CHAPTER 21: Physiology of Labor

From time immemorial inquiring minds have sought an explanation for the fact that labour usually ensues about 280 days after the appearance of the last menstrual period, but thus far no satisfactory universal cause has been discovered.

—J. Whitridge Williams (1903)

INTRODUCTION

The importance of labor physiology was highlighted in the first edition of *Williams Obstetrics*, in which an entire section was devoted to the topic. Given the science at that time, those nine chapters were concerned with the mechanics of labor and delivery. However, the current understanding of labor includes a wide spectrum of preparedness even before the first regular contractions.

Labor is the last few hours of human pregnancy. It is characterized by forceful and painful uterine contractions that effect cervical dilation and cause the fetus to descend through the birth canal. Extensive preparations take place in both the uterus and cervix long before this. During the first 36 to 38 weeks of normal gestation, the myometrium is in a preparatory yet unresponsive state. Concurrently, the cervix begins an early stage of remodeling yet maintains structural integrity. Following this prolonged uterine quiescence, a transitional phase follows during which myometrial unresponsiveness is suspended and the cervix undergoes ripening, effacement, and loss of structural cohesion.

The physiological processes that regulate *parturition*—the bringing forth of young—and the onset of labor continue to be defined. Three general contemporaneous theories describe labor initiation. Viewed simplistically, the first is the *functional loss of pregnancy maintenance factors.* The second focuses on *synthesis of factors that induce parturition.* The third suggests that the mature fetus is the source of the initial *signal for parturition commencement.* Current research supports a model that draws from all three themes. However, labor onset clearly represents the culmination of a series of biochemical changes in the uterus and cervix. These result from endocrine and paracrine signals emanating from both mother and fetus. Their relative contributions vary between species, and it is these differences that complicate elucidation of the exact factors that regulate human parturition. When parturition is abnormal, then preterm labor, dystocia, or postterm pregnancy may result. Of these, preterm labor remains the major contributor to neonatal mortality and morbidity.

MATERNAL AND FETAL COMPARTMENTS

Uterus

The myometrial layer of the uterus is composed of bundles of smooth muscle cells surrounded by connective tissue. In contrast to skeletal or cardiac muscle, the smooth muscle cell is not terminally differentiated and therefore is readily adaptable to environmental changes. Varied stimuli such as mechanical stretch, inflammation, and endocrine and paracrine signals can modulate the transition of the smooth muscle cell among phenotypes that provide cell growth, proliferation, secretion, and contractility.

In addition to this phenotypic plasticity, several smooth muscle qualities confer advantages for uterine contraction efficiency and fetal delivery. First, the degree of smooth muscle cell shortening with contractions may be one order of magnitude greater than that attained in striated muscle cells. Second, forces can be exerted in smooth muscle cells in multiple directions. This differs from the contraction force generated by skeletal muscle, which is always aligned with the axis of the muscle fibers. Third, smooth muscle is not organized in the same manner as skeletal muscle. In myometrium, the thick and thin filaments are found in long, random bundles throughout the cells. This plexiform arrangement aids greater shortening and force-generating capacity. Last, greater multidirectional force generation in the uterine fundus compared with that of the lower uterine segment permits versatility in expulsive force directionality.

Lining the thick muscular uterine walls, the endometrium is transformed by pregnancy hormones and is then termed *decidua.* Composed of stromal

cells and maternal immune cells, the decidua serves to maintain the pregnancy via unique immunoregulatory functions that suppress inflammatory signals during gestation. However, at the end of pregnancy, decidual activation ensues. With this, the decidua transitions to induce inflammatory signals and withdraw active immunosuppression, which contribute to parturition initiation.

During pregnancy, the cervix has multiple functions that include: (1) maintenance of barrier function to protect the reproductive tract from infection, (2) maintenance of cervical competence despite greater gravitational forces as the fetus grows, and (3) orchestration of extracellular matrix changes that allow progressively greater tissue compliance.

In nonpregnant women, the cervix is closed and firm, and its consistency is similar to nasal cartilage. By the end of pregnancy, the cervix is easily distensible, and its consistency is similar to the lips of the oral cavity. Observations in three-dimensional sonography and magnetic resonance imaging show increases in the cross-sectional area of the cervical canal and in the cervical stroma from early to late pregnancy (House, 2009; Lang, 2010). Concurrent with expansion of the stroma, the cervical epithelia proliferate and exert a pregnancy-specific immunoprotection.

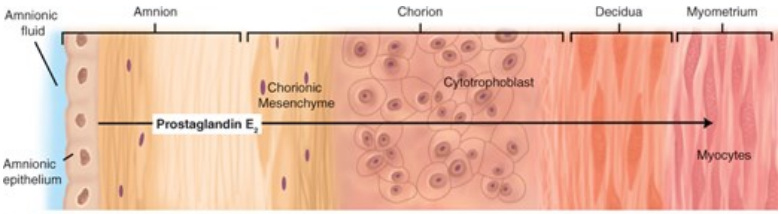
Placenta

In addition to providing the exchange of nutrients and waste between mother and fetus, the placenta is a key source of steroid hormones, growth factors, and other mediators that maintain pregnancy and potentially aid the transition to parturition. The fetal membranes—amnion and chorion and adjacent decidua—make up an important tissue shell around the fetus that serves as a physiological, immunological, and metabolic shield to protect against untimely parturition initiation.

The amnion provides virtually all of the fetal membranes' tensile strength to resist membrane tearing and rupture (Chap. 5, Amnion). This avascular tissue is highly resistant to penetration by leukocytes, microorganisms, and neoplastic cells (Fig. 21-1). It also constitutes a selective filter to prevent fetal particulate-bound lung and skin secretions from reaching the maternal compartment. In this manner, maternal tissues are protected from amnionic fluid constituents that could prematurely accelerate decidual or myometrial activation or could promote adverse events such as amnionic fluid embolism.

FIGURE 21-1

The amnion synthesizes prostaglandins, and late in pregnancy, synthesis is augmented by increased phospholipase A_2 and prostaglandin H synthase, type 2 (PGHS-2) activity. During pregnancy, the transport of prostaglandins from the amnion to maternal tissues is limited by expression of the inactivating enzymes, prostaglandin dehydrogenase (PGDH), in the chorion. During labor, PGDH levels decline, and amnion-derived prostaglandins can influence membrane rupture and uterine contractility. The role of decidual activation in parturition is unclear but may involve local progesterone metabolism and higher prostaglandin receptor concentrations, thus enhancing uterine prostaglandin actions and cytokine production. (Redrawn from Smith R: Parturition. N Engl J Med. 2007 Jan 18;356(3):271–283.)



The chorion is a primarily protective tissue layer and provides immunological acceptance. It is also enriched with enzymes that inactivate *uterotonins,* which are agents that stimulate contractions. Inactivating enzymes include prostaglandin dehydrogenase, oxytocinase, and enkephalinase (Cheung, 1990; Germain, 1994).

SEX STEROID HORMONE ROLE

In many species, the role of sex steroid hormones is clear— estrogen promotes and progesterone inhibits the events leading to parturition. And, the removal of progesterone, that is, *progesterone withdrawal,* directly precedes progression of parturition. In addition, providing progesterone to some species will delay parturition via a decline in myometrial activity and continued cervical competency (Challis, 1994). In humans, however, it seems most

likely that both estrogen and progesterone are components of a broader molecular system that maintains uterine quiescence.

Plasma levels of estrogen and progesterone in normal pregnancy are enormous and in great excess of the affinity constants for their receptors. For this reason, it is difficult to comprehend how relatively subtle changes in the ratio of their concentrations could modulate physiological processes during pregnancy. The teleological evidence, however, for an increased progesterone-to-estrogen ratio in the maintenance of pregnancy and a decline in this ratio for parturition is overwhelming. In all species studied, including humans, administration of the progesterone-receptor antagonists *mifepristone (RU-486)* or *onapristone* will promote some or all key features of parturition. These include cervical ripening, greater cervical distensibility, and augmented uterine sensitivity to uterotonins (Bygdeman, 1994; Chwalisz, 1994b; Wolf, 1993).

The exact role of estrogen in regulation of human uterine quiescence and cervical competency is less well understood. That said, estrogen can advance progesterone responsiveness and, in doing so, promote uterine quiescence. At the end of pregnancy, estrogen aids processes that mediate uterine activation and cervical ripening.

Both progesterone and estrogen bind to nuclear receptors that regulate gene transcription in a cell- and context-specific pattern. Two nuclear receptors for estrogen are estrogen receptor α (ERα) and estrogen receptor β (ERβ). Nuclear receptor isoforms of the progesterone receptor (PR-A and PR-B) are encoded by differing transcripts from a single gene (Patel, 2015).

