Measurement of cervical softness before cerclage placement with an aspiration-based device

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BACKGROUND: An abnormally soft cervix could contribute to the pathophysiology of cervical shortening and cervical insufficiency. Multiple techniques to measure cervical softness have been developed but none are used routinely in clinical practice. A clinically acceptable technique to measure cervical softness could improve identification of patients at risk for cervix-related preterm birth.

OBJECTIVE: This study aimed to measure cervical softness in patients with cervical insufficiency and in normal controls using a novel, aspiration-based device. We hypothesized that the cervix is softer in patients with cervical insufficiency.

STUDY DESIGN: This was a cross-sectional study of patients presenting for cerclage at a single academic medical center. Cervical softness was measured using a noninvasive, aspiration-based device placed on the anterior lip of the cervix during a speculum examination. The device measured the aspiration pressure required to displace cervical tissue to a predefined deformation level. Stiff tissue required increased aspiration pressure, whereas soft tissue required lower pressure values. Cerclage patients were subdivided into 3 groups, namely history-indicated, ultrasound-indicated, and examination-indicated cerclage. Controls were healthy volunteers between 12+0 weeks and 23+6 weeks of gestation without a history of cervical insufficiency and were matched by gestational age to the patients in the cerclage groups. Women with a cerclage in place, multiple gestations, active genital infection, or previous cervical excision procedures were excluded. Delivery information was subsequently recorded as well.

RESULTS: Data from 133 women were analyzed; of those, 54 patients were in the cerclage group (23 history-indicated, 12 ultrasound-indicated, and 19 examination-indicated participants) and 79 were controls (40 in the first trimester and 39 in the second trimester groups). Patients who presented for ultrasound-indicated cerclage had significantly softer cervices (median; interquartile range) than second trimester controls (62 mbar; 50.5–114 vs 81 mbar; 75–101; P=.042). The difference in cervical softness was not significantly different between the history-indicated and examination-indicated cerclage groups and their respective control groups.

CONCLUSION: Patients presenting for ultrasound-indicated cerclage had significantly softer cervices than normal controls as measured by an aspiration-based device. Quantitative measurement of cervical softness with the aspiration-based device is a promising technique for objective measurement of cervical softness during pregnancy.

Key words: cerclage, cervical insufficiency, cervical softening, cervical tissue, mechanical properties, medical device, novel aspiration device, pregnancy, softness, spontaneous preterm birth

Introduction

Cervical insufficiency (CI) is an important contributor to spontaneous preterm birth (sPTB).[1] The American College of Obstetricians and Gynecologists defines CI as the inability of the uterine cervix to retain a pregnancy in the second trimester.[2] Although the clinical features of CI are well known, the diagnosis of CI can be difficult. The current clinical algorithm for diagnosing CI is based on obstetrical history, physical examination, and cervical length measurement.[2] However, obstetrical history can be unreliable[3] and patients may present late in the pathophysiology of the disease.[4] Improved diagnosis of CI would have a significant impact on antepartum assessments of PTB risk.

Both clinical studies[5,6] and modeling studies[7–9] support the hypothesis that cervical softness is an important variable that affects cervical function during pregnancy. In clinical studies of nonpregnant women, the cervix was softer in women with CI when measured with an intracervical balloon[6] and a cervical dilator.[5] More recent studies that used computational modeling demonstrated that a soft cervix is less likely to resist cervical stresses associated with pregnancy.[7,8]

Although previous studies support the hypothesis that an overly soft cervix is associated with CI, objective measurement of cervical softness is challenging and is not part of routine clinical practice.[10] In addition, measurement of cervical properties with an intracervical balloon and cervical dilator is not practical when the patient is pregnant. Recently, investigators have used shear wave elasticity imaging to measure cervical softness during pregnancy. Investigators have reported that sPTB is associated with a softer cervix in the first trimester,[11] the second trimester,[12,13] and in twin pregnancies.[14] However, technical[15] and safety[16] questions must be addressed before shear wave elastography is used broadly. An alternate method of measuring cervical softness during pregnancy is cervical aspiration with a disposable device.[17–19] Previous studies using the aspiration technique demonstrated that cervical aspiration is more objective than a physical examination for measuring cervical softening[17] and that cervical softening begins early in the second trimester.[18] However, the aspiration technique has not been used to measure cervical softness in CI.

The objective of this study was to use the aspiration technique to compare

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AJOG MFM at a Glance

Why was this study conducted?

