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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 (SPTB). 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 from a Zonare ultrasound system with a 5-9 MHz endovaginal transducer and processed offline. Cervical ultrasonic attenuation was lower at 17-21 weeks 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 weeks in the SPTB group compared to 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.

Keywords

ultrasonic attenuation; cervical remodeling; preterm birth; cervical length

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Introduction

Preterm birth is a major public health challenge. In the United States; one in 8 pregnancies deliver prior to 37 weeks of gestation, which equates to over 447,000 preterm births annually (Martin et al. 2015). 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 (Goldenberg and Rouse 1998; Norwitz et al. 1999; Challis et al. 2000; Lemons et al. 2001; Lorenz 2001; Romero et al. 2006; Challis et al. 2009). 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.

Ultrasonic cervical length has been the standard measure to identify cervical insufficiency and to identify women who should receive preventive progestogen therapy to prevent preterm birth (Cahill et al. 2010; Campbell 2011; Werner et al. 2011; Romero et al. 2013). Progestogen therapy has shown promise to prevent preterm birth in women with cervical shortening or a history of preterm birth (DeFranco et al. 2007; Fonseca et al. 2007), although the mechanisms of how progestogens prevent preterm birth are poorly understood (Nold et al. 2013). Cervical length assessment has become a widely used clinical measure to identify 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 greatest in women with a short cervix compared to women with a longer cervix. (Campbell 2011; Romero et al. 2013). For example, in one study 34.1% of women with a cervical length of ≤1.5 cm before 34 weeks 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 exam of the cervix by palpation (Rozenberg 2008), there continues to be a need for improved noninvasive methods to detect early changes in the cervix associated with SPTB (Garfield et al. 1998; Tekesin et al. 2003; Garfield et al. 2005; Gennisson et al. 2010; Feltovich et al. 2012).

Our research 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 (Pohlhammer and O'Brien 1981; Hall et al. 2000a; Hall et al. 2000b; Hall et al. 2000c; Baldwin et al. 2007). We hypothesized that cervical ultrasonic attenuation could detect changes in water concentration and collagen organization as the cervix remodels (Leppert 1995; Leppert et al. 2000; Feltovich et al. 2005; Garfield et al. 2005; Clark et al. 2006) and hence be an early indicator for 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 (O'Brien 1977; McFarlin et al. 2006; McFarlin et al. 2010; Bigelow et al. 2011; Labyed and Bigelow 2011; Labyed et al. 2011) and others (Hall et al. 2000b; Feltovich et al. 2010; Feltovich and Hall 2013) to develop, validate and improve methods to detect microstructural tissue changes in biological tissues. For more than four decades, we have known that connective tissue has been 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 (McFarlin et al. 2006; Bigelow et al. 2008; McFarlin et al. 2010; Labyed and Bigelow 2011; Labyed et al. 2011). 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 days 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; able to read, write and understand English; did not have an immune disorder; did not use corticosteroids or have preexisting diabetes; and agreed to undergo transvaginal ultrasonic examinations at 5 planned time-points (17-21, 22-25, 26-29, 30-34, 35-39 weeks 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) with a clinical 5-9 MHz endovaginal transducer to estimate cervical ultrasonic attenuation and cervical length. Immediately following each cervical scan, using the same ultrasound system settings, a Gammex (Gammex Inc., Middleton, WI) tissue-mimicking reference phantom was scanned. The reference tissue-mimicking phantom had a known attenuation of 0.6 dB/cm-MHz from the manufacturer; as well as from independent validation measurements taken in our laboratory. The processing steps required a calibrated/standardized reference phantom in order 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 exam for this study.

Basic ultrasonic data were obtained, saved and converted to radio frequency (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 grey-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 a mean attenuation value of the entire cervix. Figure 1 displays 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 IBM SPSS 19.0 statistical software (IBM SPSS, Armonk, NY) and R version 3.0.2 (R Core Team, Vienna, Austria). Descriptive statistics were reported. ANOVA tests were used to determine patient characteristic differences 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 weeks gestation. Logistic regression modeling was conducted to determine odds ratios of preterm birth, with adjustment for repeated measures using generalized estimating equations analysis using exchangeable working correlation and robust standard errors calculated using the sandwich formula (Liang and Zeger 1986). Receiver operator characteristic (ROC) 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 received 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 multi-gravid (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 as follows: 51 (76%) delivered full term, 10 (15%) delivered spontaneously preterm and 6 (9%) delivered preterm due to medical indications such as hypertension, preeclampsia or bleeding. Table 1 displays 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. displays 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 weeks 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 weeks gestation, for cervical attenuation and cervical length outcomes. At 17-21 weeks gestation there were significant attenuation differences between SPTB and full term birth groups, $p = 0.04$. A sub-group analysis was conducted with 33 separate women who underwent a transvaginal scan of the cervix at the 17-21 weeks gestation time point. Seven of the 33 women delivered spontaneously preterm had a lower mean attenuation (1.02 dB/cm-MHz) than 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 the medically indicated preterm groups.

