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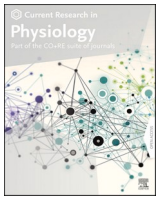

Bioengineering and the cervix: The past, current, and future for addressing preterm birth

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ABSTRACT

The uterine cervix plays two important but opposing roles during pregnancy – as a mechanical barrier that maintains the fetus for nine months and as a compliant structure that dilates to allow for the delivery of a baby. In some pregnancies, however, the cervix softens and dilates prematurely, leading to preterm birth. Bioengineers have addressed and continue to address the lack of reduction in preterm birth rates by developing novel technologies to diagnose, prevent, and understand premature cervical remodeling. This article highlights these existing and emerging technologies and concludes with open areas of research related to the cervix and preterm birth that bioengineers are currently well-positioned to address.

1. Introduction

The uterine cervix is the cylindrical connective tissue organ at the distal end of the uterus, protruding into the vaginal canal. The term cervix is derived from the Latin word "neck," which appropriately describes its shape as the pear-shaped uterus tapers into the cervical region (Fig. 1). The cervix acts as a passageway between the uterus and vagina - allowing fluids to pass from the uterus during menstruation, sperm to pass into the uterus to enable conception, and a fetus to pass from the uterus for delivery. Yet, the cervix is a selective passageway. For example, the cervix secretes mucous to simultaneously prevent pathogens from entering the uterus while facilitating sperm transport for fertilization (Martyn et al., 2014). During pregnancy, the cervix remains closed as the fetus grows and stretches the uterine cavity, a critical action that helps to prevent preterm birth.

As part of the special issue, "Physiology, Female Reproduction, and Bioengineering," the objectives of this article are.

1.) To provide an overview of the physiology of the cervix.
2.) Highlight a specific clinical need related to the cervix: preterm birth.
3.) Highlight emerging bioengineering approaches that address these needs.

The article concludes with open questions and research areas related to preterm birth and the cervix that bioengineers are well-tailored to address through interdisciplinary collaborations.

2. Physiology of the cervix

The cylindrical cervix is a distal extension of the uterus, which protrudes into the vaginal canal (Fig. 1a). Normally, the cervix has a single endocervical canal that connects the superior opening (internal os) to the lower uterine segment and the inferior end (external os) (Fig. 1b). In some cases of Mullerian (congenital reproductive tract) anomalies, where two uterine cavities are present (bicornuate uterus or uterus didelphys, there can be two cervices with two separate canals. The cervix is a layered connective tissue. Uniform, stratified, and non-keratinizing squamous epithelium lines the distal end of the cervix, termed the ectocervix (Fig. 1b). This squamous epithelium meets the mucus-secreting columnar epithelium that lines the endocervical canal at a connection called the squamocolumnar junction. Throughout the length of the endocervical canal, the columnar cells arrange into crypts that protrude into the cervical canal. Underneath the epithelial layer, the cervix maintains a subepithelial stroma and a dense, collagen-rich stroma (Fig. 1c). The nonpregnant cervix is approximately 75% hydrated. The solid component of the tissue is composed mainly of types 1 and 3 fibrous collagen, elastic fibers, proteoglycans, and glycosaminoglycans (Myers et al., 2009). The nulliparous, nonpregnant, human cervix is about 3–4 cm long and 2.5–3 cm in diameter - although its size and shape vary significantly among patients (House et al., 2009; Louwagie et al., 2021). The location of the squamocolumnar junction relative to the external os is dynamic throughout a patient's lifetime as the cervix grows and shrinks. Generally, parous patients have larger cervixes than nulliparous patients, and premenopausal patients have larger

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cervixes than postmenopausal patients (Prendiville and Sankaranarayanan, 2017). During pregnancy, the cervical length slightly decreases while the outer diameter of the cervix increases (Louwagie et al., 2021).

3. Clinical needs related to the cervix

3.1. Preterm birth

Preterm birth (PTB), defined as birth before 37 weeks of gestation, is a current clinical dilemma. PTB is the leading cause of neonatal death, and surviving babies often experience lifelong complications, including visual, learning, and hearing issues. Currently, 1 in 10 babies is born preterm worldwide, affecting about 15 million babies annually (Howson et al., 2012). PTB rates in the United States have remained above 10% since the 1990s (Prediction and Prevention of Spontaneous Preterm Birth, 2021), making it one of the highest rates compared to its economic peers.

PTBs can be categorized as induced PTB or spontaneous PTBs (sPTBs). Induced PTB encompasses induced vaginal delivery or a cesarean section before 37 weeks due to maternal or fetal indications. The discussion here focuses on sPTBs, which can occur with intact or a preterm premature rupture of membranes and accounts for 70–80% of all PTBs (Goldenberg et al., 2008). Etiologies of sPTBs are often multifactorial and do not always result from an acceleration of normal-term pregnancy. However, a soft, dilated cervix is the final common outcome of all sPTBs. Therefore, the cervix remains an essential target for sPTB prevention.

