In Vivo Characterization of the Mechanics of Human Uterine Cervices

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ABSTRACT: The uterine cervix has to provide mechanical resistance to ensure a normal development of the fetus. This is guaranteed by the composition of its extracellular matrix, which functions as a fiber-reinforced composite. At term a complex remodeling process allows the cervical canal to open for birth. This remodeling is achieved by changes in the quality and quantity of collagen fibers and ground substance and their interplay, which influences the biomechanical behavior of the cervix but also contributes to pathologic conditions such as cervical incompetence (CI). We start by reviewing the anatomy and histological composition of the human cervix, and discuss its physiologic function and pathologic condition in pregnancy including biomechanical aspects. Established diagnostic methods on the cervix (palpation, endovaginal ultrasound) used in clinics as well as methods for assessment of cervical consistency (light-induced fluorescence, electrical current, and impedance) are discussed. We show the first clinical application of an aspiration device, which allows in vivo testing of the biomechanical properties of the cervix with the aim to establish the physiological biomechanical changes throughout gestation and to detect pregnant women at risk for CI. In a pilot study on nonpregnant cervices before and after hysterectomy we found no considerable difference in the biomechanical response between in vivo and

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doi: 10.1196/annals.1389.004
ex vivo. An outlook on further clinical applications during pregnancy is presented.

KEYWORDS: uterine cervix; biomechanical properties; remodeling in pregnancy; in vivo experiment; aspiration device

INTRODUCTION

The cervix is a biochemically active tissue that changes its biomechanical properties in a remodeling process during pregnancy to be prepared for parturition. Understanding the evolution of this process during gestation is essential for acquiring more insight into the pathogenesis of conditions associated with cervical malfunction. Cervical incompetence (CI) and preterm labor are both associated with preterm cervical ripening leading to preterm birth. Despite tremendous advances in neonatal intensive care preterm birth is the greatest risk factor for infant mortality and morbidity. Among the 27,970 infant deaths in 2002 in the United States, 65% were born preterm. Once the biochemical cascade leading to cervical ripening has started, any therapeutic interventions are temporary. Hence, early detection or prediction of cervical malfunction is one of the keys to prevent preterm birth.

The methods used in clinical practice to diagnose cervical changes are digital palpation and endovaginal ultrasound. Both methods, unfortunately, detect only substantial changes of the cervix; the first method is subjective and gives information of cervical parameters summarized in the Bishop Score, whereas the second shows the length of the cervix and the shape of the internal os. Diagnostic tests that provide objective information of the biomechanical behavior of the tissue would be beneficial. Recently, instruments that indirectly measure the hydration and collagen content of the cervix were tested on human pregnant cervices in an experimental setting. Both methods, light-induced fluorescence and electrical impedance measurements, are easy to apply but have not yet found their way into clinical practice. It is, however, not clear whether these methods have negative effects on the fetus or not.

We present our data of the first in vivo application of an aspiration device on nonpregnant human cervices, which directly measures the biomechanical properties of the tissue. The aspiration test, which has the potential for application to pregnant cervices, provides information of the biomechanical properties, such as stiffness, softening, creep, and rising time. Information on the tissue structure and on these parameters will allow the design of reliable three-dimensional constitutive and computational models to better investigate the biomechanical behavior of the cervix under physiological loading condition, during pregnancy, and parturition.
THE HUMAN CERVIX—COMPOSITION AND FUNCTION

Anatomy and Histological Composition

The cervix is the cylindrical- or conical-shaped caudal part of the uterus that protrudes and opens through the upper anterior vaginal wall into the vagina. Its opening into the vagina is the external os. The cephalic end of the cervix is connected with the uterine body and the opening of the cervical canal into the uterine cavity is called internal os. The visible part of the cervix that protrudes into the vagina is referred to as the portio vaginalis. It is about 3 cm long and 2.5 cm wide, but these dimensions vary with age, parity, and hormone status. The cervical wall is about 1 cm thick throughout its length. The surface of the ectocervix (the portion of the uterine cervix extending into the vagina), is covered with squamous epithelium whereas the endocervix (the mucous membrane of the uterine cervical canal) with its glands and folds is covered with columnar epithelium (see Fig. 1).

