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Cervical strain determined by ultrasound elastography and its association with spontaneous preterm delivery

Abstract

Objective: To determine if there is an association between cervical strain, evaluated using ultrasound elastography, and spontaneous preterm delivery (sPTD) <37 weeks of gestation.

Methods: One hundred and eighty nine (189) women at 16–24 weeks of gestation were evaluated. Ultrasound elastography was used to estimate cervical strain in three anatomical planes: one mid-sagittal in the same plane used for cervical length measurement, and two cross sectional images: one at the level of the internal cervical os, and the other at the level of the external cervical os. In each plane, two regions of interest (endocervix and entire cervix) were examined; a total of six regions of interest were evaluated.

Results: The prevalence of sPTD was 11% (21/189). Strain values from each of the six cervical regions correlated weakly with cervical length (from r=−0.24, P<0.001 to r=−0.03, P=0.69). Strain measurements obtained in a cross sectional view of the internal cervical os were significantly associated with sPTD. Women with strain values ≤25th centile in the endocervical canal (0.19) and in the entire cervix (0.14) were 80% less likely to have a sPTD than women with strain values >25th centile [endocervical: odds ratio (OR) 0.2; 95% confidence interval (CI), 0.03–0.96; entire cervix: OR 0.17; 95% CI, 0.03–0.9]. Additional adjustment for gestational age, race, smoking status, parity, maternal age, pre-pregnancy body mass index, and previous preterm delivery did not appreciably alter the magnitude or statistical significance of these associations. Strain values obtained from the external cervical os and from the sagittal view were not associated with sPTD.

Conclusion: Low strain values in the internal cervical os were associated with a significantly lower risk of spontaneous preterm delivery <37 weeks of gestation.

Keywords: Cervical elasticity; cervical length; prematurity; short cervix; stiffness.

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Introduction

Cervical length evaluated by transvaginal ultrasound is currently the most powerful method for identifying women at risk of preterm delivery [8, 15, 21, 25, 26, 32, 35, 55, 56, 63, 64, 67, 79, 87, 92, 104, 126, 127]. The risk increases as the cervical length shortens [13, 17, 68, 86, 89, 113, 122, 124]. While 58% of women who deliver before 32 weeks of gestation have a cervical length ≤15 mm at 23 weeks of gestation, a large number might reach term or near term pregnancy [60, 118]. Similarly, of all women having a cervical length <25 mm in the mid-trimester, approximately 38% will have a preterm delivery [118]. Moreover, in women with a short cervix, there is evidence that vaginal progesterone, cervical cerclage, and perhaps a cervical pessary prevent preterm delivery [5–7, 14, 16, 23, 27, 31, 34, 42, 50, 59, 71, 72, 74, 78, 91, 105, 106]. Vaginal progesterone has been shown to reduce the rate of preterm birth in women with a short cervix with or without a history of previous preterm birth [19, 30, 103, 106]. Progesterone is as effective as cervical cerclage in women with a prior history of preterm birth and a short

cervix [24, 96]. Accordingly, additional parameters to cervical length are needed to improve the identification of women at risk of preterm delivery. Of particular interest is whether ultrasound elastography can provide relevant information about the risk of preterm delivery [38].

Biochemical and biophysical changes associated with cervical ripening have been described in different studies during the last decades [28, 29, 36, 47–49, 51, 57, 58, 65, 80, 81, 109–112, 115, 116, 123, 129]. Changes in collagen organization, water content, as well as concentration of proteoglycans in the extracellular matrix are considered to be the basis for the modifications in biomechanical properties that make a cervix soft or hard [2, 66, 90, 114, 128, 130]. Elastography measures the percentage of tissue deformation that occurs when oscillatory compression is applied [22, 93, 94, 97]. The degree of tissue deformation can be expressed as strain [33, 45, 46, 52]. Increased strain reflects increased deformation (therefore, softer tissue), while decreasing strain reflects reduced deformation (therefore, stiffer tissue) [52, 53]. Our team previously reported a standardized protocol for obtaining cervical strain measurements in pregnancy and demonstrated that estimated strain values differed across anatomical planes and regions of interest. Cervical strain values differed even further by patient characteristics, including parity and prior preterm delivery, gestational age at examination, and cervical length [62]. In this study, we explore whether cervical strain evaluated by ultrasound elastography is associated with spontaneous preterm delivery (sPTD).

