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The pathophysiology of human premature cervical remodeling resulting in spontaneous preterm birth: Where are we now?

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ABSTRACT

Approximately one in ten (approximately 500,000) pregnancies results in preterm birth (PTB) annually in the United States. Although we have seen a slight decrease in the U.S. PTB rate between 2007 and 2014, data from 2014 to 2015 shows the preterm birth rate has slightly increased. It is even more intriguing to note that the rate of PTB has not significantly decreased since the 1980s. In order to decrease the rate of spontaneous preterm birth (sPTB), it is imperative that we improve our understanding of normal and abnormal reproductive tissue structure and function and how these tissues interact with each other at a cellular and biochemical level. Since other chapters in this issue will be focusing on the myometrium and fetal membranes, the goal of this chapter is to focus on the compartment of the cervix. We will review the current literature on normal and abnormal *human* cervical tissue remodeling and identify gaps in knowledge. Our goal is also to introduce a revised paradigm of normal cervical tissue structure and function which will provide novel research opportunities that may ultimately lead to developing safe and effective interventions to significantly decrease the rate and complications of prematurity.

Introduction

Approximately one in ten (approximately 500,000) pregnancies results in preterm birth (PTB) annually in the United States.[1] Since premature babies are at significant risk of neonatal demise, complicated and prolonged NICU stays, lifelong disabilities, and chronic illnesses, the problem of PTB not only presents an emotionally challenging time for families impacted by a preterm birth, but it is also an enormous financial burden on US Healthcare. Caughey et al.[2] recently reported that based on cost estimates in 2006, the cost of PTB in 2015 was approximately $31 billion. Although we have seen a slight decrease in the US PTB rate between 2007 and 2014, data from 2014 to 2015 shows the preterm birth rate has slightly increased.[1,3] It is even more intriguing to note that the rate of PTB has not significantly decreased since the 1980s.[4,5]

Our field of Obstetrics has not been able to make an impactful and lasting dent in the rate of PTB in part for the following reasons. First, the etiology of sPTB likely involves extremely complex interactions between numerous factors including but not limited to genetics, hormones, the immune system, reproductive tissue properties (uterus, cervix, fetal membranes, and placenta), vascular system, nervous system,

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maternal anatomy (geometric factors), our microbiome, and the environment. In order to understand the impact of all these factors on pregnancy, we must start to look at the problem of preterm birth from a multidisciplinary perspective. Second, definitions of preterm birth (i.e., gestational age cutoffs) and outcomes of interest have not been standardized in studies making generalizability and comparability difficult. Along these same lines, there are several "phenotypes" of sPTB (i.e., those that start with premature activation of the fetal membranes leading to premature membrane rupture vs premature activation of the myometrium leading to preterm labor vs premature cervical remodeling leading to cervical failure) and we cannot assume that these phenotypes should be lumped into one category when analyzing sPTB.[6] Third, because pregnancy is a "protected state," progress in our field has been thwarted by the lack of ability to study gestational age-matched normal and abnormal human reproductive tissues (i.e., placenta, myometrium, fetal membranes, and cervical tissue) at various time points in pregnancy. The ideal progression in science is first to understand normal tissue structure and physiology, then characterize how normal tissue structure and function goes awry in disease states. Once we are able to detect these changes, we can then identify targets to alter the mechanistic pathways to either prevent or revert pathology back to the normal state. Since it is challenging, if not impossible, to obtain and test normal and gestational age-matched abnormal tissues in pregnancy, our field is left to make certain assumptions regarding mechanistic pathways leading to sPTB. This could be one reason why our current therapies are not always effective.