A primary challenge in preventing sPTB is the inability to predict its occurrence, particularly early in the pregnancy when interventions are most effective. The current gold-standard predictor of sPTB is a sonographically determined short cervix, defined as <25 mm at 24 weeks of pregnancy, using an endovaginal ultrasound (Iams et al., 1996). While many women with a short cervix do not deliver preterm (Hassan et al., 2000), clinicians measure cervical length in patients with a history of sPTB to offer cerclage interventions for those with a short cervix (Prediction and Prevention of Spontaneous Preterm Birth, 2021). A second challenge is the lack of effective prevention and management techniques. If a clinician identifies a patient at high risk for PTB, current management methods include bed rest, cervical cerclage or pessaries, and vaginal progesterone. Bed rest is ineffective in preventing sPTBs, can inversely cause harm, and is impractical for many patients (McCall et al., 2013). Cervical cerclages and pessaries are interventions designed to oppose cervical dilation physically. A cerclage is a surgical stitch inserted into and around the cervix to stitch it closed. While the effectiveness of cerclage in preventing sPTBs in patients without a history of preterm is unclear, patients with an extremely short cervix (<10 mm) may benefit (Berghella et al., 2017). Currently, cerclage is offered to patients with a history of cervical dysfunction, a history of sPTB and a short cervix, and to patients with dilated cervix prior to fetal viability (Prediction and Prevention of Spontaneous Preterm Birth, 2021). A pessary, a silicone ring placed around the cervix, is a less invasive alternative to a cerclage thought to provide physical support to the cervix. Recent randomized controlled trials of pessaries on singleton (Nicolaides et al., 2016b), singleton pregnancies with a short cervix (Hoffman, 2023) and twin pregnancies (Nicolaides et al., 2016a) demonstrate no difference in reducing the rates of sPTBs. Progesterone supplementation is an important intervention for preventing sPTBs (Care et al., 2022; De Franco et al., 2007; Hassan et al., 2011; Romero et al., 2012). The FDA recently withdrew hydroxyprogesterone caproate (Makena), an injectable synthetic form of progesterone - from the market after a randomized, double-blind clinical trial concluded that it was not effective in preventing recurrent sPTBs (Blackwell et al., 2020). However, micronized vaginal progesterone continues to be recommended for patients with a short cervix without a history of preterm birth (Prediction and Prevention of Spontaneous Preterm Birth, 2021). The mechanisms through which progesterone supplementation prevents sPTBs are currently unclear.

3.2. Other clinical needs

Clinical needs related to the cervix exist outside of PTB. Although this document will not cover these topics, readers are encouraged to explore other reviews that cover topics including, but not limited to, placenta previa (Silver, 2015), cervical cancer (Abbaspour et al., 2022; Cadena et al., 2021; Monk et al., 2022; Small et al., 2017), and cervical fibroids (Nucci, 2000).

4. Current bioengineering approaches

This section summarizes emerging bioengineering approaches that address needs related to PTBs and the cervix. These approaches are broadly categorized as diagnostic tools, preventative tools, and mechanisms of cervical remodeling and sPTBs.

4.1. Diagnostic tools for detecting PTBs

Advancements in diagnostic tools to detect patients at risk for sPTB have focused on 1.) *in vivo* devices (Table 1) that quantify cervical remodeling and 2.) biomarkers. This section provides an overview of these diagnostic tools. Detailed reviews on assessing cervical remodeling *in vivo* are available elsewhere (Bauer et al., 2007; Feltovich et al., 2012; Helmi et al., 2022; Mazza et al., 2013; O'Brien et al., 2014; Pizzella et al.,

