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● *Technical Note*

BEYOND CERVICAL LENGTH: A PILOT STUDY OF ULTRASONIC ATTENUATION FOR EARLY DETECTION OF PRETERM BIRTH RISK

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Abstract—The purpose of this study was to determine whether cervical ultrasonic attenuation could identify women at risk of spontaneous preterm birth. During pregnancy, women (n = 67) underwent from one to five transvaginal ultrasonic examinations to estimate cervical ultrasonic attenuation and cervical length. Ultrasonic data were obtained with a Zonare ultrasound system with a 5- to 9-MHz endovaginal transducer and processed offline. Cervical ultrasonic attenuation was lower at 17–21 wk of gestation in the SPTB group (1.02 dB/cm-MHz) than in the full-term birth groups (1.34 dB/cm-MHz) (p = 0.04). Cervical length was shorter (3.16 cm) at 22–26 wk in the SPTB group than in the women delivering full term (3.68 cm) (p = 0.004); cervical attenuation was not significantly different at this time point. These findings suggest that low attenuation may be an additional early cervical marker to identify women at risk for SPTB. (E-mail: bmcfar1@uic.edu) © 2015 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Ultrasonic attenuation, Cervical remodeling, Preterm birth, Cervical length.**

INTRODUCTION

Preterm birth is a major public health challenge. In the United States, one in eight pregnancies delivers prior to 37 wk of gestation, which equates to more than 447,000 preterm births annually (Martin et al. 2012). Spontaneous preterm birth (SPTB) continues to be the primary contributor to long-term morbidity, accounting for 75% of neurodevelopmental abnormalities, such as cerebral palsy and developmental delay (Goldenberg and Rouse 1998; Lemons et al. 2001; Lorenz 2001). SPTB is recognized as a syndrome that can occur through the activation of many different pathways (Challis et al. 2000, 2009; Goldenberg and Rouse 1998; Lemons et al. 2001; Lorenz 2001; Norwitz et al. 1999; Romero et al. 2006). However, the final common pathway must involve cervical remodeling to allow passage of the fetus through the cervix, and this is the focus of our research.

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Ultrasonic cervical length has been the standard measure used to identify cervical insufficiency and to identify women who should receive preventive progestogen therapy to prevent preterm birth (Cahill et al. 2010; Campbell 2011; Romero et al. 2013; Werner et al. 2011). Progestogen therapy has been promising in preventing preterm birth in women with cervical shortening or a history of preterm birth (DeFranco et al. 2007; Fonseca et al. 2007), although the mechanisms underlying its prevention of preterm birth are poorly understood (Nold et al. 2013). Cervical length assessment has become a widely used clinical measure for identifying women at high risk for preterm birth; however, it has low positive predictive value in low-risk women because the majority of individuals identified with a short cervix still deliver at term (Berghella et al. 2009; Romero et al. 2013). Generally, the risk of SPTB is greater in women with a short cervix than women with a longer cervix (Campbell 2011; Romero et al. 2013). For example, in one study, 34.1% of women with a ≤1.5-cm-long cervix before 34 wk of gestation delivered preterm (Werner et al. 2011). These findings suggest that although a shortened cervix is a risk factor for SPTB, most women with a short cervix will still deliver at term. Although a cervical length measure is more objective than a digital examination of the cervix by palpation (Rozenberg 2008), there continues to be a need for improved non-invasive methods to detect early changes in the cervix associated with SPTB (Feltovich et al. 2012; Garfield et al. 1998, 2005; Gennisson et al. 2010; Tekesin et al. 2003).

We sought to detect the likelihood of SPTB by examining cervical tissue microstructure via estimates of ultrasonic attenuation. Ultrasonic attenuation is a measure of the loss of ultrasonic energy as a function of distance (Shung and Thieme 1993). Ultrasonic attenuation is related to tissue properties of water content, collagen content and organization, which markedly change during cervical remodeling in pregnancy (Baldwin et al. 2007; Hall et al. 2000a, 2000b, 2000c; Pohlhammer and O'Brien 1981). We hypothesized that cervical ultrasonic attenuation could detect changes in water concentration and collagen organization as the cervix remodels (Clark et al. 2006; Feltovich et al. 2005; Garfield et al. 2005; Leppert 1995; Leppert et al. 2000) and, hence, be an early indicator of preterm birth. Previously we reported that cervical ultrasonic attenuation was lower in women who delivered spontaneously preterm versus term; and women with low attenuation values delivered earlier than women with higher attenuation values (McFarlin et al. 2010). We also evaluated inter-rater reliability of cervical attenuation in 13 subjects. The correlation coefficient was $r = 0.91$ ($p < 0.001$), indicating strong inter-rater reliability.