Although the inciting factors leading to sPTB vary, the final pathway to sPTB inevitably must involve premature remodeling/softening/shortening of the cervix leading to dilation of the cervix and delivery of the fetus. This point is exemplified by the fact that if the fetal membranes were to prematurely rupture or the patient went into preterm labor, the fetus would not be delivered if the cervix remained closed. In order to decrease the rate of sPTB, it is imperative that we improve our understanding of normal and abnormal reproductive tissue structure and function and how these tissues interact with each other at a cellular and biochemical level. Since other chapters in this issue will be focusing on the myometrium and fetal membranes, the goal of this chapter is to focus on the compartment of the cervix. We will review the current literature on normal and abnormal *human* cervical tissue remodeling and identify gaps in knowledge. Our goal is also to introduce a revised paradigm of normal cervical tissue structure and function that will provide novel research opportunities that may ultimately lead to developing safe and effective interventions to significantly decrease the rate and complications of prematurity.

Normal human cervical tissue structure and function—the prevailing paradigm

The cervix is the mechanical barrier located at the bottom of the uterus that keeps the uterus closed during pregnancy. As a pregnancy grows, the cervix must withstand tissue stresses generated from a complex set of forces from the weight of the growing pregnancy and pull of the uterine wall.[7] Our understanding of human cervical tissue structure was established in 1940s when Danforth[8–10] reported that the cervix is a predominantly homogenous, hydrated, collagenous structure [about 85–90% collagen/extracellular matrix (ECM) that contains proteoglycans, glycosaminoglycans, elastin, and matricellular proteins] and a minimal amount of cells (about 10–15%), which includes immune cells, fibroblasts, smooth muscle cells, and glandular/vascular cells. In addition, over time, an assumption has been made that there may be a distinct line that demarcates where the uterus (smooth muscle body) ends and the cervix (collagen/ECM) begins[11] (Fig. 1).

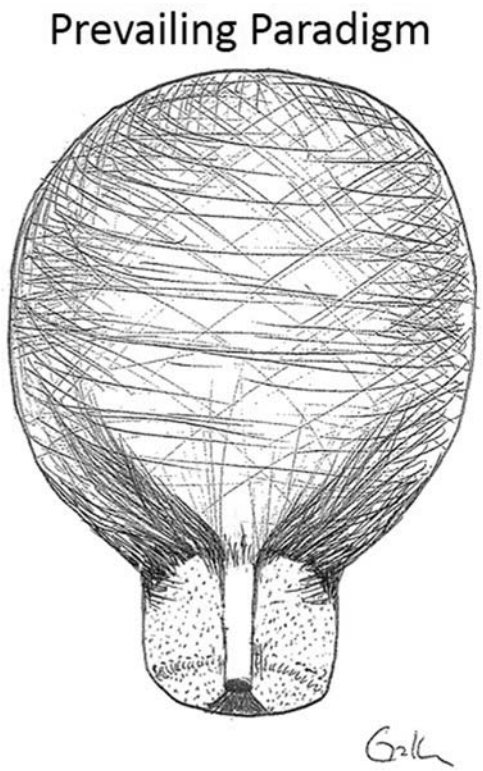

Fig. 1 – Image adapted from Vink et al.[11] showing the prevailing paradigm of cervical tissue structure. This paradigm states the cervix is mainly a homogenous collagenous structure with minimal cellular content. It also suggests a border may exist between the muscular body of the uterus and collagenous structure of the cervix.

Similar to other load-bearing tissues in the body (i.e., bone and tendon), the mechanical strength of cervix is thought to rely mainly in part on the collagen network in the ECM. Studies in the 1970s reported that the collagen network in the cervix is comprised of three distinct zones—one zone of collagen in the middle of the stroma that is oriented circumferentially around the endocervical canal (which provides resistance to cervical dilation) and an inner (toward the endocervical canal) and outer (toward the vagina) zone of collagen fibers that run parallel to the endocervical canal. These out and inner zones of collagen likely attach the cervix to the uterus[6,12,13] (Fig. 2). Recently, Yao et al.[14] used optical coherence tomography (OCT) to measure the orientation of collagen fibers and their distribution in the upper cervix using