Monitoring uterine contractions during labor: current challenges and future directions

Roger C. Young, MD, PhD; Ponnila S. Marinescu, MD; Neil S. Seligman, MD

Organ-level models are used to describe how cellular and tissue-level contractions coalesce into clinically observable uterine contractions. More importantly, these models provide a framework for evaluating the many different contraction patterns observed in laboring patients, ideally offering insight into the pitfalls of currently available recording modalities and suggesting new directions for improving recording and interpretation of uterine contractions. Early models proposed wave-like propagation of bioelectrical activity as the sole mechanism for recruiting the myometrium to participate in the contraction and increase contraction strength. However, as these models were tested, the results consistently revealed that sequentially propagating waves do not travel long distances and do not encompass the gravid uterus. To resolve this discrepancy, a model using 2 mechanisms, or a "dual model," for organ-level signaling has been proposed. In the dual model, the myometrium is recruited by action potentials that propagate wave-like as far as 10 cm. At longer distances, the myometrium is recruited by a mechanotransduction mechanism that is triggered by rising intrauterine pressure. In this review, we present the influential models of uterine function, highlighting their main features and inconsistencies, and detail the role of intrauterine pressure in signaling and cervical dilation. Clinical correlations demonstrate the application of organ-level models. The potential to improve the recording and clinical interpretation of uterine contractions when evaluating labor is discussed, with emphasis on uterine electromyography. Finally, 7 questions are posed to help guide future investigations on organ-level signaling mechanisms.

Key words: biomechanics of cervical dilation, emergent properties of the pregnant uterus, labor, mechanotransduction, monitoring uterine contractions, myometrium, organ-level signaling mechanisms, uterine models, uterine pacemaker

Introduction

Electronic fetal monitoring is performed on 80% to 90% of patients in labor.[1] The 2 main elements of the fetal monitor are fetal heart rate tracing and uterine contraction tracing. Together, they define the fetal heart rate patterns (Table)[2] that can then be interpreted as normal (Category I), indeterminate (Category II), or abnormal (Category III). Most uterine contraction tracings are recorded noninvasively, which was the focus of this review.

Contraction tracings help assess fetal status by identifying when peaks occur in relation to fetal heart rate changes. A more complete description of contractions includes the time of onset, peak height, peak duration, rest period (also called relaxation time), and baseline pressure (or tone) (Figure 1). Contraction frequency is usually reported as the number of contractions expressed within a 10-minute window.

Contraction frequency has been studied as a method to diagnose term[3] and preterm labor[4] for patients presenting with threatened labor. It also provides guidance for induction of labor.[5] Excessive frequency or uterine tachysystole (defined as >5 contractions per 10 minutes, averaged over 30 minutes[2]) is associated with adverse neonatal outcomes and should be avoided,[6,7] though the association with depressed neurologic function is controversial.[8] The presumed mechanism is that high intrauterine pressures reduce blood flow to the placenta, and too little rest between strong contractions threatens fetal well-being. The American College of Obstetricians and Gynecologists (ACOG) has provided specific management recommendations when tachysystole is observed (Figure 2).[9] The problem is that noninvasive monitoring does not reveal if intrauterine pressures are high enough to moderate placental blood flow.

In a retrospective analysis of 2355 women at term,[7] contractions were invasively recorded 30 minutes before delivery with an intrauterine pressure catheter (IUPC—the gold standard for recording contractions). Tachysystole

From PreTeL, Inc, Chattanooga, TN (Dr Young); and Department of Obstetrics and Gynecology, University of Rochester Medical Center, Rochester, NY (Drs Marinescu and Seligman).

Received Aug. 16, 2022; revised Oct. 22, 2022; accepted Oct. 27, 2022.

R.C.Y. is the Founder and Chief Medical Officer for PreTeL, Inc and holds stock in PreTeL. PreTeL is a device development company that has patent rights for monitoring of patients with uterine contractions, based on the physiology described within this presentation. No products are promoted in this manuscript. P.S.M. and N.S.S. are currently affiliated with the University of Rochester Medical Center. PreTeL, Inc has a contract with the University of Rochester by which they supply equipment used for data collection and analysis for clinical research involving uterine electromyography and by which they fund patient incentives.

R.C.Y., P.S.M., and N.S.S. received funding from the following grants submitted by PreTeL, Inc: 1. National Institutes of Health Small Business Innovation Research Grant 1R43 HD095302-01, Optimizing and validating an electromyography-based fetal monitor to identify true preterm labor; 2. National Institutes of Health Small Business Innovation Research Grant 1R43 HD098730-01, Uterine stimulation index.

Corresponding author: Roger C. Young, MD, PhD. youngschwarzenberger@gmail.com

0002-9378/$36.00 • © 2022 Elsevier Inc. All rights reserved. • https://doi.org/10.1016/j.ajog.2022.10.039

Click Supplemental Materials under article title in Contents at ajog.org

TABLE
Concepts for how the uterus creates contractions of labor

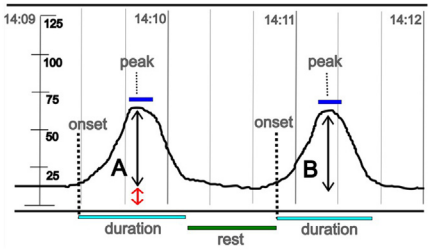
Model	Key features	Inconsistencies
Triple descending gradient	• First organ-level model to link physiology with clinical observations • Uterine pacemaker explains repetitive uterine contractions • Fixed fundal locations of 2 pacemakers explain fundal dominance • Action potential propagation is responsible for organ-level coordination • Normal labor generates high intrauterine pressures • Abnormal labor contains contractions that do not raise intrauterine pressure	• The sole mechanism for myometrial recruitment is progressive action potential propagation, but this is not observed over long distances • A fixed pacemaker is not observed • A fundal location for the pacemaker is not observed • Fundal dominance is proposed here but is not required for normal labor • A biomechanical mechanism for dilating the cervix is not explicit, though pressure is implied
Multiple pacemaker, selective dominance	• Any myocyte can function as a pacemaker, so local contractions may arise anywhere within the uterine wall • Fundal dominance is not required • During labor, 1 local pacemaker dominates; the associated local contraction expands to create a dominating contraction • Uterine synchronization is required to produce elevations of intrauterine pressure and strong contractions • Uterine synchronization is proportional to the fraction of myocytes that participate in the contraction	• Progressive action potential propagation remains the sole mechanism for myometrial recruitment • A biomechanical mechanism for dilating the cervix is not explicit, though pressure is implied • Mechanisms for pacemakers not proposed
Peristalsis/catastalsis	• This mechanism is well-established in other smooth muscle tissues, including the nonpregnant uterus • This rudimentary version of the triple descending gradient is easier to visualize and communicate	• Progressive action potential propagation remains the sole mechanism for myometrial recruitment • Fundal dominance, fixed/ fundal location of pacemaker not observed • A biomechanically reasonable mechanism for dilating the cervix is not proposed or implied
Action potential —mechanotransduction (Dual)	• Bioelectrical activity propagates (nonprogressively) throughout the uterus using mechanotransduction • Excitation-contraction coupling remains an integral component of regional contractions • Mechanosensitive myometrium serves as multiple regional pacemakers • Pressure recruits myometrium and pressure dilates the cervix • Regions are intermediate- sized functional units of uterine contractions • Uterine synchronization occurs via sequential activation of regions • Bioelectrical activity occurs without a clinical contraction when regional contractions fail to synchronize • Synchronization of regional contractions is necessary and sufficient for strong contractions of labor • Biomechanics of cervical dilation is similar to an expanding aneurism	• Mechanisms not established for myometrial mechanotransduction • Lacks proposal for initial bioelectrical event

Young. Monitoring uterine contractions: past, present, future. Am J Obstet Gynecol 2023.

was associated with adverse neonatal outcomes. However, adverse outcomes were not associated with contraction duration, rest, or baseline pressure. Although these data seem to imply that contraction frequency is the only important parameter, it should be emphasized that management decisions made earlier than 30 minutes before delivery likely have direct bearing on maternal and fetal outcomes.

It is tempting to describe the contraction pattern depicted in Figure 1 as "normal," but a pattern can be considered normal if labor is progressing and an intervention like oxytocin administration is not required. Although nationwide data are unavailable, a 2011 analysis of the Consortium on Safe Labor dataset that included 46,523 subjects found that 36.6% of singleton

FIGURE 1
Two sequential, idealized uterine contractions



A and **B,** showing the time of onset, the time the peak occurs, relative peak durations (*blue bars*), timing of peaks, the contraction duration, and the rest period between contractions. The *red arrow* represents the resting intrauterine pressure (also called "uterine tone") but is accurate only when recorded with an IUPC that has been correctly zeroed. The peak height, or peak force, (*black arrow*) is also quantifiable only with an IUPC.

IUPC, intrauterine pressure catheter.

Young. Monitoring uterine contractions: past, present, future. Am J Obstet Gynecol 2023.

pregnancies with a spontaneous onset of labor received oxytocin to augment labor.[10] These data suggest that more than 1 in 3 women do not progress normally in labor.

There are only a few preliminary studies that assess the progress of labor using features other than frequency. The ratio of the duration of the falling phase to the rising phase was found to be associated with a higher risk of cesarean delivery.[11] Contraction frequency irregularities diminish as labor progresses through the active phase or with oxytocin administration that results in vaginal delivery, but persistence of frequency irregularities is associated with oxytocin administration that results in cesarean delivery.[12] Neither of these studies nor any other alternate approach to assess contraction features has been fully developed and correlated with outcomes. Hence, there is little to no guidance for making labor management decisions based on any noninvasively recorded contraction feature other than frequency.

Recent advances in understanding how the uterus produces the forces necessary to dilate the cervix may facilitate correlating some of the features of the contraction tracing with the progress of labor and provide direction for improving how uterine contractions are measured, reported, and interpreted. This review will present an overview of uterine contractility, from cell function to organ function, with emphasis on how the uterus generates force. Clinical correlations will be presented to demonstrate how these concepts might (after additional clinical studies) be used to support selecting among the therapeutic options when interventions are considered.

Organ-level models are used to describe how cellular and tissue-level, or myometrial, contractions coalesce into clinically observable uterine contractions. More importantly, these models provide a framework for evaluating the many different contraction patterns observed in laboring patients. The ideal model would also offer insight into the pitfalls of currently available recording modalities and suggest new directions for improving recording and interpretation of the uterine contraction tracing.

In 1960, the first comprehensive model of uterine function—the "triple descending gradient"—was proposed by Caldeyro-Barcia.[13] In this model, a fundal pacemaker initiated each contraction, which then descended toward the cervix. However, studies soon indicated that a contraction could begin at many different sites and not necessarily in the fundus. This prompted Csapo[14] to propose a model of uterine function where many pacemakers are distributed throughout the uterus. Both models recruit tissue for participation in the contraction by action potentials that propagate through the uterus in waves. However, wave-like propagation over long distances has been questioned since the 1980s.[15,16] Recent studies indicate that wave-like uterine recruitment occurs over short distances but not long distances.[17,18] To integrate this new information, mechanotransduction was proposed as the essential mechanism for long distance signaling and tissue recruitment.[19] "Mechanotransduction" refers to the contraction that occurs in response to mechanical stimulation such as a brief push on the patient's abdomen.