Methods

Study design and participants

This was a cross-sectional study performed at the Center for Advanced Obstetrical Care and Research [Perinatology Research Branch of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), National Institutes of Health, Wayne State University School of Medicine, Hutzel Women's Hospital, Detroit, MI, USA]. Women with singleton pregnancies and without structural or chromosomal abnormalities were invited to participate. Patients with a short cervix or previous preterm delivery treated with vaginal progesterone or cerclage, as indicated by the treating physician, were excluded from the analysis. All patients provided written informed consent for ultrasound examination and were enrolled in research protocols approved by the Human Investigation Committee of Wayne State University and the Institutional Review Board of the NICHD. Spontaneous preterm delivery was considered as that resulting from the spontaneous onset of labor, or spontaneous rupture of membranes at <37 weeks of gestation.

Ultrasound examination

All patients were enrolled before 11 weeks of gestation when the first ultrasound was performed, and gestational age was consistent with the results of crown-rump length measurement. The cervix was evaluated at 16–24 weeks of gestation using transvaginal ultrasound (Hitachi 8–4 MHz, HI Vision 900; Hitachi Medical Corporation, Tokyo, Japan). Cervical length was measured in a sagittal view of the cervix with a clear image of the endocervical canal, the internal and external cervical os, and with a similar size of the anterior and posterior cervical lips [107]. For elastography quantification, three cervical projections were analyzed: mid-sagittal at the same level of the cervical length measurement, and two cross-sectional: one at the level of the internal os, and the other at the level of the external cervical os [62] (Figure 1). The proposed regions of interest were selected based on the feasibility of obtaining the ultrasound images and to delineate the regions of interest. The sagittal plane was the same used for cervical length measurement, and the two cross-sectional views were obtained with a 90° rotation of the ultrasound probe. Each plane was examined in two regions of interest (ROI), the endocervical canal and entire cervix, delineated as previously described [62].

Six operators, each having more than 3 years of experience in obstetrical ultrasound, acquired the elastography images. All operators were trained prior to the beginning of the study by evaluating at least 20 patients and analyzing a minimum of 120 elastography images. The reproducibility analysis showed a substantial overall agreement for considering soft/stiff estimates (kappa=0.75), matching on 82% of these classifications [62].

Measurements were performed while adjusting the region of interest to include the entire cervix and by manually applying continuous oscillatory pressure to the cervix using the ultrasound probe. The elastography equipment used in this study included a press indicator that displays the average strain in the region of interest to evaluate the condition of compression from minimal to high (levels 1–7). All measurements were performed while keeping the press indicator at a value of three (level 3). Additionally, to further standardize the method of measurement, we ensured that: (i) the posterior and anterior cervical lips in the ultrasound image had similar dimensions; (ii) the endocervical canal was completely visualized; and (iii) lateral areas of the cervix were equidistant relative to the ultrasound probe.

The measured strain values represented the percentage (%) of displacement or deformation of tissues within the cervical area averaged among consecutive ultrasound frames during manual application of oscillatory pressure. Dichotomous variables were constructed to describe whether each patient's measurement was in the bottom quartile (≤25th centile) for each cervical region determined among the entire study population. Strain values in the bottom quartile can be viewed as representing "stiff" or less tensile tissue compared to values in higher quartiles.

