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ORIGINAL ARTICLE

Fetal fibronectin, cervical length, and the risk of preterm birth in patients with an ultrasound or physical exam indicated cervical cerclage

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Abstract

Objective: The objective of this study is to estimate the risk of preterm birth in patients with an ultrasound or physical exam indicated cervical cerclage based on the results of fetal fibronectin (fFN) and cervical length (CL) screening.

Methods: Retrospective cohort of patients with a singleton pregnancy and an ultrasound or physical exam indicated Shirodkar cerclage placed by one maternal–fetal medicine practice from November 2005 to January 2015. Patients routinely underwent serial CL and fFN testing from 22 to 32 weeks. Based on ROC curve analysis, a short CL was defined as $\leq$15 mm. All fFN and CL results included are from after the cerclage placement.

Results: One hundred and four patients were included. Seventy eight (75%) patients had an ultrasound-indicated cerclage and 26 (25%) patients had a physical exam-indicated cerclage. A positive fFN was associate with preterm birth <32 weeks (15.6% versus 4.2%, $p = 0.043$), <35 weeks (37.5% versus 11.1%, $p = 0.002$), <37 weeks (65.6% versus 20.8%, $p < 0.001$), and earlier gestational ages at delivery (35.2 ± 3.9 versus 37.4 ± 2.9, $p = 0.001$). A short CL was also associated with preterm birth <35 weeks (50.0% versus 11.9%, $p < 0.01$), preterm birth <37 weeks (55.0% versus 29.8%, $p = 0.033$), and earlier gestational ages at delivery (34.8 ± 4.1 versus 37.2 ± 3.0, $p = 0.004$). The risk of preterm birth <32, <35, and <37 weeks increased significantly with the number of abnormal markers.

Conclusion: In patients with an ultrasound or physical exam indicated cerclage, a positive fFN and a short CL are both associated with preterm birth. The risk of preterm birth increases with the number of abnormal biomarkers.

Keywords

Cerclage, cervical length, fetal fibronectin, preterm birth

History

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Introduction

Preterm birth is associated with significant perinatal morbidity [1]. Cerclage has been shown to reduce the risk of preterm birth in certain high-risk patients, specifically patients with a prior preterm birth and a short cervical length (CL) detected on ultrasound (ultrasound-indicated) [2], as well as patients with cervical dilation on physical exam (physical exam-indicated) [3]. However, these patients remain at high risk of preterm birth, and identifying them with the goal to improve fetal outcome in this subset remains a challenge [4]. In other populations at risk for preterm birth, fetal fibronectin (fFN) testing and CL measurement are both significantly associated with preterm birth [5,6]. The combination of fFN and CL improves the prediction of preterm birth compared to either biomarker alone [7]. However, there is limited data comparing the role of these biomarkers, either alone or in combination, in patients who have had a cerclage [8].

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Patients who require an ultrasound or physical exam-indicated cerclage have cervical shortening at baseline, which makes the significance of a short CL after a cerclage difficult to interpret [9]. Furthermore, in non-cerclage patients, CL is inversely related to the risk of preterm delivery [10]; however, the increase in cervical length after cerclage placement does not necessarily correlate with decreased risk of preterm birth [11]. Fetal fibronectin has been shown to have a high negative predictive value but lower specificity in patients with a cerclage as compared to those without a cerclage [12]. Thus far, there are limited data evaluating the combination of fFN and CL in patients with a cerclage. Furthermore, there are limited data on the combined use of these tests in predicting preterm birth in this population.

The objective of this study is to evaluate whether positive fFN, short CL, or both are predictive of preterm delivery in patients who have had an ultrasound or physical exam-indicated cerclage.

Materials and methods

After Biomedical Research Alliances of New York Institutional Review Board approval was obtained, we reviewed the records of all patients with cerclages performed by one Maternal-Fetal

Medicine practice over a 9-year period from November 2005 to January 2015. We included all patients with a singleton pregnancy whose cerclage was ultrasound-indicated, defined as any cerclage placed during pregnancy for the indication of a short cervical length on ultrasound, or physical exam-indicated, defined as any cerclage placed in a patient with a dilated cervix on exam or membranes visible at the external os on speculum examination. We do not routinely recommend ultrasound-indicated cerclage for low-risk women with a short cervix. However, for certain high risk women, such as those with a prior preterm birth or second trimester loss, we do discuss the option of cerclage if their cervical length is 25 mm or less. Patients with asymptomatic dilation of their cervix in the second trimester are offered a physical exam-indicated cerclage, unless infection is suspected.

