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● *Technical Note*

DEVELOPMENT OF AN ULTRASONIC METHOD TO DETECT CERVICAL REMODELING *IN VIVO* IN FULL-TERM PREGNANT WOMEN

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Abstract—The objective of this study was to determine whether estimates of ultrasonic attenuation could detect changes in the cervix associated with medically induced cervical remodeling. Thirty-six full-term pregnant women underwent two transvaginal ultrasonic examinations separated in time by 12 h to determine cervical attenuation, cervical length and changes thereof. Ultrasonic attenuation and cervical length data were acquired from a zone (Zonare Medical Systems, Mountain View, CA, USA) ultrasound system using a 5–9 MHz endovaginal probe. Cervical attenuation and cervical length significantly decreased in the 12 h between the pre-cervical ripening time point and 12 h later. The mean cervical attenuation was 1.1 ± 0.4 dB/cm-MHz before cervical ripening agents were used and 0.8 ± 0.4 dB/cm-MHz 12 h later ($p < 0.0001$). The mean cervical length also decreased from 3.1 ± 0.9 cm before the cervical ripening was administered to 2.0 ± 1.1 cm 12 h later ($p < 0.0001$). Cervical attenuation and cervical length detected changes in cervical remodeling 12 h after cervical ripening administration. (E-mail: bmcfar1@uic.edu) **© 2015 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Cervical ripening, Cervical remodeling, Ultrasonic attenuation, Cervical length.**

INTRODUCTION

Globally more than 13 million infants are born pre-term each year (Harris-Requejo 2010). Pre-term birth is defined as birth before the 37th completed week of pregnancy (Martin et al. 2009). Spontaneous pre-term labor is a syndrome associated with multiple etiologies of which only a percentage may be associated with cervical insufficiency (Romero et al. 2006). Regardless of the etiology of pre-term labor, the cervix must remodel to allow the passage of the fetus. The role of the cervix during pregnancy is to maintain the fetus within the uterine cavity until fetal maturity. The strength of the cervix is due to its anatomic properties (length, thickness) and tissue composition (collagen, water and extracellular matrix) (House and Socrate 2006).

Most of our understanding of cervical remodeling in pregnancy is from animal studies and very few human studies. Thus, we describe a widely accepted hypothesis of the process of cervical remodeling in human pregnancy based on the available evidence (Danforth 1947; Feltovich et al. 2010; Leppert 1995; Owen and Iams 2003; Romero et al. 2006; Word et al. 2007). During pregnancy, total cervical collagen content increases to provide strength to the cervix (Eckman et al. 1991; Goilichkowski et al. 1980; Harkness and Nightingale 1962; Kokenyesi and Woessner 1990; Woessner and Kokenyesi 1991; Yu and Leppert 1991). Before the onset of labor contractions and over a period of weeks, the cervix remodels through a process of collagen disorganization (House and Socrate 2006; Vidaeff and Ramin 2006a, 2006b; Weiss 2000) wherein water content and proteoglycans are increased and collagen concentration is decreased (Danforth et al. 1960; Feltovich et al. 2005; Goilichkowski et al. 1980; Leppert et al. 2000; McFarlin et al. 2006; Yu and Leppert 1991), thus resulting in increased extensibility and reduced stiffness of the cervix. During this process, increased space results among the collagen fibrils (Clark et al. 2006; Feltovich et al. 2005; Leppert 1995;

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Leppert et al. 2000; Yu and Leppert 1991). The biostructure, biochemistry and biomechanics of the cervix change markedly from an unripe to a ripe cervix (Lawn et al. 2010; Leppert 1995; Leppert et al. 2000; Mahmoud et al. 2013).

