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Challenging the in-vivo assessment of biomechanical properties of the uterine cervix: A critical analysis of ultrasound based quasi-static procedures

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ABSTRACT

Measuring the stiffness of the uterine cervix might be useful in the prediction of preterm delivery, a still unsolved health issue of global dimensions. Recently, a number of clinical studies have addressed this topic, proposing quantitative methods for the assessment of the mechanical properties of the cervix. Quasi-static elastography, maximum compressibility using ultrasound and aspiration tests have been applied for this purpose. The results obtained with the different methods seem to provide contradictory information about the physiologic development of cervical stiffness during pregnancy. Simulations and experiments were performed in order to rationalize the findings obtained with ultrasound based, quasi-static procedures. The experimental and computational results clearly illustrate that standardization of quasi-static elastography leads to repeatable strain values, but for different loading forces. Since force cannot be controlled, this current approach does not allow the distinction between a globally soft and stiff cervix. It is further shown that introducing a reference elastomer into the elastography measurement might overcome the problem of force standardization, but a careful mechanical analysis is required to obtain reliable stiffness values for cervical tissue. In contrast, the maximum compressibility procedure leads to a repeatable, semi-quantitative assessment of cervical consistency, due to the nonlinear nature of the mechanical behavior of cervical tissue. The evolution of cervical stiffness in pregnancy obtained with this procedure is in line with data from aspiration tests.

1. Introduction

In normal pregnancy, a firm and closed uterine cervix is important to withstand increasing uterine pressure and allow fetal development within the uterine cavity. Spontaneous preterm parturition is a pathological condition that is defined as childbirth before completion of 37 weeks of gestation. In clinical practice, measurement of cervical length by trans-vaginal ultrasound is performed to identify women at risk, since a short cervix is related to a greater risk of preterm delivery (PTD) (Romero et al., 2006). However, most women at risk are not identified due to the low sensitivity of this parameter (Iams et al., 1996). Additional measurement of the stiffness of the cervix might be useful in the prediction of preterm delivery.

Existing data on the mechanical behavior of cervical tissue is mainly based on ex-vivo experiments with non-pregnant or at-term tissue (Fernandez et al., 2013; Myers et al., 2009, 2010, 2008; Yao et al., 2014). Characterization of the development of cervical stiffness during pregnancy remains an open challenge. Several methods have recently been proposed for quasi-static mechanical characterization of the pregnant cervix, providing measurements at different gestational ages: quasi-static elastography (Hernandez-Andrade et al., 2014, 2013; Molina et al., 2012), maximum deformability (Parra-Saavedra et al., 2011; Fruscalzo et al., 2012), and aspiration (Badir et al., 2013). The results of these studies are contradictory in that elastography indicates very modest changes in the course of pregnancy, whereas aspiration and maximum deformability show a strong decrease in stiffness, which starts early in pregnancy and continues until delivery.

Quasi-static elastography was initially introduced to differentiate malignant tumors and normal tissue by quantifying local tissue deformability (Ophir et al., 1991). Elastography measurements are performed as follows: A force is applied to the tissue by the ultrasound

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probe and the corresponding displacement or velocity field is obtained using image analysis algorithms that track the position of specific particles during their motion. Local strains are calculated from the displacement gradient and displayed in a colored image called "elastogram", indicating regions of large and small deformations, which can be a measure of local relative stiffness within the organ. Depending on the system, the force is applied by a hand-held probe, or the breathing movement of the patient and arterial pulsation is used to generate tissue motion (Bamber et. al., 2013).