The hypothesis of this study was that the pathophysiology of cervical insufficiency is related to overly soft cervical tissue. The optimal technique for measuring cervical softness has not been identified. In this cross-sectional study, a novel, aspiration-based device for measuring cervical softness was used to compare softness in patients with cervical insufficiency with controls.

Key findings

The cervix was significantly softer among patients scheduled for an ultrasound-indicated cerclage than among controls. For patients with a history-indicated cerclage or examination-indicated cerclage, no difference in cervical softness was seen when compared with controls.

What does this add to what is known?

This study suggests that a soft cervix is associated with the need for an ultrasound-indicated cerclage. This study improves our understanding of the pathophysiology of cervical insufficiency.

cervical softness in patients with CI and in normal controls. Our hypothesis was that patients with an indication for cerclage will have softer cervices than normal controls. The secondary outcome was subsequent PTB rates.

Materials and Methods

Ethics statement

This study was approved by the institutional review board. Informed consent was obtained for cervical softness measurements and medical record review from all subjects before measurements were taken.

Patient selection

Eligible patients were approached for consent by the Maternal-Fetal Medicine Clinic, the Perinatal Diagnostic Center or by the labor and delivery unit at the time of cerclage placement between January 2020 and December 2021. Cerclage patients were subdivided into the following 3 groups: history-indicated, ultrasound-indicated, and examination-indicated cerclage according to criteria defined in the American College of Obstetrics and Gynecology Practice Bulletin on the management of CI.[2]

Healthy volunteers were recruited as controls. Controls were offered a small payment as a recruitment incentive. Because cervical softness is known to be a function of gestational age,[18] 2 control groups were defined. First trimester controls (1T) were recruited between 12 and 14 weeks' gestation and were matched to patients with a history-indicated cerclage. Second trimester controls (2T) were recruited between 15 and 23 weeks' gestation and were matched to patients with an ultrasound-indicated and examination-indicated cerclage. Inclusion criteria for the control groups included women ≥18 years of age with a singleton gestation between 12+0 weeks and 23+6 weeks' gestation. Exclusion criteria included patients with a history of CI, a history of cervical surgery (conization), multiple gestations, cervical polyps, placenta previa, Müllerian anomalies, vaginal bleeding, rupture of membranes, HIV, hepatitis B, hepatitis C, or an active genital or uterine infection. Maternal demographic, obstetrical, and delivery information were collected through review of the medical record.