Currently, the most powerful risk factors for pre-term birth are assessed by patient history of a prior pre-term birth and from a shortened length of the cervix at around 20 wk of pregnancy. There is approximately a 40% recurrence of pre-term birth in women with a prior history of pre-term birth (Iams and Berghella 2010). Although cervical length assessment has become one of the most widely used tools to identify women at high risk for pre-term birth, 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). In women at low risk for pre-term birth, the positive predictive value of cervical length to predict spontaneous pre-term birth ranges from 20% to 52% (Romero et al. 2013). Generally, the shorter the cervix, the greater the probability of pre-term birth (Campbell 2011; Iams and Berghella 2010; Romero et al. 2013). There has been considerable work by our group (Bigelow et al. 2008, 2011; Labyed et al. 2011; Labyed and Bigelow 2011; Lau et al. 2013; McFarlin et al. 2006, 2010; Poellmann et al. 2013) and others (Carlson et al. 2014; Feltovich et al. 2010, 2012; Feltovich and Hall 2013; House et al. 2012; House and Socrate 2006) to develop non-invasive methods to detect and understand cervical micro-structural tissue properties associated with cervical remodeling.

Presently an *in vivo,* objective and non-invasive clinical method to determine tissue changes (increased collagen disorganization and water concentration) associated with cervical remodeling does not exist. Our research has sought to develop an ultrasonic method that could be correlated with changes associated with cervical remodeling and potentially associated with pre-term birth. We have translated promising basic science ultrasonic methods we used in an animal model (Bigelow et al. 2005, 2008; Bigelow and O'Brien 2006; Labyed et al. 2011; Labyed and Bigelow 2011; McFarlin et al. 2006) for use in human pregnancy (Bigelow et al. 2008, 2011; McFarlin et al. 2006, 2010; Labyed et al. 2011; Labyed and Bigelow 2011; Lau et al. 2013; Poellmann et al. 2013).

Estimates of ultrasonic attenuation have been used to evaluate the structure and function of tissue in health and disease (Baldwin et al. 2007; Insana 1995; Insana et al. 1992; Hall et al. 2000a, 2000b, 2000c; O'Brien et al. 1995; Wickline et al. 1992a, 1992b). Ultrasonic attenuation has been found to be related to tissue stiffness, collagen content and organization and water concentration of tissues (Baldwin et al. 2007; Hall et al. 1997, 2000a, 2000b, 2000c) and also has been found to be higher in collagen-rich tissues such as a tendon (O'Brien 1977) and rat cervix (Bigelow et al. 2008) compared with low-collagen-content tissues, such as fat (O'Brien 1977). In pregnancy, as the collagen-rich cervix remodels to prepare for labor and birth, the cervix transforms from a rigid structure to a soft, extensible structure (House and Socrate 2006; Leppert 1995). We hypothesized that by estimating changes in cervical ultrasonic attenuation we could detect and monitor these dynamic changes in tissue microstructure and function.

Our prior animal model work demonstrated that the decreased collagen concentration associated with cervical remodeling affected ultrasonic attenuation (Bigelow et al. 2008; McFarlin et al. 2006). We found that estimates of cervical attenuation were significantly correlated with gestational age in the rat cervix as ripening occurred (Bigelow et al. 2008, 2011; McFarlin et al. 2006). In a small methodology development study of the human pregnant cervix, we were able to acquire and analyze backscattered radio frequency (RF) ultrasonic signals to estimate attenuation as the cervix remodeled (McFarlin et al. 2010). There was a statistically significant relationship between decreasing attenuation and interval to delivery (McFarlin et al. 2010). Women who delivered pre-term had lower cervical attenuation values than those who delivered full term. The long-term goal of our program of research is to use ultrasonic attenuation to identify women at risk for pre-term birth. Ultrasonic attenuation is a feature that could be incorporated into clinical ultrasound systems.

During pregnancy, when labor must be medically induced, mechanical and pharmacologic agents such as prostaglandins and cervical balloons can accelerate the process of cervical remodeling before inducing labor contractions (Boulvain et al. 2008). Prostaglandins have produced marked cervical remodeling changes in times as small as 5 to 12 h (Calder et al. 2008; Leppert 1995). As a proof-of-concept study, our objective herein was to determine whether cervical attenuation was sensitive to cervical remodeling associated with medically induced cervical remodeling, a known process where cervix tissue remodels in a short time frame of 12 h rather than over many weeks during pregnancy and spontaneous labor. Our hypothesis was that a significant decrease in cervical attenuation occurs after a ripening agent was administered.