Compared to the uterine body that is primarily a muscular organ, the cervix is mainly composed of fibrous connective tissue. The main component is collagen, which is responsible for its rigidity and mechanical function. The location of type I and type III in the cervix is diffuse whereas type IV is associated with smooth muscle cells and blood vessels.

The cervical fibrous connective tissue may be considered as a fiber-reinforced composite material in which tightly packed collagen fibers are embedded in a gel-like ground substance. In the human cervix the fiber orientation is organized into three distinct zones that blend smoothly into each other on passing radially outward from the canal. Adjacent to the canal and in the outermost zone the fibrils are oriented predominantly longitudinally, that is, parallel to the canal. In the middle zone the fibers have a preferred orientation in a circumferential direction. Hence, the collagen fiber orientation changes through the thickness of the cervix, a structural feature also identified in, for example, myocardial and arterial tissues. Recently, the three-dimensional fiber architecture of the nonpregnant human uterus was determined by ex vivo magnetic-resonance diffusion tensor imaging. Circular fibers were observed in the outer and longitudinal fibers in the inner part of the cervix. The orientation of the collagen fibrils determines the directions in which the tissue can best withstand tensile stress. It is mainly the change in collagen concentration and organization in the cervix, which is responsible for the change in its mechanical properties observed during pregnancy.

Elastic fibers and smooth muscle contribute with a lower amount to the cervical stroma. Elastin is localized in specific regions of the uterine cervix and is not dispersed throughout the stroma. At the internal os more elastic fibers than collagen were identified. The smooth muscle of the U-shaped myometrium extends inferiorly to the portio supravaginalis of the cervix (part of the cervix of the uterus lying above the attachment of the vagina) and divides into two layers: one follows the vaginal reflection, the second runs at the periphery of the cervix.

Other components of the extracellular matrix are proteoglycans, containing a core protein and glycosaminoglycan chains (GAGs). As they are negatively charged they bind large amounts of water. GAGs predominantly present in the cervix are dermatan sulfate, heparan sulfate, and chondroitin sulfate. Dermatan sulfate is the most important stabilizer of cervical consistency because it shows the ability to array orthogonally at the collagenous fibril surface.

**Physiologic Function in Pregnancy**

During normal pregnancy the cervix has several demanding functions. First, it serves as a barrier that separates the vaginal bacterial flora from the uterine cavity. It has been shown that cervical mucus demonstrates antibacterial activity which may protect the fetus against ascending infections.

Second, it provides mechanical resistance to ensure a normal development of the fetus. This function is modulated by sexual steroid hormones and achieved by anabolic processes in the collagen and proteoglycan metabolism. As pregnancy advances collagen bundles, smooth muscle and fibroblasts come into alignment, presumably to increase the resistance of the tissue in response to
the increasing load of the fetus. The competent cervix is firm and its canal is closed.

Third, during the last 3–4 weeks of pregnancy, substantial remodeling of the extracellular matrix takes place to prepare the cervix to open at birth. This process, which is called cervical ripening, is controlled by hormones and involves catabolic processes leading to degradation of collagen, but the underlying biochemical mechanism is not completely understood to date.

With the onset of pregnancy vascularity and water content are increasing and a secretory transformation of fibroblasts takes place. Mediators, such as prostaglandins and interleukin-8 (IL-8, or neutrophil chemotactic factor), may induce neutrophil migration from vessels into stroma, which initiate inflammatory-like processes with release of proinflammatory cytokines and matrix-metalloproteinases (MMPs). MMPs are known to play a central role in the degradation of extracellular matrix components. They originate from cervical fibroblasts and invading leukocytes. Smooth muscle cells might also play a role in the process of cervical softening. It has been speculated that apoptotic muscle cells produce cytokines that stimulate fibroblasts to produce MMP.