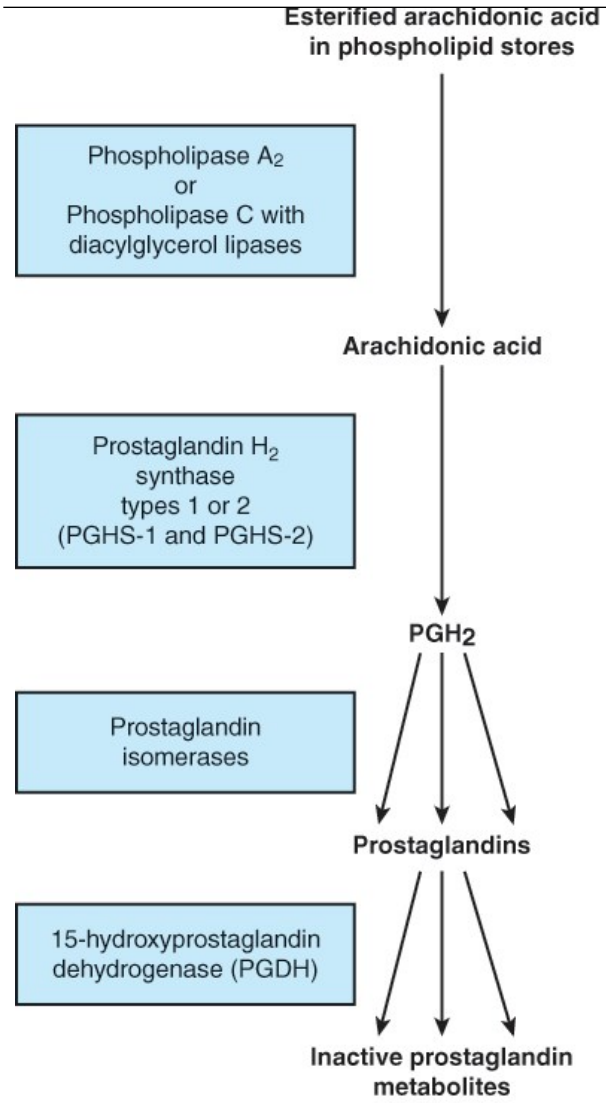
PROSTAGLANDINS ROLE

Prostaglandins are lipid molecules with varied hormone-like actions. In parturition, they play a prominent role in myometrial contractility, relaxation, and inflammation. Prostaglandins interact with a family of eight different G-protein–coupled receptors (G-Protein–Coupled Receptors), several of which are expressed in myometrium and cervix (Konopka, 2015; Myatt, 2004).

The major synthetic pathways involved in prostaglandin biosynthesis are shown in Figure 21-2. Prostaglandins are produced using plasma membrane-derived arachidonic acid, which usually is released by the action of phospholipase A_2 or C. Arachidonic acid can then act as substrate for both type 1 and 2 prostaglandin H synthase (PGHS-1 and -2), which are also called cyclooxygenase-1 and -2 (COX-1 and -2). Both PGHS isoforms convert arachidonic acid to the unstable prostaglandin G_2 and then to prostaglandin H_2. These enzymes are the target of many nonsteroidal antiinflammatory drugs (NSAIDs). Indeed, the tocolytic actions of specific NSAIDs, as discussed in Chapter 42 (β-Adrenergic Receptor Agonists), were considered promising until they were shown to have adverse fetal effects (Loudon, 2003; Olson, 2003, 2007).

FIGURE 21-2

Overview of the prostaglandin biosynthetic pathway.



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Through prostaglandin isomerases, prostaglandin H_2 is converted to active prostaglandins. These include prostaglandins E_2 (PGE_2), $F_{2\alpha}$ ($PGF_{2\alpha}$), and I_2 (PGI_2). Isomerase expression is tissue-specific and thereby controls the relative production of various prostaglandins. Another important control point for prostaglandin activity is its metabolism, which most often is through the action of 15-hydroxyprostaglandin dehydrogenase (PGDH). Expression of this enzyme is upregulated during pregnancy in the uterus and cervix, which provides the important ability to rapidly inactivate prostaglandins (Giannoulias, 2002; Kishore, 2014). Thus, myometrial responses to prostaglandins stem from a balance between prostaglandin synthesis versus metabolism, from the relative expression of various prostaglandin receptors, or from a switch in receptor-signaling pathways (Kandola, 2014; Lyall, 2002; Olson, 2007; Smith, 2001). It is entirely possible that prostanoids contribute to myometrial relaxation at one stage of pregnancy and to myometrial contractions after parturition initiation (Myatt, 2004).

In addition to the myometrium, the amnion synthesizes several bioactive peptides and prostaglandins that cause myometrial relaxation or contraction (see Fig. 21-1). Late in pregnancy, amnionic prostaglandin biosynthesis is increased, and phospholipase A_2 and PGHS-2 show greater activity (Johnson, 2002). Accordingly, many hypothesize that prostaglandins regulate events leading to parturition. The amnion is likely the major source for amnionic fluid prostaglandins, and their role in the activation of cascades that promote membrane rupture is clear. The influence of amnion-derived prostaglandins on uterine quiescence and activation, however, is less delineated. This is because prostaglandin transport from the amnion through the chorion to access maternal tissues is limited by expression of PGDH.

PHASE 1: UTERINE QUIESCENCE AND CERVICAL SOFTENING

As shown in Figure 21-3, parturition can be arbitrarily divided into four overlapping phases that correspond to the major physiological transitions of the myometrium and cervix during pregnancy (Casey, 1993, 1997; Challis, 2000; Word, 2007). These phases of parturition include: (1) a prelude to it, (2) the preparation for it, (3) the process itself, and (4) recovery. Importantly, the *phases of parturition* should not be confused with the *clinical stages of labor,* that is, the first, second, and third stages—which make up phase 3 of parturition (Fig. 21-4).

FIGURE 21-3

The phases of parturition.

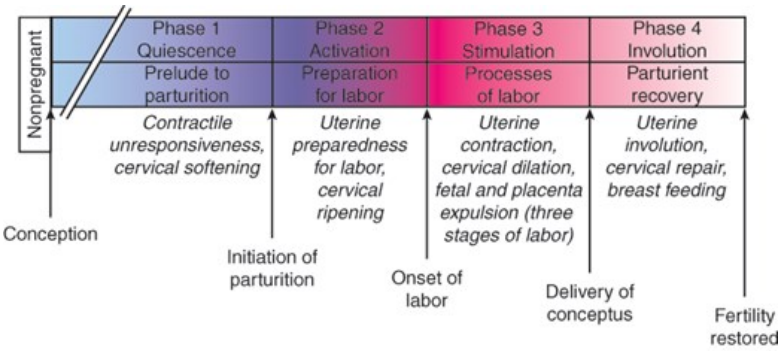
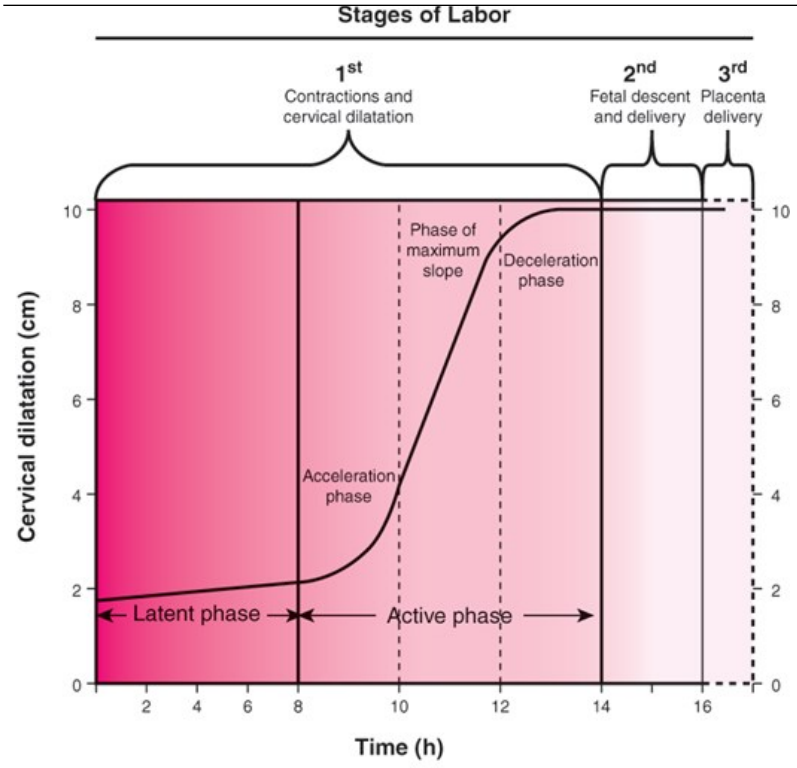


FIGURE 21-4

Composite of the average dilation curve for labor in nulliparous women. The curve is based on analysis of data derived from a large, nearly consecutive series of women. The first stage is divided into a relatively flat latent phase and a rapidly progressive active phase. In the active phase, there are three identifiable parts: an acceleration phase, a linear phase of maximum slope, and a deceleration phase. (Redrawm from Friedman EA: Labor: Clinical Evaluation and Management, 2nd ed. New York, Appleton-Century-Crofts, 1978.)



