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System-Level Biomechanical Approach for the Evaluation of Term and Preterm Pregnancy Maintenance

Preterm birth is the primary contributor to perinatal morbidity and mortality, with those born prior to 32 weeks disproportionately contributing compared to those born at 32–37 weeks. Outcomes for babies born prematurely can be devastating. Parturition is recognized as a mechanical process that involves the two processes that are required to initiate labor: rhythmic myometrial contractions and cervical remodeling with subsequent dilation. Studies of parturition tend to separate these two processes rather than evaluate them as a unified system. The mechanical property characterization of the cervix has been primarily performed on isolated cervical tissue, with an implied understanding of the contribution from the uterine corpus. Few studies have evaluated the function of the uterine corpus in the absence of myometrial contractions or in relationship to retaining the fetus. Therefore, the cervical-uterine interaction has largely been neglected in the literature. We suggest that a system-level biomechanical approach is needed to understand pregnancy maintenance. To that end, this paper has two main goals. One goal is to highlight the gaps in current knowledge that need to be addressed in order to develop any comprehensive and clinically relevant models of the system. The second goal is to illustrate the utility of finite element models in understanding pregnancy maintenance of the cervical-uterine system. The paper targets an audience that includes the reproductive biologist/clinician and the engineer/physical scientist interested in biomechanics and the system level behavior of tissues. [DOI: 10.1115/1.4023486]

1 Introduction

Preterm birth (<37 completed weeks of pregnancy) is the leading cause of neonatal death and a major contributor to both physical and developmental handicaps [1–3]. For example, survivors have higher rates of developing cerebral palsy, learning and developmental disabilities, hearing and vision impairment, and chronic lung disease compared to those delivered at term (37–42 weeks) [1,4–6].

Preterm birth is a syndrome that can occur through activation of many different pathways and these are reviewed elsewhere [7]. A variety of mechanisms have been described that lead to uterine activation and cervical change including inflammation [8], endocrine [9], and mechanical mechanisms [10]. All of these mechanisms feed into pathways that induce either uterine contractions or cervical remodeling [11] and, finally, to cervical dilation. For these reasons a mechanical approach is necessary for understanding preterm birth. This paper aims to highlight the gaps in research that exist and need to be addressed in order to develop a relevant and comprehensive mechanical approach. Despite advances in neonatal care and survival, research to predict risk and prevent preterm birth has fallen short. The preterm (less than 37 weeks of gestation) birth rate rose by more than 20% in the United States between 1990 and 2006 [12]. Most of this increase was

among infants born toward the end of the preterm period, at 34 to 36 full weeks of pregnancy, or during the period known as “late preterm” [12,13].

During gestation the uterus accommodates the growing fetus by expanding in volume. Because of their physical connection, the cervix must accommodate the uterine expansion at the uterine-cervical interface (internal os), yet maintain competency until the fetus is mature. Thus, the cervix has two opposing functions: to maintain pregnancy and to allow the fetus to pass. For a successful vaginal delivery, the cervix must first dilate to 10 cm to allow for the passing of the fetus. For this to occur, the cervix undergoes compositional, microstructural, and geometric changes (see Sec. 2), during the second and third trimesters of pregnancy [14–17]. Premature shortening, a geometric change of the cervix, is thought to be a sign of progressive mechanical failure [18]. Three factors can compromise the integrity of the cervix: loss of cervical stiffness (insufficiency), an increase in the applied tension load due to uterine contractions, or changes in volume that increase intrauterine pressure. The high incidence of preterm birth, its consequences, and the geometric and structural changes of the system make the understanding of the mechanical properties of cervical tissue a relevant subject of investigation.

The uterine corpus consists of primarily smooth muscle and is referred to as the myometrium. It, too, undergoes significant change during gestation. Synchronous and asynchronous myometrial contractions occur throughout gestation and must be accommodated for the normal progression of pregnancy. Myometrial

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tissue research has primarily focused on uterine contractions, or active forces. There are few studies on the passive mechanical properties of the uterus, as compared to the cervix, although the myometrium spends the majority of its time in a relaxed state. Moreover, the cervical-uterine interaction has largely been neglected in the literature, perhaps because of the complex relationship and challenges associated with experiments that would account for such interaction.

At present, finite element models assessing the mechanics of cervical-uterine interactions during gestation and labor are lacking. To our knowledge, a paper by House and Socrate [19] is the only one addressing the issue. The gap in research pertaining to cervical-uterine interaction is likely due to several factors, including the difficulty associated with obtaining consistent and reliable material properties as input for a model and development of an adaptive material model that can represent the evolution of the tissue over time. Another challenge is associated with accurately defining a representative geometry and the boundary conditions of the system. The interaction between the uterus and the cervix during pregnancy is a complex phenomenon that remains poorly understood.

The goals of this paper are two-fold. The first goal is to provide a broad overview of cervical-uterine changes during gestation, including geometric, biochemical, microstructural, and biomechanical changes, in order to provide the background for finite element model development. In doing so, we highlight the gaps in knowledge that need to be addressed in order to build a detailed and accurate model of the cervical-uterine system. Emphasis is placed on the mechanical behavior of both cervical and uterine tissue since the mechanical properties of the materials that make up the system are essential inputs to any model.