MATERIALS AND METHODS

Thirty-six pregnant women who were admitted for induction of labor were recruited for the study. Women were eligible to be included in the study if they were

≥18 y old; were able to read, write and understand English; were going to receive a prostaglandin cervical ripening agent for induction of labor; and agreed to twice undergo transvaginal ultrasonic examinations during labor induction. We chose to study women receiving prostaglandin cervical ripening agents for induction of labor, because marked change in cervical remodeling is known to occur within 12 h (Facchinetti et al. 2012). Women were excluded from participating in the study if they had an anomalous fetus or were too ill to give informed consent. Women were recruited once they were admitted to the Labor and Delivery unit. None of the women underwent induction of labor for the purposes of this research. The research was approved by the Human Subjects Review Boards of the University of Illinois at Chicago and Rush University Medical Center. An informed consent statement was signed by each woman participating in the study.

Thirty-six women agreed to participate in the study and underwent a transvaginal ultrasonic examination with a standard 5–9 MHz endovaginal transducer to estimate ultrasonic attenuation and cervical length before cervical ripening agents were administered and then scanned again 12 h after cervical ripening agents were administered. Immediately after each cervical scan, and without changing any scanner settings, a reference scan was recorded in a well-characterized, tissue-mimicking reference phantom with known ultrasonic properties (sound speed, attenuation coefficient, backscatter coefficient) that were comparable to average human tissue.

Cervical length was measured according to the standard method developed by Iams (Iams et al. 1996). The length of the cervix was measured with the transvaginal ultrasound probe placed in the anterior fornix of the vagina while the woman's bladder was empty. Without placing pressure on the cervix, a sagittal image of the cervix was obtained where the internal and external os were present. The cervix was measured three times along the line made by the interface of the mucosal surfaces. The shortest cervical length was recorded.

The steps for processing the data are summarized in Figure 1. In-phase Quadrature (IQ) data were obtained from z.one ultrasound system (Zonare Medical Systems, Mountain View, CA, USA) and converted to RF data (bandwidth: 3.4–7.1 MHz). The IQ data contained scans of the cervix and reference phantom. A Gammex tissue-mimicking phantom (Gammex, Middleton, WI, USA) with a known attenuation of 0.5 dB/cm-MHz was used as a reference phantom.

The RF echo data from the cervix were windowed into smaller regions of interest (sub-ROIs), and the attenuation was estimated for each sub-ROI to represent a spatial map of the attenuation throughout the closed portion of the cervix. Early in our methodology (McFarlin et al. 2010), we selected the most homogeneous appearing area of the cervix. However, we were concerned about sub-ROI selection bias and reproducibility of the measure. Thus, our approach with this and follow-up studies has been to map the entire closed portion of the cervix and use a mean attenuation value from all of the sub-ROIs as the cervical attenuation.

The spectral log difference method was used to estimate the attenuation by calculating the slope of the straight line that fits the log ratio (difference between log spectra) of the two power spectra (cervix and reference phantom spectra) from the proximal and the distal segments of the sub-ROIs (Labyed and Bigelow 2011). The spectral log difference method is one that is least susceptible to tissue heterogeneity as was observed in our previous studies (Bigelow et al. 2011; Labyed and Bigelow 2011). Our criterion for selecting the size of the sub-ROIs was to have enough tissue to make attenuation estimates with the least error, and at the same time minimize the heterogeneity of the tissue included in the sub-ROI. Figure 2 displays an attenuation image (a spatial map of the sub-ROIs) of the cervix that shows