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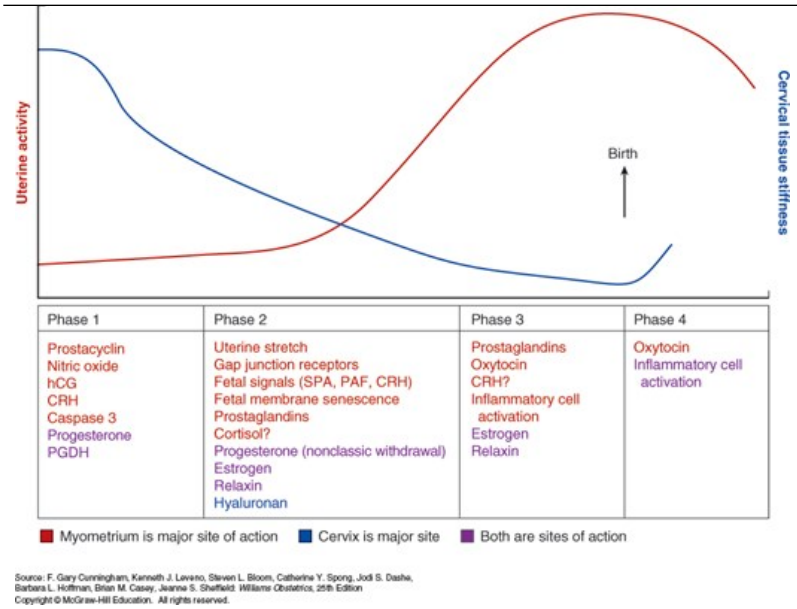
Beginning even before implantation, a remarkably effective period of myometrial quiescence is imposed. This phase 1 normally comprises 95 percent of pregnancy and is characterized by uterine smooth muscle tranquility with maintenance of cervical structural integrity (Fig. 21-5). All manner of molecular systems—neural, endocrine, paracrine, and autocrine—are likely called to implement and coordinate a state of relative uterine unresponsiveness. Moreover, a complementary "fail-safe" system that protects the uterus against agents that could perturb the tranquility of phase 1 also must be in place.

FIGURE 21-5

The key factors thought to regulate the phases of human parturition. CRH = corticotropin-releasing hormone; hCG = human chorionic gonadotropin; PAF = platelet-activating factor; PGDH = prostaglandin dehydrogenase; SPA = surfactant protein A.



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During phase 1, the myometrial cells undergo a phenotypic modification to a noncontractile state, and uterine muscle is rendered unresponsive to natural stimuli. Concurrently, the uterus must initiate extensive changes in its size and vascularity to accommodate fetal growth and prepare for uterine contractions. The myometrial unresponsiveness of phase 1 continues until near the end of pregnancy. That said, some low-intensity myometrial contractions are felt during the quiescent phase, but they do not normally cause cervical dilation. These contractions are common toward the end of pregnancy, especially in multiparas, and are referred to as *Braxton Hicks contractions* or *false labor* (Chap. 4, Uterine Contractility).

The quiescence of phase 1 likely stems from: (1) actions of estrogen and progesterone via intracellular receptors, (2) myometrial-cell plasma membrane receptor-mediated increases in cyclic adenosine monophosphate (cAMP), (3) generation of cyclic guanosine monophosphate (cGMP), and (4) other systems, including modification of myometrial-cell ion channels.

Myometrial Relaxation and Contraction

The balance between myometrial relaxation and contraction is controlled by steroid- and peptide-hormone transcriptional regulation of key genes and their protein products. Quiescence is achieved in part by: (1) diminished intracellular crosstalk and reduced intracellular Ca^{2+} ($[Ca^{2+}]_i$) levels; (2) ion- channel regulation of cell membrane potential; (3) activation of the uterine endoplasmic reticulum stress–unfolded protein response; and (4) uterotonin degradation. In contrast, contractility results from: (1) enhanced interactions between the actin and myosin proteins; (2) heightened excitability of individual myometrial cells; and (3) promotion of intracellular crosstalk that allows synchronous contractions to develop.

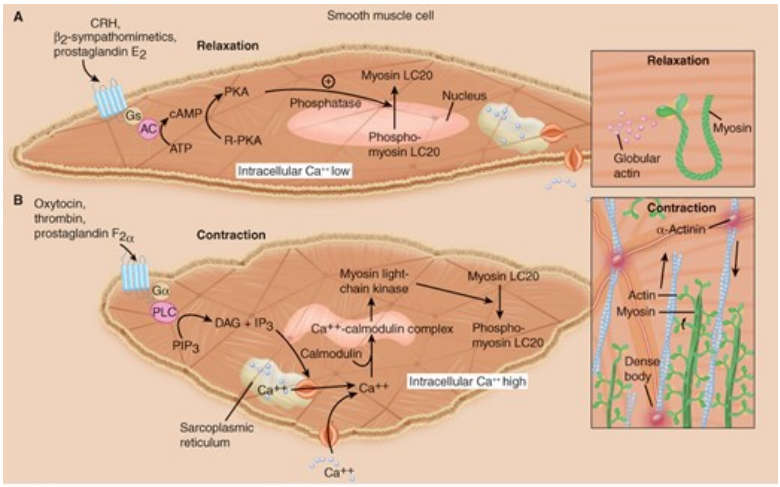
Actin-Myosin Interactions

Actin and myosin proteins are essential to muscle contraction. For this, actin must be converted from a globular to a filamentous form. Indeed, a potential mechanism for maintenance of relaxation is the promotion of actin into a globular form rather than into fibrils, which are required for contraction (Fig. 21-6). Moreover, actin must be attached to the cytoskeleton at focal points in the cell membrane to allow tension to develop.

FIGURE 21-6

Uterine myocyte relaxation and contraction. **A.** Uterine relaxation is maintained by factors that increase myocyte cyclic adenosine monophosphate (cAMP) levels. This activates protein kinase A (PKA) to promote phosphodiesterase activity with dephosphorylation of myosin light-chain kinase (MLCK). Other processes serve to maintain actin in a globular form and thus to prevent the fibril formation necessary for contractions. **B.** Uterine contractions result from reversal of these sequences. Actin now assumes a fibrillar form, and calcium enters the cell to combine with calmodulin to form complexes. These complexes activate MLCK to bring about phosphorylation of the myosin light chains. This generates ATPase activity to cause sliding of myosin over the actin fibrils, which is a uterine contraction. AC = adenylyl cyclase; Ca^{2+} = calcium; DAG = diacylglycerol; Gs and Gα = G-receptor proteins; IP_3 = inositol triphosphate; LC20 = light chain 20; PIP_3 = phosphatidylinositol 3,4,5–triphosphate; PLC = phospholipase C; R-PKA = inactive

protein kinase. (Redrawn from Smith R: Parturition. N Engl J Med. 2007 Jan 18;356(3):271–283.)



Actin must partner with myosin, which is composed of multiple light and heavy chains. The coupling of myosin and actin activates adenosine triphosphatase (ATPase), hydrolyzes adenosine triphosphate, and generates force. This interaction is brought about by enzymatic phosphorylation of the 20-kDa light chain of myosin (Stull, 1998). This is catalyzed by the enzyme *myosin light-chain kinase*, which is activated by calcium. Calcium binds to *calmodulin*, a calcium-binding regulatory protein, which in turn binds to and activates myosin light-chain kinase.

Thus, logically, uterine relaxation ordinarily is promoted by conditions that lower concentrations of $(Ca^{2+})_i$. In contrast, agents that prompt contraction act on myometrial cells to augment $(Ca^{2+})_i$ levels. Or, they allow an influx of extracellular calcium through ligand- or voltage-regulated calcium channels (see Fig. 21-6). Voltage-gated ion channels open, additional calcium ions move into the cell, and cellular depolarization follows. For example, prostaglandin $F_{2\alpha}$ and oxytocin bind their respective receptors during labor to open ligand-activated calcium channels. Activation of these receptors also releases calcium from the sarcoplasmic reticulum to lower electronegativity within the cell. Additionally, greater localization of nonselective cation channels on the cell membrane promotes Ca^{2+} entry (Ying, 2015). The rise in $(Ca^{2+})_i$ levels is often transient. But, contractions can be prolonged by inhibition of myosin phosphatase, an enzyme which dephosphorylates myosin (Woodcock, 2004).

Regulation of Membrane Potentials

As just noted, myocyte excitability is regulated in part by changes in the electrochemical potential gradient across the plasma membrane. Before labor, myocytes maintain a relatively high interior electronegativity. Maintenance of a hyperpolarized membrane potential attenuates smooth muscle cell excitation and is regulated by ion channels.

Consistent with the importance of myometrial quiescence, numerous potassium channels control membrane potential. One key regulator is the large-conductance voltage- and Ca^{2+}-activated K channel (BK_{Ca}) (Pérez, 1993). In normal physiology, the myometrial BK_{Ca} channel plays dual and opposing roles to maintain a balance between uterine quiescence and contractility. The BK_{Ca} channel is abundantly expressed in the myometrium. For most of pregnancy, opening the BK_{Ca} channel allows potassium to leave the cell to maintain interior electronegativity, thus preventing voltage-gated Ca^{2+} influx and contraction. Enhancing BK_{Ca} channel opening results in myometrial relaxation, whereas inhibition of the BK_{Ca} channel augments myometrial contractility. The ability of BK_{Ca} channel to regulate calcium dynamics and ultimately uterine contractility from early to late gestation may result from temporal changes in expression of the BK_{Ca} channel and/or BK_{Ca} interacting partners (Wakle-Prabagaran, 2016).