The second goal is to illustrate the need for numerical models that have the ability to simulate the mechanics of both the uterus and cervix, together, as a system. In doing so, the interactions and influence of one organ on the other can be modeled. An ideal model of the cervical-uterine system would take into account the possible changes in system-level interactions, resulting from evolution of the uterine corpus during gestation, uterine contractions, and cervical remodeling. Such models could, perhaps, provide insight into how changes in uterine pressure and growth influence cervical changes and mechanical function.

This paper targets both the reproductive biologist/clinician and the engineer/physical scientist interested in the mechanics of biological tissues and systems. For the former audience, we hope to convey the importance of considering the entire system, to describe the information that is needed for the models, and to point out the gaps in research in these areas. For engineers/physical scientists, we aim to highlight the biology and to point out key gaps that need to be filled in order to develop appropriate models.

2 Gestational Changes in the Uterine Corpus and Cervix

The uterine corpus and the cervix undergo marked changes in size, shape, and composition over the course of gestation. The characterization and understanding of the geometric and compositional changes as they relate to biomechanical function is important to the development of accurate models of the cervical-uterine system over the course of pregnancy. Section 2.1 describes some of the key and well-documented anatomic changes to the uterine corpus and cervix. Figure 1 shows a schematic of the anatomy of the nonpregnant and pregnant uterus and the geometrical evolution over gestation. Section 2.2 describes the “material” changes, or the changes in biochemical composition of the major extracellular matrix constituents, such as collagen and proteoglycans as human uterus and cervix increase with gestational age.

2.1 Geometric Changes in the Uterus and Cervix During Gestation

2.1.1 Geometric Changes in the Uterus. The uterus expands during gestation in order to accommodate the fetus, placenta, and

Fig. 1 Schematics showing geometric changes in the uterine and cervical anatomy. The mass and volume of the human uterus and cervix increase with gestational age. The uterus typically increases in length from 6.5 cm to 32 cm and from 60 g to 1000 g in mass. The cervix increases in overall size, but gets progressively shorter after 24 weeks, from 4–6 cm. As the cervix nears term, the internal os increases in diameter and first opens with progressive cervical shortening. The anatomy of the cervical canal is typically described in terms of its shape, beginning as a ‘T,’ opening to a ‘V,’ and finally progressing to a ‘U’ as labor nears [20].

amniotic fluid and, therefore, undergoes gross changes in its volume, mass, and shape. The shape of the entire cervical canal is often described as a ‘T’ early in term, opening to a ‘V’ and finally a ‘U’ as delivery approaches [20]. On average, the uterus increases in length from approximately 6.5 cm to 32 cm long, 4–5 cm to 24 cm in width, and 3–4 cm to 22 cm in depth [21]. At term, the uterine cavity at the fundus has a radius of approximately 7 cm. The mature nonpregnant uterus weighs an average of 60 g and its weight increases by over tenfold to approximately 1000 g at term [22]. The increase in mass is primarily due to hyperplasia and hypertrophy of the smooth muscle. Myometrial thickness varies from fundus to cervix, being thickest in the fundal region at 10–15 mm and thinnest in the lower segment at 5–10 mm near the cervix at term. As pregnancy advances, the uterine cavity changes its shape from primarily a sphere to primarily an ovoid. With the onset of labor, the lower segment thins in the isthmic region, along with effacement and dilation of the cervix.

2.1.2 Geometric Changes in the Cervix. The cervix also undergoes changes in mass, volume, length, and alignment with the uterine axis. Studies suggest that the changes in cervical volume occur mainly during the first half of pregnancy [23], and begin as early as the first trimester [24]. Recent 3D ultrasound measurements show an increase in cervical volume from 15.5 cm³ to 29 cm³ in the first trimester [24] and a modest increase to 32.1 cm³ by 32–34 weeks [24]. Ultrasound studies have shown significant correlation between cervical length and cervical volume [25]. However, cervical volume may actually decrease over the third trimester as the cervix shortens and becomes incorporated into the lower uterine segment, which is consistent with the observation that cervical length progressively diminishes after 20–24 weeks of gestation [23]. This observation that the cervix at the level of the internal os becomes incorporated into the lower uterine segment further supports the need to consider the two together as a system.

A number of studies have measured cervical length using ultrasonography in the context of preterm birth and have found an inverse correlation [26–31]. In one study, the mean cervical length at 24 weeks was 35.2 ± 8.3 mm and individuals with a cervical length ≤25 mm had a significantly higher preterm birth rate of 30% [18]. Cervical length during normal pregnancy ranges from

40–60 mm when measured before 28 weeks gestation [21]. The relative risk of spontaneous preterm birth is inversely proportional to the length of the cervix at 20–24 weeks gestation [22–25]. However, not all women with a short cervix will deliver preterm.