Statistical analysis

Strain measurements obtained at each patient's first visit during the study period were used to perform cross-sectional analyses. Binomial proportions with 95% confidence intervals (CI) and medians with interquartile ranges were calculated for categorical and arithmetic variables. Logistic regression models were fit to examine the magnitude of association between cervical tissue strain classification (±25th centile) and sPTD. Covariables considered as potential confounders
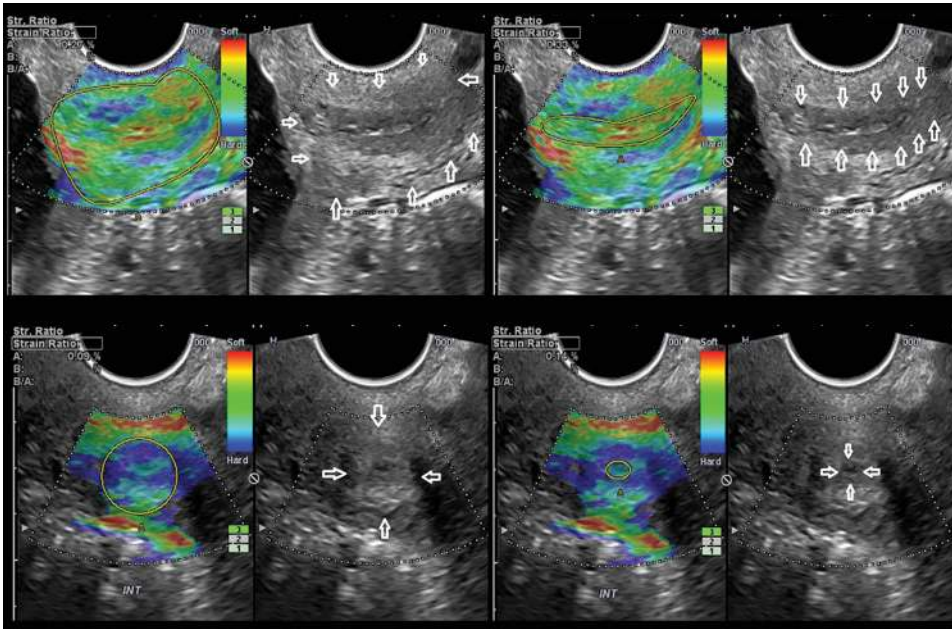
Figure 1 Cervical elastography and strain rate calculation in sagittal and cross sectional projections of the cervix. The boundaries of the endocervical canal and of the entire cervix are highlighted in the corresponding gray scale image.

in multivariable models included the following: previous preterm delivery, gestational age at examination, nulliparity, smoking status, pre-pregnancy body mass index (BMI), maternal age at study enrollment, prior preterm delivery, and race. Firth's penalized likelihood estimation [40] was performed to resolve separation issues (i.e., small cell counts in 2×2 contingency tables, representing a separation of outcomes among patients with and without a factor of interest). Statistical significance was defined as a P value <0.05. Analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

The characteristics of women who subsequently had a sPTD (n=21) and those who delivered at term (n=168)

are shown in Table 1. Women who subsequently had a sPTD had a significantly higher prevalence of cervical length <25 mm than those who delivered at term. The frequency of women with a history of a previous preterm delivery or identified as smokers was also non-significantly higher in women presenting with sPTD.

Table 2 shows the demographic characteristics of pregnant women according to the strain values from the entire cervix of the internal cervical os. Only one patient out of 51 women (2%) with strain values ≤25th centile presented with sPTD; in contrast, 20 of the 135 women (15%) whose cervical strain values were >25th centile subsequently had a sPTD.

Table 3 shows the magnitudes of association among strain values obtained in each cervical region and sPTD. Strain measurements obtained in a cross sectional view of

Table 1 Characteristics of patients presenting with spontaneous preterm delivery and patients delivering at term.