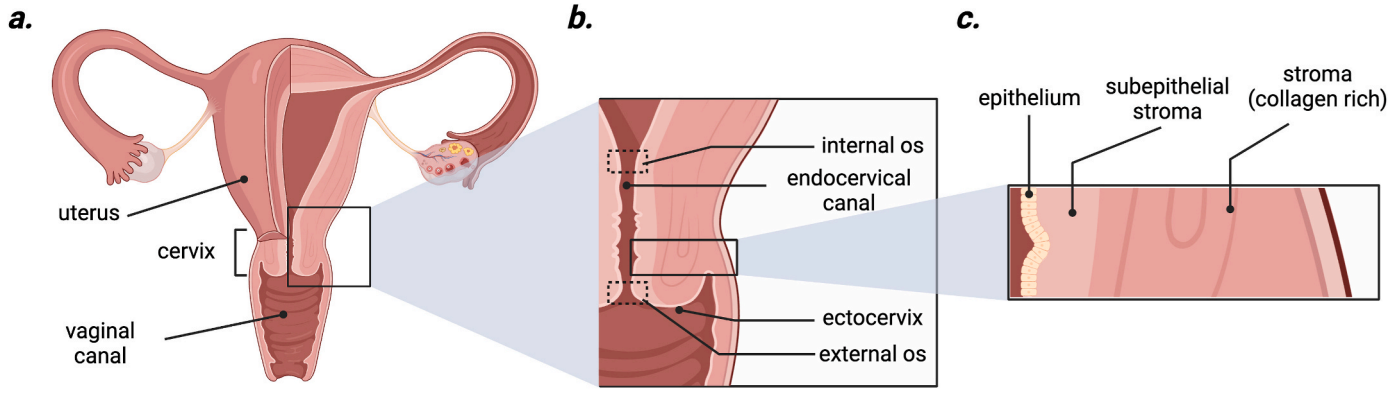

Fig. 1. Anatomy of the cervix. a.) The cervix is located on the distal end of the uterus and protrudes into the vaginal canal. The figure here shows a nonpregnant uterus and cervix **b.)** The superior and distal ends of the endocervical canal are termed the internal and external os. The distal end of the cervix is the ectocervix. **c.)** The layers of the cervix. The cervix is a connective tissue with a collagen-dense stroma. During pregnancy, the cervix undergoes microstructural changes, as its length slightly decreases, and outer diameter increases.

Table 1
In vivo devices for assessing cervical remodeling. CL: Cervical length; FFN: fetal fibronectin.

	Device dimensions	Measurement outputs	PTB prediction?
Electrical Impedance	Tip diameter, 8–12 mm	Tissue hydration	Slightly outperforms CL and FFN
Light-induced fluorescence	Tip diameter, 3 mm	Mature (crosslinked) collagen	Not yet tested
Second Harmonic Generation	Not yet developed for humans	Collagen fiber structure	Not yet tested
Raman spectroscopy	Tip diameter, 6.3 mm	Molecular fingerprint	Not yet tested
Shear wave elastography	Transvaginal ultrasound probe or around a finger	Quantitative measure of tissue stiffness	Associated with PTB
Cervical Aspiration	Tip diameter, 8 mm	Quantitative measure of tissue stiffness	In clinical trials

2020) and on biomarkers for PTB (Bastek and Elovitz, 2013).

4.1.1. Electrical impedance spectroscopy (EIS)

Electrical impedance spectroscopy quantifies the impedance of a material, or the opposition to the electrical flow, in response to an applied electrical current. Biological tissue impedance depends on its structure and hydration, including cell volumes, cell membrane capacitance, intracellular and extracellular conductivity, cellular structures, and tissue hydration. Electrical impedance has been used in the clinical setting to detect cancers, including breast, cervical, and oral (Anumba et al., 2021). To assess the electrical impedance of the pregnant cervix, a cylindrical device with a typical tip diameter of 8–12 mm applies a low current (~10μA) to the tissue and measures tissue impedance (also called resistivity) in units of Ohm × m at specific frequencies.

In clinical studies, EIS measurements at lower frequencies (4.8 kHz) indicate lower impedance in softer cervixes, with pregnant patients having lower impedance than nonpregnant patients (O'Connell et al., 2000). Similarly, patients who deliver vaginally have lower impedance than those who deliver via Caesarean section (Jokhi et al., 2009) and patients with a favorable (ripened) cervix have lower impedance than patients with an unfavorable cervix (O'Connell et al., 2003). In contrast, other studies show higher impedance in softer cervixes across frequencies (4–819 kHz), with higher impedance in third-trimester cervices compared to first and second-trimester cervices (Gandhi et al., 2006).

Recently, the ability of EIS to predict sPTB was assessed in a prospective study of 365 patients. EIS slightly outperformed other PTB assessments, including cervical length and fetal fibronectin (FFN) measurements. The study concluded that combining EIS with these measurements and a history sPTBs improved the accuracy of these predictions (Anumba et al., 2021). In summary, EIS provides an objective measure of cervical stiffness, but its ability to predict sPTB still needs to be determined. Incorporating EIS with other objective measures, like cervical length and FFN, holds promise.

4.1.2. Light-induced fluorescence (LIF)

Light-induced fluorescence (LIF) takes advantage of the natural fluorescence of collagen due to the molecular collagen crosslink, pyridinoline (Garfield et al., 1998, 2001; Schlembach et al., 2009). Typically, an optical device, termed the Collascope, measures the LIF of the cervix. The Collascope measures about 3 mm in diameter and 14 cm long and is placed on the ectocervix for about 10 s (Garfield et al., 1998). The Collascope then returns a fluorescence spectrum, and the peak of this spectrum (typically at around 390 nm) is normalized by a reference peak to calculate a LIF ratio as a measure of mature, crosslinked collagen with lower peaks correlating with a softer or ripened cervix. Clinically, LIF measurements decrease with progressing gestation (Maul et al., 2003; Zheng et al., 2020) and increase postpartum (Zheng et al., 2020). LIF ratios also decrease with labor induction with prostaglandins (Fittkow et al., 2005) and correlate positively with time to delivery (Maul et al., 2003). These data suggest that stronger, unripened cervixes have more crosslinked collagen and, thus, higher LIF measurements. The Collascope has not been tested in PTB patients, and therefore, its predictive value remains unclear. Etemadi and colleagues combined the EIS and LIF into one device, BirthAlert (Etemadi et al., 2013). Though the presented data are preliminary, they demonstrated its proof of concept in high-risk pregnant women. Currently, we know little about collagen crosslink changes in pregnant cervices, and quantitative measurements of nonpregnant human cervixes demonstrate crosslink heterogeneity, specifically from the inner endocervical canal to the outer layers of the cervix (Zork et al., 2015). Therefore, the location of the Collascope measurements could be a critical factor in LIF measurements of the cervix.