In the next sections, we present further details on these and other uterine models and how they relate to measuring and interpreting the uterine contraction tracing. However, to be able to appreciate the strengths and weakness of each model, it is necessary to examine some details on cell and tissue function.

Emergent properties of the uterus

There has been abundant research characterizing the physiology of individual uterine smooth muscle cells (myocytes), but this approach has failed to describe how the uterus functions as an organ. Part of the reason for this may be explained by the concept of "emergent properties." Emergent properties are properties of a complex system that are not possessed by any of its components individually. For the uterus, as cells are assembled to form tissue and tissue is assembled into the organ, unique properties are gained at each step. Our ability to modulate and control uterine contractions is not only dependent on understanding the properties of the constituent parts but also the emergent properties of the whole organ.

The prime example of an emergent property of the uterus is expression of an action potential. Each myocyte contains all the components necessary to produce an action potential, but isolated myocytes do not spontaneously express action potentials unless conditions are adjusted far from normal. However, small groups of myocytes express spontaneous calcium oscillations and contractions.[20] With emergent properties arising in cell groupings, emergent properties at the organ level might also be anticipated, especially regarding bioelectrical activity.

Uterine myocytes

Uterine myocytes are the smooth muscle cells that generate the contractile forces necessary for labor.[21] Intracellular free calcium—Ca_i^{2+}—is tightly regulated by redundant systems of ion channels, pumps, and exchanges (Figure 2). When concentrations of Ca_i^{2+} are below 100 nM, the cell is relaxed. The cell contracts

when calcium enters the cell or is released from intracellular stores and Ca_i^{2+} concentrations abruptly rise to near 1 μM. These increases of Ca_i^{2+} occur when the myocyte experiences an action potential, which is discussed in more detail below. Generating a contraction in response to experiencing an action potential is called excitation-contraction coupling.[22] Through these processes, the phasic uterine contractions of labor can be linked directly to the on or off oscillations of Ca_i^{2+} and bioelectrical activity.

Oxytocin directly effects uterine myocytes through 2 mechanisms. First, inositol triphosphate (IP_3) is generated, which facilitates raising Ca_i^2 and increases the so-called "excitability" of the myocyte (Figure 2). This tends to encourage action potential production and propagation of the action potential through tissue. Second, through a separate mechanism,[23] the forces produced in response to Ca_i^2 are increased by a process called "calcium sensitization" of actin-myosin interactions. Prostaglandins also use IP_3 for cell signaling, but because the receptors and other signaling mechanism differ, oxytocin and prostaglandins may have different effects on contraction force and frequency.

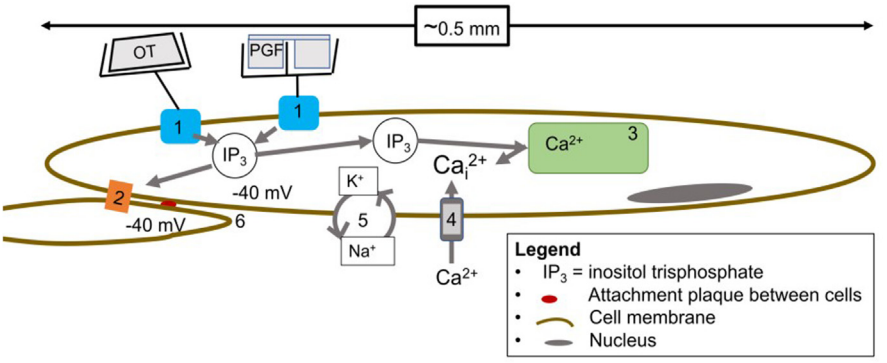
In summary, the on/off functioning of uterine myocytes means that increasing the strength of contractions requires recruiting more cells to participate in the contraction. Phrased another way, the strength of a contraction is largely proportional to the fraction of uterine myocytes that participate in the contraction,[14] though administering oxytocin increases the forces produced by the myocytes that are recruited.

Myometrium

Uterine tissue, commonly called myometrium (Figure 3), is composed mainly of myocytes but also contains connective tissue, blood vessels, and nerves. Myocytes are electrically and metabolically connected through gap junctions that are often referred to by their structural protein—connexin 43.[24] Gap junctions create the electrical syncytium of myocytes that allows the myometrium to function as a cohesive unit. Gap junctions are regulated through hormonal and mechanical mechanisms, and their expression increases before the onset of labor.[24,25] Although gap junctions are necessary for labor to occur,[26] the presence of gap junctions does not guarantee labor.

The microstructure of the myometrium begins with bundles of myocytes (Figure 3, A). The narrow, fluid filled space between myocytes is referred to as the interstitial space. The electrolyte composition of the interstitial space closely approximates serum. The bundles are grouped into fasciculata[27] (Figure 3, B). The fasciculata are separated by connective tissue, which contains blood vessels and sensory nerves. Short bridges of myocytes interconnect the fasciculata and likely assist with communication. The fasciculata diverge and converge as they travel through the uterine wall. Unlike the distinct inner and outer layers of rodent myometrium, human fasciculata travel through the uterus in a locally random but globally spiral pattern.

FIGURE 2
Calcium (Ca_i^{2+}) regulation in myocytes



During pregnancy, myocytes hypertrophy to a length of 500 μm. Ca_i^{2+} is tightly regulated through pumps, ion channels, ion exchangers, and internal storage organelles. The voltage-activated L-type Ca^{2+} channel provides the inward electrical current and calcium influx during the action potential (4). Ca^{2+} is released from the sarcoplasmic reticulum (3) by IP_3, which is produced when specific receptors (1) such as oxytocin or prostaglandin F are activated. Gap junctions (2) provide electrical and metabolic communication between cells. The potassium (K^+) and sodium (Na^+) ion gradients are necessary to establish the resting membrane potential and the action potential. These ion gradients are largely maintained by the Na^+, K^+ exchanger (5). The interstitial space between cells (6) contains an ionic composition similar to serum.

IP_3, inositol trisphosphate; *OT*, oxytocin; *PGF*, prostaglandin F2α.

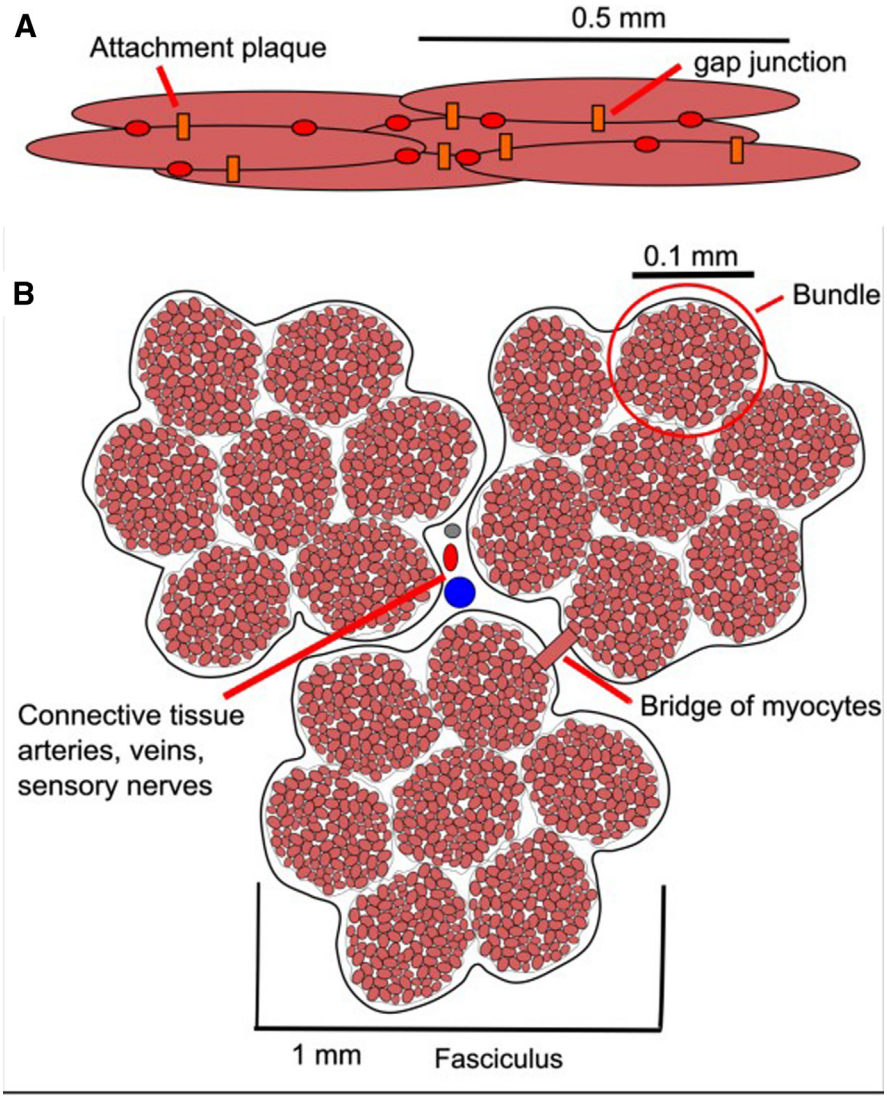
Young. Monitoring uterine contractions: past, present, future. Am J Obstet Gynecol 2023.

Action potential propagation through myometrium

When a myocyte within the myometrium expresses an action potential, Ca_i^{2+} rapidly transitions from low to high. This causes the myocyte to contract through excitation-contraction coupling. If gap junctions are present, the action potential passes from myocyte to myocyte and propagates wave-like through the myometrium. Through this mechanism, more cells are recruited to participate in the contraction, which increases the strength of the contraction.

The uterine myometrium is an unusual type of electrically active tissue, because the L-type calcium channel is the only ion channel responsible for the inward current that creates the upstroke of the action potential. The L-type calcium channel also provides a path for calcium to enter the cell from the interstitial space to raise Ca_i^{2+}. In this manner, the action potential performs double duty—it communicates the signal to contract, and it actively participates in excitation-contraction coupling.

FIGURE 3
Microanatomy of pregnant human myometrium (not drawn to scale)



A, Myocytes are mechanically linked by attachment plaques (*red*) and are electrically and metabolically linked by gap junctions. **B,** Groups of myocytes form bundles and groups of bundles form fasciculata. Bridges of myocytes periodically interconnect the fasciculata. Arteries, veins, and sensory nerves course between the fasciculata.

Young. Monitoring uterine contractions: past, present, future. Am J Obstet Gynecol 2023.

