaginosis, one group B streptococcus and two E. coli colonization treated

Table 3. — *Summary of obstetrical outcomes at selected gestational weeks and grouping.*

	Iatrogenic inductions	Spontaneous deliveries	Cerclage cases
28-32 weeks of gestation	n = 3	n = 3	n = 5
28-34 weeks of gestation	n = 17	n = 10	n = 5
28-37 weeks of gestation	n = 20	n = 35	n = 4
Deliveries ≥ 37 weeks	Iatrogenic deliveries < 37 weeks	Spontaneous deliveries and cerclage placements < 37 weeks	
Group 3*	**Group 2**	**Group 1**	
n = 341	n = 20	n = 39	

*Cerclage cases were included in group 1 to compare cervical length follow-up of cases with a preterm delivery risk to other cases.

Mullerian anomaly ($p = 0.049$), threatened abortion ($p < 0.001$) and infertility treatment ($p < 0.001$) in the studied pregnancies were significantly lower in group III compared to group I and II.

Cervical length screening, interventions and treatments of the study groups are presented in Table 2. Obstetric outcomes are presented in Table 3.

Cervical length follow-up according to groups is presented in Figure 2. The mean cervical length was significantly different in the groups at 12-14 weeks ($p = 0.007$), at 18-20 weeks ($p < 0.001$) and at 28-32 weeks of gestation ($p < 0.001$).

A total of 3.7% (15/400), 4% (16/400) and 8.1% (32/394) of the women were diagnosed with a cervical length < 30 mm at 12-14, 18-20, 28-32 weeks, respectively. The predictive value of a < 30 mm cervical length at different gestational weeks is presented in Table 4. Although the specificity of this cut-off value was high, the sensitivity and PPV was unacceptably low to justify an invasive procedure like cervical cerclage.

Using the weekly cervical screening strategy until 32 weeks of gestation in case of a cervical length < 30 mm, we performed 424 TVS scannings in addition to cervical length measurements at 12-14, 18-20 and 28-32 weeks and also, 63 vaginal cultures were performed. The total cost of extra tests after detection of a short cervix was calculated to be 2220 Euros which is much less than the cost of 8300 Euros for one surviving neonate managed in our hospital after delivering at the 25th week of gestation. On the other hand, we were able to treat five cases of cervical

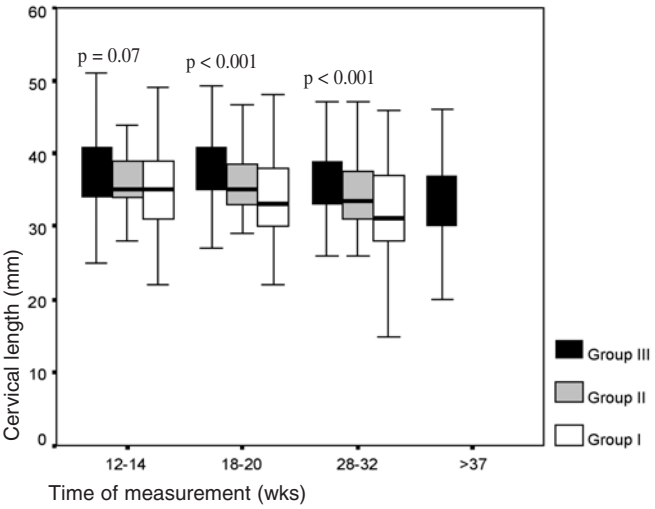

Figure 2. — Cervical length follow-up according to time and indication of delivery.

insufficiency successfully out of eight possible spontaneous deliveries < 32 weeks and 15 possible spontaneous deliveries < 34 weeks. Among the five cases with emergency cerclages performed at 20, 21, 23, 24, 27 weeks of gestation, one case (cerclage performed at 23 weeks) delivered at 35 weeks of gestation and was diagnosed as having a partial uterine septum while the other four cases delivered ≥ 37 weeks of gestation. Three of the cerclage patients were nulliparas while the patient with a partial uterine septum had two mid trimester losses and the last patient was a multipara with one live preterm delivery at 33 weeks of gestation. Preterm premature rupture of membranes with anhydramnios and intrauterine growth restriction were the indications for iatrogenic labor induction in three cases < 32 weeks of gestation. Intrauterine growth restriction, anhydramnios, preeclampsia, preterm premature rupture of membranes, and maternal heart disease were indications of iatrogenic induction of labor in 17 cases between 32 to 36 completed weeks.