4.1.3. Second harmonic generation

Due to the appreciated role of cervical collagen remodeling during pregnancy, second harmonic generation is a popular method to assess collagen fiber structure. Typically, second harmonic generation images are taken of fresh or frozen, sliced cervical tissue samples from *ex vivo* animal and human cervical tissue (Akins et al., 2010; Moghaddam et al., 2022; Myers et al., 2009). Currently, the only *in vivo* device that utilizes SHG to assess the cervix has been tested in mice (Zhang et al., 2012). This study compared *in vivo* SHG images against *ex vivo* images of mouse cervix. Further, they demonstrated the ability to image *ex vivo* nonpregnant and pregnant human cervixes. Further, SHG signal and image analysis have allowed quantitative, objective data measurements. Therefore, this technology holds promise for assessing the *in vivo* human cervix during pregnancy.

4.1.4. Raman spectroscopy

Raman spectroscopy is an optical technique that characterizes the inelastic scattering of photons by matter. An incident photon collides with molecules within the sample, shifting the photon's energy level and yielding a molecular fingerprint of samples. Typically, the Raman spectra generate multiple peaks associated with molecular bonds, which can be analyzed to determine the biochemical composition of a sample (O'Brien et al., 2014).

A Raman spectroscopy device developed for clinical assessment of the cervix consists of a 6.3 mm diameter probe placed on 3–5 locations around the ectocervix for 3 s each, totaling <10 min per visit (O'Brien et al., 2019). In a longitudinal study tracking 68 patients through the first, second, and third trimesters with a 6-week postpartum follow-up, Raman measurements showed significant changes in specific biochemical signatures, including decreasing collagen peaks and increasing blood peaks indicating more vascularization during pregnancy (O'Brien et al., 2018). In a follow-up study, the Raman spectra were acquired at 4 hour intervals throughout labor until membrane rupture in 30 patients during labor. As labor progressed, signatures associated with collagen and ECM matrix proteins decreased, blood signatures increased, as did signatures associated with lipid-based molecules (Masson et al., 2022). Although Raman's ability to predict PTB has yet to be assessed, the "molecular fingerprint" aspect of Raman makes it a promising device that provides not only objective clinical assessments but also informs cervical remodeling mechanisms during pregnancy. Of note, Raman has been successfully used to detect precancer diagnosis in the human cervix (Mahadevan-Jansen et al., 1998).

4.1.5. Ultrasound shear wave speed (SWS)

Shear wave elastography is a technique where ultrasound images are used to measure tissue stiffness. Discussions on other elastography methods to assess the cervix is available (Fruscalzo et al., 2016). With

shear wave elastography, the measured shear wave speed reflects a measure of tissue stiffness since waves travel faster in stiffer materials, and a significant advantage is an ability to create a "stiffness map" of the imaged area (Feltovich et al., 2012). An early feasibility study on *ex vivo* cervical samples demonstrated higher SWS in unripened (stiffer) than ripened cervices (Carlson et al., 2014). Several cross-sectional studies show decreased SWS with progressing gestation, indicating cervical softening (Carlson et al., 2018; Hernandez-Andrade et al., 2014, 2018; Muller et al., 2015; Ono et al., 2017) and decreased SWS in patients who deliver preterm (Feng et al., 2022; Hernandez-Andrade et al., 2018; Muller et al., 2015). A recent longitudinal study on patients demonstrated reduced SWS with gestation (Carlson et al., 2019). Recent work has also focused on further analysis of the ultrasound images to design of biomarkers based on this technique (Guerrero et al., 2019), which holds promise for assessing tissue microstructure using this technique.

4.1.6. Other optical techniques

In addition to the techniques described above, engineers are developing emerging optical methods to quantify cervical changes during pregnancy. Some examples include quantification of water content using near-infrared spectroscopy (Qu et al., 2018), the addition of a polarizer to a standard colposcope to quantify collagen content and anisotropy (Chue-Sang et al., 2018), combining ultrasound elastography with a force sensor to quantify stress-strain relationships (Hu et al., 2023), and diffusion tensor MRI to image cervical collagen microstructure (Qi et al., 2021).

4.1.7. Cervical aspiration

Unlike the above optical and imaging techniques, cervical aspiration is an *in vivo* technique designed to assess cervical mechanical properties. With cervical aspiration, a device with a tip diameter of 8 mm is inserted into the vaginal canal and placed onto the orifice of the ectocervix. The device then applies negative pressure to aspirate a portion of the ectocervix and measures the resulting deformation, similar to micropipette aspiration used to measure the mechanical properties of cells (Hochmuth, 2000). The current version of the aspiration device applies a continuous negative pressure until it achieves a 4 mm tissue displacement such that a smaller closure pressure would correspond to a softer cervix.

