Why the heart is like an orchestra and the uterus is like a soccer crowd

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The heart and the laboring uterus use different mechanisms to coordinate contractions.

This is a discussion of synchrony and coupled oscillatory behavior in the context of the physiology of the laboring uterus and the heart.

One of the great marvels of life is the degree of order that is created as life captures energy and transforms it into physiological structure and function against the forces of entropy (second law of thermodynamics[1]). Life in many ways is a battle against entropy that is inevitably lost for each individual. For human beings, this battle occurs continuously to preserve the function of each tissue. The battle is most heated in the organs that require the most energy: the brain, heart, and laboring uterus. Each uses energy to produce highly organized behavior.

During pregnancy the mother's body diverts a large amount of blood flow to the uterus. This increased blood flow carries energy that is used to create order in the developing fetus. Blood flow and energy are also required to create the regular powerful contractions required for human labor.

The human uterus has no pacemaker or motor innervation, yet develops rhythmic, powerful contractions that increase intrauterine pressure to dilate the cervix and force the fetus through the pelvis. To achieve the synchronous contractions required for labor, the muscle cells of the uterus act as independent oscillators that become increasingly coupled by gap junctions toward the end of pregnancy. The oscillations are facilitated by changes in resting membrane potential that occur as pregnancy progresses. Reductions of potassium channels in the myocyte membranes in late pregnancy prolong myocyte action potentials, further facilitating transmission of signals and recruitment of neighboring myocytes. Late in pregnancy prostaglandin production increases leading to increased myocyte excitability. Also late in pregnancy myocyte actin polymerizes allowing actin-myosin interactions that generate force, following myocyte depolarization, calcium entry, and activation of myosin kinase. Labor occurs as a consequence of the combination of increased myocyte to myocyte connectivity, increased depolarizations that last longer, and activated intracellular contractile machinery. During labor the synchronous contractions of muscle cells raise intrauterine pressure to dilate the cervix in a process distinct from peristalsis. The synchronous contractions occur in a progressively larger region of the uterine wall. As the size of the region increases with increasing connectivity, the contraction of that larger area leads to an increase in intrauterine pressure. The resulting increased wall tension causes myocyte depolarization in other parts of the uterus, generating widespread synchronous activity and increased force as more linked regions are recruited into the contraction. The emergent behavior of the uterus has parallels in the behavior of crowds at soccer matches that sing together without a conductor. This contrasts with the behavior of the heart where sequential contractions are regulated by a pacemaker in a similar way to the actions of a conductor and an orchestra.

Key words: emergent behavior, mechanotransduction, pregnancy, uterine synchronization

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Intriguingly, the human uterus displays a low level of order for the majority of pregnancy in that contractions are minimal, and activity at any one time, at different places in the uterus, is very similar. This picture changes at the time of labor in a dramatic way with an increase in contractility, energy consumption, and order, as the activity at different times is different, either relaxed or contracting.[2-4] This is quite different from the behavior of the heart. The heart and the uterus have evolved rather different ways of regulating order and contractile behavior. The heart is like an orchestra, playing continuously under the direction of a conductor. The uterus is like a soccer crowd, inactive most of the time but getting together for a song, producing a climax, and then dispersing to remain quiet until the next game.

Effective cardiac function requires the ability to rapidly change cardiac output to meet the varying needs of the corpus. When Olympic champion sprinter Usain Bolt leaves the blocks, his heart rate climbs from perhaps 50 beats per minute to well over 220, with a matching increase in cardiac output. The cardiac output of the ventricles is improved by the preceding contraction of the atria that primes the ventricular pump, increasing the ventricular volume and the efficiency of the contraction. The frequency of contractions is determined by

a specialized group of pacemaker cells, called the sinoatrial node, within the atria.[5] The pacemaker cells receive input from systemic hormonal signals and from specific neuronal connections. The sinoatrial node generates a pacemaking signal that travels through the atria and causes atrial contraction (Figure 1). Importantly, this signal is delayed at the atrioventricular node; this delay is critical in optimal function of the heart as it allows the ventricles to relax and fill with blood before initiating ventricular contraction. Thus the heart requires a highly orchestrated contraction sequence to work optimally.