Clinical correlation 1

The L-type calcium channel is notable for being blocked by nifedipine. Thus, administration of nifedipine inhibits generation of action potentials. This likely results in nifedipine functioning in 2 ways as follows: reducing the forces produced by individual myocytes (eg, impeding excitation-contraction coupling) and inhibiting recruitment of myocytes for participation in the contraction (eg, impeding action potential propagation). Arterial myocytes also contain L-type calcium channels, but arterial myocytes regulate blood pressure through graded calcium changes rather than the on/off expression of action potentials like uterine myocytes. Thus, nifedipine may modulate vascular function at lower doses than uterine function, and trials demonstrating that nifedipine does not delay preterm birth[28] do not indicate that it is ineffective as a tocolytic agent but rather that underdosing is required to avoid severe vascular effects.

Action potential propagation through the uterus

Action potentials have been observed to pass through the myometrium.[16] Early organ-level models of uterine function proposed action potential propagation as the sole mechanism of communication through the uterus. Early data in humans seemed to support this mechanism, though subsequent studies contradicted the existence of wave-like or sequential propagation over long distances.[15,16]

Uterine bioelectrical activity is commonly studied using uterine electromyography (uEMG). Like skeletal muscle EMG and electrocardiography, uEMG records voltages produced by the uterus with sensors on the skin. The technique is noninvasive, relatively unobtrusive, can be used for extended periods during labor, and can provide information on uterine contractions over time.

In 2015, a comprehensive review[18] of electrical propagation in the uterus evaluated 14 uEMG studies performed on rodents, mammals, and humans. It concluded that there are no simple propagation patterns, there is no preferential direction of propagation, and there is "special complexity" [*sic*] that poses challenges to interpretation.

As these uEMG studies were emerging, an array of 151 magnetometers that spanned the entire anterior abdominal wall[17,29] was used to investigate human uterine contractions. Magnetometers provide the same information as uEMG, except they measure the magnetic changes that occur with contractions rather than the electrical changes. With this large array, large scale images of the contracting uterus were obtained at high spatial and temporal resolutions for the first time. These data demonstrated that wave-like propagation distances are limited to approximately 10 cm over longer distances, local contractile activities suddenly appeared for no apparent reason, and the newly recruited tissue was

often located far from previously active regions.

In part to help resolve these unanticipated findings, a large scale, high resolution multichannel uEMG recording system was developed. As many as 192 sensors were used over the abdomen and midback.[30] In addition, the system compensates for patient-specific geometric variations of the uterus, fetal movements, and uterine shape changes. The analysis focused on how much of the uterus activated in contractions occurring at different dilations. Their primary finding was that contractions of nulliparous subjects tended to activate more of the uterus than contractions of multiparous subjects. Although this preliminary report did not assess how uterine wall recruitment occurs, proposed analyses will identify the local sources of uterine bioelectrical activity from early through advanced labor. These results will show where local contractions begin and how they propagate and will likely extend or contradict the magnetometer array findings.[17]

Absence of a dedicated, fixed uterine pacemaker

Because every contraction experiences a bioelectrical event with excitation-contraction coupling, there must be an initial action potential that starts the contraction. For decades, researchers have sought to identify "the" site of the initial action potential—a uterine pacemaker in analogy with the heart. However, the uterine pacemaker has not yet been located or identified.[17,31]

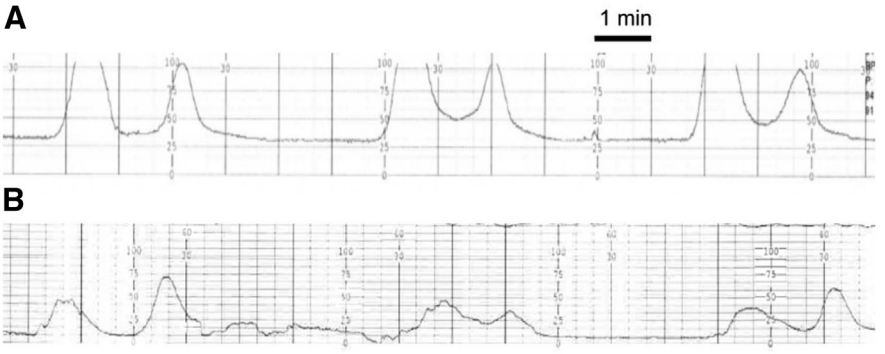
Evidence challenging the existence of a fixed uterine pacemaker in humans was reported[32] as early as 1970. In addition to abdominally placed uEMG electrodes, several electrodes were also placed through the cervix between the amniotic sac and uterine wall. By recording from multiple locations, they found that the first electrical event of a contraction occurred at different locations in different subjects. Furthermore, the location of the first event changed in a series of contractions recorded from the same subject. In the ensuing years, similar findings have been consistently reported, and as stated in a recent review,[18] "uterine pacemakers have been mostly observed to arise at random throughout the tissue and change location during the course of a single contraction or several successive contractions." In short, there is no direct evidence for a uterine pacemaker at a fixed anatomic location or that there is a predictable pattern of changing locations for the first events in a series of contractions. It seems that the uterus uses another mechanism to create the initial action potential.

Just as electrical excitability appears to be an emergent property of the myometrium, it is likely that uterine pacemaking is also an emergent property of the myometrium[33] or perhaps the uterus. Specialized placental structures[34] or cells such as telocytes[35] that could create a pacemaker-like complex of cells have also been proposed. However, none of these concepts have definitive experimental or theoretical support in humans. Further investigation to identify mechanisms that initiate the bioelectrical activity required for each contraction of labor remains critically important.

Clinical correlation 2

Figure 4 displays the uterine contraction tracings (both recorded with a tocodynamometer or TOCO) of 2 patients who presented for evaluation of labor at term. These contraction patterns may persist for many minutes or hours and are called "doubling" or "coupling." In Figure 4, A, the first contraction of the doublet is stronger than the first, whereas in Figure 4, B, the second contraction is usually stronger. The consistency of the timing within the doublet suggests that 2 contraction-initiating events are occurring at slightly different times but with the second event linked to the first. We are unaware of any clinical trials or evidence-based recommendations that address how to manage this pattern. Historically, this pattern could be explained as caused by a single pacemaker functioning abnormally and that changing the contraction pattern would require targeting the pacemaker. Because there is no known method to target the pacemaker, this pattern has been understudied. In the clinical correlations below, we discuss alternate mechanisms that may create this pattern and suggest approaches to management.

FIGURE 4
Uterine contraction patterns showing doublets, or coupling, recorded with tocodynamometry from 2 different patients



A, Patient A: the first peak of each doublet is off scale, and the second peak appears to be less strong. **B**, Patient B: the second peak of the doublet is usually stronger than the first with some variation. For both patients A and B, the rest periods between peaks of a doublet are short and incomplete. The duration of the doublets are consistently 3 minutes.

Young. Monitoring uterine contractions: past, present, future. Am J Obstet Gynecol 2023.

Biomechanics

Forces that dilate the cervix

Biomechanics investigates the mechanisms that create uterine forces and how those forces are transmitted to dilate the

cervix. Contractile forces originate with myocytes. Attachment plaques link myocytes together in bundles, which align into the fasciculata (Figure 2). Thus, fasciculata are the force-generating functional units of the uterus. Recent advances in biomechanics[36] have helped reveal the main pathways that transmit uterine forces to the cervix.

Biomechanics of directly pulling on the cervix

Many of the concepts of tissue biomechanics are counterintuitive. For example, when myocytes are arranged in series (end-to-end, chain-like), the total force they produce is only as strong as the weakest link, even if they all contract at the same time. This phenomenon directly impacts the force that is felt at the cervix when local contractions occur some distance away. A contraction expressed locally at the fundus cannot provide pulling forces on the cervix; only the fasciculata that are directly attached to the os can provide pulling forces to dilate the cervix. This requirement greatly limits the amount of force this "direct pull" mechanism is capable of producing. Biomechanical analysis[36] confirms that directly pulling on the cervix by contracting the myometrium is not the mechanism responsible for dilating the cervix.

The role of intrauterine pressure

The adequacy of labor is directly associated with contractions that raise intrauterine pressure. Montevideo units (MVU) are obtained with an IUPC and provide a measure of the time-averaged increase of intrauterine pressure that results from uterine contractions. Using Figure 1 as an example, the peak pressure of contraction A is 75, and the resting tone is 13, so the contraction pressure is 62 mmHg. The number of MVU is equal to the sum of the contraction pressures over the previous 10 minutes. The MVU provide an objective measure of uterine functioning that determines whether a patient has inadequate contractions (if $\leq$200 mmHg) or an arrest of labor (if $>$200 mmHg).[37–39] This relationship underscores the fundamental link between intrauterine pressure and progress of labor.

To raise intrauterine pressure, it is crucial that the uterus must be like a closed vessel filled with incompressible fluids (amniotic fluid, fetus, placenta). Ironically, the uterus is "closed" even after rupture of membranes. Following rupture of membranes, contractions of the lower uterine segment maintain the cervical seal around the presenting part and support the ability of the uterus to maintain pressure. This sealing process also prevents air from entering the uterine cavity, which would undermine large pressure rises, because air is compressible. Fortunately, air within the uterine cavity is rarely observed. With the uterus being a closed, pressurized vessel, Pascal's principle applies, that is, at any time, intrauterine pressure is the same throughout the uterine cavity (though possibly with minor local variations[40]).

When examining a partially dilated cervix of a patient who is experiencing strong contractions, increased tension on the cervix can be palpated soon after the contraction begins. Careful observation reveals that the forces on the cervix closely follow the profile of the uterine contraction tracing regardless of whether TOCO or an IUPC is used. This clinical observation supports the concept that forces on the cervix result from the rising intrauterine pressure.

To optimally raise intrauterine pressure and create a strong contraction, most or all the uterine wall must contract simultaneously (this has also been called uterine synchronization or uterine coordination). If the intrauterine pressure rises and much of the wall does not contract, the relaxed myometrium elongates and bulges outward. The bulging has the effect of increasing the volume of the uterine cavity at the expense of optimally increasing intrauterine pressure.

Clinical correlation 3

The TOCO tracings presented in Figure 4 display doubling caused by 2 initiating events (refer to clinical correlation 2). Because the strength of the contraction is proportional to the number of myocytes that are participating in the contraction, each peak of the doublet is created by an initiating event that recruits only a portion of the uterine wall. This "failure to synchronize" produces lower peak pressures than if a contraction were synchronized into a single peak. Assessing the intrauterine pressure is indicated, but patient perception can be hindered by systemic or regional analgesia, and palpation is inaccurate.[41] If the progress of labor is not acceptable, the clinical options would be to place an IUPC to determine the MVU, or if all other clinical assessments are reassuring, initiate or continue labor augmentation with oxytocin. The decision to use an IUPC for contraction monitoring should balance the benefits and risks.[42] The main benefit of an IUPC is that it currently is the only means to obtain MVU. In addition, an IUPC provides an optional method for recording contractions when noninvasive methods fail, which may occur with obesity. The risks include maternal fever,[42] and more rarely, bleeding complications caused during placement.[43] Further complicating the decision is that in a large prospective trial,[44] IUPC use did not improve the cesarean delivery rate or instrumented delivery rate or improve neonatal outcomes.