Importantly, if the 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 weeks gestation, the specificity = 71.4%, sensitivity = 69.2% PPV = 90% and NPV = 38.5%. The 1.15 dB/cm-MHz threshold was selected because it was approximately the half-way value between full term and preterm mean attenuation values.

There were no significant differences in cervical length (Fig 2.) among the three groups at the 17-21 weeks gestation time-point, $p = 0.46$; 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 weeks was not correlated with gestational age at delivery, $r = 0.06$, $p = 0.66$. When considering cervical length at the 22-26 weeks gestation time-point (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 weeks, 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 weeks 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 weeks gestation (full term n = 49 patients with 76 visits, spontaneous preterm n = 10 patients with 14 visits, range 17-26 weeks 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 weeks and the interaction between attenuation and the indicators for measurements prior to 22 weeks. The indicator for measurements prior to 22 weeks and the interaction effect enabled estimation of separate logistic regression response curves for attenuation prior to 22 weeks versus after 22 weeks. The attenuation interaction coefficient was approaching statistical significance ($p = 0.053$), with an estimated ratio of odds ratios of 1.89 (90% confidence interval from 1.10 to 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 association between low cervical length and preterm birth ($p=0.12$), with an estimated odds ratio of 1.75 (90% confidence interval from 0.975 to 3.14). Using the logistic regression

model as a classifier for full term versus preterm birth, the receiver-operator curve (ROC) is displayed 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 weeks and earlier.

Fifteen women received weekly 17-α hydroxy-progesterone caproate [17-OHPC] injections during pregnancy due to a history of a prior preterm birth. No women in the study received vaginal progesterone. The mean gestational age was 16 weeks when 17-OHPC was initiated. Of the 15 women with a history of preterm birth, six delivered preterm. To further understand attenuation and cervical length for women who were and were not treated without 17-OHPC, Figure 4 displays delivery outcomes for those with/without 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 the 17-21 weeks gestation time-point and before cervical length changes were detected at the 22-26 weeks gestation time-point. None of the women in our study had a cervical length less than 2.5 cm before 27 weeks of pregnancy. A cervical length less than 2.5 cm is a commonly used clinical cut-point for identifying women at risk for SPTB and eligibility for progestogen therapy (Campbell, 2011). The ultrasonic attenuation estimates of the cervix significantly provided SPTB risk assessment at the 17-21 weeks gestation time-point, weeks before the cervix shortened in length. The high positive predictive value of attenuation (PPV = 90%) at the first time-point (17-21 weeks) 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 weeks and remains fairly stable throughout pregnancy.. Presently the PPV of cervical length in low risk women ranges from 25 – 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 less than 2.5 cm before 27 weeks 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 with 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. Our sample also only included African American women who have an increased incidence of spontaneous preterm births compared to 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 weeks gestation, yet 10 women had low attenuation of the cervix at 17-21 weeks 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 to predict women early in pregnancy at risk for SPTB. The process of cervical remodeling during pregnancy makes attenuation estimates particularly attractive as a noninvasive 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 and Yu 1991; Leppert 1995; Leppert et al. 2000; Word et al. 2007). As composition of the cervix changes from a firm to a supple soft structure ultrasonic attenuation estimates can provide clinicians early tissue based information, rather than waiting for symptoms of preterm birth. Ultrasonic attenuation estimates could be an added feature added to clinical ultrasound systems.