In clinical studies, cervical aspiration measurements demonstrate decreasing tissue stiffness throughout gestation (Bauer et al., 2009), beginning in the early first trimester (Badir et al., 2013). Recently, the start-up company Pregnolia (Switzerland, https://en.pregnolia.com) commercialized the cervical aspiration device. A recent clinical study with the Pregnolia system demonstrated softer cervixes in high-risk patients with ultrasound-indicated cerclage in the second trimester (Stone and House, 2023). This device is currently in clinical trials in Europe and the United States (SoftCervix - in Europe NCT02037334, ATOPS - United States, NCT03865108, Cervical Stiffness Measurement in Cervical Insufficiency - United States, NCT04158401); therefore, more stiffness assessments, specifically in sPTB patients are forthcoming.

4.1.8. Biomarkers

Biomarkers are objective, quantifiable, and reproducible medical measurements collected from a patient (Strimbu and Tavel, 2010). Specifically for the cervix, fetal fibronectin (FFN) concentration in cervicovaginal fluid and cervical length are common biomarkers used to identify women at risk for sPTB (Son and Miller, 2017). FFN is a glycoprotein produced by the fetal cells, often described as a "biological glue" that binds the amniotic sac to the uterine lining. High levels of FFN are detected in the cervical vaginal fluid before 22 weeks of gestation are associated with sPTB. Cervical length, assessed through transvaginal ultrasound, is defined as the closed length of the cervix between the internal and external os. Typically, cervical lengths <25 mm before 24 weeks of gestation are associated with PTB. However, both biomarkers are not used to screen for sPTB because of the low positive predictive value of high FFN (14% for sPTB <37 weeks; 5.6% for sPTB <32 weeks) and cervical length (20.8% for sPTB <37 weeks and 8.6% for sPTB <32 weeks) in an observational study of 9410 nulliparous women with singleton pregnancies (Esplin et al., 2017).

Reflecting the changes in FFN (along with other possible molecules), cervical mucus properties change with labor and between normal and preterm birth patients. For example, hyaluronic acid concentration increases and its molecular weight decrease during labor (Obara et al., 2001), women at high risk for PTB have a more extensible and permeable cervical mucus (Critchfield et al., 2013), and microsphere permeability between low and high-risk women are different (Smith-Dupont et al., 2017). Further, recent work has suggested interactions between the vaginal microbiome and cervical vaginal mucus properties (Zierden et al., 2023). Together, these findings suggest exciting opportunities for cervical mucus composition or properties as a potential avenue for identifying biomarkers for sPTBs.

4.2. Preventative tools for PTBs

PTB prevention in patients remains elusive, as current strategies, including cerclage, pessaries, and progesterone supplementation, cannot prevent uterine contractions, cervical funneling, shortening, and dilation once it starts. One of the most exciting areas of bioengineering advancements in PTB includes novel tools for the prevention sPTB (Koullali et al., 2017). For example, researchers are developing an injectable cerclage as an alternative to a surgical cerclage. This therapy injects a silk, biocompatible hydrogel into the cervix to augment the tissue. In a preclinical study, the authors compared the injectable cerclage to a traditional cerclage in rabbits. They injected the injectable cerclage at gestation day 14 of a 31–32 day gestation and found that the injectable cerclage increased the tissue volume while maintaining native, compressive mechanical properties without triggering additional inflammatory response or preterm birth (Zhang et al., 2020). In addition, there are ongoing efforts to develop a medical device to improve upon the cerclage to prevent sPTBs (House et al., 2023).

In another recent preclinical study, Hoang and co-workers developed a progesterone nanosuspention that successfully prevented preterm birth in a mouse model (Hoang et al., 2019). The authors demonstrated that this new delivery mechanism was more effective than vaginal gel administration, a standard clinical method for progesterone delivery. Further, gene expression and histological analysis of the cervix showed similarities between the treated mice and gestation-matched controls. These results suggest an opportunity for bioengineers to design novel drug-delivery techniques to address sPTBs. For more discussion on this topic, the reader is referred to the review article by the authors (Zierden et al., 2021).

4.3. Identifying mechanisms of cervical remodeling

An obstacle in predicting, preventing, and treating sPTB is the limited understanding of the mechanisms involved in normal and pathological cervical remodeling. This limited understanding restricts the efficacy of the diagnostic tools and identifying appropriate therapies for individual patients. Therefore, considerable bioengineering efforts have focused on understanding of the mechanisms behind normal and abnormal cervical remodeling. This section highlights some of these advancements.

4.3.1. Cervical mechanics (structure and function)

A significant effort in understanding cervical remodeling mechanisms has focused on understanding how changes in the cervical microstructure (structure) during pregnancy result in mechanical property changes (function). Although much of this work utilizes rodent models of pregnancy (Mahendroo, 2012; Word et al., 2007; Yoshida et al., 2019), which provide access to accurately timed tissue samples

throughout pregnancy, the discussion here focuses on efforts by bioengineers to assess the structure-function relationships of the human cervix.