This bioactive environment is responsible for the breakdown of collagen fibrils. The total collagen content is decreasing whereas the collagen solubility is increasing. The total amount of glycosaminoglycans increases, with the highest values observed with the onset of labor and a relative increase in the glucuronic acid-containing GAG heparan sulfate. Because heparan sulfate is thought to be located predominantly in vessel walls its increase reflects the increased cervical vascularization. During labor the increased distensibility of the cervix is achieved by the increased concentration of hyaluronic acid, which causes the tissue to swell, and by the decreased concentration of dermatan sulfate. Dermatan sulfate is increasing until the end of the third trimester and decreases with the beginning of cervical ripening. Hyaluronic acid sharply increases with the onset of labor at the expense of dermatan sulfate. Hyaluronic acid also weakens the affinity of fibronectin to collagen, which is a contribution to the loosening of the collagen framework at term.

During labor, as the cervix effaces, the upper part of the cervix with its internal os moves laterally to become indistinguishable from the lower segment of the uterus, which suggests that the internal os of the cervix is the place of maximal softening. With the onset of labor the cervix is normally 50% effaced and the cervical canal dilated to 2 cm. The opening of the cervix from 2 to 10 cm is achieved gradually; with each contraction of the myometrium the cervix dilates, but in the interval between the contractions most of the stretching is recovered. The process of dilatation is assisted by the viscoelastic behavior of the cervix and occurs passively when the presenting part of the fetus is pushed against it during the contractions. Immediately after birth the collagen fibers
are diminished and separated into their fibrils and the cervix is extremely soft. Within 1 month the cervix returns to its nonpregnant shape.

Pathologic Conditions in Pregnancy

The prevention of preterm birth continues to be one of the most serious and complex topics in obstetrics. According to the Institute of Medicine of the National Academies, preterm birth is the leading cause of newborn deaths. In 2005, 12.5% of all live births in the United States were preterm. The incidence of preterm births has risen steadily in the United States, and has increased 27% since 1981.

CI is a clinical diagnosis defined as painless shortening, effacement, and dilatation of the uterine cervix during the second trimester of pregnancy, generally in the absence of infection, bleeding, or spontaneous preterm premature rupture of the membranes. When unrecognized and untreated this pathology leads to midtrimester spontaneous abortion and early preterm labor with the unfavorable consequences of neonatal morbidity and mortality.

Premature ripening of the cervix without uterine contractions complicates 0.5–1% of all pregnancies. The etiology is mostly idiopathic. Risk factors related to this condition include multiple pregnancies, prior cervical surgery, such as conization or repeated induced or spontaneous abortions, and the occurrence of prior spontaneous preterm births. A group of patients remains with congenital CI, which is related to congenital connective tissue disorders. Several lines of evidence indicate that in women with CI the cervical resistance is decreased. It was found that hydroxyproline extractability and collagenolytic activities were high in biopsies taken from patients with CI during the second trimester, which might reflect a decrease in the number and stability of the cross-links between the collagen molecules. Biomechanical testing revealed very low strength and high extensibility.

Elastin was found to be decreased in the incompetent cervix. A biomechanical test with a balloon placed in the cervical canal measured the pressure–volume characteristic, which indicated a significantly lower elastance in women with a previous history of one or more spontaneous midterm pregnancy losses, preterm birth, or clinically diagnosed incompetent cervix.

DIAGNOSTIC PROCEDURES ON PREGNANT HUMAN UTERINE CERVICES

This section reviews two well-established diagnostic procedures on pregnant cervices used clinically, and methods applied to animals and humans for the assessment of cervical consistency, which are not in clinical use yet.
Clinical Diagnostic Procedures

Palpation

Digital palpation of the cervix yields subjective data on effacement, dilatation, consistence and position of the cervix, and level of the presenting part. These five parameters are summarized in the Bishop score, which is used and accepted in clinical practice. Although it is a subjective method, the data are valid and comparable during late pregnancy and labor.