Increases of intrauterine pressure are created by contractions of the uterine wall, and the reverse is also true—rising intrauterine pressure increases tension on the uterine wall. As pressure equilibrates rapidly throughout the uterine cavity (Pascal's principle), any increases of intrauterine pressure quickly raise wall tension throughout the uterus. However, not all portions of the uterine wall experience the same tension.

The relationship between pressure and wall tension can be quantified by the Law of Laplace (Figure 5). This approach to analyzing the strength of uterine contractions was first presented by Csapo[14] in 1970. The Law of Laplace equation for a sphere (Figure 5, A) quantifies the relationship between wall tension, T, intrauterine pressure, P, vessel wall thickness, w, and the radius of curvature, r: $T = P \times r / 2w$. The human uterus has a more or less oblate spheroid shape (Figure 5, B). Despite experiencing similar pressures at all locations, wall

tensions vary a great deal throughout the uterus because of local differences in wall thickness and radius of curvature. At the anterior uterus, for example, wall tension, Ta, is larger than fundal wall tension, Tf, because the local radius of curvature is larger and the wall is thinner. Near the cervix, the uterine wall is thinner and as labor progresses, thins even further. The force that dilates the cervix is the local wall tension that is experienced circumferentially around the internal os. With this approach, the biomechanics for cervical dilation are similar to expansion of an arterial aneurysm.

Finally, quantifying forces using the Law of Laplace does not acknowledge the complexities of real tissue. The cervix has a complex and dynamic geometry, gradients of tissue elasticity, and anisotropy, and conditions change rapidly as the contraction progresses and pressure changes. Like the analyses required for aneurism expansion, fully addressing the biomechanics requires much more sophisticated computational methods of analysis.[45]

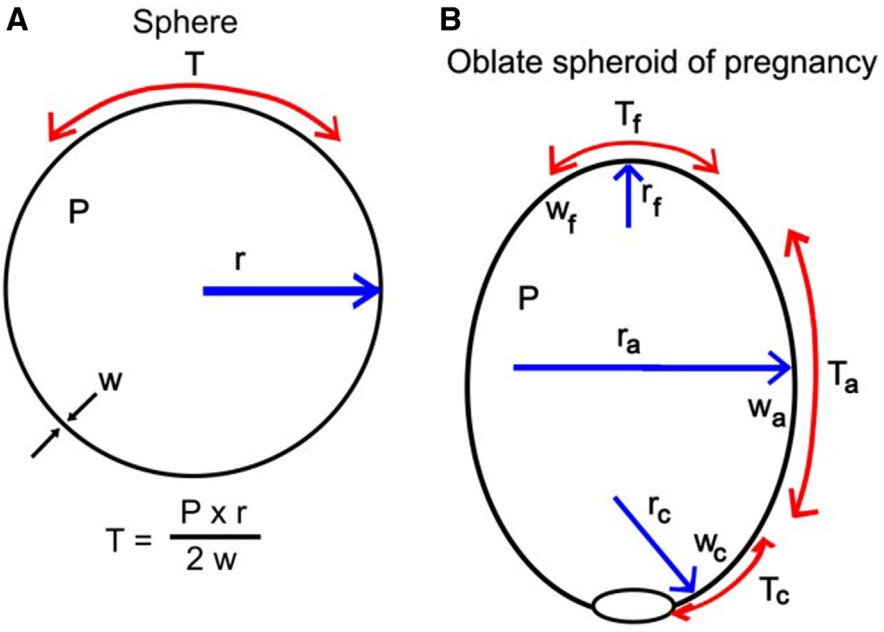
The biomechanical analysis presented above indicates that dilation of the cervix occurs primarily in response to the forces produced by elevations of intrauterine pressure.[36] The rises of intrauterine pressure during contractions are necessary to dilate the cervix rather than being an unnecessary by-product of contractions. More clearly stated, the laboring gravid uterus is a pressure-generating organ, and a realistic model of organ-level function must identify a means for raising intrauterine pressure.

Clinical correlation 4

In Figure 6, the patient is undergoing cervical ripening with the prostaglandin agonist dinoprostone in the setting of induction of labor at term. Before administration, the TOCO tracing shows contractions every 7 minutes (patient reported as mild) with interspersed small deflections. After dinoprostone, the patient experienced increasing discomfort, and the pattern changed to periods of irregular contractions that persist for more than 4 minutes without rest. Rest is seen only a small fraction of the time. These tracings could be interpreted as dinoprostone causing frequent weak contractions, or alternately, uterine tachysystole. Dinoprostone is commonly followed by induction of labor with oxytocin, but the ACOG warns against initiating oxytocin with inadequate uterine rest or tachysystole.[5] After dinoprostone administration, the irregular peak heights suggest frequent contractions without global synchronization. Without synchronization, intrauterine pressure rises are small. It is likely that dinoprostone modestly enhances myometrial excitability, and many different portions of the wall are expressing local contractions without synchronizing. This interpretation of the tracing supports initiation of oxytocin therapy despite the relative lack of uterine rest.

This assessment does not undermine the importance of uterine rest or tachysystole as key clinical parameters. However, rest and contraction frequency can also be viewed as a means to recognize persistent and excessive intrauterine pressure and that the presence or absence of uterine synchronization could also be considered when making clinical decisions.

FIGURE 5
Law of Laplace



A, This equation applies to the sphere and quantifies the relationship between tension (T), pressure (P), radius of curvature (r), and wall thickness (w). **B,** The oblate spheroid is used to approximate the shape of the pregnant uterus in vivo. The curvature and wall thicknesses vary at different locations, described here as the fundus, anterior wall, and lower uterine segment. These variations mean that the wall tension varies depending on the location, even though the pressure is constant throughout the uterine cavity.

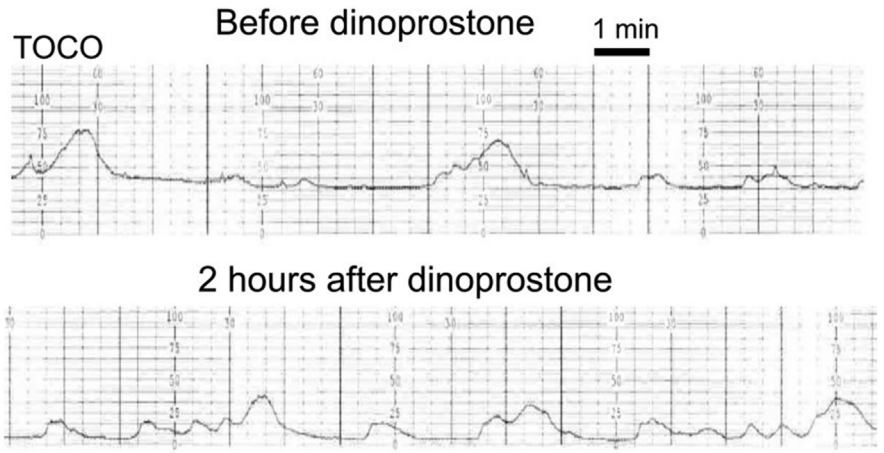
Young. Monitoring uterine contractions: past, present, future. Am J Obstet Gynecol 2023.

Organ-level models of human labor

Organ-level models seek to explain how the myometrium is recruited to create the strong uterine contractions of labor and the weaker contractions that occur in false labor. Ideally, the concepts of a pragmatic model can be extended to interpreting clinical variables and guiding evaluation and treatment options.

The "triple descending gradient" model of Caldeyro-Barcia, the Csapo model of multiple pacemakers, and the peristaltic wave model are early concepts of uterine function that have both broadened our knowledge of uterine

FIGURE 6
The effects of dinoprostone on the uterus of a patient at term



Dinoprostone was placed intravaginally for cervical ripening. Before administration of dinoprostone, uterine contractions are perceived as mild, with irregular "tightening" between contractions. Two hours after administration, contractions were perceived as slightly more frequent, but irregular activity between contractions increased.

TOCO, tocodynamometer.

Young. Monitoring uterine contractions: past, present, future. Am J Obstet Gynecol 2023.

function and guided research. Here, we present these models, how they advanced the field, and their inconsistencies. We then present a more recent organ-level model called the "dual" model that attempts to bring together available knowledge and resolve identified discrepancies. The dual model proposes 2 mechanisms of myometrial recruitment—action potential propagation and pressure-tension-mechanotransduction. The key features and inconsistencies of each model are presented in Table.

The Triple Descending Gradient model

The triple descending gradient model was the first comprehensive organ-level model of uterine function. It was proposed over 70 years ago by Caldeyro-Barcia.[13] In this model, a contraction of normal labor begins at 1 of 2 fixed pacemakers that are located on the fundus near each fallopian tube (Figure 7). The myometrium is recruited to participate in the contraction by sequential propagation of a contraction wave. *Triple descending* refers to the contraction wave, which descends toward the cervix, decreasing in both strength and duration as it progresses.

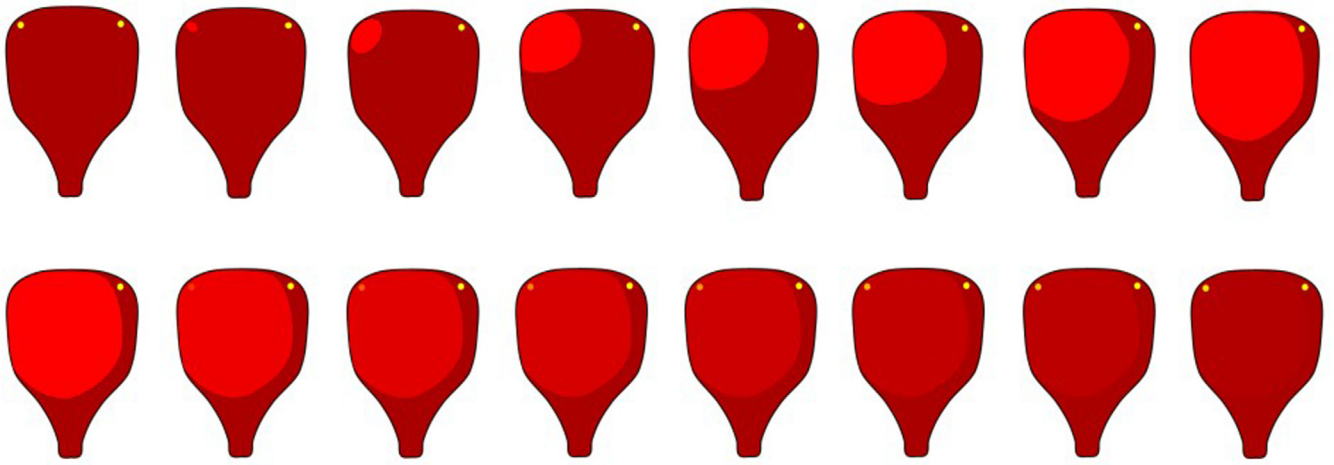
This model advocates the concept of "fundal dominance," because a normal contraction always begins at the fundus and is stronger at the fundus. If contractions progressed in any other manner,[46] they were considered abnormal and more likely to be ineffective at dilating the cervix or indicative of dystocia. The original data used to develop the model are somewhat difficult to visualize and used a limited number of sensors in a small number of subjects. In a recent preliminary report, multichannel EMG data seemed to support the association of fundal dominance and normal labor.[47] However, in a comprehensive follow-up study,[48] the same group was unable to confirm their earlier results. Other studies using either uEMG[16] or a 151 sensor-array of superconducting magnetometers[49] have failed to locate a consistent starting point for contractions or consistent directions of propagation. Despite the lack of support for fundal dominance, the importance of intrauterine pressure and uterine synchronization remain fundamental concepts and advance our understanding of labor and how to measure contractions.