	Spontaneous preterm delivery <37 weeks (n=21)	Delivery ≥37 weeks (n=168)
Maternal age, years (median, range)	23 (18–37)	23 (16–41)
African American (n,%)	21 (100%)	151 (90%)
Smoker (n,%)	9 (43%)	30 (18%)
Nulliparous (n,%)	6 (29%)	73 (43%)
Body mass index (median, range)	27 (17–48)	27 (17–48)
Cervical length <25 mm (n,%)[a]	7 (33%)	10 (6%)
Prior preterm delivery (n,%)	7 (33%)	31 (18%)
Gestational weeks at scan (median, range)	19 (17–24)	19 (16–24)
Gestational weeks at delivery (median, range)	36 (23–37)	39 (20–42)

[a]P<0.05.

Table 2 Patient characteristics according to strain values obtained in the entire cervix of the internal cervical os.

	Strain values ≤25th centile (n=51)	Strain value >25th centile (n=138)
Maternal age, years (median, range)	23 (16–41)	23 (18–37)
African American (n,%)	47 (92%)	123 (89%)
Smoker (n,%)	11 (22%)	27 (20%)
Nulliparous (n,%)	25 (49%)	52 (38%)
Body mass index (median, range)	27 (19–48)	27 (17–48)
Cervical length <25 mm (n,%)	3 (6%)	14 (10%)
Spontaneous preterm delivery[a]	1 (2%)	20 (15%)
Prior preterm delivery (n,%)	11 (22%)	26 (19%)
Gestational weeks at scan (median, range)	20 (16–24)	19 (16–24)
Gestational weeks at delivery (median, range)	39 (35–42)	39 (20–42)

[a]$P < 0.05$.

the internal cervical os were significantly associated with sPTD. The strain values corresponding to the 25th centile in the internal cervical os were 0.19 for the endocervical canal, and 0.14 for the entire cervix. Women with strain values ≤25th centile were approximately 80% less likely to subsequently deliver preterm than those whose values were >25th centile [entire cervix; odds ratio (OR) 0.17; 95% CI 0.03–0.9; endocervical canal OR 0.2; 95% CI 0.03–0.96]. Additional adjustment for gestational age at examination, maternal age, race, smoking status, parity, pre-pregnancy BMI, and previous preterm delivery did not change the magnitude of this association (entire cervix, OR 0.17; 95%

CI 0.03–0.9; endocervical, OR 0.2; 95% CI 0.04–0.9). In contrast, strain values from the external cervical os and from the sagittal view of the cervix were not associated with sPTD.

Secondary analyses revealed that women with cervical strain values ≤25th centile from the internal cervical os were 86–88% less likely to subsequently have a sPTD at <34 weeks of gestation than women with strain values >25th centile (entire cervix: OR 0.14; 95% CI 0.01–1.6; and endocervical canal: OR 0.12; 95% CI 0.01–1.6). However, these associations did not reach statistical significance, most likely due to the limited number of cases available for analysis (n=9). In contrast, none of the strain

Table 3 Magnitudes of association among strain values ≤25th centile in each cervical region and spontaneous preterm delivery (<37 weeks).

Cervical region strain	Model I		Model II	
	OR	95% CI	OR	95% CI
Internal os endocervical				
≤0.19	0.2	0.03–0.96	0.2	0.04–0.9
>0.19	1	Reference	1	Reference
Internal os entire cervix				
≤0.14	0.17	0.03–0.9	0.17	0.03–0.9
>0.14	1	Reference	1	Reference
Sagittal endocervical				
≤0.25	0.8	0.3–2.2	0.9	0.3–2.5
>0.25	1	Reference	1	Reference
Sagittal entire cervix				
≤0.2	0.7	0.2–2.0	0.8	0.3–2.4
>0.2	1	Reference	1	Reference
External os endocervical				
≤0.35	1.2	0.4–3.3	1.3	0.5–4.0
>0.35	1	Reference	1	Reference
External os entire cervix				
≤0.26	1.6	0.6–4.2	1.7	0.6–4.5
>0.26	1	Reference	1	Reference

Model I adjusted for gestational age at examination. Model II adjusted for gestational age at examination, race, smoking status, parity, maternal age, pre-pregnancy body mass index, and prior preterm delivery. OR=odds ratio, CI=confidence interval.