All cerclages were placed prior to 24 weeks. In our practice, the technique for cerclage placement has been described previously and was of the modified Shirodkar technique as described by Druzin and Berkely [13,14]. After the vaginal mucosa is dissected off of the cervix anteriorly and posteriorly, the lateral vaginal mucosa on each side of the cervix is grasped with curved Allis clamps and retracted laterally. A double needle 5 mm Mersilene suture is then passed from anterior to posterior on both the left and the right side of the cervix in the space between the cervical stroma and the retracted vaginal mucosa. The knot is then tied at 6 o'clock. The anterior vaginal mucosa is routinely reapproximated. The posterior vaginal mucosa is typically left open, unless sutures are needed for hemostasis.

After cerclage placement, patients in our practice routinely undergo concurrent cervical length and fFN screening every 2–3 weeks, beginning 1–2 weeks after cerclage placement and continuing until 31 6/7 weeks. However, fFN screening does not commence until 2–3 weeks after cerclage placement (to allow time for healing as to reduce the likelihood of a false positive result) or 22 weeks, whichever is later. Measurements of CL were performed using a 4- to 8-MHz transvaginal probe with an empty bladder according to criteria established by Iams et al. [15]. The shortest functional CL was used as this has been found to be the most reproducible measurement [16]. Fetal fibronectin testing was performed without the use of a speculum using a published protocol [17] at least 24 h from the last reported intercourse or endovaginal ultrasound. Fetal fibronectin testing was not performed in the setting of vaginal bleeding. Swabs were sent for evaluation using a fetal fibronectin assay, and a concentration of 50 ng/mL or greater was considered positive. For the purposes of this study, a short CL was established using ROC curve analysis and defined as $\leq$15 mm. Physicians were not blinded to CL or fFN results. We do not routinely recommend bedrest or hospitalization for patients with a short CL or positive fFN. In our practice, cerclages are typically removed at 36–37 weeks, or earlier as indicated in the setting of preterm labor.

We compared outcomes between patients who did and did not have a positive fFN or short CL at any time prior to 32 weeks. Only tests done after cerclage placement were included in this analysis. We analyzed fFN alone, CL alone, as well as the combined results. The primary outcome was delivery <37 weeks. We also examined the outcomes of delivery <35 weeks, <32 weeks, and gestational age at delivery. Chi-square, chi-square for trend, Student's *t*-test, and one-way ANOVA were used, as appropriate (SPSS for Windows version 22.0; IBM Corporation, Armonk, NY). A p value of <0.05 was considered significant. For the primary outcome of preterm birth <37 weeks, we calculated the screening characteristics of fFN and CL (sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), and negative likelihood ratio (−LR)). We examined four possible positive screening tests: (1) positive fFN, (2) short CL, (3) either a positive fFN or a short CL, and (4) both a positive fFN and a short CL.

Results

One hundred four patients were included. Seventy-eight (75%) patients had an ultrasound-indicated cerclage with a mean CL at placement of 16.7 mm. Twenty-six (25%) patients had a physical exam-indicated cerclage with a mean cervical dilation of 1.8 cm. The mean gestational age at cerclage placement was 20.1 weeks. The characteristics of the population are shown in Table 1. Overall, this was a high-risk population with 44.2% having a prior preterm birth, 41.3% having a prior second trimester loss, 12.5% having a prior LEEP or cone biopsy, and 5.8% having a Mullerian anomaly. 34.6% of patients delivered preterm (<37 weeks).

