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The mechanical role of the cervix in pregnancy

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ABSTRACT

Appropriate mechanical function of the uterine cervix is critical for maintaining a pregnancy to term so that the fetus can develop fully. At the end of pregnancy, however, the cervix must allow delivery, which requires it to markedly soften, shorten and dilate. There are multiple pathways to spontaneous preterm birth, the leading global cause of death in children less than 5 years old, but all culminate in premature cervical change, because that is the last step in the final common pathway to delivery. The mechanisms underlying premature cervical change in pregnancy are poorly understood, and therefore current clinical protocols to assess preterm birth risk are limited to surrogate markers of mechanical function, such as sonographically measured cervical length. This is what motivates us to study the cervix, for which we propose investigating clinical cervical function in parallel with a quantitative engineering evaluation of its structural function. We aspire to develop a common translational language, as well as generate a rigorous integrated clinical-engineering framework for assessing cervical mechanical function at the cellular to organ level. In this review, we embark on that challenge by describing the current landscape of clinical, biochemical, and engineering concepts associated with the mechanical function of the cervix during pregnancy. Our goal is to use this common platform to inspire novel approaches to delineate normal and abnormal cervical function in pregnancy.

1. Introduction

The cervix is contiguous with the lower part of the uterus. Its proximal portion is located in the abdomen and its distal portion in the vagina. It has a narrow central canal which runs along its entire length, connecting the uterine cavity and the lumen of the vagina. The opening of this canal into the uterus is called the internal os and the opening into the vagina the external os (Fig. 1A). During pregnancy, the primary biomechanical function of the cervix is to maintain the fetus within the uterus. This requires withstanding multiple forces from the uterus, including the weight of the growing fetus and amniotic sac, as well as passive pressure from the uterine wall. Then, in a dramatic reversal of roles, the cervix markedly softens, shortens and dilates to allow delivery of the fetus. Shortly after delivery, the cervix reforms into its previous shape and consistency. How the cervix manages these complex dynamic changes is an interesting and understudied biomechanics problem.

Critical problems can occur when the timing and extent of the biomechanical changes are altered. Specifically, premature softening, shortening and dilation, which may be considered early mechanical failure, occurs in cases of spontaneous preterm birth (sPTB). The underlying pathophysiology of these changes is poorly understood despite that preterm birth affects 15 million babies annually, is the leading cause of childhood (<5 years old) death, and in 2013 was responsible for 1 million deaths (World Health Organization, 2014). The rate of preterm birth has significantly decreased by 2 decades of intense research effort into its pathophysiologies and associated molecular mechanisms. We believe that this lack of progress is partly due to lack of crosstalk between clinicians, engineers and basic scientists, and that progress will require multidisciplinary collaboration between previously distinct areas of expertise such as clinical obstetrics and engineering.

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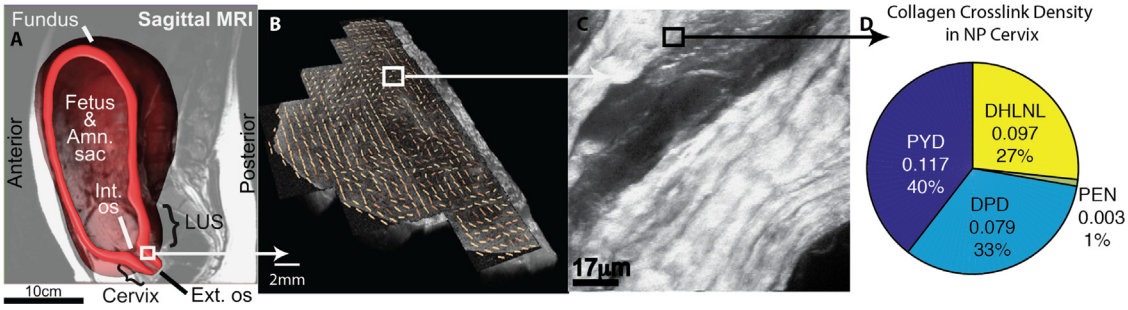

Fig. 1. Biological length scales in the human cervix. (A) The location of the uterine cervix based on segmentation of magnetic resonance imaging (MRI) data of a 22 week pregnant patient (Fernandez et al., in press). (B) Collagen fiber directionality of an axial slice of a nonpregnant (NP) cervix imaged via optical coherence tomography (Gan et al., 2015). (C) NP cervical collagen fiber imaged via second harmonic generation (Myers et al., 2009). (D) NP cervical crosslink density (mole-per-mole basis with collagen) content, pyridinoline (PYD), deoxypyridinoline (DPD), dihydroxylysinonorleucine (DHLNL), pentosidine [PEN] (Zork et al., 2015).

