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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.