Considerable ultrasonic attenuation research has been conducted in animals and humans by our group (Bigelow et al. 2011; Labyed and Bigelow 2011; Labyed et al. 2011; McFarlin et al. 2006, 2010; O'Brien 1977) and others (Feltovich and Hall 2013; Feltovich et al. 2010; Hall et al. 2000b) to develop, validate and improve methods for detecting microstructural tissue changes in biological tissues. For more than four decades, we have known that connective tissue is related to ultrasonic propagation properties such as the attenuation coefficient (Fields and Dunn 1973; O'Brien 1977). In particular, collagen concentration and water concentration have been inversely related to attenuation in animal cervix tissue (Bigelow et al. 2008; Labyed and Bigelow 2011; Labyed et al. 2011; McFarlin et al. 2006, 2010). It was thus appropriate to consider the role of connective tissue and collagen remodeling relative to attenuation in collagenous tissues such as the cervix. In our *in vivo* animal studies using timed-pregnant rats, significant correlations were found between the cervical attenuation coefficient and gestational age ($r = -0.37$, $p < 0.01$) and tropocollagen ($r = 0.35$, $p < 0.001$). Also, from 15 to 21 d of pregnancy in the rat, soluble collagen concentration and hydroxyproline decreased by 30% (F [4,31] = 7.5, $p < 0.001$), insoluble collagen decreased by 25% (F [4,31] = 6.5, $p < 0.001$) and water concentration increased from 79% on day 15 to 86% on days 20–21 (F [4,31] = 12.1, $p < 0.001$). Rats typically deliver on day 21 of pregnancy. These biochemical constituents are consistent with the biology of cervical remodeling during pregnancy (Bigelow et al. 2008). Thus, with this pilot study, our cervical attenuation findings are consistent with what has previously been observed. These promising findings led to the present study reported herein. The purpose of this study was to determine whether ultrasonic attenuation estimates of the cervix have the potential to identify women at risk of SPTB.

METHODS

Sixty-seven pregnant African American women were recruited for the study. Women were eligible if they were ≥18 years of age; were able to read, write and understand English; did not have an immune disorder; did not use corticosteroids or have pre-existing diabetes; and agreed to undergo transvaginal ultrasonic examinations at five planned time points (17–21, 22–25, 26–29, 30–34 and 35–39 wk gestation) during pregnancy. Women were recruited in the prenatal care clinics and excluded if they had an anomalous fetus or were too ill to give informed consent.

Women underwent from one to five transvaginal ultrasonic examinations (z.one, Zonare Medical Systems, Mountain View, CA, USA) with a clinical 5- to 9-MHz endovaginal transducer to estimate cervical ultrasonic attenuation and cervical length. Immediately after each cervical scan, at the same ultrasound system settings, a Gammex (Middleton, WI, USA) tissue-mimicking reference phantom was scanned. On the basis of the manufacturer's information, as well as independent validation measurements made in our laboratory, the reference tissue-mimicking phantom was considered to have an attenuation of 0.6 dB/cm-MHz The processing steps required a calibrated/standardized reference phantom to cancel out machine and operator dependencies, thus yielding ultrasonic attenuation estimates that were solely a function of the tissue under study. Women did not undergo a pelvic examination for this study.

Basic ultrasonic data were obtained, saved and converted to radiofrequency (RF) data. The RF data were windowed into smaller regions of interest (ROIs) to estimate the attenuation throughout the entire cervix. In earlier studies (McFarlin et al. 2010), the most homogeneous appearing area of the cervix was selected from the gray-scale image. However, there were concerns about ROI selection bias and measure reproducibility.

Therefore, our approach now, and used herein, has been to map the entire cervix and use the mean attenuation value of the entire cervix. Figure 1 illustrates the process of segmenting the portion of the cervix in a B-mode image that would include all of the attenuation ROIs. The spectral log difference method was used to estimate attenuation (Labyed et al. 2011). This method was selected because among the different algorithms for attenuation estimation, the spectral log difference method is one of the least susceptible to the natural heterogeneity of biological tissues (Bigelow et al. 2011; Labyed and Bigelow 2011).