To begin that dialogue, here we provide an engineering framework for studying the mechanical function of the cervix during pregnancy. The main steps include modeling the material behavior of the cervix, characterizing the pelvic anatomy, capturing the appropriate contact conditions between the pelvic soft tissues, and understanding the relevant loading and boundary conditions. Accomplishing these tasks are a challenge because, in addition to understanding the basic material and anatomical parameters, one must consider the changes that occur throughout pregnancy to accommodate the growth and ultimate delivery of the fetus. However, overcoming these engineering challenges could lead to a better understanding of normal and pathological cervical deformation.

2. The clinical problem of preterm birth

2.1. Scope of the problem

Preterm birth is defined as delivery between 20 weeks and 36 weeks+6 days gestation. Medically indicated preterm birth may result from maternal factors (e.g. preeclampsia or placenta previa) or fetal factors (e.g. oligohydramnios or growth restriction). Spontaneous preterm birth (sPTB) was formerly divided into two general categories, namely *cervical dysfunction* (*cervical insufficiency* or *cervical incompetence*) or *preterm labor* (typically thought to be the result of intrauterine infection or bleeding). A more current understanding is that sPTB from all causes can be seen as part of an extremely complex continuum involving multiple phenotypes (Barros et al., 2015; Solomon and Iams, 2014). The etiology of sPTB is multifactorial, involving diverse precipitating factors such as infection and inflammation, bleeding, poor nutrition, demographics, stress, ethnicity and race, genetic predispositions and many others, all presumably with individual, and overlapping, molecular mechanisms (Gravett et al., 2010). A recent attempt to categorize phenotypes of preterm birth showed that approximately 25% of these births are neither medically indicated nor associated with any known phenotype (Barros et al., 2015).

Organizations such as the March of Dimes have recently celebrated a decline in the preterm birth rate (from 12.8% in 2006 to 11.4% by 2013), but data from the Centers for Disease Control shows that the sPTB rate in 2012 was nearly identical to that in 1997 (Martin et al., 2013; Schoen et al., in press; Solomon and Iams, 2014). Strategies to address known risk factors (e.g. genitourinary infection and poor nutrition) have been ineffective, as have drug therapies targeted against uterine contractions, infection, or inflammation (Gravett et al., 2010; Solomon and Iams, 2014). The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine promote intramuscular progesterone treatment in patients with a history of sPTB, and vaginal progesterone supplementation or cerclage (a suture tied around the cervix) in patients with a short cervix in the current pregnancy (American College of Obstetricians and Gynecologists, 2012; Society for Maternal-Fetal Medicine Publications Committee, 2012). Importantly however, the decline in preterm birth has been attributed primarily to provider education, which has resulted in fewer nonmedically indicated deliveries $<$ 39 weeks, fewer teenage pregnancies, less smoking in pregnancy, and fewer twin and triplet pregnancies (Schoen et al., in press; Solomon and Iams, 2014). Progesterone supplementation and cerclage in selected patients are "probably contributing" according to a 2015 review (Schoen et al., in press), but this is obviously unclear, as are the mechanisms by which these treatments work, which must contribute to the reason current interventions that are ineffective in the vast majority of patients (American College of Obstetricians and Gynecologists, 2012; Conde-Agudelo et al., 2013; Grobman et al., 2012).

As stated recently by Norman and Shennan, the fact that 95% of sPTB is intractable to current therapies suggests that substantial further research is needed (Norman and Shennan, 2013). An understanding of the molecular mechanisms of the multiple pathways to sPTB is essential to the development of etiologic- and patient-specific interventions for patients at high risk and avoidance of unnecessary and potentially detrimental treatment in those at low risk (Feltovich et al., 2012; Iams and Berghella, 2010). We think the cervix is the logical place to start this investigation because cervical ripening is the last step before labor and delivery in the sPTB pathway, the final common denominator of a multitude of overlapping etiologies (Gracie et al., 2011; Gravett et al., 2010).

2.2. The role of the cervix in PTB and the importance of cervical remodeling

Clinicians use terms such as *softening*, *shortening*, *funneling*, *effacing*, and *dilating* to describe the cervical deformation that occurs during pregnancy (Fig. 2). Collectively, these changes are called *cervical remodeling* and refer to both the tissue's intrinsic material property changes and its resultant anatomical changes. Mouse models demonstrate a distinct separation between an early phase of remodeling that starts soon after conception and continues through delivery (*cervical softening*) and a later phase, near delivery, that involves rapid, marked softening and shortening (*cervical ripening*) (Akgul et al., 2012; Holt et al., 2011; Mahendroo, 2012; Read et al., 2007; Timmons et al., 2010a; Word et al., 2007). This process is not yet well characterized in human pregnancy. As in the mouse, cervical softening in human pregnancy begins early, a fact that was exploited to detect pregnancy as early as 6 weeks of gestation in the 19th century before diagnostic blood and urine tests were developed. Recent *in vivo* mechanical interrogation of the cervix (Badir et al., 2013a; Parra-Saavedra et al., 2011) supports

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