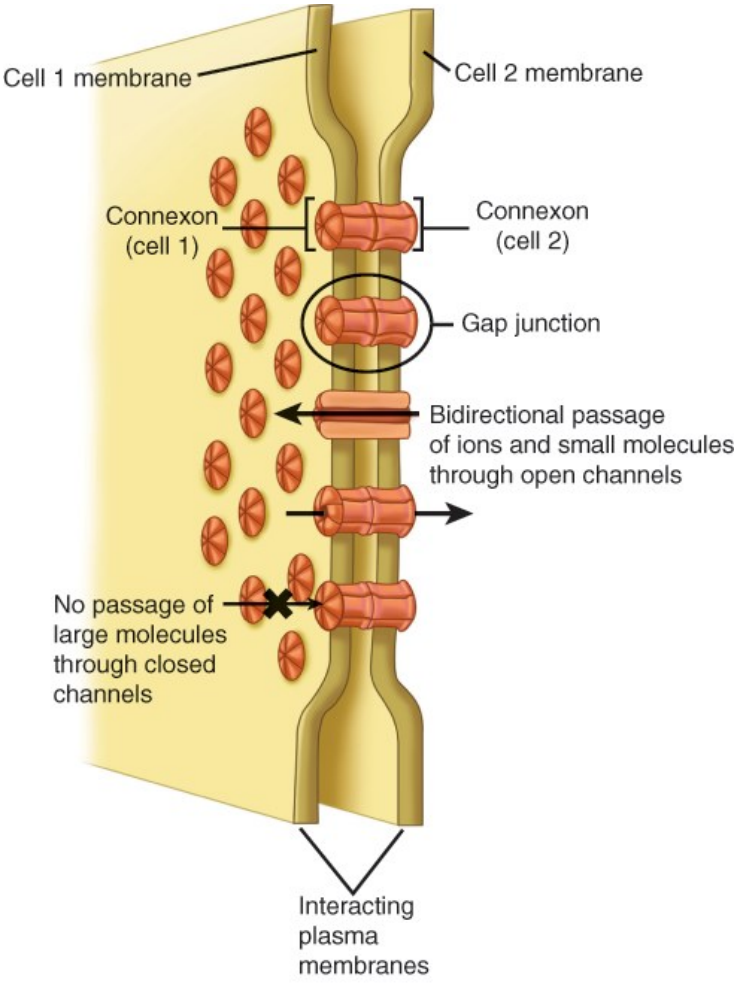
Myometrial Gap Junctions

Cellular signals that control myometrial contraction and relaxation can be effectively transferred between cells through intercellular junctional channels. Communication is established between myocytes by gap junctions, which aid the passage of electrical or ionic coupling currents as well as

metabolite coupling. The transmembrane channels that make up the gap junctions consist of two protein "hemi-channels" (Saez, 2005). These *connexons* are each composed of six *connexin* subunit proteins (Fig. 21-7). Of these, connexin-43 is expressed in myometrium, and concentrations rise near labor onset. Pairs of connexons establish a conduit between coupled cells for the exchange of small molecules that can be nutrients, waste, metabolites, second messengers, or ions. Optimal numbers and types of gap junctions are believed to be important for electrical myometrial synchrony.

FIGURE 21-7

The protein subunits of gap junction channels are called connexins. Six connexins form a hemichannel (connexon), and two connexons (one from each cell) form a gap junction channel. Connexons and gap junction channels can be formed from one or more connexin proteins. The composition of the gap junction channel is important for these channels' selectivity with regard to passage of molecules and communication between cells.



Progesterone maintains uterine quiescence in part by mechanisms that lower expression of various key proteins needed for contractility. These *contraction-associated proteins (CAPs)* include the oxytocin receptor, prostaglandin F receptor, and connexin-43. At the end of pregnancy, increased stretch along with greater estrogen dominance raises CAP levels. Integration of diverse regulatory pathways culminates in released inhibition of connexin-43 and oxytocin receptor levels to promote greater uterine contractility (Nadeem, 2016; Renthal, 2010; Williams, 2012b).

Endoplasmic Reticulum Stress Response

As another potential mechanism, progesterone maintains uterine quiescence through support of myometrial *caspase 3,* which is an anticontractile agent (Jeyasuria, 2009). This protein degrades both actin and the specific gap junction protein, connexin-43 (Kyathanahalli, 2015).

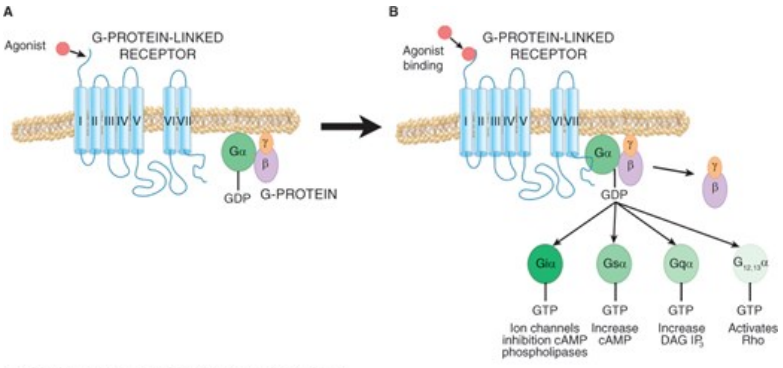
In mice, myometrial caspase 3 activation is regulated by a pregnancy-induced *endoplasmic reticulum stress response (ERSR)*. As background, the endoplasmic reticulum aids protein folding and transport. Functional irregularities cause misfolded proteins to accumulate and trigger the ERSR. The ERSR and its *unfolded-protein response (UPR)* are cellular mechanisms that work to maintain homeostasis in the face of stimuli, such as stretch and inflammation. Prolonged ERSR promotes caspase 3 activation to preserve quiescence despite these stimuli.

G-Protein–Coupled Receptors

Various cell surface receptors directly regulate myocyte contractility. Discussions thus far have described ion channel-linked receptors that regulate intracellular Ca^{2+} and membrane potential. In addition, numerous G-protein–coupled receptors appear to be modified during the phases of parturition. Several of these are present in myometrium and associated with $G_{\alpha s}$-mediated activation of adenylyl cyclase to yield higher cAMP levels. These receptors together with appropriate ligands may act with sex steroid hormones to maintain uterine quiescence (Price, 2000; Sanborn, 1998). Examples are the LH receptor and corticotropin-releasing hormone receptor 1 (CRHR1), both described in this section (Fig. 21-8). Other G-protein–coupled myometrial receptors, instead, are associated with G-protein–mediated activation of phospholipase C, which remember releases arachidonic acid. Ligands for the G-protein–coupled receptors include numerous neuropeptides, hormones, and autacoids. Many of these are available to the myometrium during pregnancy in high concentration via *endocrine* or *autocrine* mechanisms.

FIGURE 21-8

G-protein–coupled receptor signal transduction pathways. **A.** Receptors coupled to heterotrimeric guanosine-triphosphate (GTP)-binding proteins (G proteins) are integral transmembrane proteins that transduce extracellular signals to the cell interior. G-protein–coupled receptors exhibit a common structural motif consisting of seven membrane-spanning regions. **B.** Receptor occupation promotes interaction between the receptor and the G protein on the interior surface of the membrane. This induces an exchange of guanosine diphosphate (GDP) for GTP on the G protein α subunit and dissociation of the α subunit from the βγ heterodimer. Depending on its isoform, the GTP-α subunit complex mediates intracellular signaling either indirectly by acting on effector molecules such as adenylyl cyclase (AC) or phospholipase C (PLC), or directly by regulating ion channel or kinase function. cAMP = cyclic adenosine monophosphate; DAG = diacylglycerol; IP_3 = inositol triphosphate.



β-Adrenoreceptors are prototypical examples of cAMP signaling causing myometrium relaxation. β-Adrenergic receptors mediate $G_{\alpha s}$-stimulated increases in adenylyl cyclase, elevated levels of cAMP, and myometrial cell relaxation. The rate-limiting factor is likely the number of receptors expressed and the level of adenylyl cyclase expression. Agents binding to these receptors have been used for tocolysis of preterm labor and include ritodrine and terbutaline (Chap. 42, β-Adrenergic Receptor Agonists).

LH and hCG hormones share the same receptor, and this G-protein–coupled receptor has been found in myometrial smooth muscle and blood vessels (Ziecik, 1992). Levels of myometrial LH-hCG receptors during pregnancy are greater before than during labor. Chorionic gonadotropin acts to activate adenylyl cyclase by way of a plasma membrane receptor $G_{\alpha s}$-linked system. This lessens contraction frequency and force and lowers the number of tissue-specific myometrial cell gap junctions (Ambrus, 1994; Eta, 1994). Thus, high circulating levels of hCG may be one mechanism of uterine quiescence. In the mouse, variations in FSH-receptor density also regulate myometrial contractile activity (Stilley, 2016).

Prostaglandin E_2 mediates its diverse cellular effects through four G-protein–coupled receptors. Specifically, prostaglandin E receptors 1 through 4

(EP_1-EP_4) are expressed in the myometrium during pregnancy and with labor onset (Astle, 2005; Leonhardt, 2003). EP_2 and EP_4 act through $G_\alpha s$ to raise cAMP levels and maintain myometrial cell quiescence but switch to a $G_\alpha q/11$ calcium-activating pathway during labor (Kandola, 2014). EP_1 and EP_3 receptors act through $G_\alpha q$ and $G_\alpha i$ to augment intracellular Ca^{2+} and contractility.