Multiple pacemakers, expanding propagation model

Although not specifically named by Csapo,[14] the multiple pacemakers, expanding propagation model (Figure 8) incorporated the findings of Wolfs et al, who determined that the initial electrical events in the human uterus were not always in the fundus[32] (discussed above, in "Absence of a fixed, dedicated pacemaker"). Furthermore, the locations varied from contraction to contraction. This contradicted the model of Caldeyro-Barcia with fixed fundal pacemakers and the proposal that only descending contraction waves are normal.[46] The multiple pacemakers model uses many of the other basic elements of the triple descending gradient model (ie, the myometrium is recruited for participation in the contraction by sequential propagation of action potentials, not all contraction waves propagate long distances, and the progress of labor is primarily determined by the direction of propagation of the contraction wave). Instead of fixed pacemakers, Csapo proposed that any myocyte could serve as a pacemaker, and local contractions could arise at any location. With slow action potential propagation velocities, contractions remain localized rather than propagating. As labor progresses, propagation speeds become faster, and the size of the regions expands. Eventually, this results in one large dominating region initiated by a dominant pacemaker. However, because the propagation speed is limited, the entire uterus does not contract simultaneously during normal labor. Csapo emphasized that intrauterine pressure is proportional to the ratio of the number of myocytes that participate in the contraction to the number of myocytes that remain relaxed.

This model furthered understanding of labor and how to monitor contractions by accounting for the absence of a predetermined fixed pacemaker and promoting the concept of widely distributed local contractions. The concept that labor required enhancement of tissue-level propagation of action potentials was also novel. Even though intrauterine pressure was not explicitly stated to be the mechanism

FIGURE 7
Triple descending gradient proposed by Caldeyro-Barcia



A pacemaker is located near each oviduct (*small yellow circles*). A contraction begins when 1 of the pacemakers activates and creates a propagating contraction wave (*red*) that descends the uterus, decreasing in duration and strength as it travels. Strong contractions encompass most of the uterus. After the contraction peaks, myocyte relaxation occurs at approximately the same rate at all locations.

Young. Monitoring uterine contractions: past, present, future. Am J Obstet Gynecol 2023.

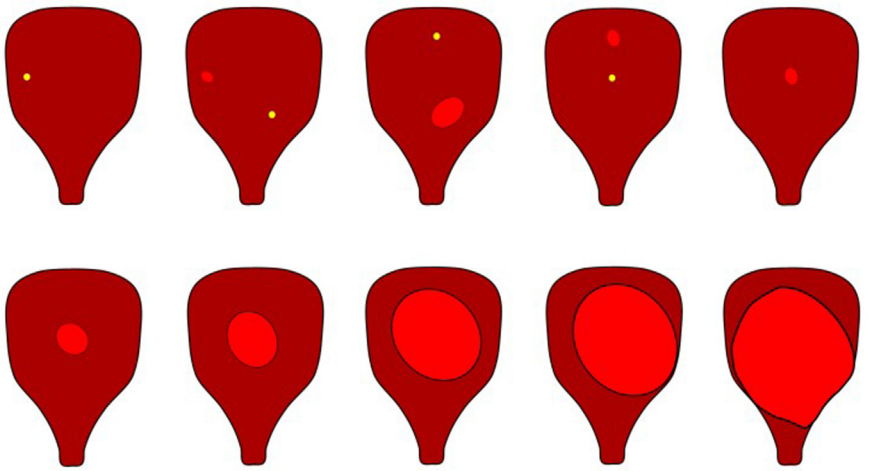
that dilated the cervix, the concept of pressure developing as a function of wall tension was a major advancement.

Uterine peristalsis

Many clinicians consider peristalsis to be a leading candidate for the mechanism of labor (Figure 9). Peristalsis can be considered a variation of the triple descending gradient model, as contractions start in the fundus and travel toward the cervix. However, peristalsis progressively pushes the fetus toward the cervix without maintaining the local contraction as the wave passes. Uterine peristalsis is well-established in the nonpregnant human uterus[50] and in other smooth muscle organs where contents are transported within an unpressurized vessel, such as the gut and ureter. Peristalsis also occurs in the pregnant rodent uterus, where the last pup must be transported through the length of the uterine horn.

There are several observations that argue against peristalsis as a mechanism for human labor. As previously discussed, fundal dominance is not supported by recent data; sequential propagation of action potentials over long distances in humans has been looked for but not found; there does not appear to be a biomechanical way for peristalsis to raise intrauterine pressure, because much of the wall is relaxed during passage of a peristaltic wave. Although the term "peristalsis" is probably most often used to refer to the triple descending gradient, care should be taken when using peristalsis as a basis for monitoring contractions or explaining clinical observations.

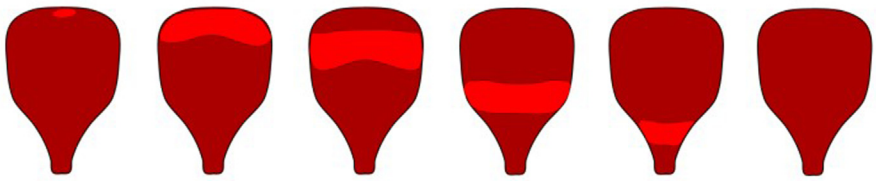
FIGURE 8
Csapo model of multiple pacemakers



There are many possible pacemakers, some of which are spontaneously active. Each pacemaker activates a small region of the myometrium and creates a local contraction. At the start of labor, the action potential propagation velocity increases, which increases the size of the local contractions. As labor progresses and contractions become stronger, 1 of the regions dominates until the propagating wave encompasses much but not all of the uterus.

Young. Monitoring uterine contractions: past, present, future. Am J Obstet Gynecol 2023.

FIGURE 9
Peristalsis model



The contraction begins in the fundus, then propagates toward the cervix. The contraction is completed when the contraction wave reaches the cervix. Unlike the triple descending gradient model, local contractions fade soon after the wave passes and do not persist for the duration of the contraction.

Young. Monitoring uterine contractions: past, present, future. Am J Obstet Gynecol 2023.

The action potential dilemma

In the models discussed above, sequential propagation of action potentials is the sole mechanism for recruiting the myometrium to participate in contraction of normal labor. In 2010, data from a high-density grid of 64 EMG sensors[51] confirmed that sequential propagation of action potentials does occur in the myometrium, though measurements were limited by the 3 cm x 3 cm grid size. In addition, there is abundant evidence showing that all contractions produce bioelectrical activity (though not all bioelectrical activity produces a contraction). However, as detailed above, there is little evidence to suggest that the myometrium is recruited in waves over long distances.[17]

Thus, the dilemma: action potentials are necessary and sufficient for myocyte and myometrial contractions at the cellular and tissue levels, but action potential propagation does not appear to be the mechanism that synchronizes organ level contractions during labor. Are there mechanisms for uterine signaling over long distances other than sequential action potential propagation? If not action potential propagation, what can account for the overwhelming data that a uterine contraction always produces bioelectrical activity and electromechanical coupling is well-established in myocytes and the myometrium?

Mechanisms for organ-level signaling other than sequential action potential propagation

Because the uterus lacks efferent nerves, central nervous system or autonomic control is unlikely. Autocrine or paracrine signaling is too slow and unpredictable to reliably regulate organ-level function. However, smooth muscle is known to contract in response to mechanical stimulation—a process called mechanotransduction. Clinical observations suggest that mechanical signaling functions in the pregnant human uterus (ie, abruptly pushing on the uterus in late pregnancy can initiate a contraction; the first line treatment for postpartum hemorrhage is uterine massage). An early publication on a pregnant rodent uterus demonstrated that contractions of 2 uterine horns could become synchronized using pressure as the sole signaling mechanism.[52] A confirmatory follow-up study demonstrated that mechanically stimulating a strip of pregnant rat myometrium with the contractions of a second strip of myometrium initiated action potentials and resulted in synchronized contractions.[53] These results also linked mechanical stimulation to synchronization of contractions through myometrial electrical excitability and outlined how mechanotransduction might be a mechanism for organ-level signaling while still relying on action potentials for myocyte- and myometrial-level signaling.

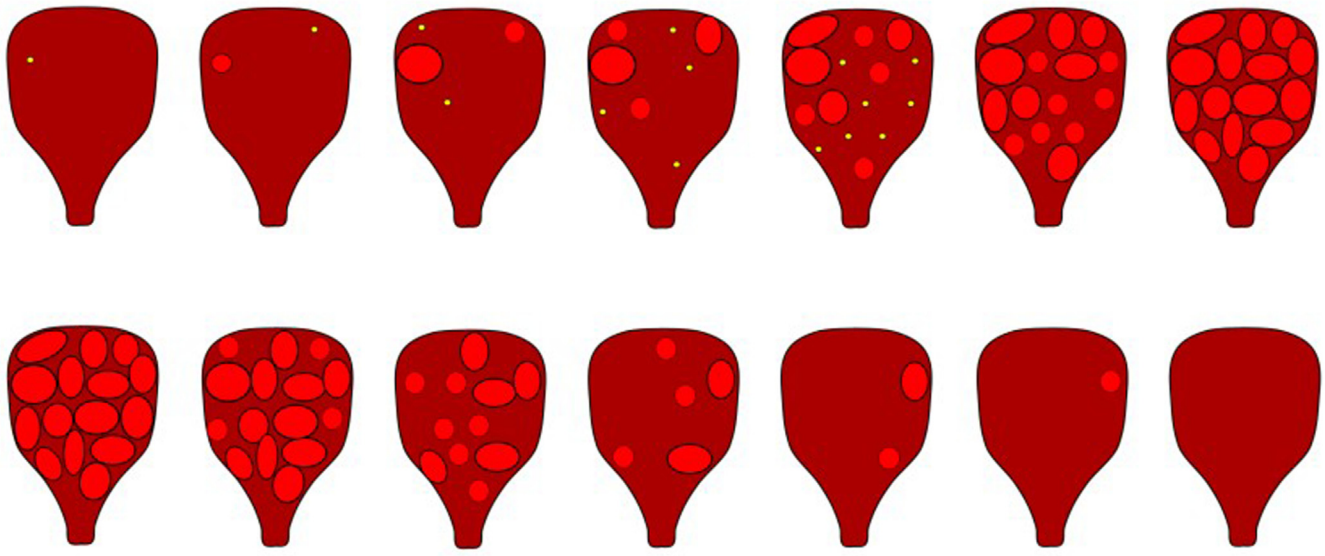
Action potentials plus pressure-tension-mechanotransduction: a dual model

A dual model of organ-level uterine signaling was proposed by the authors[19,54] in an attempt to reconcile the action potential dilemma (Figure 10). In the dual model, action potential propagation remains the primary signaling mechanism for distances less than approximately 10 cm. This distance represents the average distance an action potential propagates within the uterine wall and defines a "region." Regions are electrically independent. Over longer distances, new regions are recruited to participate in a contraction through local increases in wall tension generated by increased intrauterine pressure (eg, mechanotransduction). As noted above, all portions of the uterine wall experience much the same pressure, but local wall tensions are modified by the local radius of curvature and wall thickness. This creates a hierarchy of susceptibility to stimulation by mechanotransduction at different locations on the uterus. As rising pressure provides the signal to contract, successively recruited regions do not need to be touching or be even close to a region that is already contracting. With this mechanism, bioelectrical activity propagates throughout the uterus in what appears to be a random pattern.