The three-dimensional, anisotropic structure of the cervix makes mapping the microstructure across the cervical anatomy challenging. Bioengineers have applied emerging imaging techniques to map the complex microstructure of the cervix to address this knowledge gap. Magnetic tensor diffusion tensor imaging (DTI) on *ex vivo* (Weiss et al., 2006) and *in vivo* (Fujimoto et al., 2013) nonpregnant human uteri have revealed fiber architecture throughout the uterus and cervix, including circumferentially and longitudinally aligned fiber zones. A recent DTI study on *in vivo* nonpregnant and early pregnant uteri demonstrated structural differences in the uterine architecture, including decreased fiber density and length (Zhang and Chen, 2020). Other studies have focused on correlating microstructure to mechanical properties, typically on *ex vivo* axial cervical slices, using second harmonic generation (Hao et al., 2018; Myers et al., 2009), X-ray diffraction (Aspden, 1988a), and optical coherence tomography (OCT) (Gan et al., 2015; Yao et al., 2016). In particular, OCT analysis allows for quantitative analysis of local fiber orientation and dispersion to track heterogeneous fiber structures and heterogeneous changes during pregnancy. An advantage of OCT imaging is its non-destructive feature, allowing subsequent mechanical testing on the same sample to inform or validate sample-specific mechanics. For example, Shi et al. used OCT to determine fiber orientation, subsequently mechanically tested the tissue samples with indentation, and used the OCT data to inform an inverse finite element analysis to determine cervical material properties (Shi et al., 2019).

A first step to understanding the mechanical function of the cervix involves characterizing its physiologically relevant material properties. As mentioned, the cervix has a layered, heterogeneous, and anisotropic (direction-dependent) structure. Further, the cervix undergoes extensive deformations, dilating from 1 to 10 cm during labor. Therefore, rigorous characterization of its mechanical properties requires location and direction-specific, large deformation mechanical testing that typically requires *ex vivo* testing. However, access to human tissue samples, particularly throughout pregnancy, is challenging. Therefore, *ex vivo* mechanical data for the human cervix only exist for nonpregnant and pregnant term tissue. Additionally, the term pregnant cervix is often acquired from patients during a Caesarean section due to placenta accreta or percreta, conditions in which the placenta invades the uterine wall and may not reflect typical term conditions.

Reflecting the known microstructure, the mechanical properties of the cervix are nonlinear, viscoelastic, anisotropic, and heterogeneous (Fernandez et al., 2013; Myers et al., 2010, 2008; Birgitte S Oxlund et al., 2010; Oxlund et al., 2010; Petersen et al., 1991; Yao et al., 2014). These mechanical features have been demonstrated through uniaxial tension and compression load-unload and stress-relaxation tests (Myers et al., 2008, 2010), compressive indentation (Yao et al., 2014), and hydraulic permeability tests that quantify flow resistance of the tissue (Fernandez et al., 2013). In general, the tensile and compressive stiffness of the cervix decreases (Myers et al., 2008, 2010; Yao et al., 2014), and the permeability of the cervix increases (Fernandez et al., 2013) during gestation. One biomechanical study of cervical biopsy samples in nonpregnant women with a history of cervical insufficiency demonstrated no difference in the tensile strength of the tissue (Oxlund et al., 2010).

Bioengineers utilize constitutive modeling to connect the cervical structure to mechanical function. Generally, constitutive models, or mathematical relationships between deformation and stress, span from phenomenological to mechanistic models. For example, Aspden presented mathematical frameworks to model the cervix as a fiber-composite material (Aspden, 1988b) and to relate cervical mechanical properties to collagen fiber orientation (Aspden, 1988a). Myers et al. (2015) proposed a constitutive modeling framework incorporating fiber dispersion to model changes in collagen fibers organization with pregnancy and demonstrated the ability to capture equilibrium compression and tensile mechanical data. Other work has focused on the viscoelastic response of the cervix using the classic phenomenological models (Callejas et al., 2021; Peralta et al., 2015). Recently, Shi et al. incorporated multiscale structures from the intramolecular crosslink level, fiber dispersion, and fiber orientation to capture the 3D anisotropic equilibrium response of the human cervix (Shi et al., 2022).

While most of the research has focused on the passive mechanical properties cervix, recent work has highlighted the possible role of smooth muscle cell contractility, particularly at the internal os. Vink and co-workers (Vink et al., 2021) demonstrated that cervical smooth muscle cells (cSMCs) isolated from patients with premature cervical failure do not have inherent contractility defects. Instead, they found that cSMCs exhibit decreased contractility when exposed to soft ECM and suggested a critical "sphincter" role of the cSMCs at the internal os to prevent funneling. However, previous measurements of the contractile properties of the nonpregnant cervix did not indicate differences between the internal and external os (Petersen et al., 1991). These active properties of the cervix are an interesting and relatively unexplored topic.