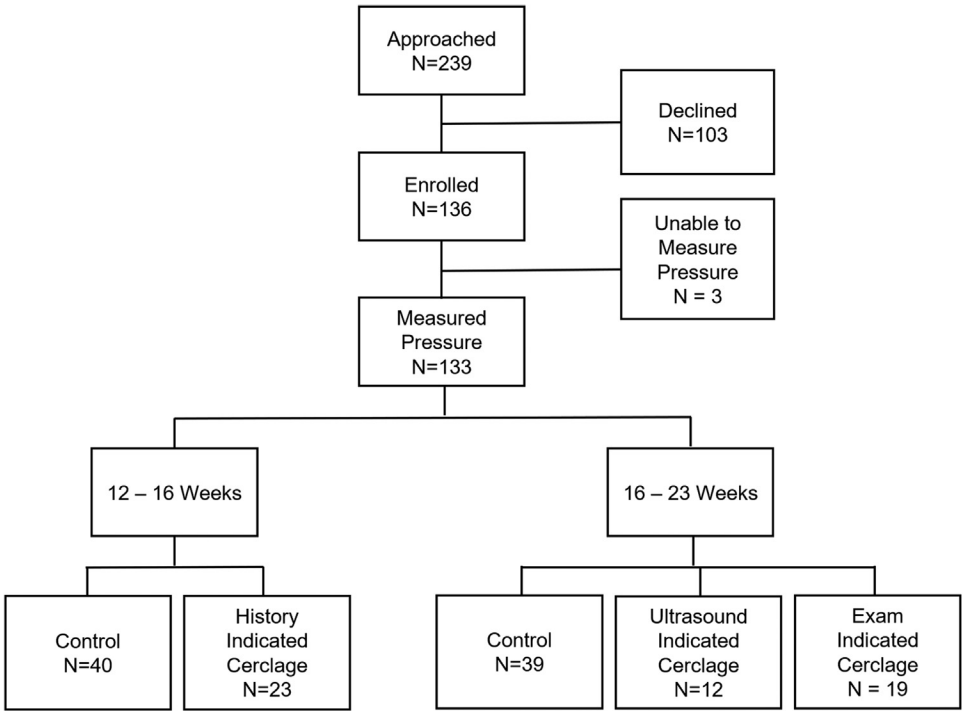
Aspiration measurements

Cervical softness was measured using an aspiration-based device (Pregnolia System; Pregnolia AG, Zurich, Switzerland). The aspiration device has 2 components, namely the control unit containing a pump and a disposable sterile device.[19] Once informed consent was obtained, the cervical softness was measured according to the instructions for use as detailed in the investigators brochure. A speculum was used to expose the cervix. The speculum examination was performed by one of the physicians on the research team. Cervical mucus was gently removed with the use of a soft cotton swab. The physician inserted the sterile aspirator device in the vaginal canal and placed the aspirator lightly on the squamous epithelium of the anterior lip of the cervix at the 12 o'clock position. A foot petal activated the vacuum system, which created a negative aspiration pressure at the tip of the device. The tip of the device has a cylindrical cavity with a depth of 4 mm. The control unit measures the aspiration pressure (P_{cl}) required to pull the tissue to the ceiling of the tip's cylindrical cavity. The vacuum pressure required to accomplish this 4 mm displacement is the closing pressure (P_{cl}). A high P_{cl} level correlates with stiff tissue and a low P_{cl} correlates with soft tissue. Up to 3 measurements were collected from the same location and an average value was calculated. The total time required to collect these aspiration measurements was <3 minutes. After the cervical softness measurement was obtained with the aspirator, the speculum was removed, and the device was discarded.

Statistics

The P_{cl} values were not normally distributed. Hence, the Mann-Whitney *U* test was used to compare P_{cl} values between patients with CI and the controls. First trimester demographic variables and delivery data were compared using *t* tests or chi-square tests as appropriate. Second trimester demographic variables and delivery data were compared using chi-square tests or analysis of variance tests, followed by a post hoc Dunnett test to compare with the control group. A *P* value of <.05 was considered significant. A power analysis was not performed because the aspiration technique is investigational and has not been tested in women with CI. Our aim was to recruit 2 healthy volunteers for each cerclage patient. Analysis was performed using GraphPad Prism 9 (GraphPad Software, San Diego, CA).

FIGURE 1
Study flow sheet



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Results

The flow diagram of the study procedure is showed in Figure 1. A total of 239 pregnant women were approached to participate. Of these, 136 provided informed consent. For 3 women, P_{cl} could not be measured because of discomfort after the speculum examination. Aspiration measurements were obtained for 133 women. No adverse outcomes related to the aspiration measurement were seen. Of the 133 women, there were 54 patients in the cerclage groups (23 history-indicated, 12 ultrasound-indicated, and 19 examination-indicated cerclage patients) and 79 controls (40 in the 1T and 39 in the 2T groups). The baseline characteristics are displayed in Tables 1 and 2. The differences in age, body mass index, and gestational age at the time of measurement between the 1T and history-indicated groups were statistically significant. Otherwise, there were no differences in the baseline demographic characteristics between the cerclage groups and the respective control groups.

The healthy volunteers seemed to tolerate the aspiration measurements without discomfort. The median P_{cl} aspiration measurements for the 1T controls (130.5 mbar) and 2T controls (81 mbar) were similar to values reported previously.[18] The P_{cl} of the 2T controls were significantly lower than that of the 1T controls as was reported previously ($P<.0001$)[18] (Figure 2).

The median (interquartile range]) P_{cl} for the ultrasound-indicated cerclage and 2T controls were 62 mbar (50.5 −114) and 81 mbar (75−101), respectively; the distributions of the 2 groups were significantly different ($P=.04$) (Figure 2). The area under the receiver operator curve was 0.70. For a P_{cl} value <69 mbar to predict the need for an ultrasound-indicated cerclage, the sensitivity was 67%, the specificity was 82%, and the likelihood ratio was 3.7.

Inspection of Table 2 reveals that race and ethnicity, nulliparity, and progesterone use were significantly different between ultrasound-indicated cerclage and 2T controls. Of note, there were too few cerclage patients for a multivariable model to adequately control for confounding. However, a sensitivity analysis was performed for race and ethnicity, nulliparity, and progesterone use. For race and ethnicity, Table 2 shows that non-Hispanic White patients were significantly overrepresented among the healthy volunteers. When non-Hispanic White patients were removed from the analysis, the *P* value increased from.042 to.07. When nulliparous controls were removed from the analysis, the *P* value increased from.042 to.09. When cerclage patients on progesterone were removed, the *P* value increased from .042 to .08.