The peptide hormone relaxin binds to the G-protein–coupled receptor named *relaxin family peptide receptor 1 (RXFP1). Binding* activates adenylyl cyclase in uterine smooth muscle cells. Adenylyl cyclase in turn prevents increased intracellular Ca^{2+} and thus promotes uterine quiescence (Downing, 1993; Meera, 1995). There are two separate human relaxin genes, designated *H1* and *H2*. Of these, *H1* is primarily expressed in the decidua, trophoblast, and prostate, whereas *H2* is primarily expressed in the corpus luteum. Relaxin in plasma of pregnant women is believed to originate exclusively from corpus luteum secretion. Plasma levels peak at approximately 1 ng/mL between 8 and 12 weeks' gestation. Thereafter, they decline to lower levels that persist until term.

Corticotropin-releasing hormone (CRH) is synthesized in the placenta and hypothalamus. Discussed in Fetal Contributions to Parturition, CRH plasma levels rise dramatically during the final 6 to 8 weeks of normal pregnancy and are implicated in mechanisms that control the timing of human parturition (Smith, 2007; Wadhwa, 1998). CRH appears to promote myometrial quiescence during most of pregnancy but then aids myometrial contractions with parturition onset. Studies suggest that these opposing actions are achieved by differential actions of CRH via its receptor CRHR1. In nonlaboring myometrium at term, the interaction of CRH with its CRHR1 receptor activates the Gs-adenylate cyclase-cAMP signaling pathway. This results in inhibition of inositol triphosphate (IP_3) and stabilization of $(Ca^{2+})_i$ levels (You, 2012). However, in term laboring myometrium, $(Ca^{2+})_i$ concentrations are augmented by CRH activation of G proteins Gq and Gi and prompts stimulation of IP_3 production and greater contractility.

Cyclic Guanosine Monophosphate

As just described, cAMP is an important mediator of myometrial relaxation. However, activation of guanylyl cyclase raises intracellular cyclic guanosine monophosphate (cGMP) levels. This also promotes smooth muscle relaxation (Word, 1993). Intracellular cGMP levels are increased in the pregnant myometrium and can be stimulated by atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) receptors, and nitric oxide (Telfer, 2001). All of these factors and their receptors are expressed in the pregnant uterus.

Accelerated Uterotonin Degradation

In addition to pregnancy-induced compounds that promote myometrial cell refractoriness, the activity of enzymes that degrade or inactivate endogenously produced uterotonins are strikingly increased in phase 1. Some of these degrading enzymes and their respective targets include PGDH and prostaglandins; enkephalinase and endothelins; oxytocinase and oxytocin; diamine oxidase and histamine; catechol *O*-methyltransferase and catecholamines; angiotensinases and angiotensin-II; and platelet-activating factor (PAF) and PAF acetylhydrolase. Levels of several of these enzymes decrease late in gestation (Germain, 1994).

Decidua

To ensure uterine quiescence, the synthesis in the decidua of prostaglandins, in particular $PGF_{2\alpha}$, is markedly suppressed. Suppression of prostaglandin production here persists throughout most of pregnancy, and suppression withdrawal is a prerequisite for parturition (Norwitz, 2015).

Phase 1 of parturition also promotes an environment of immune tolerance to protect the fetus. Namely, decidual stromal cells proactively ensure that fetal antigens do not elicit a maternal immune response. This stems from a reduced capacity to attract T cells. This limited ability derives in part from epigenetic silencing of T cell–attracting inflammatory chemokine genes (Erlebacher, 2013; Nancy, 2012; PrabhuDas, 2015).

Cervical Softening

The initial stage of cervical remodeling—termed *softening*—begins in phase 1 of parturition. It is characterized by greater tissue compliance, yet the cervix remains firm and unyielding. Hegar (1895) first described palpable softening of the lower uterine segment at 4 to 6 weeks' gestation, and this sign was once used to diagnose pregnancy. Clinically, the maintenance of cervical anatomical and structural integrity is essential for pregnancy to continue to term. Preterm cervical dilation, structural insufficiency, or both may forecast delivery.

Cervical softening results from increased vascularity, cellular hypertrophy and hyperplasia, and slow, progressive compositional and structural changes in the extracellular matrix (Mahendroo, 2012; Myers, 2015; Word, 2007). Key to matrix changes, collagen, which is the main structural protein in the cervix, undergoes conformational changes that alter tissue stiffness and flexibility (Zhang, 2012). Specifically, collagen processing and the number or type of stable covalent cross-links between collagen triple helices is altered. Mature cross-links between newly synthesized collagen monomers are reduced due to diminished expression and activity of the cross-link-forming enzymes beginning in early pregnancy (Akins, 2011; Drewes, 2007; Yoshida, 2014). These enzymes are lysyl hydroxylase and lysyl oxidase. Together, these early pregnancy changes contribute to greater tissue compliance.

Clinical evidence for the importance of matrix changes to cervical softening is supported by in vivo mechanical evaluation of the cervix (Badir, 2013; Parra-Saavedra, 2011). The prevalence of cervical insufficiency is also higher in those with inherited defects in the synthesis or assembly of collagen or elastic fibers (Anum, 2009; Hermanns-Le, 2005; Rahman, 2003; Wang, 2006). Examples are Ehlers-Danlos and Marfan syndromes, discussed in Chapter 59 (Hereditary Connective Tissue Disorders). Concurrent with matrix remodeling in the softening period, genes involved in cervical dilation and parturition are actively repressed (Hari Kishore, 2012).

PHASE 2: PREPARATION FOR LABOR

To prepare for labor, the myometrial tranquility of phase 1 of parturition must be suspended—so-called *uterine awakening* or *activation.* This phase 2 of parturition is a progression of uterine changes during the last few weeks of pregnancy. Importantly, shifting events associated with phase 2 can cause either preterm or delayed labor.

Progesterone Withdrawal

Key factors in uterine activation are depicted in Figure 21-5. In species that exhibit progesterone withdrawal, parturition progression to labor can be blocked by administering progesterone to the mother. Whether progesterone administration in the absence of classic progesterone withdrawal in pregnant women can delay the timely onset of parturition or prevent preterm labor continues to be investigated. The possibility that progesterone-containing injections or vaginal suppositories may prevent preterm labor has been studied in several randomized trials conducted during the past 15 years. These are discussed in Chapter 42 (Prophylaxis with Progestogen Compounds), and their use in preventing recurrent preterm birth continues to be debated (Norman, 2016).

Classic progesterone withdrawal resulting from decreased secretion does not occur in human parturition. However, a mechanism for progesterone inactivation, whereby the myometrium and cervix become refractory to progesterone's inhibitory actions, is supported by studies using progesterone-receptor antagonists. Mifepristone is a classic steroid antagonist, acting at the level of the progesterone receptor. Although less effective in inducing abortion or labor in women later in pregnancy, mifepristone appears to have some effect on cervical ripening and on increasing myometrial sensitivity to uterotonins (Berkane, 2005; Chwalisz, 1994a).

The diverse mechanisms by which functional progesterone withdrawal or antagonism is achieved is an active area of research. These include: (1) changes in the relative expression of the nuclear progesterone-receptor isoforms, PR-A, PR-B, and PR-C; (2) differential interaction of PR-A and PB-B with enhancers and inhibitors of gene expression; (3) alterations in PR activity through changes in the expression of coactivators or corepressors that directly influence receptor function; (4) local inactivation of progesterone by steroid-metabolizing enzymes or synthesis of a natural antagonist; and (5) microRNA regulation of progesterone-metabolizing enzymes and transcription factors that modulate uterine quiescence (Condon, 2003; Mahendroo, 1999; Mesiano, 2002; Nadeem, 2016; Renthal, 2010; Williams, 2012a). Taken together, these observations support the concept that multiple pathways exist for a functional progesterone withdrawal.

Myometrial Changes

Phase 2 myometrial changes prepare it for labor contractions. This results from a shift in the expression of key proteins that control uterine quiescence to an expression of contraction-associated proteins, described earlier (Myometrial Gap Junctions) (Renthal, 2015). Of these CAPs, myometrial oxytocin receptors and gap junction proteins, such as connexin-43, markedly rise in number. These CAPs increase uterine irritability and responsiveness to *uterotonins.*

Another critical change in phase 2 is formation of the lower uterine segment from the isthmus. With this development, the fetal head often descends to

or even through the pelvic inlet—so-called *lightening*. The abdomen commonly undergoes a shape change, sometimes described by women as "the baby dropped." It is also likely that the lower segment myometrium is unique from that in the upper uterine segment, resulting in distinct roles for each near term and during labor. This is supported by human studies that demonstrate differential expression of prostaglandin receptors and CAPs within the upper- and lower-segment myometrial regions (Astle, 2005; Blanks, 2003; Sparey, 1999). Near term, elevated expression of the *HoxA13* gene in the lower myometrial segment compared with the upper segment also induces CAP expression and regionalized contractility of the lower segment (Li, 2016).