The behavior of the heart parallels the behavior of an orchestra under the guidance of a conductor. Each musician is capable of independent activity and rhythm, but if each played without knowledge of the others, there would be a low level of order. For the orchestra to function effectively the conductor invests energy to regulate the activity of individual musicians to achieve coherence and synchrony of behavior. Connectivity of individual musicians is provided by visual cues from the conductor and by visual and aural cues from other musicians. The actual output of any given musician is determined by the score and by that individual's ability. The operation of a conductor allows an individual to influence the behavior of a large number of components in a wide range of behaviors, changing tempo, mood, and volume.

The contrast between the heart and the human uterus is quite stark. The heart is equipped with specialized pacemaker and conducting systems while the human uterus has no innervation regulating contractility. Most smooth muscle cell organs or tissues demonstrate spontaneous contractility, especially in response to stretch, such as the bowel or bladder. The reproductive tract of mammals is rather different. A key aspect of the evolution of amniotes, of which primates are an order, is the ability to lay eggs on dry land that are impermeable to water yet permeable to oxygen. These eggs have a tough outer membrane that is formed inside the reproductive tract. To form this specialized egg the conceptus must be retained in the reproductive tract and contractions of the tract must be arrested. Mammals have taken this process further and the conceptus is retained with amniotic membranes within the reproductive tract while additional nutrition for fetal development is provided by the placenta. Throughout this period of fetal development the contractile activity of the reproductive tract must be suppressed, and in particular its response to stretch.

In the human being, contractility of the uterus is suppressed at the beginning of pregnancy to allow implantation. Hormonal signals suppress uterine contractility. The signals come from the maternal ovary that produces progesterone and the developing morula of fetal and trophoblastic cells that secretes chorionic gonadotrophin.[6] The progesterone and the chorionic gonadotrophin together suppress myometrial contractility, providing a "brake" on the uterus. The brake reduces uterine contractility for the vast majority of pregnancy. The brake mechanism includes keeping individual myocytes disconnected from one another. This is achieved by reducing gap junctions between individual myocytes.[7] Gap junctions are connections between individual cells that are formed by the protein connexin 43 (Cx43). These junctions allow the passage of small molecules, such as inositol trisphosphate, and facilitate electrical connection. The formation of Cx43 is inhibited by a transcription factor called zinc finger E-box binding homeobox (ZEB)1, which is stimulated by progesterone.[8] As pregnancy proceeds the production of progesterone gradually increases and the enlarging placenta becomes the major source of progesterone. The suppression of Cx43 expression ensures that even if a myometrial cell depolarizes, the electrical signal does not travel far and no increase in intrauterine pressure occurs.

Depolarization and contraction of uterine myocytes during pregnancy are also suppressed by other mechanisms. Progesterone has antiinflammatory effects and suppresses production of prostaglandins that stimulate myocyte depolarization.[9,10] Hormones produced by the placenta also act to reduce contractile pathways within myometrial cells.[11] Chorionic gonadotrophin acts on the myocytes through 7 transmembrane domain receptors that link to $G_{\alpha s}$ proteins that activate adenylate cyclase to stimulate production of the intracellular messenger cyclic AMP (cAMP). cAMP activates protein kinase A (PKA), which activates phosphatases that reduce myosin light chain kinase phosphorylation, decreasing the myosin-actin cross-bridge cycling that underlies muscle contraction. The cAMP-activated pathways also likely reduce formation of actin fibers that are required for the development of tension.[12,13] Chorionic gonadotrophin is not the only placental hormone that can affect these pathways to promote relaxation. The placenta also produces corticotrophin-releasing hormone (CRH), which increases exponentially through pregnancy[14] and promotes relaxation of myometrial myocytes through cAMP-dependent pathways.[15]