All data were entered into an electronic database and analyzed with SPSS Version 19.0 statistical software (IBM, Armonk, NY, USA) and R Version 3.0.2 (R Core Team). Descriptive statistics were reported. Analysis of variance (ANOVA) tests were used to determine differences in patient characteristics by group, with α set at 0.05. Two-tailed unpaired *t*-tests were used to determine differences in attenuation and cervical length at 17–21 and 22–26 wk of gestation. Logistic regression modeling was conducted to determine odds ratios of preterm birth, with adjustment for repeated measures with generalized estimating equation analysis using exchangeable working correlation and robust standard errors calculated with the sandwich formula (Liang and Zeger 1986). Receiver operating characteristic (ROC) curve analysis of the logistic regression model was conducted using the *lroc* function in the R package *epicalc* (Chongsuvivatwong 2012).

This study was approved by the Human Subjects Review Board of the University of Illinois at Chicago. All research participants submitted written informed consent prior to participating in the study.

RESULTS

All of the women in our study were African American and received their prenatal care at a tertiary medical center with maternal fetal medicine physicians or certified nurse midwives. Most women were multigravid (56/67, 84%), and 34% (23/67) had a history of at least one prior preterm birth. Of the 67 women in the study, delivery data were available for 51 (76%) delivered full term, 10 (15%) delivered spontaneously preterm and 6 (9%) delivered preterm because of medical indications such as hypertension, pre-eclampsia and bleeding. Table 1 summarizes patient characteristics by group.

A total of 239 transvaginal ultrasonic examinations were conducted for attenuation and cervical length. Each woman had from one to five scans during pregnancy. The reasons for the missed scans were: preterm birth, missed appointments, moved away, or delivery for medical indications. Figure 2a illustrates mean cervical attenuation and mean cervical length for all of the women in the study over the course of pregnancy. For women who delivered full term, attenuation remained relatively constant with a small standard error of the mean until about 36 wk of gestation, when there was a decline. Women delivering spontaneously preterm and medically indicated preterm had different patterns of attenuation over the course of pregnancy.

The analyses focused on the early gestational ages, namely, 17–21 and 22–26 wk of gestation, for cervical attenuation and cervical length outcomes. At 17–21 wk of gestation, there were significant attenuation differences between the SPTB and full-term birth groups ($p = 0.04$). A subgroup analysis was conducted with 33 separate women, who underwent a transvaginal scan of

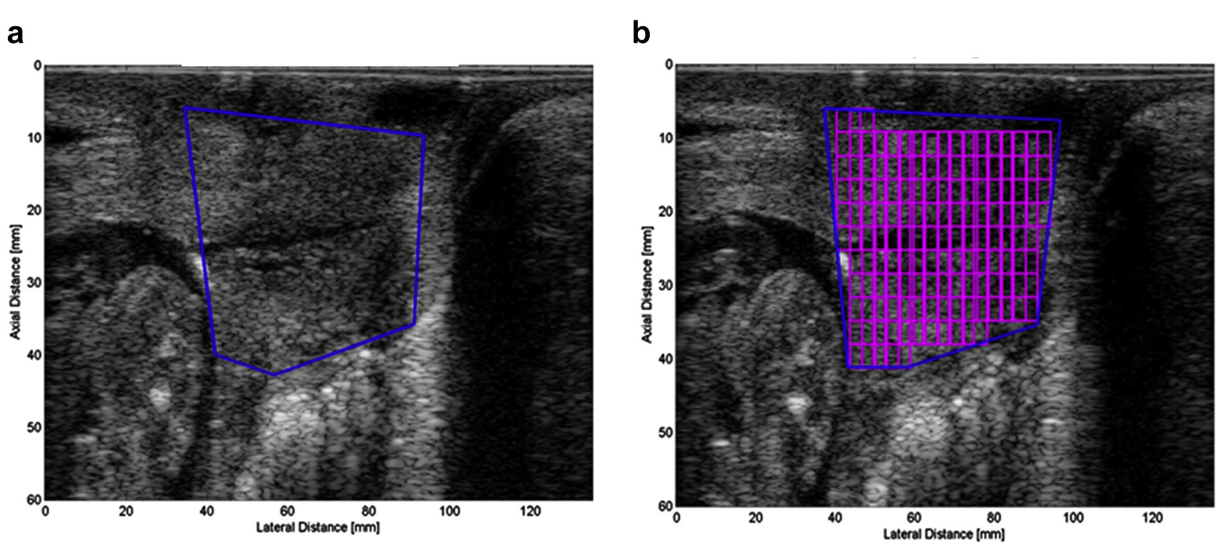

Fig. 1. (a) How the examiner outlines the portion of the cervix that will be processed for attenuation. (b) Regions of interest within the segmented cervix.