The difference in P_{cl} was not significantly different for the history-indicated and examination-indicated cerclage groups when compared with their respective control groups (Figure 2).

The PTB rate before 35 weeks' gestation was significantly higher among the patients with a history-indicated cerclage than among the 1T controls (21.7% vs 2.9%; $P=.03$) (Table 1). The PTB rate

TABLE 1
Baseline demographics and delivery data: history-indicated cerclage[a]

Variable	History-indicated cerclage n=23	Controls n=40	*P* value
Age (y)	33.6±4.6	30.1±5.7	.02
Race and ethnicity, n (%)			
Non-Hispanic White	5 (21.7)	18 (45.0)	NS
Non-Hispanic Black	8 (34.8)	9 (22.5)	
Hispanic	8 (34.8)	6 (15.0)	
Asian	0	5 (12.5)	
Not reported	2 (8.7)	2 (5.0)	
BMI (kg/m^2)	34.4±6.9	28.3±7.0	.002
GA at measurement (wk), median (IQR)	13.3 (12.3–14.1)	12.5 (12.1–12.7)	.001
Nulliparous, n (%)	0 (0.0)	15 (37.5)	<.001
History of spontaneous preterm birth >14 wk, n (%)	22 (95.6)[b]	0 (0.0)	<.001
History of cerclage, n (%)	15 (65.2)	0 (0.0)	<.001
Progesterone use, n (%)	4 (17.4)	0 (0.0)	.01
Delivery data			
GA at delivery (wk), median (IQR)	38.1 (35.1–39.0)	39.0 (38.1–39.7)	.002
Preterm birth <35 wk, n (%)[c]	5 (21.7)	1 (2.9)	.03

BMI, body mass index; *GA*, gestational age; *IQR*, interquartile range; *NS*, not significant.

[a] The ± values are presented as mean±standard deviation;; [b] This number is not 100% because 1 patient received a history-indicated cerclage for a previous examination-indicated cerclage with delivery at term;; [c] One control patient and 1 cerclage patient delivered prematurely because of preeclampsia with severe features. The remaining preterm births were the consequence of spontaneous preterm birth.

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before 35 weeks' gestation was significantly higher among patients with an ultrasound-indicated cerclage than among 2T controls (33.3% vs 0%; *P*=.002). The PTB rate for examination-indicated controls (10.5%) was not significantly different when compared with 2T controls (Table 2).

Comments

Principal findings

Patients presenting for ultrasound-indicated cerclage had significantly softer cervices than normal controls when measured using an aspiration-based device. The difference in cervical softness was not significantly different for the history-indicated and examination-indicated cerclage groups when compared with their respective controls.

Results in the context of what is known

Before the widespread adoption of transvaginal measurements of cervical length, various tests of the cervical function in nonpregnant women were proposed to aid the diagnosis of CI.[5,6,20,21] Easy cervical passage of an 8 mm Hegar dilator[20] or #16 Foley catheter[21] provided evidence of a wide uterine isthmus and supported the diagnosis of CI. To measure the mechanical properties of cervical tissue, investigators used (1) a calibrated dilator to measure the cervical resistance index (CRI)[5,22] and (2) an intracervical balloon to measure the elastance.[6] When compared with healthy controls, patients with a history of CI demonstrated decreased CRI and elastance values.[5,6,22] These previous studies and the present study add support to the hypothesis that CI is caused, in part, by overly soft cervical tissue.

It is known that the mechanical properties of the cervical tissue arise from its fibrous extracellular matrix.[9,23] It is also known that the strength of cervical tissue is related to the composition and organization of cervical collagen.[24] Cervical collagen experiences significant remodeling during pregnancy to accommodate fetal growth and, ultimately, parturition.[23] Although the molecular events that cause cervical remodeling are under active investigation, the final outcome is decreased collagen organization with concomitant loss of tissue strength.[25,26] This study confirms an earlier report[18] that cervical remodeling occurs early in pregnancy and significant softening can be detected by the early second trimester.

Clinical implications

The diagnostic algorithm for the diagnosis of CI could be improved. The mainstay of diagnosis is an obstetrical history.[2] When the obstetrical history is unclear, cervical length surveillance is used to monitor for cervical shortening.[3] However, obstetrical history and cervical length surveillance are not useful for primiparous patients. In addition, patients can present with a dilated cervix when cerclage treatment is more difficult. An improved algorithm for detecting patients at risk for CI would be highly clinically significant.