The likelihood of a myometrial cell depolarizing and contracting is related to the electrical potential difference it maintains across its plasma membrane. The membrane potential is created and maintained by an energetically driven process; sodium ions (Na^+)/potassium ions (K^+) adenosine triphosphatase moves K^+ into the cell and Na^+ ions out of the cell against their ionic gradients. K^+ then diffuse out of the cell down the concentration gradient to generate an electrochemical gradient, leaving the inside of the cell relatively negative compared to the outside. Intracellular calcium concentrations rise when a cell expresses an action potential, voltage-activated calcium channels open, and calcium ions (Ca^{2+}) move into the cell through the channels.[9] Rises of intracellular free Ca^{2+} then lead to active contraction through the activation of myosin light chain kinase, effective myosin-actin interaction, and production of tension.[16]

During pregnancy the relatively high K^+ gradient makes it difficult to depolarize the cell and thereby assists in maintaining quiescence.[17] Therefore, multiple pathways interact during pregnancy to prevent the development of uterine contractions and to promote

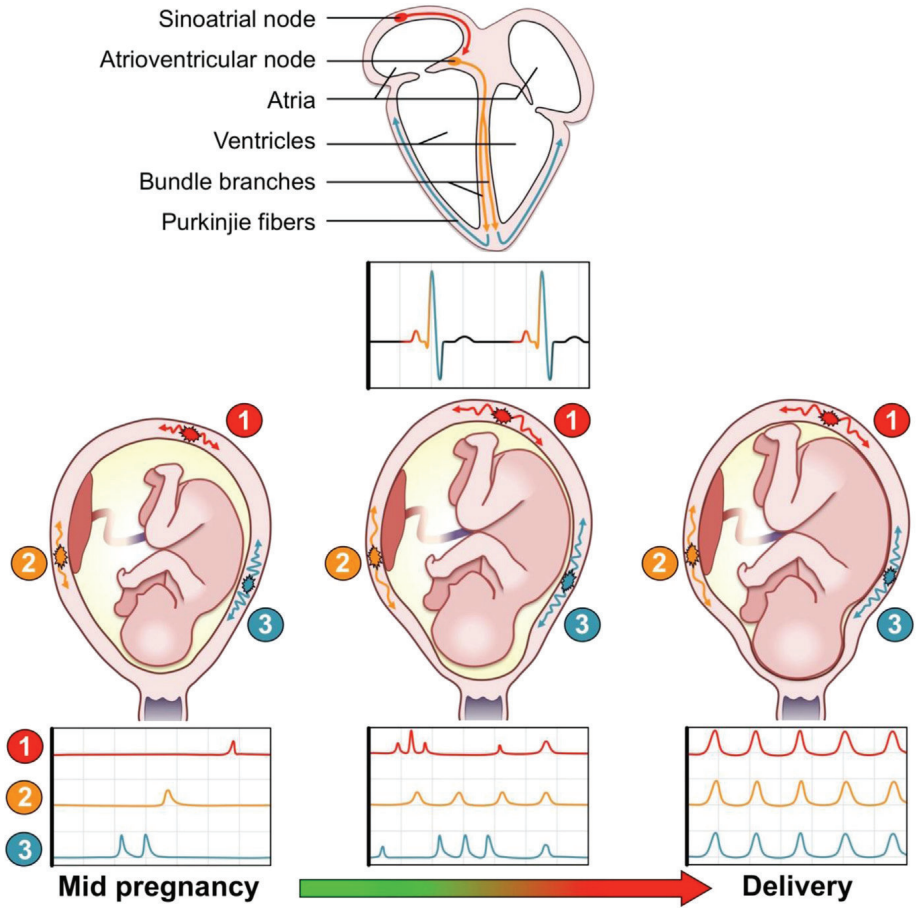
the quiescent state within the myometrium of the uterus as fetal development and growth occur within the amniote membranes.

One of the puzzles of human pregnancy is the mechanism that generates the onset of labor. The available data strongly support the presence of a brake on uterine contractility provided by progesterone and other agents such as CRH. The hypothesis of the progesterone block was developed by Csapo[18] in the middle of last century and for many years little further progress occurred. A primary problem was how the block was removed. In many mammals processes occur at the end of pregnancy to reduce maternal or placental production of progesterone so that maternal circulating concentrations of progesterone fall dramatically precipitating labor; but this does not happen in human beings.[19,20] In human beings, maternal circulating concentrations of progesterone rise progressively across pregnancy and only decline with the delivery of the placenta. It seems that in human beings, estrogen action may increase to override the action of the progesterone brake.