Table 4 Cervical length and strain values ≤25th centile of the entire cervix from the internal cervical os in women with spontaneous preterm delivery.

Patient	Gestational weeks at scan	Cervical length (mm)	Strain ≤0.14 (yes/no)	Gestational weeks at delivery
1	18	18	No	22
2	16	27	No	23
3	17	36	No	24
4	19	16	No	25
5	22	6	No	25
6	18	29	No	27
7	18	36	No	33
8	21	32	No	33
9	21	5	No	33
10	18	35	No	34
11	16	39	No	35
12	16	42	Yes	35
13	21	22	No	35
14	21	28	No	35
15	23	36	No	35
16	24	22	No	35
17	18	32	No	36
18	18	35	No	36
19	19	16	No	36
20	19	37	No	36
21	20	44	No	36

Strain was estimated using a cross sectional projection of the entire cervix at the level of the internal os.

estimations performed in sagittal or external views was significantly associated with sPTD at <34 weeks.

Table 4 shows the characteristics of women who subsequently presented with sPTD. Of these 21 patients, 33% (n=7) had a cervical length <25 mm, and all but one (95%) had cervical strain values above the 25th centile.

Table 5 shows the correlations between cervical length (mm) and strain values from each of the six cervical regions of interest. Strain values from the internal cervical os showed a weak negative correlation with cervical length, whereas strain values from the external cervical os

Table 5 Correlation between strain estimations obtained in the different cervical regions and cervical length.

Variable	Correlation	95% Confidence intervals		P-value
Internal endocervical	−0.24	−0.37	−0.10	<0.001
Internal complete	−0.22	−0.36	−0.08	0.002
Sagittal endocervical	−0.13	−0.27	0.01	0.08
Sagittal complete	−0.07	−0.21	0.07	0.34
External endocervical	−0.03	−0.17	0.12	0.69
External complete	−0.06	−0.20	0.09	0.43

and the sagittal plane were not correlated with the cervical length.

Discussion

Principal findings of the study

Cervical elastography performed at 16–24 weeks of gestation showed that: (i) low strain values estimated in a cross sectional view of the internal cervical os were significantly associated with a lower risk of spontaneous delivery <37 weeks of gestation. Women with values ≤25th centile, representing stiff or less tensile tissue, were 80% less likely to subsequently have a sPTD than women with strain values >25th centile; (ii) only one patient with a strain value ≤25th centile subsequently had a sPTD, whereas 15% of patients with strain values >25th centile subsequently had a sPTD; and (iii) the association between strain values ≤25th centile in the internal cervical os and sPTD remained significant when adjusting for potential confounders.

Elastography of the uterine cervix and spontaneous preterm delivery

The relationship of cervical strain evaluated by elastography to the risk of preterm delivery is of considerable interest. Prior reports of elastography of the uterine cervix have focused on measurement standardization or assessment of reproducibility [43, 73, 88, 117, 120, 121]. Only two articles have reported the relationship between cervical elastography and clinical outcome. Swiatkowska-Freund et al. [117] used ultrasound elastography in the evaluation of women with post-term pregnancies, and reported that a soft endocervical canal was associated with successful induction of labor. Additionally, Khalil et al. [73] suggested that ultrasound elastography might have potential value in predicting the risk of preterm delivery, although few patients (n=12) were examined. Our results show that strain values in the internal cervical os are associated with a risk of sPTD. When strain values in the internal cervical os were ≤25th centile, only one woman had a spontaneous preterm delivery. Despite the finding that strain values >25th centile were significantly associated with a risk of sPTD, a clear separation between those who will and who will not deliver preterm is still a goal. There was a modest correlation between cervical length and strain values in the internal cervical os. This is consistent with our previous report in uncomplicated women delivering at

term [62]. Cervical strain seems to provide different information about cervical characteristics from cervical length. The association with cervical length, as well as biochemical markers in a larger population, might improve the discrimination of women with a higher/lower risk of preterm delivery.