This study highlights the complexity of CI. Like previous studies of the mechanical properties of cervical tissue in CI,[5,6,22] we found significant overlap in cervical softness between patients who were scheduled for cerclage and healthy controls. Indeed, the P_{cl} was not significantly different between patients with a history-indicated cerclage and controls. The finding that the cervix was softer for patients scheduled for ultrasound-indicated cerclage suggests that accelerated cervical remodeling could be an important factor in CI. Future studies will need to decipher the relative contributions of baseline cervical softness and accelerated remodeling for cervical dysfunction.

TABLE 2
Baseline demographics and delivery data: ultrasound-indicated and examination-indicated cerclage[a]

Variable	US-indicated cerclage n=12	Examination-indicated cerclage n=19	Controls n=39	*P* value US-indicated vs controls	*P* value examination-indicated vs controls
Age (y)	29.2±6.1	30.3±5.7	30.4±4.9	NS	NS
Race and ethnicity, n (%)					
Non-Hispanic White	1 (9.1)	5 (26.3)	21 (53.8)	.02[b]	NS
Non-Hispanic Black	4 (27.3)	4 (21.1)	6 (15.4)		
Hispanic	4 (36.4)	7 (36.8)	3 (7.7)		
Asian	3 (18.2)	1 (5.3)	3 (7.7)		
Not reported	0 (0.0)	2 (10.5)	6 (15.4)		
BMI (kg/m^2)	29.2±5.2	28.5±4.7	29.5±6.3	NS	NS
GA at measurement (wk), median (IQR)	19.0 (17.9–20.2)	20.6 (19.3–22.0)	19.6 (18.6–20.1)	NS	NS
Cervical length at measurement (cm)	1.5±0.8	0.8±1.0	4.0±0.6	<.001	<.001
Cervical dilation at measurement, n (%)	4 (25.0)	15 (79.0)	0 (0.0)	0.01	<.001
Nulliparous, n (%)	0 (0.0)	6 (31.6)	12 (30.8)	<.001	NS
History of spontaneous preterm birth >14 wk, n (%)	12 (100)	1 (5.3)	1 (2.6)	<.001	NS
Progesterone use, n (%)	4 (33.3)	9 (47.4)	0 (0.0)	<.001	<.001
Delivery data					
GA at delivery (wk), median (IQR)	38.4 (31.0–39.9)	38.0 (37.3–39.1)	39.1 (37.8–39.6)	NS	NS
Preterm birth <35 wk, n (%)[c]	4 (33.3)	2 (10.5)	0 (0)	.002	NS

BMI, body mass index; *GA*, gestational age; *IQR*, interquartile range; *NS*, not significant; *US*, ultrasound.

[a] The ± values are presented as means ± standard deviation;; [b] To perform the chi-square tests, the data were dichotomized to non-Hispanic White vs not non-Hispanic White;; [c] Preterm birth was a consequence of spontaneous preterm birth.

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There was no difference in cervical softness among patients presenting for examination-indicated cerclage and among the 2T control group. We observed a large variation in P_{cl} measurements for examination-indicated cerclage patients−−the distribution of P_{cl} values seemed to be bimodal in our study. We speculate that cervical dilation caused tissue stretching, which altered the biomechanics of the cervix and led to an abnormally high P_{cl} measurement in some patients.