Table 1. Characteristics of women in the study*

Patient characteristic	Full term (N = 51)	SPTB (N = 10)	MI PTB (N = 6)	Statistics F	Statistics p
Age	26 (6)†	25 (5)	30 (9)	1.279	0.285
Total number of pregnancies	3	4	4	1.568	0.216
Number of births					
Full term	1	0.7	1	0.287	0.751
Preterm	0.4	1	1	4.651	0.023
Abortion	—	1.4	1.4	1.791	0.196
Living children	1.3	1.2	1.7	0.526	0.541
Number of women who received 17-OHPC	9	6	1	5.928	0.013
Gestational age at birth (wk)	38.9 (1)	29.3 (6)	33.1 (1)	47.383	0.0001
Infant birth weight (g)	3133 (531)	1645 (1202)	2.046 (845)	23.49	0.0001

MI PTB = medically indicated preterm birth; 17-OHPC = 17-hydroxyprogesterone caproate; SPTB = spontaneous preterm birth.
* Differences among the groups were evaluated with an analysis of variance test.
† Values are means or means (SD).

the cervix at 17–21 wk of gestation. Seven of the 33 women delivered spontaneously preterm had a lower mean attenuation (1.02 dB/cm-MHz) than the women in the full-term birth groups (1.34 dB/cm-MHz) (p = 0.04). At this time point, there was little difference in attenuation between the full-term and medically indicated preterm groups.

Importantly, if a true case is a full-term delivery and a false case is a spontaneous preterm delivery, then at a threshold attenuation of 1.15 dB/cm-MHz (above this value is true or full-term delivery) for 17–21 wk of gestation, specificity = 71.4%, sensitivity = 69.2%, positive predictive value (PPV) = 90% and negative predictive value (NPV) = 38.5%. The 1.15 dB/cm-MHz threshold was selected because it was approximately the halfway value between full-term and preterm mean attenuation values.

There were no significant differences in cervical length (Fig. 2) among the three groups at 17–21 wk of gestation (p = 0.46); there also was no difference in cervical length between the spontaneous preterm and full-term birth groups (p = 0.39). Cervical length at 17–21 wk was not correlated with gestational age at delivery (r = 0.06, p = 0.66). With respect to cervical length at 22–26 wk of gestation (full term n = 49 and spontaneous preterm n = 8), women who delivered preterm had significantly shorter cervical lengths (3.16 cm) than women delivering full term (3.68 cm) (t = 3.04, p = 0.004). None of the women in the study had cervical lengths <2.5 cm before 27 wk, a common definition of a "short cervix" (Romero et al. 2013). These findings suggest that cervical tissue properties, as detected by attenuation, are sensitive to remodeling by 17–21 wk in women who will deliver spontaneously preterm, and before cervical shortening.

The data were filtered to extract all measurements for each patient in the range 17–26 wk of gestation (full term

