**Pregnancy and the Myometrium**

Despite its crucial role in pregnancy, the smooth muscle layer of the uterus – the myometrium – has been understudied. In rodents, myocytes are organised into longitudinal and circular layers, whereas in humans, they are intermingling and spiralling. These smooth muscle cells, which lack sarcomeres, produce some of the strongest phasic contractions in the body. These contractions must occur at the correct time and be of sufficient strength and frequency to cause the cervix to thin and shorten during the first stage of labour and to expel the baby in the second stage. Finally, myometrial contractions must change from phasic to tonic to deliver the placenta without causing maternal haemorrhage.

Contributors to this volume have written expert reviews describing how the myometrium accomplishes the activities described above. However, we start by considering the complexity of pregnancy with reviews examining the influence of environment and general health on myometrial function. Next, we delve into myocytes, electrical activity, hormonal influences, and myometrial physiology. Finally, we conclude with reviews covering approaches that will lead to further insights into the myometrium: phytobiology, drug discovery, and mouse models. We are grateful to all the authors for focusing their reviews on new findings and unresolved issues, and highlighting areas where our understanding of myometrial physiology and pathophysiology would benefit from further study.

Our first four reviews explore the effects of the environment, health factors, and their intersections on the myometrium. First, Leimert and Olson examine the effect of race on uterine function, specifically the elevated risk for preterm delivery among black women in the USA. With the title "*Allostatic Load and Race in Pregnancy Outcomes",* the authors point out that “race is a social construct, and evidence suggests that in the United States, the effect of Black race on preterm birth is environmental, not genetic”. They review a wide body of literature and conclude that an accumulation of lifetime and generational stress produces an allostatic load that, through epigenetic mechanisms, affects pregnancy outcomes. Fortunately, they note that some of these effects may be reversible.

Second, we present Prendergast's review, "*Maternal phenotype: How does age, obesity and diabetes affect myometrial function?"* In this era of personalised medicine, we must consider how maternal health factors affect myometrial contractility, response to drugs, and labour outcomes. This is especially pressing, as the prevalence of older mothers, obesity, and diabetes are increasing. It is clear that obesity and its associated inflammatory responses have deleterious effects on myometrial contractility. In contrast, the data appear insufficient to confirm that maternal age affects contractility.

Third, "*In utero circadian changes: facing light pollution"*, is the intriguing title of the review by [Torres-Farfan](file:///%5C%5Ctorres-Forfen) et al. The authors elegantly present the evidence that increased nocturnal light pollution – a feature of modern life – is likely to damage our health. Crosstalk between maternal and fetal circadian systems is crucial to fetal development, and thus to adult health. However, disruption of circadian rhythms can reduce the normal nocturnal peak of the hormone melatonin, leading to negative health consequences for mothers and babies.

Finally, in this section, Stout et al. summarize our knowledge of the human vaginal microbiome and its correlations with clinical outcomes. Additionally, they review recent studies that have expanded our understanding of population-level differences in the vaginal microbiome that may affect both *in vitro* fertilization success and preterm birth. Deciphering the interactions between the micro- and myco-biomes is also emerging as a key area for further study.

Our next set of three reviews focuses on myocytes. First, Kajuluri, Li, and Morgan write about the important recent literature on contractile proteins in *"The uterine myocyte, contractile machinery and proteins of the myometrium and their relationship to the dynamic nature of myometrial function"*. This review describes the ways in which uterine function is controlled by contractile protein isoforms, the electrical activity of myocyte plasma membranes, intracellular calcium concentration, and signal transduction pathways, all of which are regulated by hormones.

In the second article on myocytes, Parkington, Siriwardhana, and Coleman describe the importance of mitochondria, the sarcoplasmic reticulum, and the invaginated areas of plasma membrane known as caveolae. Recent literature highlights potentially key roles of these organelles in calcium homeostasis, and thus myometrial excitability and contractility.

The final article on myocytes is not about the uterus, but about the cervix. Although we have known for many years that the top of the cervix contains numerous myocytes, Vink reviews the data indicating that these myocytes form a physiological sphincter. Whereas the cervix has long been thought to respond to uterine contractions, Vink presents potentially paradigm-shifting evidence that this sphincter contributes to activating the myometrial myocytes, and hence contributes to labour.

Next, we include three reviews discussing hormonal influences on the myometrium. First, Condon et al. present "*Estrogen/Estrogen Receptor Action and the Pregnant Myometrium"*. Estrogen has long been known to be required for hyperplastic and contractile responses. Here, the authors review recent literature investigating the function of estrogen receptor alpha splice isoforms in uterine contractility. Additionally, they discuss the role of insulin like growth factor 1 in myometrial hyperplasia during pregnancy.

The second review in this section discusses the major pregnancy-associated hormone progesterone. In their article, Wilson and Mesiano describe how progesterone withdrawal occurs at molecular and physiological levels. They then discuss recent data suggesting that parturition involves “specific changes in myometrial cell PR-A activity which abrogates the progesterone-PR anti-inflammatory effects and is induced in myometrial cells when the extent of pro-inflammatory stimuli exceeds a threshold level”. This is relevant to our understanding of how inflammation and stress contribute to or even cause term and preterm births.