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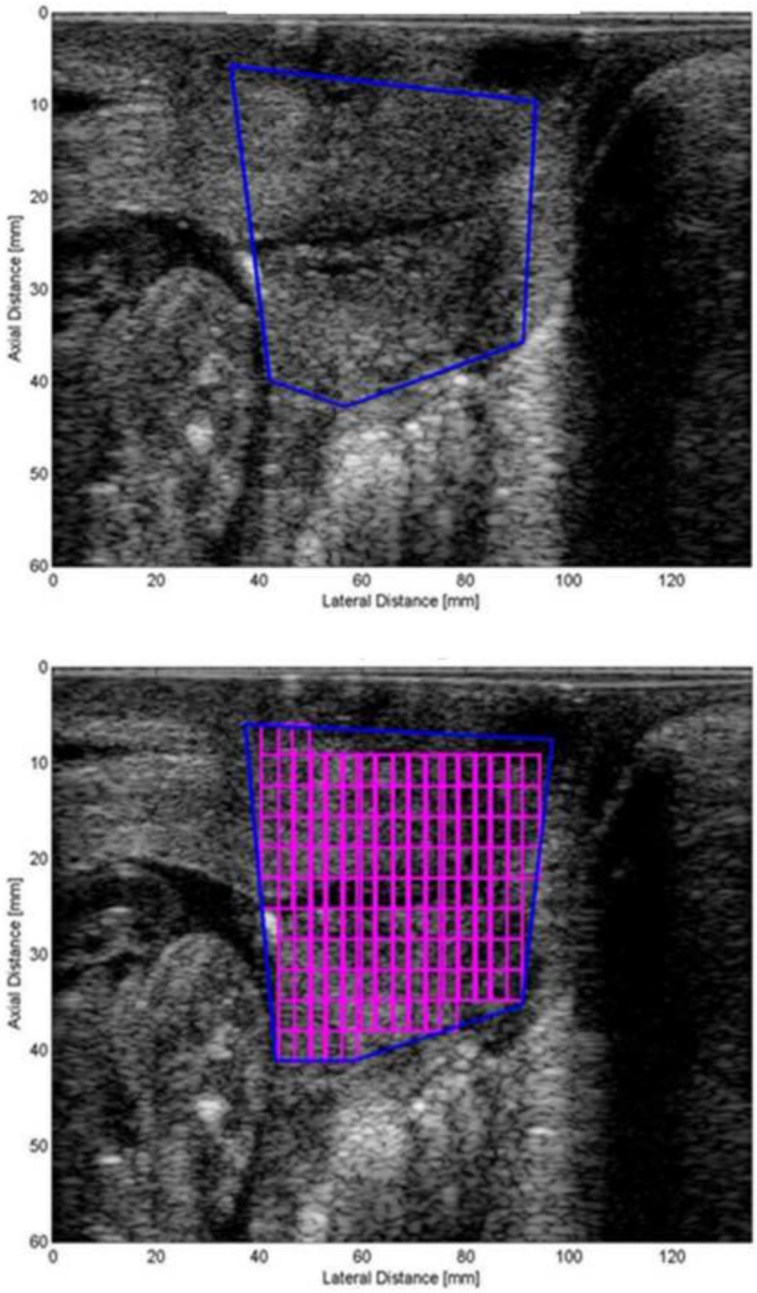

Figure 1.

a. Figure displays how the examiner outlines the portion of the cervix that will be processed for attenuation.

Figure 1.b. Figure displays the Regions of Interest within the segmented cervix..