The importance of evaluating cervical characteristics besides cervical length, such as deformation, elasticity, ultrasound attenuation, strain, and collagen composition, is to provide information on the tensile properties of the cervix during pregnancy and before the onset of preterm or term labor [9, 10, 12, 41, 44, 70, 75, 76, 82, 84, 98, 99, 102, 119, 131]. Changes in such cervical characteristics can be related to the content and organization of collagen and proteoglycans in the extracellular matrix [1, 49, 66, 77, 80, 95, 100, 101, 123]. In particular, there is a relationship between collagen fiber cross links and the degree of tissue stiffness. In experimental models, changes in tissue stiffness induced by increasing the number of collagen cross links have been demonstrated with ultrasound techniques [3, 54].

Regional differences in cervical tissue characteristics have been previously described. Feltovich et al. [37] suggested that the lack of homogeneity of cervical tissue could be related to differences between the alignment and organization of the collagen network. Carlson et al. [20] reported a higher shear wave speed in the proximal (internal os) cervical segment when compared with the distal (external os) segment of the cervix in studied specimens obtained after hysterectomy. McFarlin et al. [84] reported that the lack of homogeneity of the cervix might be a limitation when studying ultrasound properties such as attenuation. Using elastography Molina et al. [88] also reported an apparent lack of homogeneity in the measurable stiffness of the cervix. Therefore, inherent strain differences in cervical regions are not surprising, and might be related to differences in tissue composition; whereas the internal cervical os is mainly formed by simple columnar epithelium, the external os has non-keratinized stratified squamous epithelium [108]. It may be possible that different tissue characteristics are affected in different cervical regions in relation to sPTD.

Technical issues

By following a standard protocol for image acquisition and strain calculation, we were able to reduce the variability of elastography estimations [62]. Reproducibility is facilitated by the relatively easy identification of the proposed planes for elastography evaluation. The sagittal projection is obtained in the same image as that used to measure the cervical length; then by rotating the ultrasound probe 90°, the transverse planes for the internal and external cervical os are obtained. These transverse planes are located immediately below the transducer, assuring a more homogenous pressure distribution. Nevertheless, two technical aspects should be considered when manual compression is applied for ultrasound elastography: (i) ultrasound cannot directly measure pressure; it can evaluate changes in frequency or amplitude of the backscattered radiofrequency signals. Therefore, strain measurements and color elastograms are directly related to the movement or displacement of the structures [11]; and (ii) the variability of compression applied by the operator can lead to differences in the displacement of structures; slight compression may create a mild displacement in stiff areas; strong compression can produce large displacements in soft areas. Therefore, a standardized method, independent of the operator, is desirable. The ultrasound equipment used for elastography herein has a press indicator, displaying the average displacement of the structures ranging from mild to high (levels 1–7, respectively). We used an intermediate level (bar level 3) for all examinations; this value represents a moderate compression applied to the region of interest. In addition, we ensured that the anterior and posterior cervical lips had similar dimensions; we obtained adequate visualization of the endocervical canal, and located the lateral parts of the cervix equidistant from the ultrasound probe.

The current study was not designed to assess test performance in a large number of patients. Rather, this is the first step to evaluate the association between cervical strain estimated using elastography and sPTD. Our findings suggest that elastography may have value as a tool in clinical risk assessment of sPTD. Further investigation is required to examine whether it improves sPTD risk assessment when performed in combination with cervical length and/or other biochemical parameters, particularly for early preterm delivery [4, 18, 39, 61, 69, 83, 85, 102, 125, 132].

In conclusion, the risk of spontaneous preterm delivery is significantly lower in women with low strain values obtained in the internal cervical os. Ultrasound elastography may have a role in the assessment of risk for preterm delivery.

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