Oxytocin Receptors

Because of its long-standing application for labor induction, it seemed logical that oxytocin must play a central role in spontaneous human labor. Myometrial oxytocin receptor levels do rise during phase 2 of parturition, and the level of oxytocin receptor mRNA in human myometrium at term is greater than that found in preterm myometrium (Wathes, 1999). However, it is unclear whether oxytocin plays a role in the early phases of uterine activation or whether its sole function is in the expulsive phase of labor. Most studies of regulation of myometrial oxytocin receptor synthesis have been performed in rodents. Disruption of the oxytocin receptor gene in the mouse does not affect parturition. This suggests that, at least in this species, multiple systems likely ensure that parturition occurs.

Progesterone and estradiol appear to be the primary regulators of oxytocin receptor expression. Estradiol treatment in vivo or in myometrial explants raises myometrial oxytocin receptor concentrations. This action, however, is prevented by simultaneous treatment with progesterone (Fuchs, 1983). Progesterone also may act within the myometrial cell to enhance oxytocin receptor degradation and inhibit oxytocin activation of its receptor at the cell surface (Bogacki, 2002). These data indicate that one of the mechanisms whereby progesterone maintains uterine quiescence is through inhibition of a myometrial oxytocin response.

Cervical Ripening

Before contractions begin, the cervix must undergo extensive remodeling. This eventually leads to the cervix yielding and dilating from forceful uterine contractions. Cervical modifications during phase 2 principally involve connective tissue changes—termed *cervical ripening.* The transition from the softening to the ripening phase begins weeks or days before labor. During this transformation, the cervical matrix changes its total amounts of *glycosaminoglycans*, which are large linear polysaccharides, and *proteoglycans,* which are proteins bound to these glycosaminoglycans.

Many of the processes that aid cervical remodeling are controlled by the same hormones regulating uterine function. That said, the molecular events of each are varied because of differences in cellular composition and physiological requirements. For example, the hormone relaxin regulates myometrial quiescence. It also regulates cervical ripening, but through cell proliferation and modulation of extracellular matrix components (Park, 2005; Soh, 2012). The uterine corpus is predominantly smooth muscle. In contrast, the cervix has a high ratio of fibroblasts to smooth muscle cells, and extracellular matrix contributes significantly to overall tissue mass. Recent studies in the nonpregnant human cervix report a spatial gradient of smooth muscle cells. Specifically, smooth muscle cells make up approximately 50 percent of stromal cells at the internal os but only 10 percent at the external os (Vink, 2016).

Cervical Connective Tissue

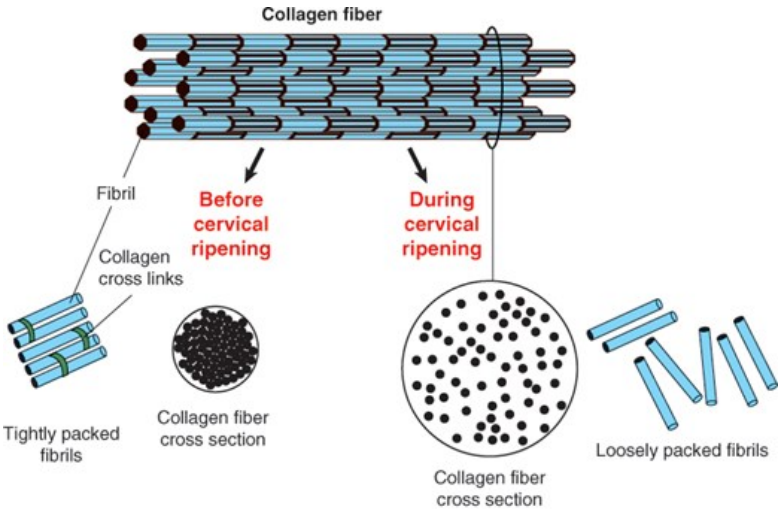
Collagen

The cervix is an extracellular-matrix-rich tissue. Constituents of the matrix include type I, III, and IV collagen, matricellular proteins, glycosaminoglycans, proteoglycans, and elastic fibers. Of these, collagen is largely responsible for the structural disposition of the cervix. During collagen assembly, multiple collagen triple-helical molecules are cross-linked to one another by the actions of lysyl oxidase to form fibrils. In addition, fibril size, packing, and organization determine the strength and mechanical properties of the cervix. These properties are regulated in part by collagen-binding proteoglycans such as decorin or biglycan, as well as matricellular proteins such as thrombospondin 2 (Fig. 21-9).

FIGURE 21-9

The collagen fiber architecture is reorganized in phases 1 and 2 of parturition to allow a gradual increase in mechanical compliance of the cervix. A collagen fiber is made up of many fibrils. Fibril size and packing are regulated in part by small proteoglycans such as decorin and by the density of collagen cross-links. In phase 1, fibril size is uniform and fibrils are well organized, although a decline in cross-link density aids softening. During

cervical ripening in phase 2, fibril size is less uniform, and spacing between collagen fibrils and fibers is greater and disorganized.



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Higher turnover of collagen during pregnancy likely allows the gradual replacement of mature cross-linked collagen fibrils with poorly cross-linked fibrils, which yield greater collagen disorganization. This increased turnover, rather than loss of collagen to achieve cervical remodeling, is supported by mouse and human studies that document no changes in collagen content between nonpregnant states and term pregnancy (Akins, 2011; Myers, 2008; Read, 2007; Yoshida, 2014). In further support, polymorphisms or mutations in genes required for collagen assembly are associated with an elevated incidence of cervical insufficiency (Anum, 2009; Rahman, 2003; Warren, 2007).

Glycosaminoglycans and Proteoglycans

Hyaluronan is a high-molecular-weight polysaccharide that functions alone, whereas most other glycosaminoglycans (GAGs) complex with proteins to form proteoglycans. Hyaluronan is a hydrophilic, space-filling molecule, and thus greater hyaluronan production during cervical ripening is thought to increase viscoelasticity, hydration, and matrix disorganization. Hyaluronan synthesis is carried out by hyaluronan synthase isoenzymes, and expression of these enzymes is elevated in the cervix during ripening (Akgul, 2012; Straach, 2005).

Although not well defined, changes in proteoglycan composition are also suggested to accompany cervical ripening. At least three small leucine-rich proteoglycans are expressed in the cervix—decorin, biglycan, and fibromodulin (Westergren-Thorsson, 1998). In other connective tissues, decorin interacts with collagen to regulate the packing, order, and strength of collagen fibrils (see Fig. 21-9) (Ameye, 2002). In addition to the cervix, these proteoglycans are expressed in the fetal membranes and uterus.

Inflammatory Changes

In phase 2, resident immune cells are localized to the cervical stroma, although a functional role for these cells in this phase of remodeling has been challenged. Microarray studies comparing gene expression patterns at term both before and after cervical ripening show little rise in proinflammatory gene expression. In contrast, proinflammatory and immunosuppressive gene expression in the cervix after delivery increases markedly compared with that during cervical ripening (Bollapragada, 2009; Hassan, 2006, 2009). Further, detailed studies in mice provide evidence that leukocyte migration but not activation takes place before labor. Once labor is underway, activation of neutrophils, proinflammatory M1 macrophages, and tissue repair M2 macrophages in the cervix is augmented. This suggests a role for inflammatory cells in postpartum cervical remodeling and repair (Mahendroo, 2012).

Induction of Cervical Ripening

No therapies prevent premature cervical ripening. In contrast, treatment to promote cervical ripening for labor induction includes direct application of prostaglandins PGE_2 and $PGF_{2\alpha}$. Prostaglandins likely modify extracellular matrix structure to aid ripening. Although the role of prostaglandins in the normal physiology of cervical ripening remains unclear, this property is useful clinically to assist labor induction (Chap. 26, Preinduction Cervical Ripening).

In some nonhuman species, the cascades of events that allow cervical ripening are induced by dropping serum progesterone concentrations. And in humans, administration of progesterone antagonists causes cervical ripening.

Endocervical Epithelia

In addition to matrix changes, during pregnancy, endocervical epithelial cells proliferate such that endocervical glands account for a significant percentage of cervical mass. The endocervical canal is lined with mucus-secreting columnar and stratified squamous epithelia. These cells form both a mucosal barrier and a tight junctional barrier that protect against microbial invasion (Akgul, 2014; Blaskewicz, 2011; Timmons, 2007). The mucosal epithelium recognizes and deters pathogen invasion via expression of toll-like receptors that identify pathogens and via antimicrobial peptides and protease inhibitors. In addition, these epithelia express signals to underlying immune cells when a pathogenic challenge exceeds their protective capacity (Wira, 2005).

Fetal Contributions to Parturition

It is intriguing to envision that the mature human fetus provides the signal to initiate parturition, and evidence for fetal signaling is mounting (Mendelson, 2017). The fetus may give signals through blood-borne agents that act on the placenta or through secretion into the amnionic fluid.

Uterine Stretch

Fetal growth is an important component in uterine activation in phase 2 of parturition. With uterine activation, stretch is required for induction of specific CAPs. Namely, stretch increases expression of connexin-43 and oxytocin receptors. Levels of gastrin-releasing peptide, a stimulatory agonist for smooth muscle, are also augmented by stretch in the myometrium (Tattersall, 2012).

Clinical clues for a role of stretch come from the observation that multifetal pregnancies carry a much greater risk for preterm labor than singleton ones. And, preterm labor is also significantly more common in pregnancies complicated by hydramnios. Although the mechanisms causing preterm birth in these two examples are debated, a role for uterine stretch must be considered.

