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Review

Future directions in preterm birth research

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SUMMARY

The problem of preterm birth continues to pose one of the most significant research challenges that we face due to its immense scope and complexity. With evidence that 95% of cases of spontaneous preterm birth are intractable to current interventions, our best hope in resolving this problem may lie in new, innovative ideas. Novel approaches to researching preterm birth are currently underway, building upon our prior discoveries and probing into the unknown on multiple fronts. Here we discuss some of the major focuses of future investigation that provide a promising outlook for discovery, including advanced techniques to evaluate the cervix, new strategies to identify the role of the microbiome, and advances in molecular and epigenetic-based research.

1. Future directions

The problem of preterm birth continues to pose one of the most significant research challenges that we face due to its immense scope and complexity. To date, we have made important progress in our understanding of the pathophysiology and its multifactorial etiology. The results of this work have led to the establishment of some preventive strategies; yet the complex nature of the problem has allowed it to remain elusive to our currently available interventions. In order to make a meaningful impact in dealing with the problem of preterm birth, which remains the leading global cause of neonatal death, we are in need of a substantial amount of further research [1].

One of the challenges inherent to investigating a problem of such a large scope is the uncertainty of whether or not we are asking the right questions. Prior research has developed a framework for us to build upon; however, with evidence that 95% of cases of spontaneous preterm birth are intractable to current interventions, our best hope in resolving this problem may lie in new, innovative ideas [2].

Novel approaches to researching preterm birth are currently underway, building upon our prior discoveries and probing into the unknown on multiple fronts. Here we discuss some of the major focuses of future investigation that provide a promising outlook for new discovery.

2. The cervix

The role of the cervix in spontaneous preterm birth has been an important area of focus for research; a sonographic short cervix detected in the second trimester remains our best predictor of spontaneous preterm birth [3]. But we have struggled to translate our knowledge of the cervix into the development of an unequivocal and efficacious treatment modality. New approaches to studying the role of the cervix use technological advancements, such as mechanical engineering, to reassess the anatomic considerations of the cervix and to identify how they relate to pathologic changes.

Investigation of cervical remodeling and the associated biomechanical processes that lead to premature softening, shortening, and dilation, represents a promising area for exploration. A recent comprehensive review by Myers et al. details current investigations into the clinical, biochemical, and engineering concepts associated with the mechanical function of the cervix during pregnancy [4]. Using advanced imaging techniques and mechanical tissue tests in the form of quantitative ultrasound and mechanical aspiration measurement procedures, we may soon be able to gain a more comprehensive understanding of the three-dimensional anatomy of the cervix, the changes it undergoes during pregnancy, and the characteristics that are associated with pathology. This can allow us

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to make significant progress in developing a comprehensive understanding of the three-dimensional anatomy of the cervix.

Quantitative ultrasound has been described as a useful, non-invasive tool in assessing the collagen-rich cervical microstructure [5]. The advantage that quantitative ultrasound techniques provide over standard ultrasound methods is their ability to address soft tissue characteristics directly, with less reliance on operator or system settings. Techniques for evaluating the cervix with quantitative ultrasound include palpation-type elastography, shear-wave elastography, acoustic attenuation, and acoustic backscatter measurements. Each technique uses a different modality to assess cervical properties, with each being used to primarily detect changes in the time-dependent material tissue response, tissue hydration status, or extracellular matrix structure [6]. Standardization and the establishment of normal control parameters are common needs for developing technologic modalities. Once these are developed, further studies can be undertaken to use these techniques to detect the pregnancy-related changes in cervical collagen and microstructure, and ultimately provide useful information in comparing normal and abnormal changes in cervical architecture.

Additional imaging techniques currently under development seek to build upon the use of elastography and overcome the inherent limitations. These include an ultrasonic sensor that is able to quantify the circumferential shear modulus of the cervix, and elasticity imaging methods based on 'remote palpation' that could assess the softness or stiffness of cervical tissue [6]. These systems have shown some promise outside of the field of obstetrics, and translating them to new roles in an assessment of the cervix may provide useful new information.