2.1.3 Geometric Changes Associated With the Uterine–Cervical Relationship. The geometrical and/or structural changes likely impact mechanical function. For example, the uterine cavity is spherical during the first and early second trimesters. As the fetus continues to grow, however, the uterine volume increases, which causes an elongation of the cavity into an ovoid [21]. With complete expansion of the uterine isthmus, the cervix must now accommodate the tensile forces imposed by the growing fetus and uterine sac. The expansion of the uterus results in displacement of the internal cervical os anteriorly and inferiorly [32] and these changes are likely to alter the forces imposed on the cervix. The cervical canal is typically pointed posteriorly and is generally not aligned with the uterine axis (Fig. 2). This relationship has been recognized indirectly in the Bishop score (see Table 1) [33], which is a clinical assessment tool used to evaluate the readiness of the cervix for labor induction. As the cervix moves anteriorly, the likelihood for a successful vaginal delivery increases. This displacement brings the cervical canal in alignment with the uterine axis and likely improves the efficiency of uterine contractions on cervical dilation and effacement. This uterine–cervical relationship has not been extensively evaluated in prior studies assessing preterm or term labor.

2.2 Compositional and Microstructural Changes in the Uterus and Cervix During Gestation

2.2.1 Compositional and Microstructural Changes in the Uterus. Uterine remodeling during pregnancy serves two main purposes. One is to accommodate the growing fetus. The other is to develop the force capacity required to expel the fetus during labor. The uterine corpus is 70% smooth muscle with 30% extracellular matrix (ECM) [34] and this composition is believed to remain stable throughout pregnancy. Few studies have focused on the ECM changes that occur in the myometrium during gestation.

The relative composition of the myometrium is not thought to change significantly during pregnancy. Myometrial smooth muscle cells increase the production of both α and γ actin, which are responsible for the contractile activity of the uterus [35]. In

Fig. 2 Schematic of the forces that act on the uterus and cervix before (left) and during dilation (right) include myometrial contraction, gravitational force, and boundary conditions from round, broad, and uterosacral ligaments. Cross-sections of the cervix illustrate the changes in dilation, collagen fiber arrangement, and lateral boundary conditions from the ligaments.

Table 1 The Bishop score [34]: a metric to assess the readiness of the cervix for labor assessed by a vaginal examination

Score	0	1	2	3
Dilation (cm)	Closed	1–2	3–4	≥ 5
Effacement (%)	0–30	40–50	60–70	≥ 80
Fetal station	–3	–2	–1, 0	+1, +2
Cervical consistency	Firm	Medium	Soft	
Position of cervix	Posterior	Mid-position	Anterior	

addition, the cells increase the production of ECM components, such as collagen and elastin. The increase in elastin appears to be regulated by mechanical stretch to a greater extent than the increase in collagen [36]. However, the functional contribution of the changes in elastin is not known.

The total amount of collagen in the uterus also increases during pregnancy, although its concentration decreases as the tissue enlarges [37,38]. The predominant forms of fibrillar collagen in the uterus are Type I and Type III. Increased production of collagen and overall turnover contributes to the increase in extractability. Collagen is secreted into the extracellular matrix where it must crosslink with other collagen molecules to form the fibrils that provide tissue support. Soluble collagen that has not formed into fibrils is not believed to provide mechanical support.

Proteoglycans are also important constituents of the myometrial ECM. Measurements of hyaluronic acid and sulfated glycosaminoglycans (GAGs) show a decline from nonpregnant levels [37]. Both increase with labor but remain below levels measured in nonpregnant myometrium [37]. Decorin is the predominant proteoglycan found in the myometrium and the proteoglycans biglycan and versican are also present [39]. Decorin content is slightly lower in the myometrium than in the cervix, making up about 63% of the total GAG content.

2.2.2 Compositional and Microstructural Changes in the Cervix. Similar to the uterus, the cervix also undergoes significant remodeling during pregnancy (see Fig. 3). Throughout most of pregnancy, the cervix serves a structural role; its purpose is to maintain the fetus within the uterine cavity until the fetus has developed. At the end of pregnancy, the cervix must allow passage of the fetus for birth to occur. These are two divergent roles, forcing the cervix to undergo dramatic changes in microstructure and composition. This evolution in the function of the cervix is possible because of both compositional and structural changes [40]. In turn, these physiological modifications result in a change in the mechanical properties of the tissue [17].

The main structural constituents in the cervix are collagen, proteoglycans, and the GAG hyaluronan. Collagen and proteoglycans are the two main extracellular components that maintain the

Fig. 3 Cervical remodeling in normal pregnancy starts with cervical softening very early in pregnancy. Later in pregnancy, the collagen disorganizes and collagen fibers disorganize [48].

structural integrity of load bearing tissue, such as bone, cartilage, tendons, and cervix [41]. Both directly contribute to maintain tissue structure and resist compressive and tensile forces [42]. Recent studies of proteoglycan knockout mice indicate that proteoglycans regulate collagen fibrillogenesis and are involved in cross-linking collagen fibers [43–47]. In the cervix, these interactions help maintain cervical integrity, resisting both transient (uterine contractions) and constant (intrauterine pressure, gravity) forces.