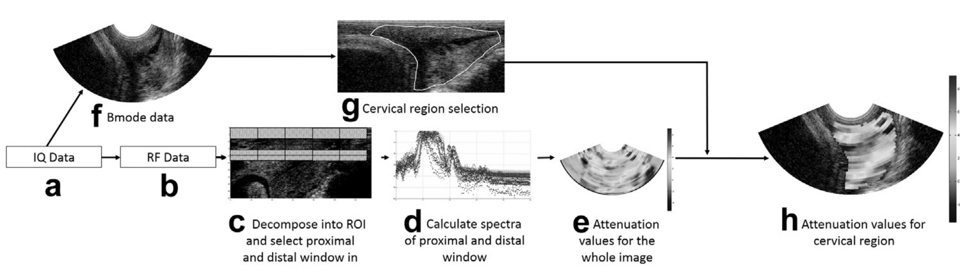

Fig. 1. Step by step process for estimating cervical attenuation coefficient. (a) IQ data obtained from machine, (b) IQ data converted to RF data, and (c) RF data decomposed into ROIs based on the pulse length and number of echoes. Spectral difference algorithm used; hence proximal and distal windows for each ROI are identified. (d) Spectrograms of proximal and distal windows are calculated. (e) Estimate the attenuation coefficient for the entire image. (f) IQ data converted to B-mode image. (g) User selects the cervical region from the B-mode image. (h) Attenuation coefficients estimated for the selected cervix region. ROI = region of interest.

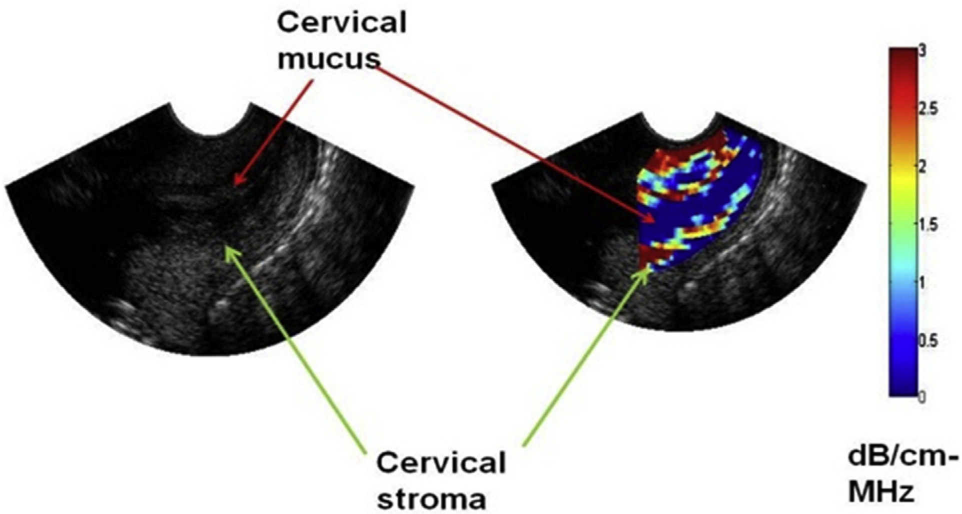

Fig. 2. Scan of the cervix displaying tissue architecture *via* attenuation mapping. The colored pixels represent attenuation values the stroma of the cervix and the blue pixels in the cervical canal (mucus, which is almost totally water) have an attenuation value close to 0, consistent with the attenuation of water.

consistency with known tissue layers of the human cervix (Leppert 1995). For example, the image shows the attenuation of the cervical mucus layer to be essentially zero, which is consistent with the known attenuation of water (Shung et al. 1992), whereas the tissue layers in the cervix have an attenuation range from 0 to 2.5 dB/cm-MHz.

We evaluated the inter-rater reliability of attenuation mapping of the cervix by having 50% of the scans mapped and reprocessed independently by a second examiner and found an inter-rater reliability of $r = 0.97$, $p < 0.001$. All data were entered into an electronic database and analyzed with SPSS 19.0 software (IBM Inc., Armonk, NY, USA) statistical software. Analysis included descriptive statistics, paired two-tailed *t*-tests, Pearson correlation and ANOVA; $\alpha < 0.05$ was considered significant.

RESULTS

The 36 women participating in the study were at full-term pregnancy (≥39 wk of gestation). Table 1 displays maternal characteristics of study participants. Elective induction of labor and post-dates pregnancy were the most common indications listed for labor induction. Although the majority of women in the study delivered vaginally, 16 (44%) delivered by cesarean section. There was no significant difference in attenuation and cervical length at each time point among the women delivering vaginally or by cesarean (Table 2). The main indication for cesarean section was arrest of labor.