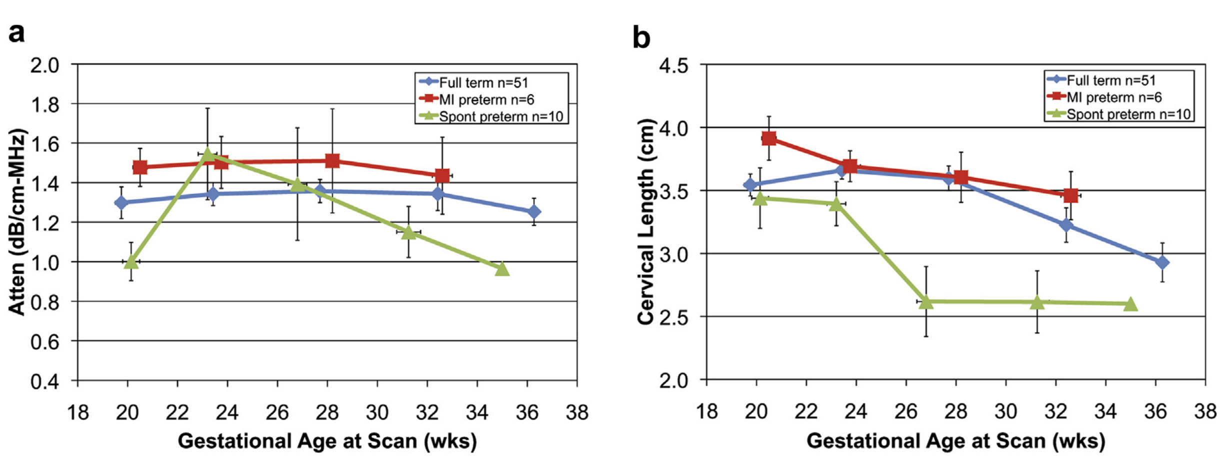

Fig. 2. (a) Attenuation coefficient over the course of pregnancy for 68 African American women by birth outcome (full-term, MI preterm and Spont preterm). (b) Cervical length over the course of pregnancy for 67 African American women by birth outcome (full term, MI preterm and Spont preterm). Error bars are SEM. MI = medically indicated; Spont = spontaneous.

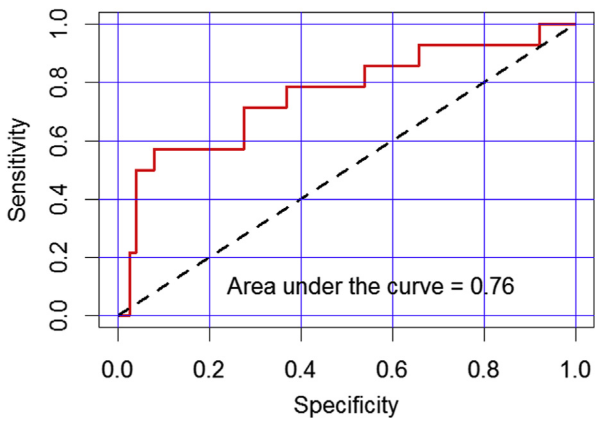

Fig. 3. Receiver operating characteristic curve for the logistic regression model (attenuation and cervical length) based on visits during 17–26 wks of gestation. The model accounts for 76% of the area under the curve (red line).

n = 49 patients with 76 visits, spontaneous preterm n = 10 patients with 14 visits, range: 17–26 wk of gestation). A logistic regression model with exchangeable correlation structure was calculated to model the log odds of preterm birth as a function of scan attenuation, cervical length, an indicator for measurements prior to 22 wk and the interaction between attenuation and the indicators for measurements prior to 22 wk. The indicator for measurements prior to 22 wk and the interaction effect enabled estimation of separate logistic regression response curves for attenuation prior to 22 wk versus after 22 wk. The attenuation interaction coefficient was approaching statistical significance ($p = 0.053$), with an estimated ratio of odds ratios of 1.89 (90% confidence interval: 1.10–3.25), suggesting an association between low early attenuation measurements and preterm birth. Cervical length was not statistically significant in the model, but suggestive of an association between short cervical length and preterm birth ($p = 0.12$), with an estimated odds ratio of 1.75 (90% confidence interval: 0.975–3.14). Using the logistic regression model as a classifier for full-term versus preterm birth, the ROC curve is provided in Figure 3. The estimated 76.0% area under the curve (AUC) is the estimated probability of correctly classifying two randomly selected patients, one of whom delivers preterm and the other who does not, suggesting some predictive capability based on the measurements ≤26 wk.

Fifteen women received weekly 17-α hydroxyprogesterone caproate (17-OHPC) injections during pregnancy because of a history of a prior preterm birth. No women in the study received vaginal progesterone. The mean gestational age was 16 wk when 17-OHPC was initiated. Of the 15 women with a history of preterm birth, 6 delivered preterm. To further understand attenuation and cervical length for women who were and were not treated without 17-OHPC, Figure 4 illustrates delivery outcomes for those who did and those who did not received 17-OHPC. However, the sample sizes were too small to yield any conclusions.

DISCUSSION

The results of this pilot study suggest that for women who will deliver spontaneously preterm, ultrasonic attenuation was lower at 17–21 wk of gestation and before cervical length changes were detected at 22–26 wk. None of the women in our study had a cervical length <2.5 cm before 27 wk of pregnancy. A cervical length <2.5 cm is a commonly used clinical cutoff point for identifying women at risk for SPTB and eligibility for progestogen therapy (Campbell, 2011). The ultrasonic attenuation