A negative effect of digital examination is, however, the introduction of vaginal organisms into the cervical canal, which is independent of the state of the fetal membranes (ruptured or intact). Inoculation of bacteria is in particular a problem in pregnancies with increased risk of preterm birth. Another drawback of the method is that no data are obtained from the total length of the cervix and the shape of the internal os.

Endovaginal Ultrasound

The cervical length and anatomy of the internal os can be objectively assessed by endovaginal ultrasound examination. Some experience is needed to avoid artificial elongation of the cervix caused by pressing the vaginal probe on the anterior cervix. In contrast to digital palpation endocervical inoculation of bacteria is not an issue with endovaginal ultrasound examinations. Studies of cervical ultrasound revealed a median cervical length of 35–40 mm at 24–28 weeks and of 30–35 mm after 32 weeks of gestation, respectively.

Cervical effacement starts at the internal os and is described as T, Y, V, U shapes of the internal os relative to the remaining closed segment of the cervix. This ultrasound finding is called funneling and is characterized by a dynamic opening and closing of the internal os. The risk of preterm birth increases with decreasing cervical length at 24–28 weeks. Two findings, funneling and a cervical length less than 30 mm, diagnosed before 32 weeks, are associated with increased risk of preterm birth. In a retrospective analysis a cervical length of less or equal to 15 mm seen on a second-trimester sonogram had a positive predictive value for early preterm delivery of 47.6%, a negative predictive value of 96.7%, a sensitivity of 8.2%, and a specificity of 99.7%. Hibbard et al. also confirmed that cervical length measured during routine ultrasound at 16–22 weeks’ gestation is a significant predictor of preterm birth before 35 weeks. The sensitivity in their study ranged from 13–44%, specificity 90–99%, positive predictive value 15–47%, and negative predictive value 80–98%. Both studies calculated a positive predictive value around 50%, which means that 50% of women with shortened cervix will deliver at
term. A study investigating the diagnostic accuracy of endovaginal ultrasound and digital examination of the cervix in the prediction of preterm delivery in patients presenting with preterm labor and intact membranes indicated a significant relationship between the occurrence of preterm delivery and endovaginal cervical parameters as cervical length and funneling. In contrast, no correlation was found between the results of digital examination and the occurrence of preterm delivery.40

**Experimental Diagnostic Procedures**

*Light-Induced Fluorescence*

Garfield et al.41 described an instrument, called collascope, to measure changes in collagen content during gestation and labor by means of light-induced fluorescence. The noninvasive method is based on the characteristic fluorescence spectrum of collagen, with a peak around 390 nm. The ratio between the fluorescence signals obtained from the tissue to a reference signal serves as an indirect estimate of collagen concentration. *In vivo* studies on humans2 and rats42 showed a decrease in fluorescent intensity in late gestation and at parturition, which reflects the decrease in collagen content. In addition, light-induced fluorescence correlated positively with time-to-delivery interval and was significantly lower in women who delivered less than 24 h compared with those patients who delivered more than 24 h.2

*Electrical Current and Impedance*

This method is based on the resistance of tissue to electrical current. Electrodes are placed on the surface of the cervix3 or even penetrate the cervical surface to a depth of 4 mm,43 and measure the potential that results when an electrical current is passed. Because hydration results in changes in electrical impedance, cervical ripening reduces the resistance to conduction of electrical current. Avis et al.44 described the *in vitro* application of multifrequency electrical impedance measurements on preterm and term cervices. They described the ratio of extra- versus intracellular impedance, which was lower for term cervices.