The fibrous cervix contains much less muscle than the uterine corpus. The cervix contains approximately 10% smooth muscle [15,48,49], 2% elastin, with the remainder collagen and proteoglycans. Smooth muscle content decreases over the length of the cervix and is greatest at the internal os and least at the external os. The elastin content does not change with pregnancy [15]. Similar to the myometrium, the two main fibrillar components of collagen are Types I and III in a 3:1 ratio and this ratio remains constant throughout pregnancy [50]. It is established that the collagen concentration in the cervix, though not total collagen content, decreases as pregnancy progresses. Collagen crosslinking is believed to provide the structural stability of load bearing tissues. Specific types of collagen crosslinks, which stabilize fibers and fibrils, have not been well characterized. Indirect assessments suggest that crosslink frequency does not vary through gestation [51,52]. Cervical collagen fibers become more dispersed with cervical ripening at term [53,54]. In most soft tissues, collagen undergoes continuous turnover. This turnover process in the cervix results in a large proportion of extractable (acetic acid and pepsin soluble) collagen near term. Since only fibrillar collagen provides load-bearing function, total collagen assays, i.e., soluble collagen and fibrillar collagen, may not accurately reflect the potential load-bearing capacity of the tissue.

Proteoglycans (PGs) are another important ECM constituent that is involved in structural support and both directly and indirectly contribute to structural integrity. Studies of PG knockout mice indicate that small leucine rich PGs (decorin, biglycan) regulate collagen fibrillogenesis and are involved in organizing collagen fibers [55]. The family of large aggregating PGs, which include aggrecan and versican, contain multiple linear and branched GAG chains. The large aggregating PGs function by accommodating compressive loads. The GAG component is important in determining a variety of mechanical properties [56]. The GAG chain length and sulfation of disaccharide subunits contribute to their molecular interactions [41,53,57–59].

Some functions of PGs include regulating fibrillogenesis, cross-linking collagen fibers, and regulating turnover [55]. Decorin is the predominant PG and primarily contains the GAG dermatin sulfate, accounting for approximately 75% of the total GAG content. Decorin associates with collagen fibers and influences fibril formation and organization. Dermatin sulfate is closely associated with collagen stability and the decrease in dermatin sulfate as the cervix softens is consistent with the decrease in both the decorin and collagen content. Many other GAGs are present in the cervix including heparan sulfate, chondroitin sulfate, and keratan sulfate, which all increase over gestation. The GAGs heparin sulfate and hyaluronic acid (hyaluronan) are equally abundant, making up around 10% of the total GAG content.

Hyaluronan has been shown to have many functions including mediating inflammatory responses and regulating protease activity. One of its principal functions is to regulate tissue hydration and osmotic force in addition to tissue fluidity in response to compression [57,60,61]. Increases in cervical hydration and cervical softening are associated with increases in hyaluronan content. Hyaluronan has a high affinity for water due to its high electro-negative charge and is generally thought to contribute to the textural softening of the cervix during ripening [62].

3 Mechanical Testing and Mechanical Properties of Uterine and Cervix Tissue

Mechanical property data for cervical and uterine tissues are essential to the development of accurate and physiologically relevant

mechanical models of the cervical-uterine system. Such models will lead to a better understanding of the physical factors that can lead to preterm birth and could be used to evaluate interventions that are aimed at predicting the risk and reducing the incidence of preterm birth.

The mechanical properties of tissue, in general, change not only in the presence of pathologic processes, but also under normal physiological processes such as growth and development. The mechanical properties of the cervix and uterus change over the course of pregnancy, adapting to the changing physical requirements imposed by the fetus and in preparation for birth. The compositional and microstructural changes in the cervical and uterine tissue, described in Sec. 2, dictate these changes in mechanical properties. Perhaps the most accepted evidence of this change is the softening of the cervix as delivery becomes eminent. The Bishop score qualitatively and subjectively reflects this change. It is generally accepted that early remodeling and softening of the cervix can lead to preterm birth [63]. However, the changes in mechanical properties associated with remodeling and softening of the cervix are not well-characterized for either term or preterm pregnancies. The data available on the uterus are also lacking.

The cervix and uterus are complex organs, owing to the fact that they are heterogeneous tissues with structure, composition, and mechanical properties that change dramatically in a relatively short period of time and that also vary with location in the organ. This complexity contributes to the difficulty in their characterization and, consequentially, leads to the knowledge gap in understanding their mechanical behavior. Like many other soft tissues, the mechanical behavior of cervical and uterine tissue is anisotropic, viscoelastic, and nonlinear elastic in addition to being heterogeneous [64,65]. Their properties are also asymmetric in tension versus compression [64,66].

Sections 3.1 and 3.2 provide an overview of the current literature on mechanical testing, including test methods that have been used for uterine and cervical tissue and the mechanical properties that have been measured, pointing out important gaps in knowledge. To date, data on the mechanical property of uterine tissue are very limited and exist primarily for nonpregnant human tissue for obvious ethical reasons. While there are significantly more data in the literature for cervical tissue, the mechanical behavior remains poorly understood.