Finally, bioengineers use finite element modeling to understand how material property changes affect cervical dilation (Mahmoud et al., 2013; Westervelt and Myers, 2017). In these models, constitutive relationships are applied to isolated cervical geometry (Gou et al., 2020) or patient-derived anatomies that include the uterus and cervix from imaging data, such as MRI (Fernandez et al., 2015) or ultrasound (Louwagie et al., 2021; Westervelt et al., 2017). Continued developments with these techniques have the exciting potential to incorporate patient-specific anatomical and mechanical changes (informed by the *in vivo* tools outlined previously) to predict the trajectory and timing of cervical dilation during pregnancy.

4.3.2. *Hormonal, inflammatory, and mechanical effects on cervical remodeling*

Another open question related to cervical remodeling is: *how* or *what* cues do cells respond to remodel the cervix? To answer this question, House and co-workers used a 3-D tissue culture system as a platform to investigate how cervical fibroblasts respond to hormones and remodel their environment. They found that dynamically loading the constructs increased collagen and sulfated glycosaminoglycan synthesis leading to a stiffer matrix (House et al., 2010), increasing progesterone concentrations led to less collagen synthesis (House et al., 2014), while the addition of progesterone and estrogen also decreased collagen production leading to a softer matrix (House et al., 2018).

In a different study, Shukla et al. (2018) investigated the effects of progesterone and IL-beta, a proinflammatory cytokine, on ECM remodeling, cell traction force generation, cell-ECM adhesion, and tissue contractility. They found that IL-β treatment reduced cell traction force and cell-ECM adhesion, reducing cell-level contractility. At the same time, progesterone did not affect cell traction force and cell contractility while increasing cell-ECM adhesion. Together, these experimental data suggest the responsiveness of cervical fibroblasts to adapt to hormonal, inflammatory, and mechanical cues. How these cues interact, however, is unclear and would be an interesting topic to investigate, especially given the dynamic hormonal, inflammatory, and mechanical environment of pregnancy.

5. Future approaches and open areas related to the cervix and PTB

As summarized above, bioengineers have and continue to contribute solutions for PTB centered around the cervix. This section suggests open areas of research that bioengineers are now well-positioned to address.

5.1. Cervical mechanobiology

Based on the efforts towards characterizing the mechanics of the cervix, we are starting to understand how much the cervix remodels *in vivo*. Data from *in vitro* experiments have provided insight into what cues cervical cells respond to. However, *how* cells integrate these cues to remodel the cervix is less clear. Cells are known mechanosensors. When they sense changes in mechanics, for example, increased stretch or stress, these signals will trigger a biochemical response, triggering signaling pathways that ultimately lead to various behaviors, including, but not limited to, cell growth, differentiation, shape changes, apoptosis, or transcriptional changes (Vogel and Sheetz, 2006). Importantly, cells can partially adapt to changes in mechanics by remodeling their ECM through matrix protein deposition, rearrangement, or removal to return to a homeostatic mechanical state (Humphrey et al., 2014). In addition to mechanics, cells respond to hormonal and inflammatory cues, which also trigger similar responses.

During pregnancy, uterine cavity volumes increase dramatically, from <10 mL in the nonpregnant state to 20,000 mL by the end of pregnancy. Simultaneously, pregnancy hormone levels continually change (Tulchinsky et al., 1972), as do immune responses (Mor and Cardenas, 2010). In other tissue organs and systems, emerging engineering approaches integrate biological and mechanical cues to elucidate *how* cells respond to mechanical cues and remodel their environment. For example, tissue engineering and *in vitro* experimental methods where cervical cells are seeded on 3-D tissue constructs under different levels, directions, and patterns of stretch and different types and levels of hormones or cytokines could characterize how cervical cells respond to mechanical, hormonal, and inflammatory cues. These data would generate a set of "rules" that cervical cells follow to inform computational approaches, like agent-based modeling, a common method to understand other remodeling processes, including infarct remodeling (Richardson and Holmes, 2016; Rouillard and Holmes, 2014), tendon wound healing (Chen et al., 2018), and arterial remodeling in response to hypertension (Hayenga et al., 2011).

Finally, another important aspect of mechanobiology is the feedback loop where tissue and cell growth and remodeling, in turn, alter *in vivo* mechanical cues, thus modifying future behavior. Bioengineers have developed computational approaches for other tissue systems to understand these feedback loops. For example, the kinematic growth framework (Rodriguez et al., 1994) has been widely used in cardiovascular research to understand how cell growth (through hypertrophy or hyperplasia) and mechanical loading affect *in vivo* elastic stretch, representing the stretches that cells experience. To incorporate hormonal and mechanical interactions, we developed a multiscale model that couples a cell-signaling network model to a kinematic growth framework to simulate heart growth during pregnancy (Yoshida et al., 2022). Alternatively, agent-based models can be coupled to finite element models to simulate this mechanical feedback loop. Leveraging these new computational approaches and integrating them with existing mechanical models would allow biological and mechanical data integration and enable bioengineers, clinicians, and biologists to collaborate to understand how the significant mechanical and biological changes interact to drive cervical remodeling and mechanical function during pregnancy (Fig. 2).