Table 1. Characteristics of the sample

Variable	All participants N = 36
Maternal age y (m, SD)	29.4 (6.7)
Race/ethnicity (number)	
Black	13
White	11
Latina	3
Asian	9
Gravida (m, SD)	2.2 (1.5)
Living children (m, SD)	0.7 (1.2)
Gestational age, wk (m, SD)	39.6 (1.3)

Figure 3 displays individual attenuation (Fig. 3a) and cervical length (Fig. 3c) outcomes. The women who had the highest attenuation at the pre-cervical ripening time point were those who also had the greatest decrease in attenuation at the second scan 12 h later. Initial attenuation values pre- and post-cervical ripening were similar among nulliparous and multiparous women (Fig. 3b). Cervical attenuation significantly decreased ($p < 0.0001$) in the 12 h between the pre-cervical ripening attenuation time point and 12 h later. The mean cervical attenuation of these full-term women was 1.1 ± 0.4 dB/cm-MHz before cervical ripening agents were used and 0.8 ± 0.4 dB/cm-MHz 12 h later. Thus, by using ultrasonic attenuation, we were able to detect changes in cervical remodeling in a short period, suggesting that ultrasonic attenuation is sensitive to tissue property changes.

As expected, mean cervical length also decreased from 3.1 ± 0.9 cm before the cervical ripening was administered to 2.0 ± 1.1 cm 12 h later ($p < 0.0001$). Pre-cervical ripening, cervical length ranged from 2.0 to 5.5 cm (Fig. 3c). Initial cervical lengths pre- and post-cervical ripening were similar among nulliparous and multiparous women (Fig. 3d). There was no correlation between cervical attenuation and cervical length,

Table 2. Cervical attenuation and cervical length at both time points and mode of delivery

Cervical variable	NSVD, mean (SD)	Cesarean, mean (SD)	*t*	*p*
Cervical length initial (cm)	2.9 (0.9)	3.0 (0.8)	0.04	0.83
Cervical length at 12 h (cm)	1.9 (1.1)	2.1 (1.0)	0.89	0.77
Attenuation initial (dB/cm-MHz)	1.08 (45)	1.20 (0.39)	0.80	0.37
Attenuation at 12 h (dB/cm-MHz)	0.88 (0.33)	0.76 (0.32)	1.15	0.29

suggesting that these measures may be independently detecting different structures in the cervix.

DISCUSSION

In this study, we were able to detect changes in ultrasonic attenuation of the cervix at 12 h after a cervical ripening agent was administered. Our previous work found a relationship between cervical tissue properties and attenuation (McFarlin et al. 2006, 2010; Labyed et al. 2011). Interestingly, ultrasonic attenuation was not correlated with cervical length, thus suggesting that cervical attenuation and cervical length are likely independent measures because each may be sensitive to different structures and/or spatial scales of the cervix. One can think about spatial scales between cervical attenuation and cervical length. Ultrasonic attenuation is a measure of cervical tissue at a scale of around the ultrasonic wavelength—that is, about 300 μm—and is affected by tissue hydration and density. For example, the attenuation of water and cervical mucus is about 0 dB/cm-MHz (Fig. 2). On the other hand, ultrasonic cervical length is a measure at a larger scale, around a couple of centimeters (about 100 times greater than the ultrasonic wavelength). It is not surprising that the attenuation coefficient ranges from 0 to 2.5 dB/cm-MHz; cervical tissue is heterogeneous in nature (Feltovich et al. 2010; Lau et al. 2013). Thus, to address the heterogeneity issue we averaged all of the attenuation values within the selected portion of the cervix.