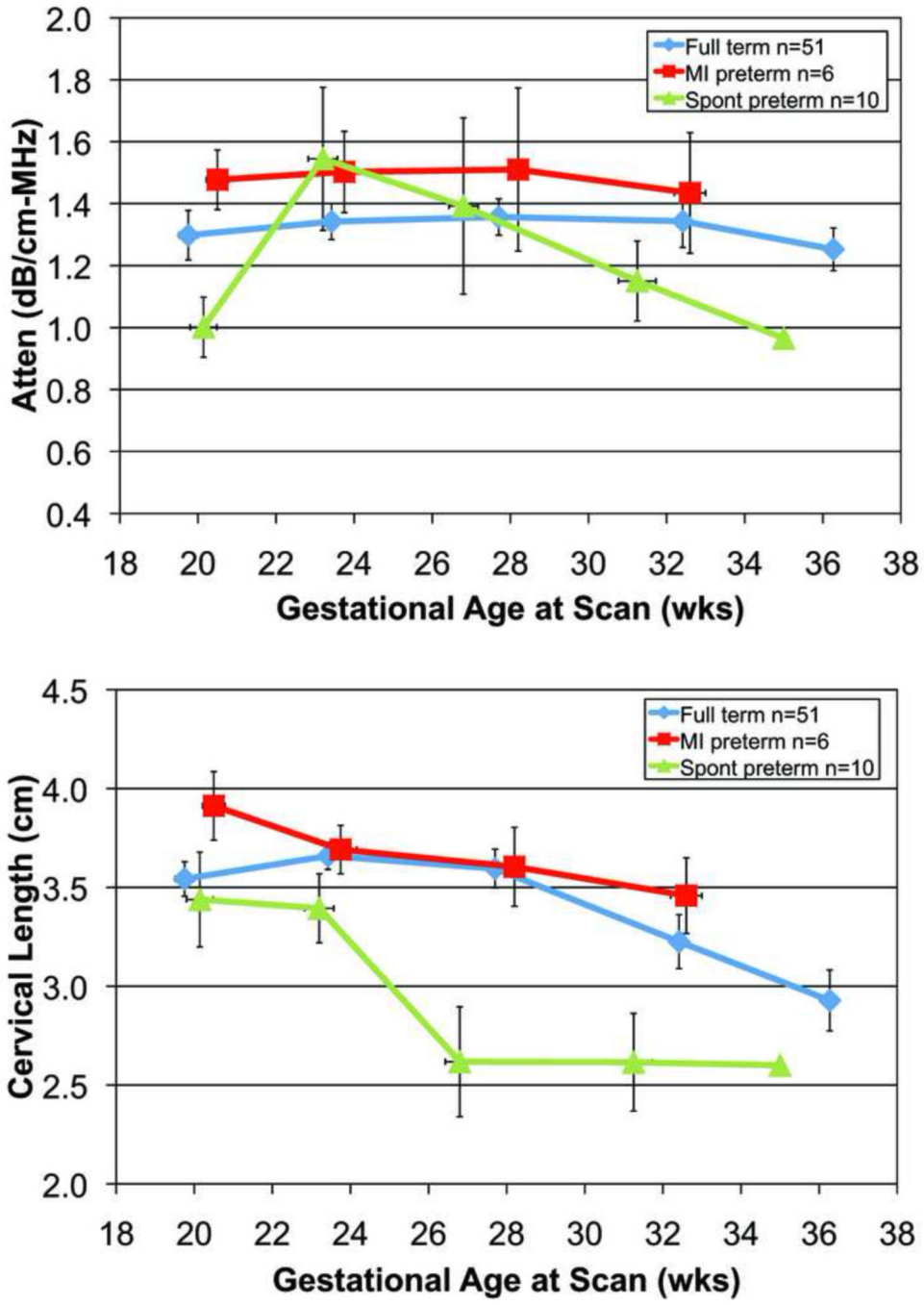

Figure 2.

a. Attenuation coefficient over the course of pregnancy for 68 African-American women by birth outcome (full term, medically indicated preterm and spontaneous preterm). Error bars are SEM.

Figure 2. b. Cervical length over the course of pregnancy for 67 African-American women by birth outcome (full term, medically indicated preterm and spontaneous preterm). Error bars are SEM.

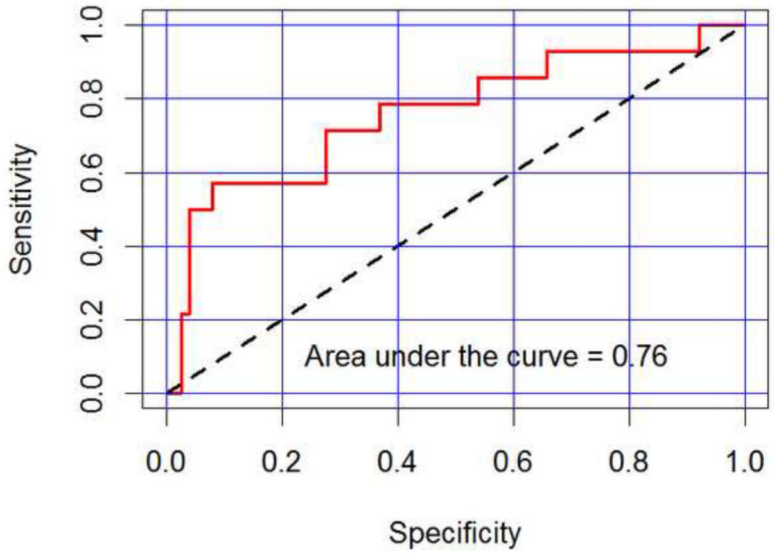

Figure 3.