3.1 Mechanical Testing and Properties of Uterine Tissue. Despite the extensive research that has been done on the active forces that occur during contractions [67,68], there are few data available on the passive mechanical properties of uterine tissue. This represents a significant gap in research that, if addressed, could contribute to major advances in the ability to model the cervical-uterine system. Some of the data that are available are described in the following text.

Whole uterine tissue, i.e., at the organ level, has not been characterized. There are no data available on animal uterine tissue, to the best of our knowledge. Uterine tissue has been tested in tension [66,69,70] and in static and dynamic compression [66,71] using either traditional mechanical testing system or ultrasound methods [72], as summarized in Table 2. While mechanical testing of uterine tissue in tension may yield the most physiologically

Table 2 Selection of literature, *ex vivo* uterine mechanics

Measured property	Test method	Reference
Stiffness	Tension, displacement control	[69]
	Compression	[66]
Failure properties	Tension, displacement control	[66]
	Ultrasound	[72]
Complex modulus	Ultrasound	[71]
	Ultrasound	[72]

relevant data, these tests are difficult to conduct because of challenges associated with mounting tissue samples. Planar biaxial testing of uterus is also complicated due to its thickness. Samples for compression testing [60,71,72] are more easily prepared, however, this deformation mode may be less relevant.

Techniques that use ultrasound may potentially be used *in vivo* in the clinic, but cannot measure all deformation modes. In particular, tensile properties are difficult to measure using ultrasound. Therefore, these approaches may not provide sufficient data for comprehensive mechanical models. The pulse-echo technique and ultrasound elastography are the two methods that use ultrasound to measure the elastic properties of uterine tissue. The former determines Young's modulus by evaluating the transmitted pulse through tissue and the velocity of the propagating pulse. The speed of sound through the tissue v is related to the modulus E by $E = v^2 \rho$, where ρ is the density of the sample [72]. Elastography uses ultrasound imaging in conjunction with mechanical deformation in order to differentiate between tissues of different stiffness, such as healthy and cancerous breast tissues [73]. Kiss et al. [71] used this method to identify uterine pathologies such as leiomyomas, which are benign fibrous tumors of the uterus. While ultrasound elastography is a reasonable method to identify such regions, it is not as useful in quantifying the absolute mechanical properties for input into mechanical models. The method is perhaps most useful for differentiating between softer and stiffer tissue within a region of interest.

The data in Fig. 4(a) illustrate the nonlinear elastic behavior of the uterine tissue, along with differences between pregnant and nonpregnant tissue tested in tension [69]. Figure 4(b) highlights the anisotropy and viscoelasticity. The complex modulus is higher when loaded parallel to collagen fibers, as would be expected from a fibrous material. The tissue is stiffer in tension than compression, owing to the fact that fibrous collagen is optimized for tensile loading. The variation in properties with cyclic loading frequency, shown in Fig. 4(b), is one measure of viscoelastic behavior [71]. The data support the variability of results that are due to the complexity and heterogeneity in composition and structure, which also contribute to the difficulty in obtaining accurate and relevant experimental data for models.

Uterine samples from the inner and outer layers of the uterus were tested in tension and compression by Pearsall and Roberts. They found that the outer layer was more compliant in compression,

but was stiffer in tension [66]. The alignment of the smooth muscle fibers and the ECM along the long axis of the uterus is consistent with the uterine tissue being stiffer in tension.

3.2 Mechanical Testing and Properties of Cervical Tissue.

Studies of the mechanical properties of cervical tissue often aim to address cervical insufficiency [74–76]. Cervical insufficiency is the painless, contraction-free, dilation of the cervix at midgestation. While there has been significantly more characterization of the cervix compared to uterine tissue, there remain large gaps in the literature. The knowledge is essential for developing comprehensive models of the relationship between the cervical structure, composition, and mechanical properties. First, there is no standardized or universally accepted procedure by which to measure cervical mechanical properties. Second, the property (or properties) most appropriate for diagnosing cervical insufficiency or characterizing cervical remodeling has (have) not been established. As a result, investigators have used different test protocols to measure a range of properties, making it difficult to directly compare results across studies. Third, nearly all of the tests have been conducted *in vitro* and/or without directly considering the relationship or interactions between the cervix and the uterus during gestation and labor. Only one mechanical model exists that considers both the cervix and uterus [19]. The lack of appropriate models of cervical and uterine mechanics likely results from the aforementioned gaps in knowledge. Thus, there is a significant need for both the experimental testing and theoretical modeling of the mechanical behavior of the tissue.

Despite the significant shortcomings in the mechanical test data, some basic trends of the mechanical properties of the cervix do emerge from the literature. The goal here is to give a general overview of those studies and the corresponding trends, as shown in Tables 3 and 4 [77–104]. The aim is not to report on the specifics of all the work to date. The properties of cervical tissue change with gestation, age, and the health of the individual. Researchers have measured properties of human, mouse, rat, and sheep cervixes and have tested cervical tissue primarily in tension and *in vitro* (see Table 3). Some data date back several decades. Tensile tests of small animal tissue are typically conducted using the entire cervix, while samples from larger animals consist of strips or biopsied tissue cut to a specific test geometry. Only a couple of studies, to our knowledge, have tested cervical tissue in

Fig. 4 Representative data from the literature showing the complex mechanical behavior of uterine tissue. (a) The nonlinear elastic behavior in the stress-elongation data and differences for pregnant versus non pregnant tissue [69]. Nonpregnant uterine tissue is stiffer than pregnant tissue for the entire range of stress and elongation shown. (b) Representative examples of anisotropic and viscoelastic behavior in uterine tissue. The complex modulus depends, to a great extent, on the collagen fiber orientation, loading frequency, and amount of precompression. In addition to the complex modulus being greater for loading parallel to fibers, it also increases with increasing loading frequency [71].