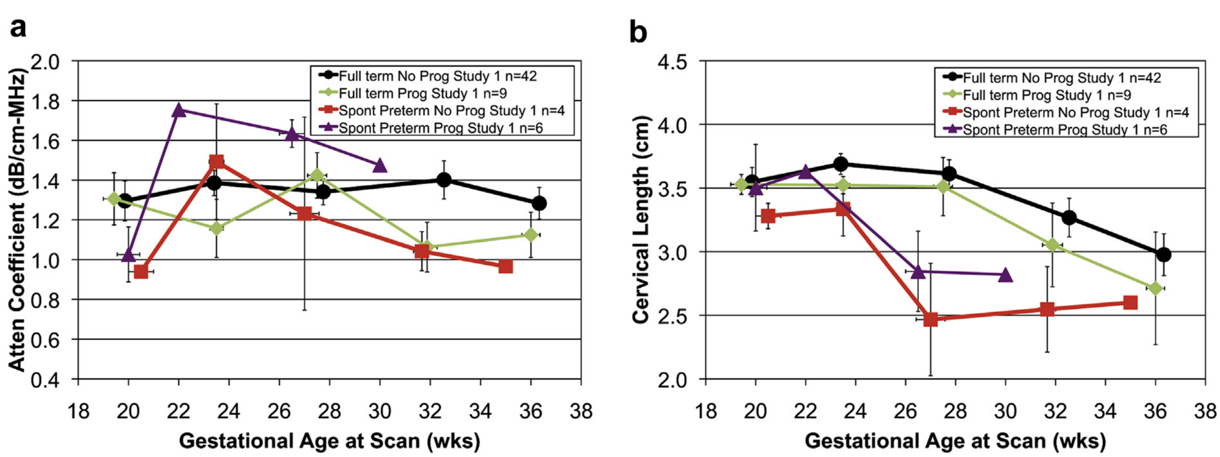

Fig. 4. (a) Attenuation coefficient over the course of pregnancy for 61 African American women by birth outcome and 17-hydroxyprogesterone caproate (Prog) therapy. The medically indicated preterm birth group (n = 6) was not included. (b) Cervical length over the course of pregnancy for 6 African American women by birth outcome and Prog therapy. The medically indicated preterm birth group (n = 6) was not included. Error bars are SEM.

estimates of the cervix significantly provided SPTB risk assessment at 17–21 wk of gestation, weeks before the cervix shortened in length. The high positive predictive value of attenuation (PPV = 90%) at the first time point (17–21 wk) to determine which women will deliver spontaneously preterm is encouraging. Our data suggest that for women who will deliver full term, attenuation of the cervix is high at 17–21 wk and remains fairly stable throughout pregnancy. Presently, the PPV of cervical length in low-risk women ranges from 25% to 52%, although it is the current standard of care (Romero et al. 2013). It is possible that cervical length and attenuation estimates of the cervix may detect different groups of women at risk for preterm birth, as none of the women in our study had a cervical length <2.5 cm before 27 wk of gestation.

Limitations

This pilot study had several limitations. Human research is important for translating our basic science animal findings to clinical practice in humans, but is relatively expensive. Therefore, the sample size was small, especially for the number of women delivering spontaneously preterm. Not all women kept their appointments to be scanned at the five time points. The findings will provide data for sample size and effect size estimates to conduct a more focused study with a greater number of spontaneous preterm births. Also, our sample included only African American women, who have an increased incidence of spontaneous preterm births compared with white women.

CONCLUSIONS

Quantitative ultrasound technology has the capability to take cervical assessment and preterm birth risk beyond the present macrostructure cervical length measures. In this study, none of the women had a short cervix (<2.5 cm) before 27 wk of gestation, yet 10 women had low attenuation of the cervix at 17–21 wk of gestation and delivered preterm. These findings suggest that low attenuation may be an additional early cervical marker for preterm birth risk. Further research with a larger sample size will be needed to determine whether cervical attenuation estimates during pregnancy have the potential to be clinically useful in predicting women early in pregnancy at risk for SPTB. The process of cervical remodeling during pregnancy makes attenuation estimates particularly attractive as a non-invasive method to detect tissue changes that reflect early preparation and readiness for labor and birth. The cervix microstructure of collagen content and organization and tissue composition of water and proteoglycan content markedly change during pregnancy (Leppert 1995; Leppert and Yu 1991; Leppert et al. 2000; Word et al. 2007). As the cervix changes from a firm to a supple soft structure, ultrasonic attenuation estimates can provide clinicians with early tissue-based information, rather than waiting for symptoms of preterm birth. Ultrasonic attenuation estimates could be a feature added to clinical ultrasound systems.

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