In addition to imaging, new mechanical testing technologies allow for in-vivo tissue analysis an area of further investigation. These include the EndoFLIP® balloon inflation device described by Hee et al. in 2014, and mechanical pipette aspiration devices used in multiple prior studies [7–11]. The utility of these devices may lie mainly in their ability to characterize the influence of the non-collagenous part of the extracellular matrix on the mechanical response of the pregnant cervix to strain [12]. The potential clinical importance of this has led to investigations that are currently ongoing.

A comprehensive understanding of the cervical microstructure will ultimately require a reliable, accurate method of evaluating the pregnant cervix. Table 1 includes a summary of the methods that are most recently described in the literature. Although these techniques provide promise for an accurate characterization of the microstructure of the pregnant cervix, most of them are still in need of significant development. The comprehensive understanding that we seek is likely to require further investigation of these methods, exploration into possible combinations of them, and perhaps even the development of novel approaches not yet discovered. Further investigation in the area of the cervical biomechanics will likely require an interdisciplinary approach that involves a collaboration of advanced imaging techniques, in-situ mechanical examination studies, material modeling, and biochemical analysis. The combination of these investigations is hoped to aid in our understanding of cervical remodeling and the intrinsic tissue property changes that occur during the process, in turn leading to an improved recognition of its role in spontaneous preterm birth.

Table 1
Methods for assessing the cervix in pregnancy.

Method	In vivo/ex vivo	Modality	References
Balloon inflation (EndoFLIP®)	In vivo	Mechanical	Aspden [13] Hee et al. [7] Liao et al. [14]
Mechanical aspiration	In vivo	Mechanical	Mazza et al. [8] Bauer et al. [9] Parra-Saavedra et al. [15] Badir et al. [10] Badir et al. [11] Mazza et al. [16] Maurer et al. [17]
Palpation-type elastography	In vivo	Ultrasound	Swiatkowska-Freund and Preis [18] Molina et al. [19] Hee et al. [20] Fruscalzo et al. [21] Hernandez-Andrade et al. [22]
Shear wave elastography	In vivo	Ultrasound	Palmeri et al. [23] Carlson et al. [24]
Acoustic attenuation	In vivo	Ultrasound	Labyed et al. [25] Guerrero et al. [26]
Acoustic backscatter power loss	In vivo/ex vivo	Ultrasound	Feltovich et al. [5]
Gray-level histogram	In vivo	Ultrasound	Kuwata et al. [27]
Second harmonic generation	Ex vivo	Microscopy	Akins et al. [28]
Raman spectroscopy	In vivo/ex vivo	Spectroscopy	Vargis et al. [29]

3. The microbiome

The human microbiome consists of the aggregate of micro-organisms and their genomes that naturally reside within the various systems of the human body. The relationship between preterm birth and microbial colonization of the normally sterile intrauterine environment has long been established [30]. Microbial invasion of the amniotic cavity is often subclinical in nature, and has been shown to occur in one of every four preterm deliveries [31]. However, as opposed to acquired infection being the sole etiology, bacterial species associated with the microbiota of the genitourinary, gastrointestinal, and pulmonary systems, as well as those involved in periodontal disease, have been shown to enter the amniotic cavity and predispose women to preterm birth [32]. Aagard et al. have also demonstrated an association between the unique composition of the placental microbiome and preterm birth, further highlighting this as an area of further investigation [33].

Further, the question of commensal versus pathologic microbes is one which we are now beginning to address. Although microbial invasion has been thought to exert a pathologic effect by inducing inflammatory cascades that lead to preterm birth, recent discoveries have suggested that not all microbes exert this effect. Stout et al. have illustrated this by identifying the presence of intracellular bacteria in the placental basal plate of term placentas, in addition to noting the absence of bacteria in preterm placentas [34]. Further investigations are needed to discover the identity and origin of micro-organism species that are potentially pathologic, and those that are commensal and exert no effect.

Ongoing advances in metagenomics and the enhanced ability to perform DNA sequencing studies are allowing us to obtain more information on the composition of the microbial community of various body sites and the changes that occur in them during pregnancy. As an example, studies of the vaginal microbiome in pregnant and non-pregnant women have demonstrated that a considerable decrease in species diversity occurs as pregnancy progresses [32]. Studies of the gastrointestinal microbiome have also demonstrated changes in species differentiation with pregnancy. The significance of these biological changes and their role in the induction or prevention of intrauterine infection leading to preterm birth has yet to be identified, but represents a promising area for further investigation.