Table 3 Selection of literature, *ex vivo* cervix mechanics

Measured property	Test method	Species ^a	Sample	Correlation ^b				Reference
Stiffness	Tension, load control	S	Partial hysterectomy	M	T	[54]		
	Tension, displacement control	R	Whole canal	A	G	S	[86]	[87]
				A	G		[88]	[89]
				A			T	[90]
				A			T	[72]
				A			T	[76]
		M	Partial hysterectomy	A		M	T	[91]
				A	B	G		[92]
				A		M	T	[93]
							T	[94]
					B	H		[64]
	Compression, displacement control	H	Biopsy (NP)	B		S		[95]
					H	M	S	[65]
				B	H	M		[96]
				B	H			[97]
							T	[94]
				B	H			[64]
					H	M	S	[65]
								[77]
				A	B	G		[100]
				A		G		[101]
Creep or stress Relaxation	Tension, load control	R	Whole canal	A	B	G		[102]
				A			M	[53]
				A			M	[75]
				A			M	[103]
					B			[92]
					B			[104]
					B			[86]
					B			[95]
					B	H		[64]
					H	M	S	[65]
	Tension, displacement control	H	Partial hysterectomy					[77]
								[94]
								[97]
								[96]
								[64]
Failure properties	Tension, load control	R	Whole canal	A	B	G		[95]
								[77]
								[94]
								[97]
								[96]
Complex modulus	Ultrasound	H	Partial hysterectomy					[64]
								[95]
								[72]
								[95]
								[71]

^aR = rat; M = mouse; S = sheep; and H = human.

^bA = gestational age; B = biochemistry (ECM composition); G = geometry (usually cervical diameter); H = patient history (including previous births, abortion, cervical instability, etc.); M = mouse; S = anatomical site (usually internal versus external); and T = treatment (including drug, hormone, surgery, etc.).

Table 4 Selection of literature, *in vivo* human cervix mechanics

Measured property	Test method	Pregnant ^a	Correlation ^b	Reference
Stiffness	Aspiration	NP		[85]
				[84]
	Dilation	P	A	[83]
		NP		[78]
		P		[79]
Creep or stress relaxation	Balloon catheter	NP	G	[81]
		NP		[85]
	Aspiration			[84]
				[82]
				[82]

^aP = pregnant; NP = nonpregnant.

^bA = gestational age; G = geometry (usually cervical diameter); and H = patient history (including previous births, abortion, cervical instability, etc.).

compression and, in these studies, small samples were cut from different locations in the human cervix in order to capture any anisotropy and heterogeneity in the mechanical properties [65,71].

In cervix animal studies, typically conducted on rats or mice, a pair of parallel rods are passed through each of the cervical canals (mice and rats have two canals) and then mounted in a testing device [77]. This approach, however, does not abide by some basic rules of mechanical testing in tension; the material or tissue between the rods should have a smaller cross-sectional area than the material or tissue close to the grips in order to ensure that deformation is confined to the region between the rods, or the gauge section. With the described approach, the thicker portion of the sample is within the gauge section, while the thinner weaker tissue is near the grips. Thus, while relative properties may show consistent trends, absolute properties may not translate well across studies and the data cannot really report material properties *per se*.

Measures of viscoelasticity that have been used to characterize the properties of cervical tissue include creep and stress relaxation (see Table 3). The complex modulus has also been measured for

the cervix [71]. Lumped parameter models, consisting of springs and dashpots, which represent the elastic and viscous (time/frequency dependent) response of the tissue, respectively, offer a more comprehensive description of viscoelastic behavior [65].

The trends in the mechanical properties of the cervix with gestational age are that stiffness decreases, extensibility increases, creep rate increases, and the load to failure, or strength, decreases (see Table 3 for a selection of studies). An early comprehensive study of rat cervical tissue was published in 1959 by Harkness and Harkness [77]. This paper detailed the change in stiffness with gestational age and cervical circumference using creep tests and also measured the collagen content and concentration in cervical tissue. Since that time, a wide number of studies have looked at how stiffness or creep correlate with gestational age, cervical geometry, obstetric history, biochemical composition, collagen microstructure, or with the application of some treatment. The most quantitative and comprehensive research published on cervix mechanics to date is a pair of papers published by Myers et al. on human tissue [64,65]. The earlier of these papers reported correlations between several quantitative mechanical properties and the biochemical composition of the obtained cervix tissue, with the goal of establishing structure-function relationships, including capturing tissue anisotropy.