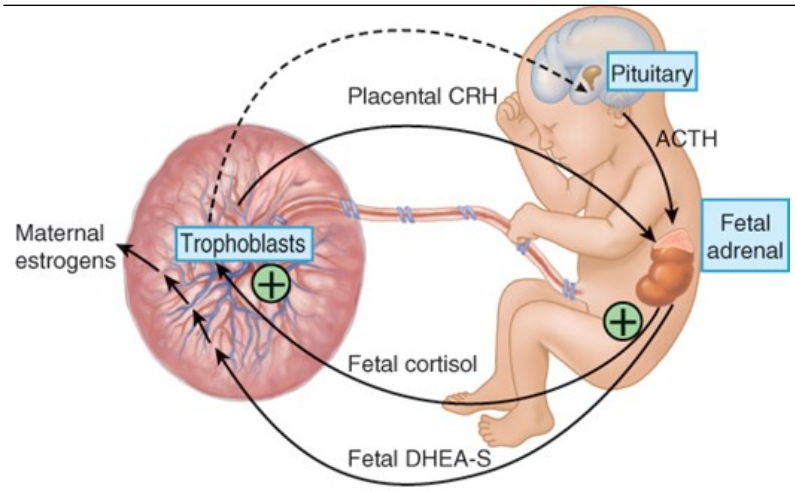
Cell signaling systems that are influenced by stretch to regulate the myometrial cell continue to be defined. This process—*mechanotransduction*—may include activation of cell-surface receptors or ion channels, transmission of signals through extracellular matrix, or release of autocrine molecules that act directly on myometrium (Shynlova, 2007; Young, 2011).

Fetal Endocrine Cascades

The ability of the fetus to provide endocrine signals that initiate parturition has been demonstrated in several species. However, evidence suggests that it is not regulated in the same manner in humans. That said, the human fetal hypothalamic-pituitary-adrenal-placental axis is considered a critical component of normal parturition. Moreover, premature activation of this axis is considered to prompt many cases of preterm labor (Challis, 2000, 2001). As in the sheep, steroid products of the human fetal adrenal gland are believed to have effects on the placenta and membranes that eventually transform the myometrium from a quiescent to a contractile state. A key component in the human may be the unique ability of the placenta to produce large amounts of CRH (Fig. 21-10).

FIGURE 21-10

The placental–fetal adrenal endocrine cascade. In late gestation, placental corticotropin-releasing hormone (CRH) stimulates fetal adrenal production of dehydroepiandrosterone sulfate (DHEA-S) and cortisol. The latter stimulates production of placental CRH, which leads to a feed-forward cascade that enhances adrenal steroid hormone production. ACTH = adrenocorticotropic hormone.



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A CRH hormone that is identical to maternal and fetal hypothalamic CRH is synthesized by the placenta in relatively large amounts (Grino, 1987; Saijonmaa, 1988). However, unlike hypothalamic CRH, which is under glucocorticoid negative feedback, cortisol instead *stimulates* placental CRH production. This ability makes it possible to create a feed-forward endocrine cascade that does not end until delivery.

Maternal plasma CRH levels are low in the first trimester and rise from midgestation to term. In the last 12 weeks, CRH plasma levels rise exponentially, peak during labor, and then fall precipitously after delivery (Frim, 1988; Sasaki, 1987). Amnionic fluid CRH concentrations similarly increase in late gestation. CRH is the only trophic hormone-releasing factor to have a specific serum binding protein. During most of pregnancy, CRH-binding protein (CRH-BP) binds most maternal circulating CRH, and this inactivates it (Lowry, 1993). During later pregnancy, however, CRH-BP levels in both maternal plasma and amnionic fluid decline, leading to markedly greater levels of bioavailable CRH (Perkins, 1995; Petraglia, 1997).

In pregnancies in which the fetus can be considered "stressed" from various complications, concentrations of CRH in fetal plasma, amnionic fluid, and maternal plasma are greater than those seen in normal gestation (Berkowitz, 1996; McGrath, 2002). The placenta is the likely source of this elevated CRH concentration. For example, placental CRH content is fourfold higher in placentas from women with preeclampsia than in those from normal pregnancies (Perkins, 1995).

Placental CRH is thought to play several roles in parturition regulation. It may enhance fetal cortisol production to provide positive feedback so that the placenta produces more CRH. Late in pregnancy—phase 2 or 3 of parturition—modification in the CRH receptor favors a switch from cAMP formation to increased myometrial cell calcium levels via protein kinase C activation (You, 2012). Oxytocin acts to attenuate CRH-stimulated accumulation of cAMP in myometrial tissue. CRH acts to augment myometrial contractile force in response to $PGF_{2\alpha}$ (Benedetto, 1994). Finally, CRH stimulates fetal adrenal C_{19}-steroid synthesis, thereby increasing substrate for placental aromatization.

Some have proposed that the rising CRH level at the end of gestation reflects a *fetal-placental clock* (McLean, 1995). CRH concentrations vary greatly among women, and the rate of rise in maternal CRH levels is a more accurate predictor of pregnancy outcome than is a single measurement (Leung, 2001; McGrath, 2002). In this regard, the placenta and fetus, through endocrinological events, influence the timing of parturition at the end of normal gestation.

Fetal Lung Surfactant and Platelet-Activating Factor

Surfactant protein A (SP-A) produced by the fetal lung is required for lung maturation. SP-A is expressed by the human amnion and decidua, is present in the amnionic fluid, and prompts signaling pathways in human myometrial cells (Garcia-Verdugo, 2008; Lee, 2010; Snegovskikh, 2011). The exact mechanisms by which SP-A activates myometrial contractility in women, however, remain to be clarified. One mode may be its effects on prostaglandins. Namely, SP-A selectively inhibits prostaglandin $F_{2\alpha}$ in the term decidua, but SP-A levels drop in the amnionic fluid at term (Chaiworapongsa, 2008). In addition to SP-A, the fetal lung makes the uterotonic agent platelet-activating factor (Frenkel, 1996; Toyoshima, 1995). This factor and SP-A play a role in fetal–maternal signaling for parturition (Gao, 2015).

Fetal-Membrane Senescence

Toward the end of pregnancy, fetal membranes undergo physiological aging termed cellular senescence (Menon, 2016). In human fetal membranes and animal models, stretch and oxidative stress induce senescent fetal membrane to manifest a form of sterile inflammation termed senescent-associated secretory phenotype (SASP). This in turn propagates inflammatory signals that further weaken the fetal membrane and activate signals in the decidua and myometrium to initiate parturition. Thus, as the functional necessity of fetal membranes declines at term, they are able to promote signals that contribute to parturition initiation.

Fetal Anomalies and Delayed Parturition

Some evidence shows that pregnancies with markedly diminished estrogen production may be associated with prolonged gestation. These "natural experiments" include women with inherited placental sulfatase deficiency and fetal anencephaly with adrenal hypoplasia. The broad range of gestational length seen with these disorders, however, calls into question the exact role of estrogen in human parturition initiation.

Other fetal abnormalities that prevent or severely reduce the entry of fetal urine or lung secretions into amnionic fluid do not prolong human pregnancy. Examples are renal agenesis and pulmonary hypoplasia, respectively. Thus, a fetal signal through the paracrine arm of the fetal–maternal communication system does not appear to be mandated for parturition initiation.

Some brain anomalies of the fetal calf, fetal lamb, and sometimes the human fetus delay the normal timing of parturition. More than a century ago, Rea (1898) observed an association between fetal anencephaly and prolonged human gestation. Malpas (1933) extended these observations and described a pregnancy with an anencephalic fetus that was prolonged to 374 days—53 weeks. He concluded that the association between anencephaly and prolonged gestation was attributable to anomalous fetal brain-pituitary-adrenal function. Indeed, the adrenal glands of the anencephalic fetus are very small and, at term, may be only 5 to 10 percent as large as those of a normal fetus. This is caused by developmental failure of the fetal zone that normally accounts for most of fetal adrenal mass and production of C_{19}-steroid hormones (Chap. 5, Fetal Adrenal Gland–Placental Interactions). Such pregnancies are associated with delayed labor and suggest that the fetal adrenal glands are important for the timely onset of parturition.

PHASE 3: LABOR

This phase is synonymous with active labor, which is customarily divided into three stages. These compose the commonly used labor graph shown in Figure 21-4. The first stage begins when spaced uterine contractions of sufficient frequency, intensity, and duration are attained to bring about cervical thinning, termed *effacement*. Several uterotonins may be important to the success of this stage of active labor (see Fig. 21-5). These have been shown to stimulate smooth muscle contraction through G-protein coupling. This labor stage ends when the cervix is fully dilated—about 10 cm—to allow passage of the term-sized fetus. The first stage of labor, therefore, is the *stage of cervical effacement and dilation.* The second stage begins when cervical dilation is complete and ends with delivery. Thus, the second stage of labor is the *stage of fetal expulsion.* Last, the third stage begins immediately after delivery of the fetus and ends with the delivery of the placenta. Thus, the third stage of labor is the *stage of placental separation and expulsion.*

First Stage: Clinical Onset of Labor

Uterine Labor Contractions

In some women, forceful uterine contractions that effect delivery begin suddenly. In others, labor initiation is heralded by spontaneous release of a small amount of blood-tinged mucus from the vagina. This extrusion of the mucus plug that had previously filled the cervical canal during pregnancy is referred to as "show" or "bloody show." Its passage indicates that labor is already in progress or likely will ensue in hours to days.