Thomas et al. (2007) published the first elastography measurements on pregnant cervices and calculated an elasticity tissue quotient (TQ). These results demonstrated no correlation of the TQ with the duration of pregnancy. Similar findings were reported by Hernandez-Andrade et al. (2013) and by Molina et al. (2012). In both studies, pregnant subjects were included in the study. Slow loading cycles were applied to obtain the strain maps. Since the applied force cannot be measured in current ultrasound systems, different standardization procedures were proposed aiming at a repeatable loading of the cervix in different measurements. Molina et al. (2012) controlled the procedure by limiting the probe displacement up to one centimeter. Hernandez-Andrade et al. (2013) used the provided "pressure bar" on the ultrasound monitor of their equipment to control compression. The question of how to standardize elastography measurements on the cervix has been discussed in recent review publications (Feltovich et al., 2012; Feltovich and Hall, 2013). Hee et al. (2013) manufactured a soft elastomer to be applied on the vaginal probe and used it to provide a reference.

Ultrasound measurement of the maximum deformability of the cervix was first introduced by Parra-Saavedra et al. (2011) and later Fruscalzo et al. (2012). This trans-vaginal ultrasound based procedure does not use the elastography strain maps to determine cervical consistency. For the measurement the sagittal plane of the cervix is visualized, as during cervical length measurements. The cervix is then manually compressed with the probe until no further cervical deformation is observed in the ultrasound monitor image (maximum deformation). The ratio of the anterior–posterior distance (thickness) before (reference configuration) and after compression application (compressed configuration) is calculated and quantifies maximum deformability of the cervix. In Parra-Saavedra et al. (2011) this measure is called cervical consistency index (CCI). The differences in the procedure of Parra-Saavedra et al. (2011) and Fruscalzo et al. (2012) is that the latter limits maximum compression of the anterior lip instead of the whole cervix. The results of both methods are consistent (Mazza et al., 2014) and have shown an increase in compliance with gestational age. These findings are in line with those obtained with aspiration measurements (Badir et al., 2013) on the pregnant ecto-cervix indicating a progressive decrease of stiffness during gestation. This indicates that biomechanical characterization might contribute to the detection of increased risk of preterm delivery, while clinical studies using quasi-static elastography could so far not show a potential for diagnosis.

The objective of the present study is to rationalize the findings obtained with the different quasi-static procedures based on a simple mechanical analysis of each configuration and corresponding simulations. These simulations are not aimed at an accurate representation of the complex anatomy of the cervix and its surroundings, but rather focus on demonstrating fundamental mechanical principles and qualitatively representing the effects of geometrical and material related nonlinearities on the mechanical response of the cervix.

2. Methods

Two approaches were used for the present analysis: (i) Quasi-static elastography was conducted on phantoms with known mechanical properties, to evaluate the effectiveness of the compression standardization procedure proposed in Hernandez-Andrade et al. (2013) and Molina et al. (2012). (ii) Finite element simulations of a representative system were performed to rationalize the maximum deformability measurements from Parra-Saavedra et al. (2011) and Fruscalzo et al. (2012) as well as the findings of Hee et al. (2013) using a reference elastomer on the ultrasound probe.

2.1. *Elastography on reference phantoms*

Two tissue-mimicking ultrasound phantoms (Hall et al., 1997) were manufactured using agar powder hydrated in boiling water. The stiffness of the phantoms was controlled by the amount of powder (0.002 g/ml, 0.001 g/ml) mixed into the solution. While the gel solution was liquid, Metamucil fibers were added to increase the absorption and scattering characteristics for ultrasound imaging. The mixture was stirred to obtain a homogenous material. The solution was then poured into a cylindrical container with 80 mm inner diameter and 60 mm depth. In this container gelation occurred at room temperature overnight. A thin plastic film covered the containers to assure hydrated surfaces.

The phantoms were mechanically characterized prior to elastography measurements using our indentation setup. The indenter tip with diameter of 25 mm (similar dimensions as ultrasound probe) was positioned centrally on the phantoms with ultrasound coupling gel between the transducer and the phantom to reduce friction. The tip was indented up to 15 mm into the samples with a strain rate of 0.1%/s. Compressive strains under the indenter would thus be in the range of

Fig. 1. Experimental setup for elastography measurements on phantoms using Hitachi VISION Preirus. Left: Hitachi ultrasound machine and test bench. Right: elastography measurement on phantom placed on balance.