Like Csapo's model, the dual model proposes that each contraction begins with the spontaneous expression of an action potential, not necessarily at a specific location. The action potential sequentially propagates approximately 10 cm and produces the first regional contraction. The first contraction raises intrauterine pressure only slightly, because most of the uterine wall is relaxed and stretches as the pressure rises. The slight rise of pressure increases wall tension throughout the uterus, modified by local wall thickness and local radius of curvature.

The next steps in the dual mechanism diverge from previous models. If there is myometrium that is sufficiently susceptible to a slight rise in tension, then mechanotransduction initiates another action potential at that location and another regional contraction occurs. This raises pressure and wall tension even further, which initiates more action potentials and recruits more regions. As more regions participate in the contraction, pressure continues to rise, wall tensions increase, and even lesser susceptible

FIGURE 10
Dual mechanism of uterine signaling



Action potential propagation and pressure/ tension/mechanotransduction. An initial action potential arises at an unspecified location on the uterine wall. Action potential propagation recruits all tissue within a 10 cm diameter, creating the first regional contraction. The slight pressure rise caused by the first regional contraction increases tension throughout the uterine wall, with local modifications according to the Law of Laplace. The increased tension initiates a second action potential at the location most susceptible to mechanotransduction, though the location is not necessarily near the first regional contraction. The second action potential propagates, creating the second regional contraction, which raises pressure slightly more. This positive feedback process repeats, resulting in recruitment of most or all the uterine wall. Shape change occurs as pressure rises, and pressure rises as more regions are recruited. At the peak of the contraction, most of the uterine wall contracts synchronously. After the peak of the contraction, regions independently relax, though not necessarily in the order of recruitment.

Young. Monitoring uterine contractions: past, present, future. Am J Obstet Gynecol 2023.

regions become activated. Converting a relaxed region into a contracting region decreases the compliance of the uterus, which also serves to raise intrauterine pressure. Together, these steps manifest positive feedback and cooperativity.

Strong contractions occur when most parts of the uterine wall simultaneously participate in the contraction. However, if the initial pressure rises are not sufficient to initiate additional action potentials through mechanotransduction, the process stops, preventing development of a strong contraction even though bioelectrical activity has been expressed in some parts of the uterine wall.

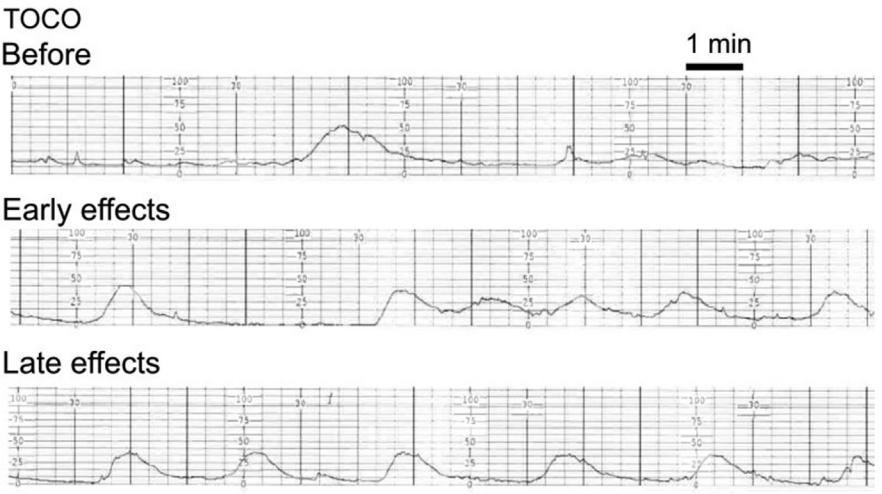
The dual model requires further refinements, 2 of which are listed in Table. First, mechanically induced contractions have been described in the myometrium, but the mechanism has not been established. Possibilities include stretch-activated ion channels, tension-activated release of IP_3, or production of prostaglandins with increasing tension. Second, the dual model utilizes a mechanotransduction mechanism for initiating regional contractions as the contraction progresses, but mechanisms that initiate the first regional contraction are not addressed.

Clinical correlation 5

In Figure 4, the doublets were caused by 2 initiating events, with each event recruiting a portion of the uterine wall (see clinical correlations 2 and 3). The triple descending gradient model interprets these tracings as abnormal functioning of a single pacemaker, though it is unlikely that a fundal uterine pacemaker exists in humans. The multiple pacemaker model suggests that 2 pacemakers are active but similarly cannot explain how the pacemakers can be dependent on one another. The dual model interprets the tracing as one region producing an initiating local contraction. The remaining regions have slightly different sensitivities to mechanotransduction (according to Laplace's Law, Figure 5), and these differences create 2 groups. The first group responds quickly to the pressures created by the initiating event, whereas the second group takes slightly longer to activate. Although the dual model requires some speculation about regional responses to mechanotransduction, it offers a plausible physiological explanation for how doublet contraction patterns are created.

The triple descending gradient interprets Figure 6 as dinoprostone enhancing the irregular firing of 1 or both pacemakers, with action potentials

FIGURE 11
Oxytocin for induction of labor at term



Uterine activity is recorded with tocodynamometry. Before initiating the oxytocin infusion, infrequent mild to moderate contractions are perceived by the patient, with some irregular activity seen on the contraction tracing. At low doses of oxytocin early in the induction, an irregular contraction pattern is seen without rest for 6 minutes. The oxytocin infusion rate was increased, resulting in expression of stronger contractions at a consistent frequency of 4 every 10-minutes (late effects).

TOCO, tocodynamometer.

Young. Monitoring uterine contractions: past, present, future. Am J Obstet Gynecol 2023.

propagating only short distances. Alternately, dinoprostone may be initiating action potentials in other, aberrant locations, which create ineffective contractions. The multiple pacemaker model suggests that many different pacemakers are firing irregularly, also with limited action potential propagation. The dual model would interpret the tracing in Figure 6 as dinoprostone causing increased tissue excitability with initiation of spontaneous contractions of many regions but without mechanotransduction signaling that is necessary for uterine synchronization.

Clinical correlation 6

Oxytocin is administered to half of all women in labor in the United States. It increases both the strength and frequency of contractions. Figure 11 displays tracings recorded from a patient who was undergoing induction of labor with oxytocin at term. Because the recording is performed with TOCO and several hours had elapsed, it was not possible to reliably compare the contraction strength among the 3 tracings. Before oxytocin, contractions were irregular and reported by the patient to be mild. Early in the induction, the contraction pattern was similar to the pattern seen after dinoprostone administration (Figure 6). Continuing to increase oxytocin dosage resulted in expression of a regular pattern with a frequency of 4 contractions per 10 minutes and adequate rest between contractions (late effects).

Both the triple descending gradient and multiple pacemaker models could be interpreted to indicate that the early effects of oxytocin show excessive stimulation of one or more pacemakers and the lack of rest is a potential problem. This may introduce hesitancy to continue or increase the dosage of oxytocin. The dual model interprets the early effects as many regions producing many unsynchronized local contractions that do not raise intrauterine pressure to high values and hence are unlikely to risk fetal status. In contrast, the transition from early to late effects is caused by oxytocin increasing myocyte excitability and contractility, which together elevate intrauterine pressure in the rising phase of the contraction. Higher pressures facilitate the mechanotransduction signaling and synchronization. Because synchronization also increases pressure, oxytocin creates a positive feedback loop that can create excessive intrauterine pressure if administered in excess.

Clinically monitoring uterine contractions

The 4 techniques currently used to clinically monitor uterine contractions during pregnancy have recently been reviewed[55] to compare their virtues and pitfalls. These 4 techniques are palpation, TOCO, IUPC, and uEMG. The biomechanics and organ-level models discussed above are relevant to the following observations and concerns raised in that review.

- TOCO reports the change of contour of the abdomen, not intrauterine pressure.

It reflects the change of uterine shape by measuring the abdominal contour changes, but it does not measure intrauterine pressure. In most cases, TOCO qualitatively follows the uterine contraction tracing of an IUPC fairly closely, because the uterus changes shape as pressure increases and decreases. This serves its primary function of locating the contraction peak, as the rising phase of a contraction is almost the mirror image of the falling phase. However, TOCO deviates from the true pressure profile, because once shape change has fully occurred, additional pressure rises are not recorded by TOCO. This may result in TOCO reporting a more flattened peak, whereas the IUPC reports a more rounded peak. These distortions of the contraction profile make it difficult, or perhaps impossible, to correlate the shape or duration of a TOCO tracing with uterine function. Thus, TOCO is useful for identifying when contraction peaks occur and measuring contraction frequency, but it is unlikely that additional information on the effectiveness of uterine contractions can be obtained from a TOCO tracing.

Clinical correlation 7

Because TOCO measures uterine shape change, the TOCO tracing is highly dependent on where it is placed. Changing the location of the transducer changes the size of the deflections. TOCO often detects artifacts such as patient respiration and movement. Rarely, "inverted" TOCO deflects are seen (Figure 12) where the contractions are recorded as downward deflections. Of note, these downward deflections are consistent in frequency and amplitude, similar to the upward deflections of most TOCO tracings. This emphasizes that even though TOCO is not quantitative, the relative strength of contractions recorded over short periods can be inferred as long as there are no changes in patient position or transducer adjustments. This rationale justifies inferring the relative strengths of the 2 peaks of the doublets in Figure 4.

- There is dissociation between labor progress and the force of contractions.

Although the precise relationship between contractions and forces on the cervix is unclear, Laplace's Law or more advanced computational methods provide a basis for a pressure-tension model that can be tested and refined. Recent advances in the biomechanics of pregnancy have addressed some of the complexities of relationship between the uterine corpus and cervix.[36] Even when pressures are measured with an IUPC, there are many other clinical variables that influence the progress of labor (ie, cervical compliance, pelvic structure, and pain relief interventions). Until there is clarity on the relationship between contractile forces and cervical forces, it will be difficult to define the importance of nonuterine factors.

- Fetal monitors based on fetal electrocardiogram (ECG) and uEMG are cleared by the US Food and Drug Administration (FDA).