Thirty-two (30.8%) patients had a positive fFN after the cerclage placement. These patients were significantly more likely to deliver <37 weeks, <35 weeks, <32 weeks, and delivered at significantly earlier gestational ages (Table 2). Based on the ROC curve analysis, a CL cutoff of $\leq$15 mm was used to define a short CL (AUC 0.690, 95% CI 0.547–0.834, $p = 0.008$). Twenty (19.2%) patients had a CL $\leq$15 mm after the cerclage placement. These patients were also significantly more likely to deliver <37 weeks and <35 weeks, and delivered at significantly earlier gestational ages (Table 3). When we examined combined fFN and CL screening, 63 (60.6%) patients never had a positive fFN or CL $\leq$15 mm after

Table 1. Demographics of the population.

Characteristic	
Total patients	104
Age	33.1 ± 5.8 years
Prior preterm birth	46 (44.2%)
Prior second trimester loss	43 (41.3%)
Prior LEEP/Cone	13 (12.5%)
Cerclage in prior pregnancy	22 (21.2%)
Mullerian anomaly	6 (5.8%)
Progesterone use in pregnancy	63 (60.6%)
White race	80 (76.9%)
Ultrasound-indicated cerclage	78 (75.0%)
Cervical length at cerclage placement	16.7 ± 6.1 mm
Physical exam-indicated cerclage	26 (25.0%)
Cervical dilation at cerclage placement	1.8 ± 1.1 cm
Gestational age at cerclage placement	20.1 ± 2.1 weeks
Fetal fibronectin positive*	32 (30.8%)
Cervical length ≤15 mm*	20 (19.2%)
Gestational age at delivery (mean)	36.7 ± 3.4 weeks
Gestational age at delivery (range)	24 4/7–41 2/7 weeks
Delivery <32 weeks	8 (7.7%)
Delivery <35 weeks	20 (19.2%)
Delivery <37 weeks	36 (34.6%)

*Only tests that were performed after cerclage placement are included.

cerclage placement, 30 (28.8%) patients had either a positive fFN or a CL ≤15 mm after cerclage placement, and 11 (10.6%) patients had both a positive fFN and a CL ≤15 mm after cerclage placement. The risk of preterm birth <37 weeks, <35 weeks, and <32 weeks increased significantly across these three groups, and the gestational age at delivery decreased significantly across these three groups (Table 4). For example, a patient with both a negative fFN and a CL >15 mm delivered on average at 37.6 weeks and only had a 19% likelihood of delivering preterm, whereas a patient with both a positive fFN and a CL ≤15 mm delivered on average at 33.4 weeks and had a 72.7% likelihood of delivering <37 weeks.

The screening characteristics of fFN and CL as predictors of preterm birth <37 weeks are shown in Table 5.

Discussion

In this study, we found that in patients with an ultrasound or physical exam-indicated cerclage, either a positive fFN or a short CL ≤15 mm between 22 and 32 weeks is associated with preterm birth, and the risk increases further if both markers are positive. Prior studies have shown the association between either biomarker and preterm delivery in patients with cerclage [5,8,15]; however, our study demonstrates that having both biomarkers positive is associated with a higher risk of preterm birth than either alone and that the number of positive biomarkers is inversely associated with gestational age at delivery.

These results of fFN and CL testing could potentially help obstetricians counsel patients more accurately on the expectations of the pregnancy. The results may allow planning ahead for what may be an earlier delivery with consideration to transfer of care to a tertiary facility, administration of antenatal steroids to accelerate fetal maturation, and/or magnesium sulfate exposure to reduce the risk of cerebral palsy in early preterm births. Improved ability to accurately predict which patients will undergo preterm delivery may also help avoid unnecessary treatments including modified activity levels, hospitalization, and tocolysis. The high negative predictive value of one or both markers is also useful in providing patient reassurance of a likely term delivery, the psychological value of which should not be underestimated. However, at this time, it is uncertain if these tests actually improve clinical outcomes in patients given the disappointing lack of efficacy of treatments to prolong gestation, such as bedrest and tocolysis. It is also uncertain if serial testing, as we did, has any advantages or disadvantages as compared to testing at a single point in time, such as at 28 weeks, for example. Therefore, until prospective studies demonstrate clinical benefit to these tests, at this time, they should be considered optional and discussed with the patient as a potential adjunct to her care, if she desires this testing.

