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Computer modeling tools to understand the causes of preterm birth

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ABSTRACT

The mechanical integrity of the soft tissue structures supporting the fetus may play a role in maintaining a healthy pregnancy and triggering the onset of labor. Currently, the level of mechanical loading on the uterus, cervix, and fetal membranes during pregnancy is unknown, and it is hypothesized that the over-stretch of these tissues contributes to the premature onset of contractility, tissue remodeling, and membrane rupture, leading to preterm birth. The purpose of this review article is to introduce and discuss engineering analysis tools to evaluate and predict the mechanical loads on the uterus, cervix, and fetal membranes. Here we will explore the potential of using computational biomechanics and finite element analysis to study the causes of preterm birth and to develop a diagnostic tool that can predict gestational outcome. We will define engineering terms and identify the potential engineering variables that could be used to signal an abnormal pregnancy. We will discuss the translational ability of computational models for the better management of clinical patients. We will also discuss the process of model validation and the limitations of these models. We will explore how we can borrow from parallel engineering fields to push the boundary of patient care so that we can work toward eliminating preterm birth.

Introduction

Preterm birth (PTB) is defined as a live birth that occurs before 37 weeks' gestation.[1] It is the leading cause of death in children under the age of five, reaching 1.1 million annually.[2] Each year there are an estimated 500,000 cases of preterm birth in the US.[1] As many as 95% of cases are intractable to current therapies,[3] suggesting the need for continued investigations and medical discoveries. The average cost of a preterm newborn's first year of life is over 10 times that of a normal term baby's ($49,000 vs. $4,500).[4] Furthermore, PTB often leads to lifelong health complications such as cerebral palsy, asthma, and numerous learning disabilities, and has an estimated societal cost of at least $26 billion in the United States each year.[5]

Throughout gestation, the fetus is supported and protected by biologically active soft tissue structures. These structures send mechanical signals that can trigger tissue remodeling and contractility through mechanosensitive cells (e.g., mechanotransduction). The mechanical integrity of the uterus, cervix, and fetal membranes are critical for a successful pregnancy, where the loss of structural integrity of these tissues is believed to contribute to spontaneous PTB. For

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example, in the case of cervical insufficiency (CI) the cervix dilates and shortens painlessly in the absence of uterine contractions.[6] CI is hypothesized to be caused by premature cervical remodeling and softening of the tissue. Preterm labor is believed to be caused, in part, by uterine overdistention, as evidenced by the higher rate of preterm labor for multiple gestations or excessive amniotic fluid.[7,8] A recent study investigated uterine overdistention in nonhuman primates by inflating intra-amniotic balloons. Results showed uterine overdistention caused preterm labor triggering a cascade of cytokines and prostaglandins associated with inflammation.[9] Premature preterm rupture of membranes (PPROM) occurs due to damage of the collagen in the chorioamnion, causing a mechanical tear in the membrane. Clinical studies show excessive collagen degradation in chorioamnion and amniotic fluid samples that have experienced PPROM.[10] The hypothesized causes of PPROM include an insufficient cervix, hydramnios, trauma, and amniotic fluid infection.[11]

Characterizing reproductive tissues in real time and accessing organs to measure anatomical and tissue properties throughout gestation is challenging. Hence, a driving engineering motivation is to use biomechanical models of pregnancy to understand the mechanical functions and dysfunctions of the tissues during pregnancy. The purpose of this review article is to introduce and discuss engineering analysis tools to evaluate and predict the mechanical loads on the uterus, cervix, and fetal membranes. Medical imaging such as magnetic resonance imaging (MRI) and ultrasound are minimally invasive, yet provide thorough anatomies of a patient's anatomy. These anatomies can be implemented in biomechanical models to simulate gestational scenarios without providing any harm to pregnant patients. Here we will explore the potential of using computational biomechanics and finite element analysis to study the causes of preterm birth and to develop a diagnostic tool that can predict gestational outcome.

Engineering definitions

A biomechanical model quantitatively represents the geometry and mechanical properties for a single tissue, organ, or a system of load-bearing tissues and organs. The model aims to solve for the amount of tissue stress and stretch as the result of external mechanical loading. Mechanical models depend on strict definitions of force, deformation, stress, strain, and stretch. We briefly explain them here. The term stress represents the amount of force carried within the tissue normalized by its geometry. It is a three-dimensional term, where the amount of stress will vary depending on the direction. Simply put, stress (σ) is defined as a force (F) per unit area (A), $\sigma = F/A$, with units of pressure N/m^2 or Pa in metric and lb/in^2 or psi in the English unit system. Due to its direction-dependence, there are multiple types of stress: normal stress occurs when the force vector is perpendicular to the surface, and shear stress occurs when the force vector is parallel to the surface. If the force vector is somewhere in between perpendicular and parallel to the surface, both stress components are present. Strain (ε) is a measure of deformation of the tissue due to stress, and it is also normalized by geometry. Because stress is direction-dependent, strain is also direction-dependent. Simply put, it can be expressed as the change in tissue length (Δl) over the original length (l_0), $\varepsilon = \Delta l/l_0$. Strain is often reported as a percentage. Stretch is similar to strain and is typically used for materials that undergo large deformations, such as soft biological tissues. Stretch (λ) is the ratio between the current length at a given applied force (l) and the original length (l_0) of the material, $\lambda = l/l_0$. It is reported as a unitless ratio and not a percentage.

In addition to accurately describe the shape and size, a biomechanical model also requires the mechanical properties of the tissues in the system. Tissue mechanical properties are the quantitative values that relate the amount of tissue stress σ with the amount of strain ε (or stretch λ). This mathematical relationship is called a material model, and the equation parameters are the material properties of the tissue. Material properties are found by isolating the tissue and conducting a series of mechanical tests. The most basic, and often most informative, mechanical test is a uniaxial tensile test. In this test, a uniform piece of tissue is gripped within a material tester by each of its end. The material tester displaces the grips by prescribed displacement values Δl, and the force F is measured as the tissue is pulled in tension. The material tester records force F as a function of grip displacement Δl, and stress σ and strain σ are then derived from these values and are normalized by the cross-sectional area A of the tissue.

The shape and magnitude of the experimental stress σ versus strain ε curve for a given material is the material behavior of the tissue. The mathematical equation describing the material behavior is the material model, where model parameters are *tissue material properties* (or tissue mechanical properties). Material properties must be strictly defined within each modeling context because the terms such as stiffness and strength have specific meanings in the field of mechanics. The simplest of material behavior is linear elastic, where there is a linear relationship between stress σ versus strain ε This type of material is described by two material parameters: the Young's modulus E and the Poisson's ratio ν. The Young's modulus E of a material is often referred to as the stiffness of a material, and is the slope of the stress σ versus strain ε curve. Material compliance is the inverse of material stiffness $1/E$, often thought of as the material's flexibility. A material that deforms easily is said to be compliant, while a material that resists deformation is said to be stiff. Also identifiable on a stress–strain curve is the strength of a material. Yield strength is the point at which the stress–strain curve begins to deviate from a straight line, and represents the lowest stress that produces permanent deformation of a material. Poisson's ratio of a material (ν) is the ratio of lateral strain to axial strain when a material is in tension: $\nu = -(\varepsilon_{yy}/\varepsilon_{xx})$. In other words, it is the amount of transverse extension divided by the amount of axial compression. For example, when you stretch a rubber band, the band will become longer, but the width of the band will become narrower. Materials that are truly incompressible have a Poisson's ratio ν of 0.5, since the sum of all their strains result in zero volume change.

Soft biological tissues have a complex material behavior because the material is made of an intricate network of long-