Arrowsmith provides the final discussion of hormones in her review*, "Oxytocin and vasopressin signalling and myometrial contraction".* Because these two hormones differ by only two of their nine amino acids, it is challenging to elucidate their separate physiological effects on myometrium. Recent progress in designing more selective and potent agonists and antagonists of these hormones is helping clarify their signalling and effects on the myometrium. In addition, Arrowsmith describes emerging roles for oxytocin as an inflammatory mediator and transcription regulator. This work leads her to suggest that we may be on the brink of expanding the therapeutic potential of oxytocin and vasopressin.

We next turn to two excellent reviews on electrical signalling, which is necessary for uterine activity in both non-pregnant and pregnant states. Garfield et al. review some of the classical work on electrical activity in their review, "*Monitoring the Onset and Progress of Labor with Electromyography in Pregnant Women".* They also discuss some recent data suggesting that monitoring both uterine and abdominal muscle activity may be useful for diagnosing and treating labour progression to improve maternal and fetal outcomes. Along the same lines, Blanks and Eswaran review the current state of the field of uterine electrophysiological activity. They posit that a combination of structural knowledge and electrical knowledge attained either by electromyography or by magnetomyography will be important for diagnosing aberrant uterine activity.

The next three reviews focus on the basis for uterine electrical activity – ion conductance through various channels on the myometrial cell membrane. First, Amazu et al. present evidence that sodium channels are active in myometrial cells and discuss a recently described channel that allows sodium ions to "leak" into myometrial cells. This slow influx of positive charge allows the cell to reach a threshold at which an action potential is generated. Second, Greenwood describes the role of potassium channels in "*Trying to keep calm in troubled times: The role of K channels in uterine physiology".* The review describes the multiple types of potassium channels in the myometrium and the diverse mechanisms by which they modulate uterine excitability. Lastly, Dunford et al. review calcium-activated chloride channels, focusing on the Anoctamin 1 channel. Although this channel clearly modulates myometrial excitability and contractility, its mechanisms of action have yet to be unmasked.

After ion channels, we turn to two reviews focusing on other pathways that can affect the state of the myometrium. In their review, "*Non-conventional signaling in human myometrium by conventional pathways",* Butler et al. revisit the complex inter-play of conventional pro-relaxation signaling and explore the concept that progesterone, cAMP, glucocorticoids, and possibly gasotransmitters work synergistically to dampen intrinsic myometrial contractility to allow pregnancy to progress without incident. The loss of this restraint restores myometrial contractility and allows labour to initiate. Next, in "*Mechanisms of Normal Labour"*, Nguyen-Ngo and Lappas summarize the mechanisms underlying myometrial contractility at the molecular, cellular, and organ levels. They focus on the interconnected cross-talk between key pathways leading to labour. This review both details the mechanisms of normal labour and highlights the significant differences between normal term and pathologic preterm labour.

Our next two reviews go beyond muscle cells in the myometrium. First, like other tissues, the myometrium contains numerous types of immune cells. For example, leukocytes are presumed to contribute to both host defense and tissue remodeling and repair. Siewiera and Erlebacher's review provides an overview of this understudied aspect of myometrial physiology, with special emphasis on the potential role of myometrial leukocytes in pregnancy and parturition. Clearly, a greater appreciation of the relationship between distinct classes of immune cells and the myometrium will be essential in understanding the complexities of uterine function.

In addition to immune cells, cyclic nucleotides in the myometrium modulate contractility and timing of parturition. The review by Guerra, et al. focuses on integrating established and recent findings regarding the roles of cyclic adenosine monophosphate, cyclic guanosine monophosphate, and phosphodiesterases in changes in myometrial contractility. The review specifically describes the transition from quiescence to active labour and some controversies in this field. A deeper understanding of the complex roles of cyclic nucleotides in both normal and aberrant contractile states would be of great benefit to the field.

Lastly, we conclude this issue with three reviews covering novel topics and areas for further investigation. First, the review, "*Uterine transplantation: the science and clinical update",* by Brännström et al. will likely excite the readers. Recent studies have highlighted the success of using this experimental clinical procedure in women lacking a functional uterus. The translation from animal models to humans took 20 years, but in the last five years, several live human births have been reported from uterine transplantation. This review describes the procedure and the development of this burgeoning field, as more and more clinical programs are performing uterine transplants.

The next two reviews focus on novel strategies to combat the problem that current tocolytics and uterotonics are limited by their off-target effects, lack of efficacy, or both. However, since prehistoric times, medicinal plants have been widely used as remedies, especially in developing countries. In their review, Bafor and Kupittayanant describe the evidence that several medicinal plants affect uterine contractility through a variety of mechanisms that involve calcium channels and several receptors. Medicinal plants should be further considered as ways to discover new uterotonic or tocolytics to be used in addition to or instead of modern therapeutics. In "*Drug discovery strategies for the identification of novel regulators of uterine contractility"*, Siricilla et al. define the ideal tocolytic or uterotonic as a drug that would be uterine-selective with rapid onset and long-duration efficacy. Additionally, they discuss strategies and limitations as we search for new therapeutics to treat aberrant uterine activity.

In the last review of this series, Wu et al. discuss using genetically engineered mice to dissect the pathways controlling myometrial contractility. By combining various applications of next generation sequencing and genome editing, researchers are now using mice to explore both the coding and noncoding genomes. The authors thoroughly review novel technologies in this field that will allow us to better understand the crosstalk between the endometrial and myometrial compartments to support the fetus.

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