During human pregnancy 2 major estrogens are produced: estriol and estradiol. Estriol is produced in the placenta from 16-hydroxy-dehydroepiandrostenedione (DHEAs), a steroid created by the action of the fetal liver on DHEAs produced in the fetal adrenal. The production of fetal DHEAs is partly regulated by CRH, which increases exponentially across pregnancy[21]; consequently estriol levels rise markedly at the end of pregnancy. Estradiol is also made in the placenta from DHEAs that has not been 16-hydroxylated, and the majority of this comes from the maternal adrenal and levels of estradiol increase more slowly in late pregnancy. A consequence of these events is that the ratio of estriol to estradiol increases late in pregnancy. This changing ratio appears critical and occurs in singleton and twin pregnancies and in those delivering preterm.[20] The ratio is relevant because while both estriol and estradiol are effective agonists at estrogen receptors, when present at equimolar concentrations they block their respective actions by the formation of heterodimers.[22] Thus, when late in pregnancy estriol becomes dominant over estradiol, the formation of estriol homodimers allows the environment to become estrogenic.

Estrogen has many actions on the uterine myometrium. Acting via microRNA species estrogen action reduces the formation of ZEB transcription factors that inhibit production of Cx43.[23,24] The estrogens also turn on expression of cyclooxygenase 2 that enzymatically generates prostaglandins that promote uterine myocyte depolarization and contraction.[25] At the same time that these events are occurring, there is a decline in the concentrations within the myometrial cells of components of the $G\alpha_s$-adenylate cyclase-cAMP-PKA pathway that promotes relaxation.[26,27] The decline in the PKA pathway leads to actin fiber formation.[12] The ion channels that participate in cellular action potentials are also important regulators of labor. For example, the expression of many types of potassium channels vary as pregnancy progresses, which modulates myocyte excitability and action potential duration.[28-30] These events combine at the end of pregnancy to dramatically increase the connectivity of myometrial

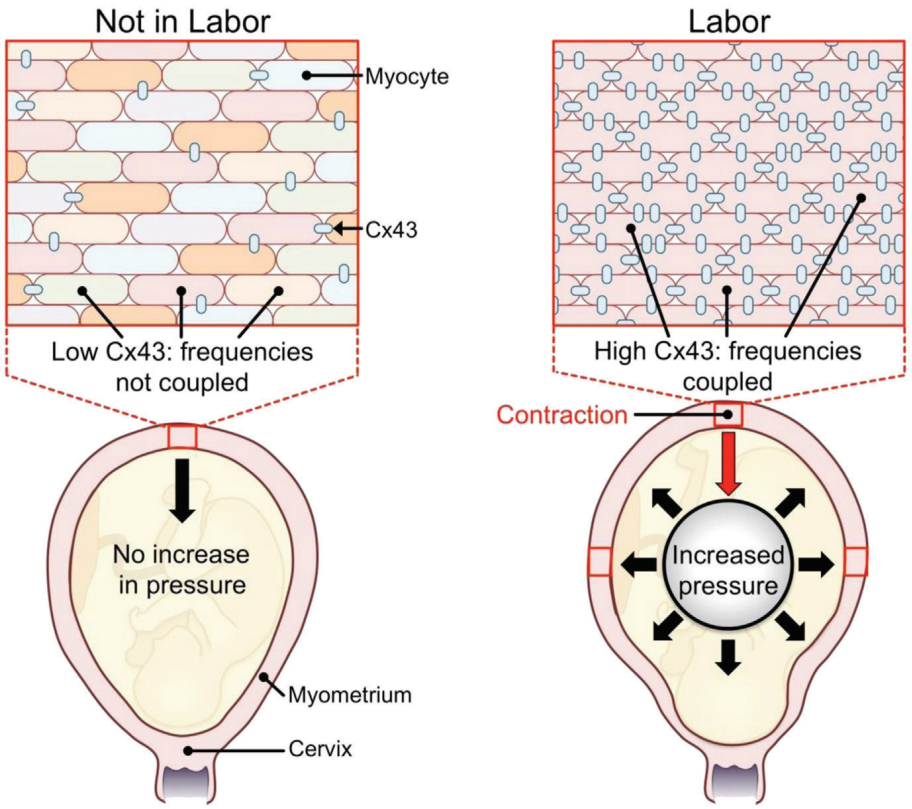
FIGURE 1
Regulation of cardiac and uterine contractility