Several ECG/uEMG-based fetal monitor devices have been cleared by the FDA, and 1 is currently available for clinical use in the US. Important advantages of this class of monitors are patient comfort and improved performance with obesity. The uterine contraction tracings are created by recording the uEMG, then converting the signals into an output tracing familiar to practicing obstetrical providers. Currently, contraction monitoring is limited to reporting when contractions occur and defining the temporal relationship between the fetal heart rate and contractions, essentially providing the same information as TOCO. Reporting contractions from uEMG signals seems to produce an excessive number of false positive contraction. However (see below):

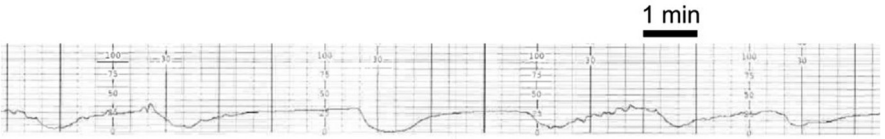
- uEMG has the potential to provide more information than the timing of contractions.

A variety of numeric methods have been used to analyze uEMG signals to identify changes that associate with specific abnormalities of labor, such as true vs false labor, obstructed labor, and prolonged labor, among others.[56] Most techniques have focused on frequency or power analyses of the uEMG signals produced by the myometrium. This approach assumes, perhaps incorrectly, that the important information resides at the tissue-level rather than being an emergent property of the uterus. For whatever reason, uEMG signal analysis techniques that go beyond reporting when contractions occur are not yet clinically available.

One uEMG technology developed to measure uterine function as opposed to myometrial function is "action potential propagation velocity"[57]. The data recording and analysis were designed to diagnose true vs false preterm labor and were based on a combination of the triple descending gradient and the multiple pacemaker model (Figures 7 and 9). In both models, sequential action potential propagation is the mechanism for organ-level signaling. As noted by Csapo,[14] faster speeds were envisioned to indicate more optimal organ-level coordination and a stronger contraction indicative of true preterm labor. However, the measured propagation speeds[57] exceeded anticipated values 10-fold and undermined the concept that action potential propagation was responsible for long distance signaling.[58] As the technology was based on sequential action potential propagation, questions arose regarding both data collection and analysis.[58] Further development of the propagation velocity technology seems to have stopped when the complexity of the uEMG signal propagation patterns became apparent.[18]

In retrospect, the concept of measuring organ-level coordination as a surrogate for contraction strength is compelling but should not be based on the premise that action potentials propagate long distances. As the dual model offers an alternative to action potential propagation, measuring uterine coordination with uEMG techniques based on this model may provide a clinically useful approach to noninvasively measure

FIGURE 12
TOCO reporting an inverted tracing



Correlating the tracing with palpation and patient discomfort confirmed the contractions were correctly recorded, though the contractions were represented as a downward deflection. This appearance of the tracing persisted until the TOCO transducer position was changed. Note that each contraction is represented by similarly shaped deflection and a relatively consistent peak magnitude.

TOCO, tocodynamometer.

Young. Monitoring uterine contractions: past, present, future. Am J Obstet Gynecol 2023.

contraction strength (see future directions below).

- uEMG detects more false positive contractions than TOCO

"False positive" refers to a deflection on the uEMG uterine contraction tracing that does not correspond to a deflection on the IUPC tracing.[59] uEMG measures signals arising from myometrial contractions. However, as predicted by all 3 uterine models presented, myometrial contractions do not always produce organ-level contractions that raise intrauterine pressure. Hence, uEMG recordings might be predicted to contain signals that may not correlate with uterine contractions. If these signals are not correctly interpreted, the uEMG tracing may contain many false positive contractions. All uEMG-based uterine contraction monitors currently cleared by the FDA carry a warning that false positive contractions are frequently reported.[59] Moreover, a high rate of reporting false positive contractions is stated by the FDA to be the reason that no uEMG-based device is currently cleared for use in preterm patients.

The dual model (Figure 10) may suggest a method to minimize reporting false positive contractions using uEMG. The dual model predicts that local contractions produce uEMG signals, but these contractions do not raise intrauterine pressures to high values unless many local contractions synchronize into a global contraction. Thus, to minimize reporting false positive contractions, uterine activities could be measured at several different locations, then a deflection could be reported only when the uEMG signals are synchronized.

- uEMG correctly detects more contractions than TOCO, especially in patients with obesity.[60,61]

Obesity makes recording of any surface signal challenging, because the increased thickness of the anterior abdominal wall distorts and attenuates all signals. TOCO measures uterine shape changes, and uEMG records bioelectrical signals from the uterus, and both signals must be transmitted to the abdominal surface. Given the purely mechanical nature of TOCO, it is markedly disrupted by obesity. uEMG-based devices are becoming a promising alternative for noninvasive contraction monitoring in this group of patients.

Key questions; outline for future investigations

Next, we present 7 questions selected only because they are relevant to topics in this review. With dozens of researchers active in the field, each would likely have their own list.

What triggers the onset of labor? (Or, is there a trigger?)

There has been great progress in understanding cellular function but no clear answers for what triggers labor. Although it is satisfying to believe that a single triggering cellular event activates and converts uterine quiescence to active labor, there is no evidence to support that supposition. There may be many events that initiate labor, or the trigger may involve 1 or more emergent properties. The dual model predicts that mechanotransduction is both necessary and sufficient for labor, suggesting that expression of the mechanotransduction pathway triggers labor. Further investigation is required to support or refute this prediction.

Is it possible to use uterine electromyography to detect uterine activation?

In addition to evaluating the contractions of labor, uEMG may also be useful for evaluating uterine activation before labor begins. Specific classes of uEMG signals are seen as early as 16 to 22 weeks gestation.[62] Interestingly, in patients with cervical shortening, distinct patterns of uEMG signals are observed that exhibit a signal expression similar to those preceding the onset of labor. Consequently, these data offer a plausible biophysiological link to cervical shortening in this population, may aid in the development of tools to individualize care in patients at risk of preterm labor, and improve outcomes.

Is it possible to reliably assess the strength of contractions using uterine electromyography?

As described above, measuring the characteristics of uEMG signals or action potential propagation velocities do not appear to be able to reliably assess uterine coordination and contraction strength. However, designing a monitoring system based on mechanotransduction (dual model, Figure 10) rather than action potential propagation offers a different approach to measuring uterine coordination. From the dual model, local uterine activities could be measured with several widely separated uEMG sensors. Then, if the local uterine activities occur simultaneously, the dual model predicts that the contraction is strong. If the local activities are unsynchronized, the dual model predicts the contraction is weak. In addition, by rejecting solitary uEMG signals, it should be possible to report fewer false positive deflections on the uterine contraction tracing.

What are the cellular mechanisms of mechanotransduction in the myometrium?

Smooth muscle mechanotransduction is an established phenomenon, and how acute or abrupt mechanotransduction events of the myometrium may affect uterine contractions have been investigated.[19,63–65] However, the cellular mechanisms of acute mechanotransduction have yet to be adequately addressed. If mechanotransduction is the last necessary step before the onset of labor as proposed in the dual model, understanding how these mechanisms activate will help define the events involved with the onset and maintenance of labor.

What determines the frequency of contractions?

Most of the research on uterine function has focused on understanding how strong contractions are generated. Understanding what determines the frequency of these contractions has

received much less attention. This imbalance is perhaps unwarranted, as strong contractions must occur with adequate frequency to dilate the cervix, and contraction frequency is the one clinical parameter that is easily quantified. As labor progresses, contractions become stronger and more frequent. However, the precise relationship between contraction strength and frequency is very poorly understood. Contraction frequency might primarily depend on cellular processes or it may reflect an emergent property of the tissue or organ.

Do patients in preterm labor and term labor activate the same mechanisms to express contractions?

A common assumption is that idiopathic preterm labor and term labor share similar myometrial activation pathways. However, a recent gene expression analysis[66] suggests that preterm labor and term labor are initiated differently. An even broader approach may be required, such as considering preterm labor to be a syndrome with a spectrum of causes and phenotypic expressions. This approach adds complexity and requires a structure to organize the mechanisms, including the influence of nonmyometrial factors such as cervical, amnion, and fetal biology.[67]

What are the important clinical questions that contraction monitoring should address?

Practitioners of obstetrics have done an exceptional job of adapting to knowledge gaps to provide optimal care for current patients. However, it is important that those accommodations do not obscure the knowledge gaps or mask the clinical needs. Except for the need to noninvasively assess contraction strength, monitoring uterine contractility has few well-articulated questions and an excess of need. Technology awaits the questions, and future patients await the solutions.

In this review, we present the core elements of myocyte contractility, myometrial structure and function, and uterine signaling during pregnancy. Although knowledge of cellular- and tissue-level function has steadily advanced through many refinements and developed into a substantial base, our understanding of the mechanisms that create organ-level contractions has not kept pace. Concepts from early models of organ function have persisted, likely because until recently, there has been only indirect evidence that these models have intrinsic shortcomings. However, studies now confirm that wave-like uterine recruitment occurs over short distances but not long distances. To integrate this new information, mechanotransduction was proposed as the essential mechanism for long distance communication and uterine synchronization. Developing a more rigorous understanding of how the uterus contracts and produces cervical dilation has direct relevance to clinically measuring and interpreting uterine contraction patterns. This is particularly important for uEMG technology, which may offer new information on myometrial and uterine function and enhance our opportunity to improve methods for diagnosing abnormalities of labor. ■