5.2. Cervical structure and uterine interactions

While the passive mechanics of the cervical stroma is well characterized, understanding the full mechanical function of the cervix – including how it prevents funneling and dilation – likely requires an appreciation of its whole structure. For example, the cervical epithelium is an immunologic and physical barrier (Nallasamy and Mahendroo, 2017). In mice, a disruption in the cervical epithelial organization alone increases susceptibility to PTB (Akgul et al., 2014). Further, two PTB mouse models (hormone-mediated through RU486 and inflammation-mediated through lipopolysaccharide, LPS) exhibit distinct mechanical and ECM structures, yet both mouse models lead to premature cervical dilation and delivery (Jayyosi et al., 2018; Willcockson et al., 2018). Finally, recent reports of cervical smooth muscle cell populations (Vink et al., 2016), its altered contractility in response to substrate stiffness (Vink et al., 2021), and altered fibroblast-ECM adhesion in response to cytokines and progesterone (Shukla et al., 2018) suggest that other mechanisms besides ECM remodeling could be involved in sPTB. Therefore, considering its layered structure and multiscale mechanical behavior to connect cell-level mechanics to tissue mechanics could provide more insight into how the cervix behaves at the organ level.

Second, the cervix is not an isolated organ. Its connection to the uterus is a critical aspect of its mechanical behavior. During pregnancy, the uterus grows and stretches to accommodate the growing fetus, likely affecting the mechanical loading of the cervix. During the first stage of

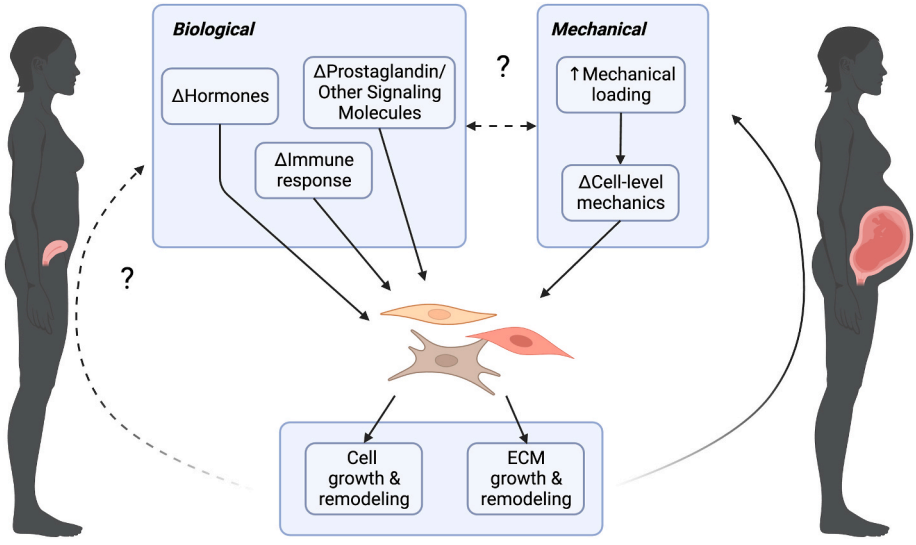

Fig. 2. Understanding cervical mechanobiology during pregnancy. Pregnancy presents dynamic changes in biology (hormones, immune response, etc.) and mechanics (from the growing fetus). These cues affect cervical cell (fibroblasts, smooth muscle cells, etc.) behavior and resulting cell and extracellular matrix (ECM) growth and remodeling, but how the cues interact are unclear. Further, changes in cell and ECM growth and remodeling can feedback to alter cell-level mechanics and potentially biological responses. Understanding these feedback loops can help answer *how* the cervix remodels itself during normal and pathological pregnancies.

labor, the uterus produces forceful contractions that pull on, thin, efface, and dilate the cervix. Further, recent studies demonstrate a gradient of smooth muscle cells – comprising 50–60% of the tissue at the internal and approximately 10% at the external os (Vink et al., 2016). Therefore, understanding the mechanical interactions between the uterus and cervix is important for pregnancy biomechanics. A limitation in understanding the mechanical interactions between the uterus and the cervix is that uterine biomechanics, particularly its growth and remodeling during pregnancy, is currently understudied (Myers and Elad, 2017). Understanding how the structure-function relationship changes of the uterus, lower uterine segment, and cervix work together could help identify better therapies for preventing cervical dilation.

5.3. *Precision medicine for pregnancy*

There are multiple etiologies of PTB that can differ between patients (Frey and Klebanoff, 2016; Goldenberg et al., 2008; Vink and Feltovich, 2016). Therefore, effective solutions for diagnosing and treating PTB likely require patient-specific considerations. For example, computational approaches that can account for patient-specific biology, anatomy, and physiology could help us understand which specific PTB etiologies a patient might experience or which drugs or interventions would be most effective for preventing PTB (Quinney et al., 2014).

CRediT authorship contribution statement

Kyoko Yoshida: Visualization, Conceptualization, Writing - original draft, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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