The figure illustrates the 'Conductor' like role of the sinoatrial node in regulating the order of contractile behavior in the atria and ventricles of the heart. The *lower illustration* shows the gradual development of synchronous behavior in areas of the uterus that eventually lead to the widespread rhythmic contractions of the uterus that increase intrauterine pressure and dilate the cervix at the time of labor. This has parallels with the development of hand waving and singing by members of soccer crowds who achieve synchrony of behaviour without a conductor.

Smith. Heart like an orchestra, uterus like a soccer crowd. Am J Obstet Gynecol 2015.

FIGURE 2
Myometrial activity before and after the onset of labor



Not in Labor illustrates the low level expression of Cx43 during the majority of pregnancy that prevents the development of synchronized myocyte contractions that are required to increase intrauterine pressure. *Labor* illustrates how increased expression of Cx43 channels allows the development of synchronous contractile activity in patches of the myometrium that are large enough to raise intrauterine pressure. The rise in intrauterine pressure causes and increase in tension throughout the uterine wall providing a signal that allows the whole uterus to synchronize contractile activity, generating the rhythmic contractions required to dilate the cervix.

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myocytes, which makes them more likely to concurrently depolarize and to remain depolarized for longer (Figure 2).[31]

The increase in connectivity between individual myocytes at the end of pregnancy and the increase in myocyte excitability allows the myocytes to behave as coupled oscillators and generate coordinated contractions. This coupled oscillatory behavior is similar to that shown by fireflies that synchronize their light flashes.[32] This process has been observed in women using the array of superconducting magnetometers in Little Rock, AR, which has been used to monitor synchronous activity in the human uterus as women approach labor.[33] The recordings demonstrate no evidence of a localized pacemaker, but areas of the uterus progressively become more synchronized in association with faster conduction of electrical signals across the uterus. Further, this behavior can be modelled in silico by varying connectivity, excitability, refractory period, and action potential duration to produce the same behaviors observed in Little Rock, AR.[34] In this work, the area over which an action potential could spread was a key determinant of the development of synchronous contractions. If the area over which an action potential could spread was large enough, contraction of this region or patch of tissue would increase intrauterine pressure leading to an increase in uterine wall tension.[35] Increased uterine wall tension then provoked widespread synchronous contraction of myocytes. If the area over which an action potential propagated was too small to raise intrauterine pressure then no synchronous contractions of the whole uterus would occur. Synchronous contractions across the uterus raise the intrauterine pressure leading to dilatation of the cervix; when the membranes rupture pressure is maintained by occlusion of the pelvic outlet by the fetal head.

This type of behavior is also similar to that observed in crowds at soccer matches that develop synchronized activities such as hand waving and the singing of songs. These patterns of singing and waving may begin in any part of the stadium and are determined by the connectivity of the members of the crowd and by the level of excitability of the crowd.[36,37] The difficulty of synchronizing a large crowd mitigates against high-frequency activity such as might be required in an orchestra or in the heart but provides resilience as it is not dependent on a pacemaker. Thus, a conductor orchestrates the rapid rhythms of the heart but human birth (Video) has the excitement of a soccer crowd to maintain contractions with the goal of birth and the creation of order.

Self-organizing systems are optimal for mechanisms requiring progressive development and are robust, yet allow different input conditions to yield the same output.[38] Perhaps the challenge for uncovering the regulator of human birth has been quixotic in the sense that the uterus is self-organizing. Recent discoveries of cellular and organizational mechanisms have highlighted how the heart and the uterus use different solutions for creating order from entropy. Further understanding and development of these concepts are expected, as we search for the biological causes of adverse pregnancy outcomes. ■

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