A number of techniques have been developed to quantitatively measure stiffness *in vivo* in humans (see Table 4), including cervical dilators that stretch the cervical canal [78–80], balloon catheters that inflate within the canal [81,82], and aspirators that apply suction to a small part of tissue and measure deflection of the tissue in the aspirator [83–85]. The balloon catheters and cervical dilators measure the resistance, i.e., stiffness, of the cervix during dilatation. While the dilators and aspirators make some measure of the stiffness of the cervix *in vivo*, they do not measure “material properties,” which are independent of the sample geometry and size. Therefore, data obtained using these approaches cannot be used as input in mechanical models.

4 Utility of Finite Element Modeling for Assessing the Response of the Uterus and Cervix as a System

One of the goals of this paper is to illustrate the need and the utility for continuum finite element (FE) models that have the ability to simulate the interactions between the cervix and the uterus during pregnancy and labor. Previous research has primarily focused on evaluating the mechanical properties of cervical tissues with very little research on the mechanical properties of the uterus. Still, neither tissue is adequately characterized.

There is but one FE model for preterm birth in the literature that includes both the uterus and the cervix [19]. While this was a critically important initial step in modeling this system, the details of the model were few; the presentation of the model did not provide details on the assumptions, boundary conditions, or material properties and the details of the results were not presented. A separate group of studies modeled the system in simulated automobile crashes [105,106] and studied the interaction between the uterus, ligaments, and other organs in that context. These highlight the need to consider all of the boundary conditions in the system, but because they treat the uterus and cervix as a single material, the model is not useful in the context of preterm birth.

Intuitively, there must be a mechanical interaction between the cervix and the uterus; two connected components in a structure must interact and the specifics of the interaction depend on the connection at their interface, their connection with surroundings (i.e., boundary conditions), and on loading. Therefore, an accurate assessment of cervical deformation during pregnancy and labor requires modeling the uterus and cervix, together as a system, while taking into account the appropriate loading, such as those caused by the weight of the baby or due to contractions, along with other boundary conditions, such as the attachments of ligaments and the constraints they impose.

For this paper, we develop two simplified 2D FE models to illustrate the possible utilization of a simplified numerical model to address the complex issue of uterine-cervical interaction. The model is used to demonstrate the influence of the material properties and shape of the cervix, T versus U (Fig. 1), on the separation of the cervical canal walls along the length of the canal during physiological loading (i.e., not labor contractions). (It is important to note that the model is used in this paper for illustrative purposes and is not intended to provide a detailed evaluation of the uterine-cervical interaction.) The reason for developing 2D models is because they are much more efficient, as compared to 3D models, if the problem investigated is planar or could be idealized as planar. Three-dimensional models are computationally expensive and rather impractical, particularly when used in parametric studies. Indeed, in some cases the idealization of a 3D problem into a 2D one could result in a loss of accuracy in the simulations. This is particularly the case when large out-of-plane deformations are expected, which is not the case for this analysis. Here, we subject the models to varying levels of hydrostatic pressure in order to assess the susceptibility for cervical dilation and preterm birth at an early gestational age, i.e., prior to the active labor phase of pregnancy.

4.1 Description of the 2D Model. This 2D finite element model evaluates morphological changes in the cervix under two different geometries to demonstrate how small differences can cause a predisposition to advancing cervical dilation. The first geometry is what is considered normal for most gravid women, the ‘T’ or closed cervix (see Fig. 1). The second geometry, the ‘U’ geometry, is associated with cervical funneling or cervical shortening (see Fig. 1). The model is based on an illustration in Williams [107] and was scaled such that the length of the uterocervix was 35 cm and the width 23 cm. The finite element software package ABAQUS [108] was used to develop the models. Both the ‘T’ and ‘U’ models are shown in Fig. 5.

In order to demonstrate the utility of a finite element model in investigating uterine-cervical interactions, we evaluate the differences associated with changes in hydrostatic pressure as the loading condition. There are a number of sources of changing hydrostatic pressure during pregnancy, independent of labor contractions. The uterine wall is subjected to hydrostatic pressure early in pregnancy due to expansion of the amniotic sac [109]. Situations that are associated with increases in hydrostatic pressure during pregnancy such as polyhydramnios, a condition of excessive amniotic fluid, are associated with preterm birth [110]. An increase in intrauterine hydrostatic pressure occurs with the application of fundal pressure (pushing on the top portion of the uterus), and can also be associated with cervical change and deformation [111]. It is well documented that the uterus irregularly contracts throughout gestation [112]. These irregular nonlabor contractions will also increase the hydrostatic pressure. Understanding the role of hydrostatic pressure on the uterine cervical interaction under different geometric constraints or in relationship to changes in tissue property can provide useful insight into understanding mechanisms involved in preterm birth and term labor.