The first study on women that used this method *in vivo* showed a significant difference in the resistance between nonpregnant and pregnant cervices.3 *In vitro* data on hysterectomy specimens revealed a good correlation between resistance measurement and cervical consistency assessed by digital palpation.43
EXPERIMENTAL DIAGNOSTIC PROCEDURE BASED ON ASPIRATION TESTS

This section discusses a novel method recently introduced at the Department of Obstetrics and Gynecology, Medical University Graz. A study was performed with the aim to verify the feasibility of in vivo measurements on human uterine cervices using the aspiration method, and to identify the normal biomechanical behavior of nonpregnant cervices in vivo versus ex vivo.45

The Aspiration Device

The method of the aspiration device is based upon a pipette aspiration technique.46 We used an improved version of the device, which was originally developed by Vuskovic.47 The technique is based on the application of a predefined pressure function in the pipette attached to the cervix, causing tissue deformation that is dynamically registered in two dimensions. The device consists of an aspiration tube with a video camera fixed at its top (see Fig. 2 for the aspiration device and a sketch illustrating the working principle). The diameter of the aspiration cavity is 10 mm. The tube is gently pushed against the tissue to ensure a good initial contact between the tissue and the aspiration cavity into which tissue is sucked by creating a vacuum. A personal computer controls the pressure inside the device by means of a pump, an air reservoir and two valves.

Under the assumption that the tissue is isotropic and homogeneous, a description of the deformed tissue can be given by simply monitoring the side-view profile of the tissue during its deformation. An optical fiber is connected

FIGURE 2. Aspiration device: an image of the instrument and a sketch illustrating the working principle (adopted from Mazza et al.45).
to an external source of light and provides the necessary illumination inside the tube. The images of the side view are reflected by a mirror and are captured at a frequency of 25 Hz by a digital camera. The grabbed images are processed off-line in order to extract the profiles of the deformed tissue.

**The Experiments**

**Patients**

Menopausal women were recruited before hysterectomy with informed consent. The following data were recorded for each patient: age, obstetric history including number of births and abortions, uterine pathology, and medication such as hormonal replacement therapy. Hysterectomy was performed for prolapsed uterus and vagina in 4 cases, for endometrial cancer in 2 cases, and for uterine fibroids in 2 cases. Six of the uteri were extracted by vaginal and two by abdominal hysterectomy.

**Procedure**

Before the *in vivo* experiments some presurgical procedures were performed after anesthetization of the patient. The urinary bladder was catheterized to evacuate the urine. Specula were inserted and the cervix and vagina were cleaned and disinfected. Under visualization of the cervix the device was placed at its anterior lip at the 12 o’clock position, and was then kept in contact with the tissue without pressure (on the same spot) to achieve optimal results.

Eight uteri were tested *in vivo* before hysterectomy; four of them were also tested *ex vivo*, approximately 1.5 h after extraction. The remaining four were lost for *ex vivo* testing because the cervix was dissected during the vaginal extraction procedure. The *in vivo* and *ex vivo* tests were always performed at the same location, that is, on the anterior lip of the cervix. This was achieved because a slight marking remained on the tissue after the aspiration experiment, which made the identification of the testing location easier. This marking might have been remained due to the stopped blood supply after the surgical extraction of the uterus, which was performed immediately after the testing. On gross examination the squamous epithelium was not injured by the aspiration. For an image of a whole uterus of a menopausal woman in contact with the aspiration device see Figure 3. After the procedure the device was cleaned mechanically with special brushes and towels to remove the mucus. Then it was soaked in a disinfectant solution and rinsed with sterile water. Subsequently the device was gas sterilized.
FIGURE 3. Image showing a whole uterus of a menopausal woman in contact with the aspiration device.

Protocol

For the in vivo experiments the following protocol was adopted:

1. A single loading–unloading cycle: starting from atmospheric pressure and reaching a (negative relative) pressure of $P_{\text{min}} = 220$ mbar. This pressure level (oscillating around 220 mbar) was kept for about 8 sec, and then returned to atmospheric pressure.

2. Repetition of the first loading–unloading cycle: this experiment was performed to assess the repeatability of the results by a direct comparison with the first test.