Newborns of women that had cerclage were followed for 12 to 18 months of life and were completely healthy.

Table 4. — *Predictive value of a < 30 mm cervical length at different gestational weeks.*

Measurement time	Spontaneous preterm birth < 34 weeks (n = 15)				Spontaneous preterm birth < 37 weeks (n = 39)			
	Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV
12-14 weeks (n = 400)	26.7	97.1	26.7	97.1	15.4	97.5	40	91.4
18-20 weeks (n = 400)	26.7	96.9	25	97.1	17.9	97.5	43.8	91.7
28-32 weeks (n = 394)*	11.1	91.9	3.1	97.8	39.4	94.7	40.6	94.5

Sens = Sensitivity; Spec = Specificity; PPV = positive predictive value; NPV= negative predictive value; *Predictive values of 28-32 weeks screening were calculated for 9 and 33 cases for birth < 34 and < 37 weeks, respectively, as four cerclage and two spontaneous deliveries occurred until screening.

Discussion

Using assessment of cervical length measurement at the 12-14th, 18-20th and 28-32nd weeks of gestation strategy, we were able to postpone five inevitable extreme premature preterm deliveries until after 34 weeks of gestation without fetal morbidity and mortality.

Our data supports the notion that short cervices do not necessarily indicate the risk of preterm delivery. Prophylactic cerclages based solely on this finding would be an over-treatment in a considerable number of patients as the sensitivity and the PPV of a diagnosed short cervix as the above-mentioned screening intervals are low. Also, different than most cerclage studies conducted in the literature we screened all women including nulliparas which constituted 48% of our study population. As a result of that three of the five emergency cerclage cases were nulliparas. Several prior case control studies, reviews, and metaanalyses have suggested that only high-risk women with one or two mid trimester losses should be screened for cervical length measurement, and prophylactic cerclage placement should be performed after these losses [2, 5, 22]. Although this might be a statistical fact it underscores the physiological burden of one or more prior mid trimester losses on both the couple and their obstetrician.

Cervical length is a continuum and might be influenced by sociodemographic factors like race, stress, and occupation across the gestation [23]. Bacterial vaginosis, microbial invasion of the amniotic cavity and intra-amniotic inflammation might also cause cervical insufficiency through IL-8 mediated degradation of the cervical matrix [24]. Whether a predisposing factor or a result, women with cervical length < 25 mm have 9% microbiologically proven intraamniotic infection, < 20 mm have a higher rate of placental inflammation and if cervical dilatation is present, microbial invasion of amniotic cavity might be as high as 51.5% [1, 15, 25]. These findings formed the background of our vaginal culture and bacterial vaginosis screening of short cervices which might be the contributing factor for the high success rate of emergency cerclages placed. A study published after the start of this study showed that vaginal povidone iodine, also used in our study, normalizes IL-8 concentrations in 23.2% of patients and decreases preterm delivery rates before 34 weeks of gestation [26].

A high rate of surveillance after emergency cerclage in a small number of patients in this study might be due to the attempt of controlling vaginal microbial flora via antibiotic use before and after the operation or use of agents that suppress uterine contractility and enhance cervical remodeling such as cyclooxygenase inhibitors and progesterone. Cerclage in our population was performed on pregnant women with well identified poor prognostic factors for successful operations such as visible membranes, cervical length < 5 mm, cervical dilatation ≥ 3 cm, and nulliparity [14, 27]. Fetal salvage in these cases of emergency cerclage is reported to be 46-50%, most of which are delivered preterm due to short operation delivery interval [14, 28].

Our study indicates two important measures: 1) follow-up of short cervices until clinically advanced cervical dilatation is a safe procedure after which a successful cerclage operation can be performed. This is proven by the fact that prophylactic cerclage placement for incidental detection of cervical length < 25 mm in the early second trimester does not improve pregnancy outcome [29], and 2) cervical length is probably influenced by factors not yet defined as women with poor obstetric performances have shorter cervices since the end of first trimester across the gestation. This latter proposal is evidenced by shorter cervices identified in cases of iatrogenic induction of labor due to early rupture of membranes, chronic maternal illness and evidence of placental insufficiency.

Conclusion

The management algorithm proposed in this study resulted in prevention of one very early premature delivery for every 85 additional US measurements performed and 13 vaginal cultures obtained in addition to ideal current antenatal US screening. Routine cervical length measurement combined with serial TVS and vaginal microbial monitoring of the short cervices will avoid unnecessary prophylactic cerclages while increasing the success of emergency cerclages performed upon solid clinical findings.

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