The main strength of this study is the combination of fFN and CL testing in a large cohort of patients in one practice who underwent a standardized cerclage placement on indications most commonly accepted in routine clinical practice (a high-risk patient with a short cervix, or an asymptomatic patient with a dilated cervix). Our subsequent management was similar across patients. Another strength of this study is

Table 2. Risk of preterm birth in patients with a cervical cerclage using fetal fibronectin testing (fFN) alone.

	fFN positive, *n*=32	fFN negative, *n*=72	*p**
Gestational age at delivery	35.2 ± 3.9	37.4 ± 2.9	0.001
Preterm birth <32 weeks	5 (15.6%)	3 (4.2%)	0.043
Preterm birth <35 weeks	12 (37.5%)	8 (11.1%)	0.002
Preterm birth <37 weeks	21 (65.6%)	15 (20.8)%	<0.001

*Student's *t*-test or Chi-square.

Table 3. Risk of preterm birth in patients with a cervical cerclage using cervical length (CL) measurement alone.

	CL ≤15 mm, *N*=20	CL >15 mm, *N*=84	*p**
Gestational age at delivery	34.8 ± 4.1	37.2 ± 3.0	0.004
Preterm birth <32 weeks	3 (15.0%)	5 (6.0%)	0.172
Preterm birth <35 weeks	10 (50.0%)	10 (11.9%)	<0.001
Preterm birth <37 weeks	11 (55.0%)	25 (29.8%)	0.033

*Student's t-test or Chi-square.

Table 4. Risk of preterm birth in patients with a cervical cerclage based on the combined fetal fibronectin (fFN) and cervical length (CL).

	Both tests positive, *N*=11	One test positive, *N*=30	Both tests negative, *N*=63	*p**
Gestational age at delivery	33.4 ± 4.5	36.3 ± 3.1	37.6 ± 2.9	0.001
Preterm birth <32 weeks	3 (27.3%)	2 (6.7%)	3 (4.8%)	0.031
Preterm birth <35 weeks	7 (63.6%)	8 (26.7%)	5 (7.9%)	<0.001
Preterm birth <37 weeks	8 (72.7%)	16 (53.3%)	12 (19.0%)	<0.001

Positive tests = fFN positive, CL ≤15 mm.

*One-way ANOVA or Chi-square for trend.

Table 5. Test characteristics of fetal fibronectin (fFN) and cervical length (CL) as a screening test for preterm birth <37 weeks in patients with a cerclage.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	+LR	−LR
fFN positive	58.3	83.8	65.6	79.2	3.6	0.50
CL ≤15 mm	30.6	86.8	55.0	70.2	2.3	0.80
Either fFN positive or CL ≤15 mm	66.7	75.0	58.5	81.0	2.7	0.44
Both fFN positive and CL ≤15 mm	22.2	95.6	72.7	69.9	5.0	0.81

the sample size with minimal loss to follow up. Also, because all the cerclages were of the Shirodkar type and placed by only a few highly skilled providers within a single practice, there is less potential for confounding by provider technique.

The limitations of the study include a relatively homogeneous population with limited ethnic diversity with private health insurance. However, comparing our population with that of the published meta-analysis on ultrasound-indicated cerclage [2], our rate of preterm birth was statistically similar to theirs (delivery <35 weeks in our study was 20/104 (19.2%), whereas in Berghella et al., it was 71/250 (28.4%), Chi-square p values = 0.096). The retrospective study design, including a period of 9 years, is also a limitation of this study as all screening and management decisions were part of the patients' routine obstetrical care. It is possible that clinical guidelines and management trends may have changed during the 9-year period, which could have affected the timing of delivery. Also, since patients and obstetricians were not blinded to the results, the results of the tests could have influenced outcomes. However, we believe that the likelihood of this is low as the only evidence-based treatment for women at increased risk for preterm birth would be antenatal corticosteroids, and the administration of steroids should not affect the timing of delivery.

Future studies, perhaps with larger sample sizes, are necessary to confirm and increase the generalizability of these findings. Additional studies may also investigate the role of quantitative fFN and its relationship with CL in predicting preterm delivery [18].

In conclusion, in patients with an ultrasound or physical exam-indicated cerclage, a positive fFN and a short CL are both associated with preterm birth. The risk of preterm birth increases with the number of abnormal biomarkers.

Declaration of interest

The authors report that they have no conflicts of interest.

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