Receiver Operator Curve for the logistic regression model (attenuation and cervical length) based on first-visit data only at 20.5±3.5 weeks gestation. The model accounts for 76% of the area under the curve (red line)

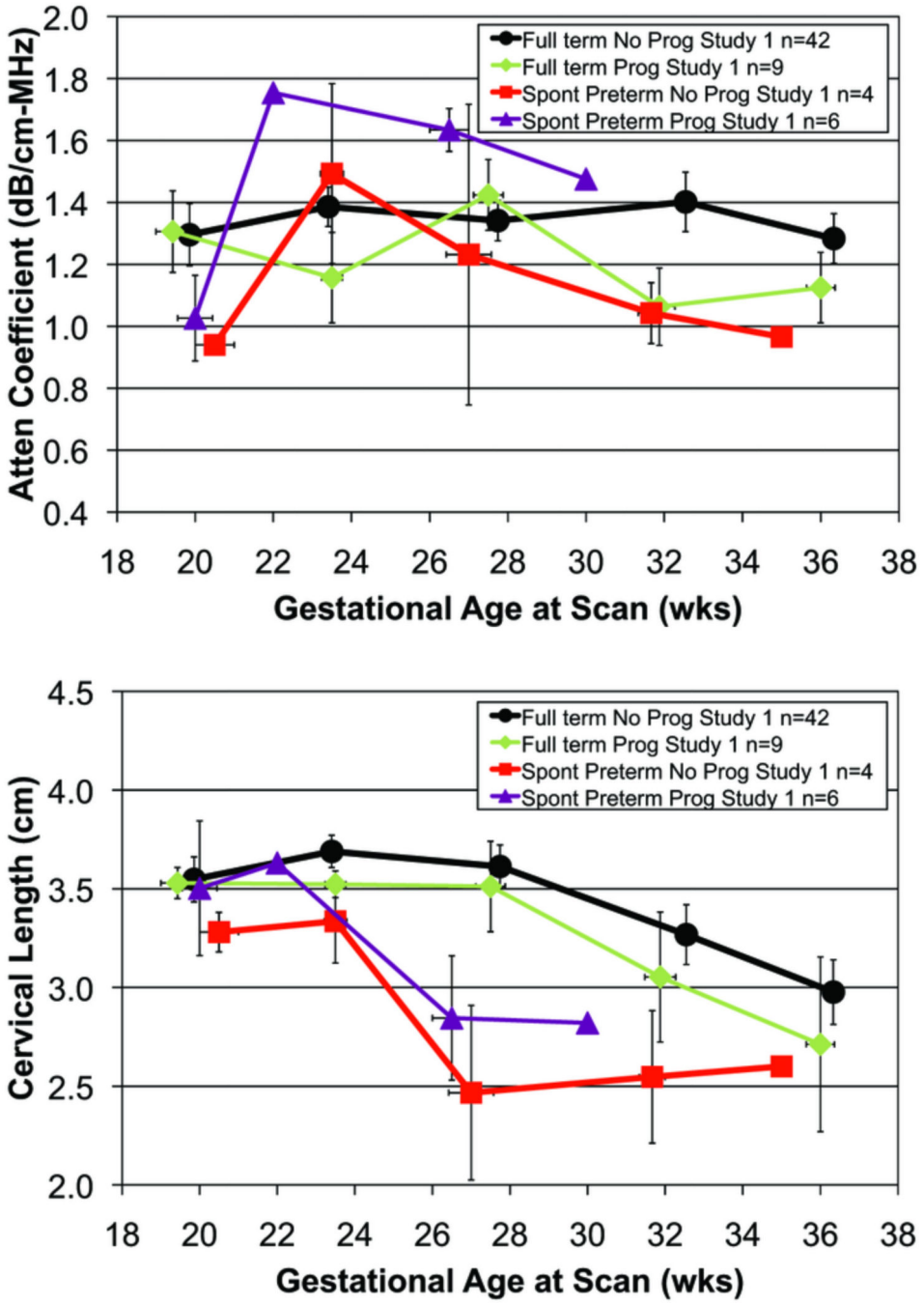

Figure 4.

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

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

Table 1

Characteristics of women in the study. Differences among the groups were evaluated with an ANOVA test. (m= mean; SD= Standard deviation; SPTB = spontaneous preterm birth; MI PTB = Medically indicated Preterm birth; g= grams)

Patient characteristics	**Full term N=51**	**SPTB N=10**	**MI PTB N=6**	***Statistic F***	***p***
Age (m ± SD)	26 (6)	25(5)	30 (9)	1.279	0.285
Number of total	3	4	4	1.568	0.216
pregnancies (m)					
Number of births:					
Full term (m)	1	0.7	1	.287	0.751
Preterm (m)	0.4	1	1	4.651	0.023
Abortion (m)		1.4	1.4	1.791	0.196
Living children (m)	1.3	1.2	1.7	0.526	0.541
Number of women	9	6	1	5.928	0.013
who received 17-OHPC	38.9 (1)	29.3(6)	33.1 (1)	47.383	0.0001
Gestational age at birth (weeks, ±SD)	3133 (531)	1645	2046	23.49	0.0001
Infant Birth weight (g, ±SD)		(1202)	(845)		