The model consists of a continuum, 2D, plane strain elements for the uterus, the cervix, and the bony tissue. The uterosacral and cardinal ligaments are modeled using truss elements that will only take axial tension (i.e., no compression). The cervix itself has a Young’s modulus of 40 MPa, which is in the range of that for tissue from a nonpregnant woman, or 2 MPa, which is abnormally soft and similar to tissue immediately post-partum [97]. The resistance of the cervical canal to opening under hydrostatic pressure is modeled using a series of spring elements with spring constants chosen to match the load-deformation relationship for the rest of the cervix. The models are analyzed under two different hydrostatic pressures, selected based on pressures observed commonly in labor (45 mm Hg) and during induced preterm labor (95 mm Hg). The Young’s modulus of the uterus is 566 kPa [105]

Fig. 5 The 2D finite element models of the 'T' and 'U' geometries

in all of the analyses. The modulus of a short transition region between the cervix and uterus is assigned the average of the two tissues. The Poisson's ratio used in the model is 0.40. Pinned boundary conditions were applied around the bony tissue (see Fig. 5) and at the bottom of the cervix in order to prevent translation of the system.

4.2 Finite Element Model Results and Discussion. In these illustrative simulations, we focus on the widening of the cervical canal at several points along its length. We evaluate the absolute change in width rather than strain because this value has greater clinical relevance. In managing preterm labor, a change in cervical diameter from 3 to 6 cm (a 100% change) would indicate that delivery is imminent and no intervention could delay it. A change

from 1 to 2 cm (also 100% change) would still allow clinical interventions that could effectively delay delivery.

Hydrostatic pressure applied to the interior surfaces of the uterus and cervix causes a widening of the cervical canal in all four cases (see Fig. 6). As would be expected, the canal widens more for the higher pressure, 95 mm Hg, as compared to the lower pressure, 45 mm Hg. In fact, the increase is almost double. In all four cases shown, the canal for the softer cervix widens much more than for the stiff one and the difference between them is approximately an order of magnitude. Widening for the 'T' cervix is greatest near the internal os, although small changes in width occur along the entire length of the canal. For the stiff cervix at both pressures, the increase in width would not be measurable by the clinician making an evaluation based on the Bishop score and the patient would certainly not be considered at risk. This is not

Fig. 6 Deformation (widening) of the seven springs representing the cervical canal. An increase in the pressure results in increased widening ((a) versus (b), (c) versus (d)), as does softening of the tissue ((a) versus (c), (b) versus (d)). The greatest deformation of 'T' cervixes is located at the internal os, while the greatest deformation of 'U' cervixes is shifted towards the external os.

the case for the soft cervixes, where changes at the external os for the 'U' cervix approach a quarter of a centimeter. The final observation is that the canal does not widen uniformly for any of the four cases.

The model clearly demonstrates that opening of the cervical canal is influenced by each of the individual variables: soft versus stiff cervix, 'T' versus 'U' shape, and increasing hydrostatic pressure. The values chosen are relatively conservative and we argue that these are reasonable representations of physiological conditions, although we do recognize that we have not taken the complex viscoelastic behavior of these tissues into account.

The final observations are in regard to clinical implications of the results. We note that the soft, T-shaped cervix at high pressure will open at the internal os, over 0.25 cm, which would not be detected digitally by the clinician, but that could still have implications to preterm birth. Similarly, for the soft, U-shaped cervix, the maximum opening is approximately 0.5 cm, which is twice the change observed in the T-shaped cervix, demonstrating the importance of geometry on the risk of preterm birth. In our comparisons of stiff versus soft, 'T' versus 'U' geometry, and low and high pressure, the observed changes in cervical stretch are what would clinically be expected. These examples further highlight the clinical utility of such models in understanding the factors associated with changes in the cervical canal and the associated risk for preterm birth.

5 Summary and Conclusions

In this paper, we review the literature on the mechanical properties and mechanical testing of cervical and uterine tissue in order to highlight the gaps in knowledge in these areas. We also describe the geometric, compositional, and microstructural changes of these two organs during pregnancy and assert that these changes are interrelated and, together, all significantly influence the mechanics of the cervical-uterine system. Developing models that include all of these factors are critically needed in order to make progress in understanding the mechanics of preterm birth. Finally, we present a 2D model that highlights several of these important factors, such as the pressure, cervix geometry, and cervical stiffness, under physiologic, nonlabor, loading conditions.

One of the major gaps in the conduct of preterm labor and birth research is the lack of appropriate animal and theoretical models to test hypotheses. Animals do not typically deliver preterm [113]. Thus, in animals, preterm birth conditions need to be induced or stimulated by various methods. Animal models can be expensive and their anatomy and physiology may not directly relate to the human condition [113]. Our ability to assess the uterine cervical interaction in humans is limited by ethical issues in imaging and obtaining human tissue during pregnancy. In addition, conducting experiments to induce preterm birth in an otherwise normal pregnancy would not be acceptable. Finite element modeling of human parturition is important because it has the potential to simulate clinical scenarios, tissue properties, and functions without the use of humans or animals.

Research on the mechanical properties of the tissues and the interactions between the cervix and uterus are critical for developing accurate models for evaluating premature birth, which is still a major problem in the U.S. and worldwide. Much more research needs to be done to understand the mechanics of this process. More extensive and uniform characterizations of the mechanical properties of cervical and uterine tissue are needed in order to develop accurate models that capture cervical-uterine interactions and the evolution of the geometry, composition, microstructure, and properties of the system over the course of the pregnancy.

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