Seminars in Perinatology ▮ (2017) ▮▮▮–▮▮▮

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Seminars in Perinatology

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Regular Articles

Prevention of preterm birth: Novel interventions for the cervix

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ARTICLE INFO

Keywords:
Preterm birth
Cervix
Remodeling
Cerclage
Pessary

ABSTRACT

Preterm birth is the leading cause of neonatal mortality and morbidity worldwide. Spontaneous preterm birth is a complex, multifactorial condition in which cervical dysfunction plays an important role in some women. Current treatment options for cervical dysfunction include cerclage and supplemental progesterone. In addition, cervical pessary is being studied in research protocols. However, cerclage, supplemental progesterone and cervical pessary have well known limitations and there is a strong need for alternate treatment options. In this review, we discuss two novel interventions to treat cervical dysfunction: (1) injectable, silk protein-based biomaterials for cervical tissue augmentation (injectable cerclage) and (2) a patient-specific pessary. Three-dimensional computer simulation of the cervix is performed to provide a biomechanical rationale for the interventions. Further development of these novel interventions could lead to new treatment options for women with cervical dysfunction.

Clinical background

Preterm birth, defined as birth before 37 weeks of gestation, is the major contributor of neonatal mortality and morbidity worldwide.[1] It can cause respiratory immaturity, intracranial hemorrhages and infections, and these conditions can result in a range of long-term complications such as intellectual impairment, cerebral palsy, chronic lung disease, deafness and blindness.[2] The frequency and severity of adverse outcomes of children born preterm increase with decreasing gestational age at birth.[1] Preterm birth is an important complication of both singleton and multifetal pregnancies and preventing preterm birth remains a challenge in clinical obstetric care.[1,2]

The worldwide incidence of preterm birth is 11.1%, which varies between countries within a range of 5–13% and results in

Supported in part by the Tissue Engineering Resource Center (TERC) from the National Institute of Biomedical Imaging and Bioengineering (EB002520) and by the March of Dimes Transdisciplinary Research Center for Preterm Birth at the University of Pennsylvania (21-FY15-002).

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http://dx.doi.org/10.1053/j.semperi.2017.08.009
0146-0005/

approximately 15 million children born preterm each year.[3] The highest rates occur in Southeastern and South Asia where 13.4% of the children are born preterm. Approximately 1.2 million preterm births occur in high-income countries, of which more than 0.5 million occur in the United States where the estimated preterm birth rate is 11–12%.[1]

Although preterm birth is a complex, multifactorial condition, in some women, cervical dysfunction plays an important role.[4] The composition and structure of the cervix controls its ability to remain closed during pregnancy to promote fetal development. In normal delivery, cervical effacement and dilation occurs at term. In preterm delivery, cervical effacement and dilation occurs prior to term, which can lead to a premature birth. Cervical dysfunction is detected by measuring a short cervix with transvaginal ultrasound.[5–7] The risk of preterm birth is inversely proportional to the length of the cervix, with a shorter cervix conferring a higher risk.[6]

Various treatment strategies to prevent preterm birth in women with suspected dysfunctional cervix have been studied, including cervical cerclage, cervical pessary and progesterone.[8] However, these treatment strategies are not effective in all patient populations at risk for preterm birth. There remains a strong need for alternative, effective therapies for preventing preterm birth in women with a dysfunctional cervix. In this review, we discuss two novel interventions to treat cervical dysfunction that are currently being studied; injectable, silk protein-based biomaterials for cervical tissue augmentation (injectable cerclage) and a patient-specific pessary. We also demonstrate a three-dimensional computer simulation of the interventions to provide a biomechanical rationale for efficacy. These complementary interventions aim to address the pathogenesis of cervical dysfunction and to support the native, physiological properties of the cervix.

Injectable biomaterials for cervical augmentation

Cervical remodeling

In spontaneous preterm birth, the final common event is softening, shortening, and dilation of the cervix, also referred to as cervical remodeling. Cervical remodeling relates to both changes in (1) the material properties of the stroma (i.e., softening) and (2) the anatomical shape of the cervix (i.e., shortening, effacement, and dilation).[4] There is a strong relationship between cervical remodeling and the organization and composition of the cervical extracellular matrix (ECM). The cervical ECM plays a key role in the maintenance of appropriate mechanical function of the cervix.[9] Excessive cervical softening appears to be related to preterm birth.[9] Preventing excessive softening, i.e., reestablishing the normal properties of the stroma, is a promising clinical target for the development of interventions that aim to prevent cervical dysfunction and preterm birth.[4]

Cervical cerclage

Currently, a cervical cerclage is an important treatment option for the prevention of preterm birth in women with suspected cervical dysfunction.[10–13] The fact that cervical cerclage is an effective treatment for a short cervix[13] suggests that cervical dysfunction is causally related to preterm birth in some women. A cervical cerclage is a surgical procedure in which a suture is placed in the stroma to provide added support for the cervix, as proposed by Shirodkar in 1955[14] and by McDonald in 1957[15]. Although a cerclage was efficacious in some studies,[13] no efficacy was seen in other studies.[16] In twins, cerclage may be associated with increased risk of adverse neonatal outcomes.[17] Moreover, placing a cerclage is not without risk. Complications of cerclage include preterm premature rupture of membranes (PPROM), infection, preterm labor, suture displacement, and bleeding.[18] In addition, cerclage is associated with an increased risk of cervical laceration, both in nulliparous and multiparous women.[19]

It is hypothesized that a cervical cerclage prevents premature cervical remodeling by providing support to the cervix. The exact mechanism, however, by which a cerclage provides support and prevents premature cervical remodeling remains unclear. In addition, a cerclage does not address excessive cervical softening, which likely relates to cerclage failure in some women. A comprehensive understanding of the complex process of cervical remodeling and the relationship between biochemical and mechanical properties of the cervix could lead to a more effective intervention to prevent spontaneous preterm birth.[4]

Cervical shortening—cause or consequence of preterm birth

Whether a short cervix causes preterm birth or is a consequence of a different pathophysiology is difficult to determine in individual patients. When a cerclage is not successful, it suggests either (1) the cerclage did not provide adequate support or (2) the cause was unrelated to cervical dysfunction. The most common pathophysiology associated with cervical shortening is infection and inflammation. Among women with clinically diagnosed cervical insufficiency (defined as cervical dilation ≥1.5 cm), the risk of intrauterine infection is 8–51%.[20,21] Among women with a short cervix, the levels of inflammatory cytokines (i.e., MMP-8 and IL-6) are increased.[22–24] In addition, the risk of adverse pregnancy outcomes are increased when cervical dysfunction and intrauterine infection/inflammation are present.[20,21,23,24]

Although infection and inflammation may be present in cases of cervical dysfunction, it is difficult to know the natural history of ascending infection in pregnancy. It is possible that ascending infection leads to subsequent cervical shortening/insufficiency. It is also possible that infection occurs as a consequence of a short cervix. If ascending infection is a consequence of a short cervix, a therapy that prevents cervical shortening could help prevent ascending infection. A hypothesis of this research is that, in some cases, a short cervix leads to an impaired cervical barrier to infection. We advocate for the importance of a detailed study of cervical biomechanics of cervical shortening, which could reveal interventions that provide better support for the cervix compared to present therapies. Improved interventions for the cervix could not only treat cases of cervical insufficiency but also prevent ascending infection in cases where a short cervix is the cause.