3. Four to five loading–unloading cycles: they were applied consecutively with a resting time of approximately 10 sec between the individual cycles. For the ex vivo testing the same tests 1–3, as described above, were performed with the addition of the following:

4. Three loading–unloading cycles: resting time of approximately 30 sec between the individual cycles.

Data Analysis

The displacement history of the highest point of the obtained deformation profiles was analyzed (for representative plots see Fig. 4). The locations at characteristic changes in the displacement-time plots were labeled by points A, B, C, D:

Point A: displacement before the pressure decreases.

Point B: displacement at which the pressure was held constant.

Point C: maximum displacement in the first load cycle (before pressure increase).
**FIGURE 4.** Displacement history: single cycle (A); multiple cycles (B). The locations A–D are used for data analysis and comparison purposes (adopted from Mazza et al.45).

**Point D:** maximum displacement at the fourth load cycle.

In addition, we define the following parameters: $d_0 = \text{displacement at B} - \text{displacement at A}$; $d_1 = \text{displacement at C} - \text{displacement at A}$; $d_4 = \text{displacement at D} - \text{displacement at A}$ (see Fig. 4). We propose that the curve between the locations B and C is interpolated by an exponential function, with the origin shifted to location B, that is,

$$f(t) = A_0[1 - \exp(-t/\tau)], \quad A_0 = (d_1 - d_0)/[1 - \exp(-t_0/\tau)],$$

where $\tau$ is the characteristic time, subsequently referred to as the “rising time,” and $t_0$ is the time between the points B and C. The parameters $d_0, d_1, d_4, \tau$ are determined from measured values and characterize the displacement history.

For subsequent data analysis additional parameters are introduced: that is, the “stiffness” $\eta$ (in bar/mm) and two dimensionless quantities, the “softening” $\gamma$ and the “creep” $\delta$, defined to be

$$\eta = p_{\text{min}}/d_1, \quad \gamma = (d_4 - d_1)/d_1, \quad \delta = d_1/d_0.$$

For data analysis of the *ex vivo* test 4 the dimensionless softening parameter $\gamma_3 = (d_3 - d_1)/d_1$ is introduced, where $d_3$ is the maximum displacement of the third cycle. The parameters $\eta, \delta, \tau$ are analyzed from a statistical point of view. To eliminate the organ-to-organ variability, the measured values of each organ were normalized with respect to the organ specific average *in vivo* value.

**RESULTS AND INTERPRETATION**

**Stiffness $\eta$**

From the two single loading–unloading cycles (tests 1, 2) and from the first cycles of the repetitive loading–unloading cycles (tests 3, 4) several values of
The values of the stiffness parameter $\eta$ vary from a minimum of 0.065 to a maximum of 0.315 bar/mm, which gives a factor of 4.8 between these values. The mean values of each uterus range from 0.095 to 0.24 bar/mm, which gives a factor of 2.5. The maximum SD for each organ is 30%. It turns out that the scatter of the stiffness parameter between the different organs is larger than the scatter of the measurement results obtained from one single organ.

The variability of measured data can be defined as (i) the standard deviation $\sigma_A$ for the eight uteri (which depends on the uterus-to-uterus variability), and (ii) the standard deviation $\sigma_B$ for each organ (a measure of the errors in the measurement procedure). We calculated the following standard deviations of $\eta$ for the eight uteri: $\sigma_A = 32\%$ and $\sigma_B = 22\%$. Based on these results predictions can be made on the capability of this experimental procedure to detect a certain change in the parameter $\eta$. In a clinical study the initial average stiffness value of one specific organ (one patient) can be determined by repeating the measurement several times (for instance, five times). The results also suggest that there is no significant difference between in vivo and ex vivo with respect to $\eta$.

