In vivo evaluation of cervical stiffness evolution during induced ripening using shear waves elastography: insight from an animal model

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Statement of Purpose: The characterization of tissue mechanical properties can provide significant insight on the ability of biological tissues to perform their function. For example, despite numerous advances and intensive research in perinatal medicine, spontaneous preterm birth (PTB) is the leading global cause of neonatal mortality and morbidity. On the other hand, labor has to be induced in approximately 23% of the pregnancies, worldwide. Both issues may be related to the distensibility of the cervical tissue. Quantitative and objective monitoring of the cervix ripening may provide a method to identify cases at risk of PTB and assess the likelihood of successful induction of labor. Currently, however, no reliable clinical tools for such a quantitative and objective evaluation exist. Elastography aims at imaging tissue stiffness. Supersonic Shear Imaging (SSI) is a dynamic Elastography method, that uses the propagation of shear mechanical waves to excite the tissue. The shear wavespeed is subsequently tracked by ultrafast ultrasonic imaging, allowing characterization of stiffness (Bercoff, 2004). This technique has been thoroughly used for diagnosis of breast cancer (Tanter 2008) or liver fibrosis (Muller et al., 2009). Understanding the mechanisms that take place in normal pregnancy will allow a better understanding of the cervical remodeling and lead to better methods of diagnosis of PTB and successful induction of labor. In this work, we propose a preliminary assessment of the evolution of stiffness during the cervical maturation process in the sheep. The main goal was to study the feasibility of elastography using SSI to quantify the cervical stiffness during the maturation process, and to assess the potential of this technique for the diagnosis of preterm labor and for labor induction success.

Methods: The cervical stiffness was quantified by two different operators, in 9 pregnant ewes *in vivo* by using SSI. The cervical ripening was artificially induced by a dexamethasone injection in 5 randomly assigned animals, while 4 constituted the control group. The stiffness of the second ring of the cervix was quantified over a circular region of interest of ∅ 5 mm during vaginal ultrasound examination. Images were acquired every 4 hours during 24 hours to monitor the cervical maturation induced by the dexamethasone injection. In the dexamethasone group, 8 ml (2 mg) of Dexadreson was administrated intramuscularly after the first elastographic imaging was acquired. Following the last examination, the cervices were recovered for further histological study.

Elastography was performed by two expert veterinarians, using a 7-MHz conventional endocavitary ultrasonic probe (SE 12-3, Supersonic Imagine, Aix-en-Provence, France). These data were used to determine the interobserver reproducibility. Both operators performed the examination in a standardized pattern. The ewes were placed on an examination table, immobilized with their hindquarters elevated for proper placement of the probe. Transvaginal ultrasound imaging was performed in the cervix of the animal in a dorsal plane. After the dexamethasone injection, elastographic and conventional B-mode images of the cervix were acquired in all the animals (both control and dexamethasone group). Images were acquired every 4 hours during 24 hours in order to follow the cervical maturation induced by the dexamethasone injection.

Results: Wilcoxon signed-rank tests with a Bonferroni-Hochberg correction were run. The results showed a significant difference between the control and dexamethason groups ($p<1e-6$). In addition, the cervical stiffness was found to decrease significantly throughout the cervical ripening (from 9.5 kPa ± 0.9 kPa to 5.0 kPa ± 0.8 kPa). A significant decrease of the cervical stiffness was observed as early as within the first 4 hours after the injection ($p<5e-3$). The intraobserver and interobserver repeatability of measurements were assessed using Bland-Altman analysis with 95% CI.

Conclusions: First, elastography measurements of the cervix obtained using the SSI technique were highly reproducible. Second, stiffness of the uterine cervix was observed to decrease throughout the maturation process induced by the dexamethasone injection. Finally, it was possible to quantify the decrease of stiffness through the cervical maturation process. Elastography may be a valuable method to quantify objectively and noninvasively the cervical stiffness in vivo, and ultimately could be a useful tool for the diagnosis of PTB and the assessment of labor induction success.

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