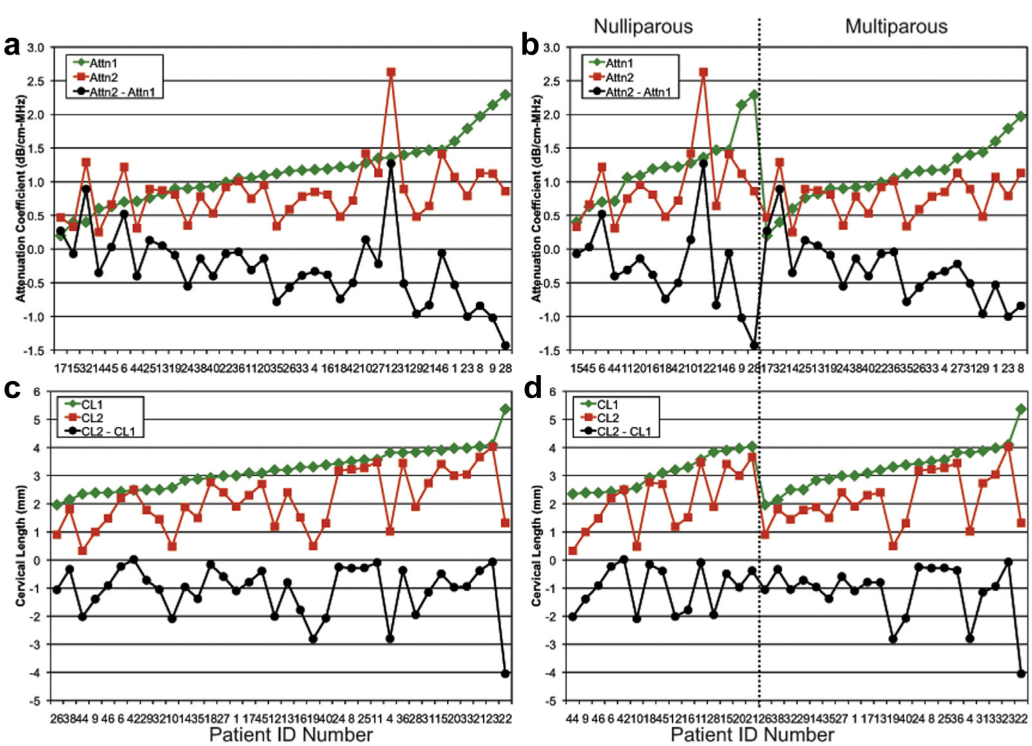

Fig. 3. Thirty-six patients each scanned twice and approximately 12 h apart, for which ultrasonic Attn and CL were determined. Attn1 and CL1 denote before a cervical ripening agent was administered, Attn2 and CL2 denote 12 h after the administration of a cervical ripening agent, and Attn−Attn1 and CL2−CL1 denote the changes between the two attenuation and cervical length outcomes. Figures 3a and 3c are ordered by increasing Attn1 and CL1. Figures 3b and 3d segmented by parity into nulliparous and multiparous, and then for each, into their respective ordering by increasing Attn1 and CL1. Attn = attenuation; CL = cervical length.

Both cervical length and attenuation decreased significantly from the initial scan to the scan 12 h after a cervical ripening agent was administered. We hypothesized that there would be a significant decrease in cervical attenuation after the cervix was exposed to a ripening agent. We did not power the study, nor was it our intention in this study to use this technology to predict mode of delivery (cesarean or vaginal birth). Cervical remodeling is only one factor when determining whether a woman will deliver vaginally or by cesarean. Factors such as the size and position of the fetus, size of the maternal pelvis, strength of uterine contractions and fetal tolerance of labor also need to be clinically considered.

Our previous animal study results indicated a decrease in attenuation with gestational age of rat pregnancy; marked cervical collagen content and water increase in pregnancy; and increased collagen disorganization during the process of cervical remodeling. In human pregnancy (Bigelow et al. 2011; McFarlin et al. 2006), ultrasonic attenuation has been related to the number of weeks to delivery and risk of pre-term birth in a pilot study (McFarlin et al. 2010). The attenuation values in this study are similar to attenuation values during pregnancy in our previous study (McFarlin et al. 2010). Thus, ultrasonic attenuation may have the potential to be an additional objective measure of cervical tissue remodeling. Although macro-structural changes of the cervix can be quantified with cervical length (Berghella et al. 2009; Iams et al. 1996; Iams and Berghella 2010; Romero et al. 2013) and cervical consistency index (Parra-Saavedra et al. 2011), there is currently no method to objectively estimate cervical tissue property changes non-invasively at a microstructural level.

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