**Softening $\gamma$**

The values of $\gamma$ obtained from in vivo experiments range from 0.05 to 0.19, whereas the corresponding values from ex vivo tests are between 0.11 and 0.29. The variability of $\gamma$ is comparable with that of the stiffness parameter $\eta$. A significant difference was observed between the in vivo and ex vivo mechanical response. The ex vivo values of $\gamma$ were larger than in vivo by a factor of approximately two.

**Creep $\delta$ and Rising Time $\tau$**

The time dependence of the mechanical response is evaluated from the displacement history of the time period with “constant” pressure during the first loading cycle. The average value of the normalized creep parameter is smaller for ex vivo tests, whereas the corresponding normalized rising time is larger. However, the differences between in vivo and ex vivo are small and cannot be regarded as significant for the given scatter of the measured values.

**Short vs. Long Resting Times**

We observed a difference for the softening parameter $\gamma_3$ for long and short resting times in ex vivo experiments. The softening parameter was always larger for short resting times. This might be attributed to the recovery characteristics
of the tissue. With longer resting times microstructural processes lead to partial preservation of the initial material characteristics.

**ASPIRATION TESTS ON PREGNANT CERVICES: FUTURE PROMISE AND OPEN PROBLEMS**

To prevent preterm birth early detection of cervical changes due to CI and preterm labor is mandatory. An instrument that indicates beginning changes in the biomechanical properties toward cervical ripening would be beneficial. To date endovaginal ultrasound is the only instrument in clinical use that detects progressive, in many cases therapy-resistant, conditions.

We attempt to introduce an aspiration test in clinical practice; therefore, we initiated a study at the Department of Obstetrics and Gynecology, Medical University Graz, with the aim to establish the normal biomechanical behavior of pregnant cervices throughout gestation. The study is approved by the ethics committee of the Medical University Graz. Beginning with the second trimester, every 4 weeks pregnant women are followed longitudinally to monitor the physiological and biomechanical behavior of their cervices. Knowledge of the physiological variation at a defined gestational age is crucial to recognize early changes associated to possible pathological conditions.

Issues of importance for the aspiration test on pregnant women are:

1. *The choice of the maximum negative pressure.* Aspiration tests on pregnant cervices indicate that a (negative) relative pressure of 220 mbar, as used on nonpregnant cervices, is too high for cervices tested in the third trimester. Due to the physiological softening of the cervix in the later state of pregnancy, the deformation of the sucked tissue exceeds the area of the mirror, which makes it impossible to capture an image. Therefore, we reduced the maximum relative pressure to 80 mbar.

2. *Experimental protocol.* The protocol needs to be easily carried out. It should also not be too time consuming to minimize the discomfort to which the women are exposed during the time the specula are inserted. For the use on pregnant women the diameter of the aspiration tube was diminished by 50% to a diameter of 15 mm.

3. *Vulnerable cervix areas.* During gestation the cervix is more vulnerable due to increased vascularity, and the presence of vulnerable columnar epithelium around the external os. Again, especially in the third trimester, a superficial, harmless bleeding can be triggered by the aspiration. Therefore, a vulnerable cervix may limit the use of the device, but when the device is placed to the cervix under visualization vulnerable areas may be avoided.

The results of the stiffness parameter on nonpregnant cervices showed a scatter of the measured *in vivo* data up to 19% for one organ, which in part
can be attributed to experimental uncertainties. A source of that scatter in the aspiration experiment is the external force required to bring the device in contact with the tissue, which determines the initial deformation of the tissue, typically within the range of 1–2 mm, and any variation of this (compressive) force during the measurement. Modifications of the aspiration devices are under consideration to reduce and/or quantify the contact force and its influence on the measured results, and to also identify the anisotropic tissue behavior through deformation measurements.

Our test series will demonstrate the applicability of the aspiration device for diagnostic purposes. A next step is the use of aspiration test data in combination with endovaginal ultrasound obtained from women at risk of CI. In the future we will correlate the biomechanical properties obtained by the aspiration test with the collagen content of the cervix indirectly measured by the light-induced fluorescence method.

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