REFERENCES

1. Ananth CV, Chauhan SP, Chen HY, D'Alton ME, Vintzileos AM. Electronic fetal monitoring in the United States: temporal trends and adverse perinatal outcomes. Obstet Gynecol 2013;121:927–33.
2. ACOG Practice Bulletin No. 106: intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. Obstet Gynecol 2009;114:192–202.
3. Pates JA, McIntire DD, Leveno KJ. Uterine contractions preceding labor. Obstet Gynecol 2007;110:566–9.
4. Chao TT, Bloom SL, Mitchell JS, McIntire DD, Leveno KJ. The diagnosis and natural history of false preterm labor. Obstet Gynecol 2011;118:1301–8.
5. ACOG Practice Bulletin No. 107: induction of labor. Obstet Gynecol 2009;114:386–97.
6. Heuser CC, Knight S, Esplin MS, et al. Tachysystole in term labor: incidence, risk factors, outcomes, and effect on fetal heart tracings. Am J Obstet Gynecol 2013;209:32. e1–6.
7. Frey HA, Tuuli MG, Roehl KA, Odibo AO, Macones GA, Cahill AG. Can contraction patterns predict neonatal outcomes? J Matern Fetal Neonatal Med 2014;27:1422–7.
8. Reynolds AJ, Geary MP, Hayes BC. Intrapartum uterine activity and neonatal outcomes: a systematic review. BMC Pregnancy Childbirth 2020;20:532.
9. American College of Obstetricians and Gynecologists. Practice Bulletin No. 116: management of intrapartum fetal heart rate tracings. Obstet Gynecol 2010;116:1232–40.
10. Zhang J, Branch DW, Ramirez MM, et al. Oxytocin regimen for labor augmentation, labor progression, and perinatal outcomes. Obstet Gynecol 2011;118:249–56.
11. Galinimoghaddam T, Moslemizadeh N, Seifollahpour Z, Shahhosseini Z, Danesh M. Uterine contractions' pattern in active phase of labor as a predictor of failure to progress. Glob J Health Sci 2014;6:200–5.
12. Oppenheimer LW, Bland ES, Dabrowski A, Holmes P, McDonald O, Wen SW. Uterine contraction pattern as a predictor of the mode of delivery. J Perinatol 2002;22:149–53.
13. Caldeyro-Barcia R, Poseiro JJ. Physiology of the uterine contraction. Clin Obstet Gynecol 1960;3:386–410.
14. Csapo A. The diagnostic significance of the intrauterine pressure. I. Obstet Gynecol Surv 1970;25:403–35.
15. Parkington HC, Harding R, Sigger JN. Coordination of electrical activity in the myometrium of pregnant ewes. J Reprod Fertil 1988;82:697–705.
16. Lammers WJ. The electrical activities of the uterus during pregnancy. Reprod Sci 2013;20:182–9.
17. Zhang M, La Rosa PS, Eswaran H, Nehorai A. Estimating uterine source current during contractions using magnetomyography measurements. PLoS One 2018;13:e0202184.
18. Rabotti C, Mischi M. Propagation of electrical activity in uterine muscle during pregnancy: a review. Acta Physiol (Oxf) 2015;213:406–16.
19. Young RC, Barendse P. Linking myometrial physiology to intrauterine pressure; how tissue-level contractions create uterine contractions of labor. PLoS Comput Biol 2014;10:e1003850.
20. Bru-Mercier G, Gullam JE, Thornton S, Blanks AM, Shmygol A. Characterization of the tissue-level Ca2+ signals in spontaneously contracting human myometrium. J Cell Mol Med 2012;16:2990–3000.
21. Wray S, Prendergast C. The myometrium: from excitation to contractions and labour. Adv Exp Med Biol 2019;1124:233–63.
22. Shmygol A, Blanks AM, Bru-Mercier G, Gullam JE, Thornton S. Control of uterine Ca2+ by membrane voltage: toward understanding the excitation-contraction coupling in human myometrium. Ann N Y Acad Sci 2007;1101:97–109.
23. Blanks AM, Shmygol A, Thornton S. Regulation of oxytocin receptors and oxytocin receptor signaling. Semin Reprod Med 2007;25:52–9.
24. Garfield RE, Sims S, Daniel EE. Gap junctions: their presence and necessity in myometrium during parturition. Science 1977;198:958–60.
25. Tabb T, Thilander G, Grover A, Hertzberg E, Garfield R. An immunochemical and

immunocytologic study of the increase in myometrial gap junctions (and connexin 43) in rats and humans during pregnancy. Am J Obstet Gynecol 1992;167:559–67.
26. Garfield RE, Thilander G, Blennerhassett MG, Sakai N. Are gap junctions necessary for cell-to-cell coupling of smooth muscle?: an update. Can J Physiol Pharmacol 1992;70:481–90.
27. Lutton EJ, Lammers WJ, James S, van den Berg HA, Blanks AM. A computational method for three-dimensional reconstruction of the microarchitecture of myometrial smooth muscle from histological sections. PLoS One 2017;12:e0173404.
28. Hawkins JS, Wells CE, Casey BM, McIntire DD, Leveno KJ. Nifedipine for acute tocolysis of preterm labor: a placebo-controlled randomized trial. Obstet Gynecol 2021;138:73–8.
29. Eswaran H, Preissl H, Murphy P, Wilson JD, Lowery CL. Spatial-temporal analysis of uterine smooth muscle activity recorded during pregnancy. Conf Proc IEEE Eng Med Biol Soc 2005;2005:6665–7.
30. Cahill AG, Wen Z, Wang H, et al. Analysis of electrophysiological activation of the uterus during human labor contractions. JAMA Netw Open 2022;5:e2214707.
31. Young RC. The uterine pacemaker of labor. Best Pract Res Clin Obstet Gynaecol 2018;52:68–87.
32. Wolfs G, Rottinghuis H. Electrical and mechanical activity of the human uterus during labour. Arch Gynakol 1970;208:373–85.
33. Sheldon RE, Baghdadi M, McCloskey C, Blanks AM, Shmygol A, van den Berg HA. Spatial heterogeneity enhances and modulates excitability in a mathematical model of the myometrium. J R Soc Interface 2013;10:20130458.
34. Lammers WJ, Stephen B, Al-Sultan MA, Subramanya SB, Blanks AM. The location of pacemakers in the uteri of pregnant guinea pigs and rats. Am J Physiol Regul Integr Comp Physiol 2015;309:R1439–46.
35. Banciu A, Banciu DD, Mustaciosu CC, et al. Beta-estradiol regulates voltage-gated calcium channels and estrogen receptors in telocytes from human myometrium. Int J Mol Sci 2018;19.
36. Fernandez M, House M, Jambawalikar S, et al. Investigating the mechanical function of the cervix during pregnancy using finite element models derived from high-resolution 3D MRI. Comput Methods Biomech Biomed Engin 2016;19:404–17.
37. American College of Obstetricians and Gynecologists (College), ; Society for Maternal-Fetal Medicine, Caughey AB, Cahill AG, Guise JM, Rouse DJ. Safe prevention of the primary cesarean delivery. Am J Obstet Gynecol 2014;210:179–93.
38. Hauth JC, Hankins GD, Gilstrap LC, Strickland DM, Vance P. Uterine contraction pressures with oxytocin induction/augmentation. Obstet Gynecol 1986;68:305–9.
39. American College of Obstetrics and Gynecology Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin Number 49, December 2003: Dystocia and augmentation of labor. Obstet Gynecol. 2003;102:1445–1454.
40. Knoke JD, Tsao LL, Neuman MR, Roux JF. The accuracy of measurements of intrauterine pressure during labor: a statistical analysis. Comput Biomed Res 1976;9:177–86.
41. Arrabal PP, Nagey DA. Is manual palpation of uterine contractions accurate? Am J Obstet Gynecol 1996;174:217–9.
42. Harper LM, Shanks AL, Tuuli MG, Roehl KA, Cahill AG. The risks and benefits of internal monitors in laboring patients. Am J Obstet Gynecol 2013;209:38.e1–6.
43. Wilmink FA, Wilms FF, Heydanus R, Mol BW, Papatsonis DN. Fetal complications after placement of an intrauterine pressure catheter: a report of two cases and review of the literature. J Matern Fetal Neonatal Med 2008;21:880–3.
44. Bakker JJ, Verhoeven CJ, Janssen PF, et al. Outcomes after internal versus external tocodynamometry for monitoring labor. N Engl J Med 2010;362:306–13.
45. Humphrey JD, Taylor CA. Intracranial and abdominal aortic aneurysms: similarities, differences, and need for a new class of computational models. Annu Rev Biomed Eng 2008;10:221–46.
46. Alvarez H, Caldeyro-Barcia R. [The normal and abnormal contractile waves of the uterus during labour]. Gynaecologia 1954;138:190–212.
47. Euliano TY, Marossero D, Nguyen MT, Euliano NR, Principe J, Edwards RK. Spatiotemporal electrohysterography patterns in normal and arrested labor. Am J Obstet Gynecol 2009;200:54. e1–7.
48. Edwards RK, Euliano NR, Singh S, et al. Evaluating fundal dominant contractions on spatiotemporal electrohysterography as a marker for effective labor contractions. Am J Perinatol 2019;36:924–9.
49. Escalona-Vargas D, Govindan RB, Furdea A, Murphy P, Lowery CL, Eswaran H. Characterizing the propagation of uterine electrophysiological signals recorded with a multisensor abdominal array in term pregnancies. PLoS One 2015;10:e0140894.
50. Myers KM, Elad D. Biomechanics of the human uterus9. Wiley Interdiscip Rev Syst Biol Med; 2017.
51. Rabotti C, Mischi M, Oei SG, Bergmans JW. Noninvasive estimation of the electrohysterographic action-potential conduction velocity. IEEE Trans Biomed Eng 2010;57:2178–87.
52. Takeda H. Generation and propagation of uterine activity in situ. Fertil Steril 1965;16:113–9.
53. Young RC, Goloman G. Mechanotransduction in rat myometrium: coordination of contractions of electrically and chemically isolated tissues. Reprod Sci 2011;18:64–9.
54. Young RC. Mechanotransduction mechanisms for coordinating uterine contractions in human labor. Reproduction 2016;152:R51–61.
55. Cohen WR. Clinical assessment of uterine contractions. Int J Gynaecol Obstet 2017;139:137–42.
56. Vlemminx MWC, Rabotti C, van der Hout-van der Jagt MB, Oei SG. Clinical use of electrohysterography during term labor: a systematic review on diagnostic value, advantages, and limitations. Obstet Gynecol Surv 2018;73:303–24.
57. Lucovnik M, Maner WL, Chambliss LR, et al. Noninvasive uterine electromyography for prediction of preterm delivery. Am J Obstet Gynecol 2011;204:228.e1–10.
58. Rabotti C, Oei SG, van 't Hooft J, Mischi M. Electrohysterographic propagation velocity for preterm delivery prediction. Am J Obstet Gynecol 2011;205:e9–10.
59. Monica AN24 uterine electromyographic monitor 510(k) premarket notification, K112390. 01/02/2011. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K101801. Accessed January 2, 2011.
60. Vlemminx MWC, Thijssen KMJ, Bajlekov GI, Dieleman JP, Van Der Hout-Van Der Jagt MB, Oei SG. Electrohysterography for uterine monitoring during term labour compared to external tocodynamometry and intra-uterine pressure catheter. Eur J Obstet Gynecol Reprod Biol 2017;215:197–205.
61. Vlemminx MWC, Thijssen KMJ, Bajlekov GI, Dieleman JP, Van Der Hout-Van Der Jagt MB, Oei SG. Could electrohysterography be the solution for external uterine monitoring in obese women? J Perinatol 2018;38:580–6.
62. Marinescu PS, Young RC, Miller LA, Llop JR, Pressman EK, Seligman NS. Midtrimester uterine electromyography in patients with a short cervix. Am J Obstet Gynecol 2022;227:83.e1–17.
63. Young RC. Synchronization of regional contractions of human labor; direct effects of region size and tissue excitability. J Biomech 2015;48:1614–9.
64. Yochum M, Laforêt J, Marque C. Multi-scale and multi-physics model of the uterine smooth muscle with mechanotransduction. Comput Biol Med 2018;93:17–30.
65. Garfield RE, Murphy L, Gray K, Towe B. Review and study of uterine bioelectrical waveforms and vector analysis to identify electrical and mechanosensitive transduction control mechanisms during labor in pregnant patients. Reprod Sci 2021;28:838–56.
66. Phung J, Wang CA, Reeders J, et al. Preterm labor is a distinct process from term labor following computational analysis of human myometrium. Am J Obstet Gynecol 2022;226:106.e1–16.
67. McLean M, Bisits A, Davies J, Woods R, Lowry P, Smith R. A placental clock controlling the length of human pregnancy. Nat Med 1995;1:460–3.