Research implications

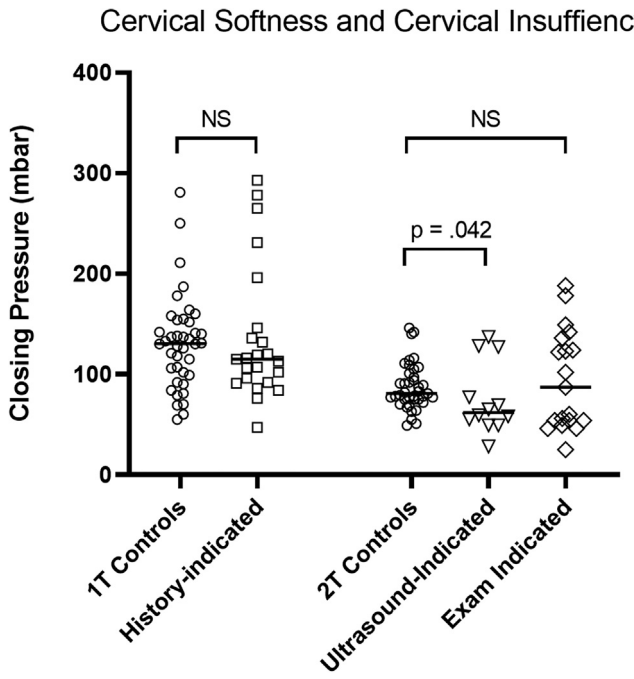
Computational[7,8,19,27,28] and clinical studies[29–32] highlight the complexity of the biomechanical environment of the cervix. Computational modeling studies demonstrated that the mechanical properties of cervical tissue have an important impact on tissue stretch in response to cervical loading.[7] In addition to tissue properties, variables that also affect tissue stretch are the loading environment, the anatomic parameters, the adhesion of the membranes, and the tissue microstructure.[7,28] Clinical studies demonstrate that intrauterine infection and inflammation are commonly seen in the setting of cervical dysfunction.[29–32] Whether cervical biomechanical dysfunction is a cause or a consequence of ascending infection and intrauterine inflammation is an important unanswered question in PTB research. Data from this study could inform a future prospective trial aimed at studying the natural history of cervix-related PTB.

Strengths and limitations

The main strength of this study is that a novel measurement of cervical softness was performed in patients with CI. In our hands, the aspiration method for measuring cervical softness was quick and easy to perform. The measurement seemed to be well tolerated, and no adverse effects were seen. An additional strength is that this study was careful to distinguish between patients with different indications for cerclage. In contrast with previous studies of the mechanical properties of CI,[5,6,22] patients in this study were separated into history-indicated, ultrasound-indicated, and examination-indicated groups.

A significant limitation of this study is that it was underpowered to control for confounding. Healthy control patients were significantly more likely to be non-Hispanic White and nulliparous. Cerclage patients were significantly more likely to be using progesterone. Sensitivity analyses in

FIGURE 2
Cervical softness and cervical insufficiency



The cervix was softer among patients scheduled for an ultrasound-indicated cerclage than among second trimester controls. No significant differences in softness were seen among patients scheduled for a history-indicated cerclage or an examination-indicated cerclage and their respective controls.

1T, first trimester; *2T*, second trimester; *mbar*, millibar; *NS*, not significant.

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which these variables were removed demonstrated an attenuation of the significance of the *P* value. The sensitivity analysis demonstrated that race and ethnicity, nulliparity, and progesterone use could have a meaningful impact on aspiration measurements. Future, adequately powered studies should take this into consideration.

A second limitation of this study is its cross-sectional study design. Because aspiration measurements were performed after CI was diagnosed, no information regarding the temporal relationship between cervical softness and CI was obtained. In addition, the rate of PTB was too low to know whether the aspiration method predicted subsequent PTB. Last, this was a single center study, and the results may not be generalizable to other centers.

The most significant limitation of the aspiration method is that a speculum is needed to perform the measurement. The requirement for a speculum examination was the most common reason patients declined to participate in the study. In addition, the aspiration method may not give useful results when there is significant cervical scarring. Anecdotally, several of the abnormally high P_{cl} measurements in the history-indicated group (eg, >200 mbar) were seen in patients with a history of cerclage procedures, which may be associated with cervical scarring. Last, cervical trauma or an abnormally wide isthmus may not be detected with cervical aspiration because the measurement of cervical softness could be normal.

An additional limitation of the aspiration method is that the sampling area is limited to a column of tissue at the external os. In a previous study, a finite element simulation of tissue aspiration showed that a column of approximately 8 to 10 mm of tissue is mechanically affected by the aspiration.[33] That column of tissue is composed of the squamous epithelium, fibrous stroma, smooth muscle, and vessels. It is likely that the fibrous stroma dominates the mechanical response. The squamous epithelium is <0.5 mm thick[34] and smooth muscle and vessels are not prominent components of the cervical stroma.[24] Although the stroma of the external os is adequately sampled, the aspiration device does not sample the internal os of the tissue, which is where cervical shortening is initiated.

Conclusions

Objective measurement of cervical softness with the aspiration-based device is a promising technique for antepartum assessment of patients at risk for cervical dysfunction. The cervix was softer in the ultrasound-indicated cerclage group than in the gestational age–matched control patients. Future studies of the aspiration method are needed to assess its value in the prediction of cervical shortening and, ultimate, its prediction of PTB. ■

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