Unique among physiological muscular contractions, those of uterine smooth muscle during labor are painful. Several possible causes have been suggested: (1) hypoxia of the contracted myometrium—such as that with angina pectoris; (2) compression of nerve ganglia in the cervix and lower uterus by contracted interlocking muscle bundles; (3) cervical stretching during dilation; and (4) stretching of the peritoneum overlying the fundus.

Of these, compression of nerve ganglia in the cervix and lower uterine segment by the contracting myometrium is an especially attractive hypothesis. Paracervical infiltration with local anesthetic usually produces appreciable pain relief with contractions (Chap. 25, Neuraxial Analgesia). Uterine contractions are involuntary and, for the most part, independent of extrauterine control. Neural blockade from epidural analgesia does not diminish

their frequency or intensity. In other examples, myometrial contractions in paraplegic women and in women after bilateral lumbar sympathectomy are normal but painless.

Mechanical stretching of the cervix enhances uterine activity in several species, including humans. This phenomenon is the *Ferguson reflex* (Ferguson, 1941). Its exact mechanism is unclear, and release of oxytocin has been suggested but not proven. Manipulation of the cervix and "stripping" the fetal membranes is associated with a rise in blood levels of prostaglandin $F_{2\alpha}$ metabolites.

The interval between contractions narrows gradually from approximately 10 minutes at the onset of first-stage labor to as little as 1 minute or less in the second stage. Periods of relaxation between contractions, however, are essential for fetal welfare. Unremitting contractions compromise uteroplacental blood flow sufficiently to cause fetal hypoxemia. In active-phase labor, the duration of each contraction ranges from 30 to 90 seconds and averages 1 minute. Contraction intensity varies appreciably during normal labor. Specifically, amnionic fluid pressures generated by contractions during spontaneous labor average 40 mm Hg, but vary from 20 to 60 mm Hg (Chap. 24, Patterns of Uterine Activity).

Distinct Lower and Upper Uterine Segments

During active labor, the anatomical uterine divisions that were initiated in phase 2 of parturition become increasingly evident (Figs. 21-11 and 21-12). By abdominal palpation, even before membrane rupture, the two segments can sometimes be differentiated. The upper segment is firm during contractions, whereas the lower segment is softer, distended, and more passive. This mechanism is imperative because if the entire myometrium, including the lower uterine segment and cervix, were to contract simultaneously and with equal intensity, the net expulsive force would markedly decline. Thus, the upper segment contracts, retracts, and expels the fetus. In response to these contractions, the softened lower uterine segment and cervix dilate and thereby form a greatly expanded, thinned-out tube through which the fetus can pass.

FIGURE 21-11

Sequence of development of the segments and rings in the uterus at term and in labor. Note comparison between the uterus of a nonpregnant woman, the uterus at term, and the uterus during labor. The passive lower uterine segment is derived from the isthmus, and the physiological retraction ring develops at the junction of the upper and lower uterine segments. The pathological retraction ring develops from the physiological ring. Anat. I.O. = anatomical internal os; E.O. = external os; Hist. I.O. = histological internal os; Ph.R.R. = physiological retraction ring.

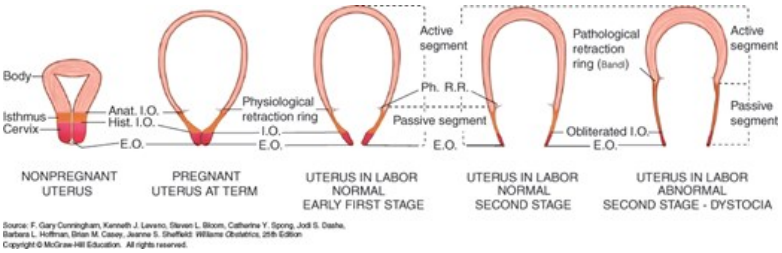
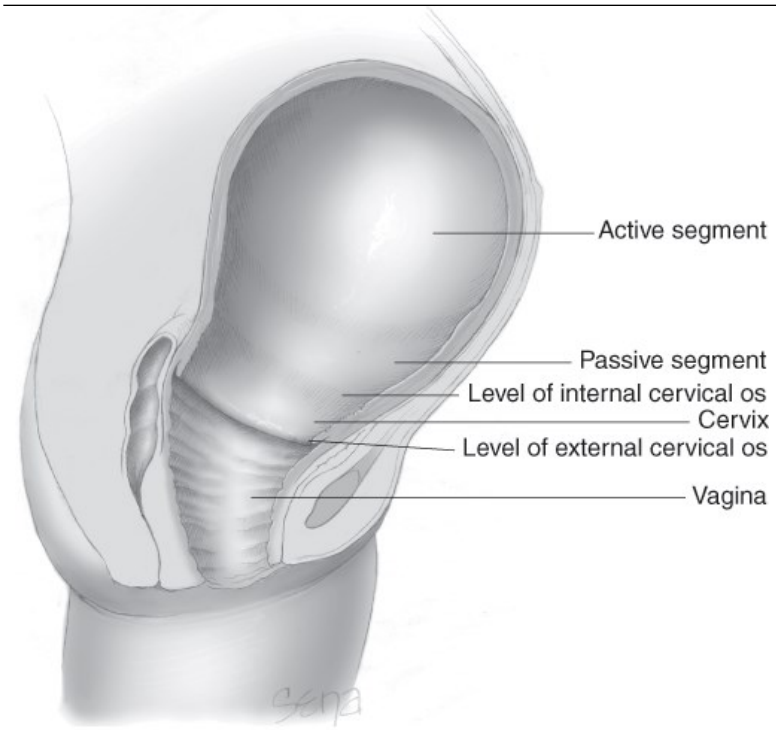


FIGURE 21-12

The uterus at the time of vaginal delivery. The active upper segment retracts around the presenting part as the fetus descends through the birth canal. In the passive lower segment, there is considerably less myometrial tone.



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The myometrium of the upper segment does not relax to its original length after contractions. Instead, it becomes relatively fixed at a shorter length. The upper active uterine segment contracts down on its diminishing contents, but myometrial tension remains constant. The net effect is to take up slack, thus maintaining the advantage gained in expulsion of the fetus. Concurrently, the uterine musculature is kept in firm contact with the uterine contents. As the consequence of retraction, each successive contraction commences where its predecessor left off. Thus, the upper part of the uterine cavity becomes slightly smaller with each successive contraction. Because of the successive shortening of the muscular fibers, the upper active segment becomes progressively thickened throughout first- and second-stage labor (see Fig. 21-11). This process continues and results in a tremendously thickened upper uterine segment immediately after delivery.

Clinically, it is important to understand that the phenomenon of upper segment retraction is contingent on a decrease in the volume of its contents. For this to happen, particularly early in labor when the entire uterus is virtually a closed sac with only minimal cervical dilation, the musculature of the lower segment must stretch. This permits a greater portion of the uterine contents to occupy the lower segment. The upper segment retracts only to the extent that the lower segment distends and the cervix dilates.

Relaxation of the lower uterine segment mirrors the same gradual progression of retraction. Recall that after each contraction of the upper segment, the muscles do not return to their previous length, but tension remains essentially the same. By comparison, in the lower segment, successive lengthening of the fibers with labor is accompanied by thinning, normally to only a few millimeters in the thinnest part. As a result of the lower segment thinning and concomitant upper segment thickening, a boundary between the two is marked by a ridge on the inner uterine surface—the *physiological retraction ring.* When the thinning of the lower uterine segment is extreme, as in obstructed labor, the ring is prominent and forms a *pathological retraction ring*. This abnormal condition is also known as the *Bandl ring,* which is discussed further in Chapter 23 (Perinatal Complications).

Changes in Uterine Shape

Each contraction gradually elongates the ovoid uterine shape and thereby narrows the horizontal diameter. This change in shape has important effects on the labor process. First, there is greater *fetal axis pressure,* that is, the smaller horizontal diameter serves to straighten the fetal vertebral column. This presses the upper pole of the fetus firmly against the fundus, whereas the lower pole is thrust farther downward. The lengthening of the ovoid shape has been estimated at 5 to 10 cm. Second, with lengthening of the uterus, the longitudinal muscle fibers are drawn taut. As a result, the lower segment and cervix are the only parts of the uterus that are flexible, and these are pulled upward and around the lower pole of the fetus.

Ancillary Forces

After the cervix is dilated fully, the most important force in fetal expulsion is produced by maternal intraabdominal pressure. Contraction of the abdominal muscles simultaneously with forced respiratory efforts with the glottis closed is referred to as *pushing*. The force is similar to that with defecation, but the intensity usually is much greater. The importance of intraabdominal pressure is shown by the prolonged descent during labor in paraplegic women and in those with a dense epidural block. And, although increased intraabdominal pressure is necessary to complete second-stage labor, pushing accomplishes little in the first stage. It exhausts the mother, and its associated elevated intrauterine pressures may be harmful to the fetus.

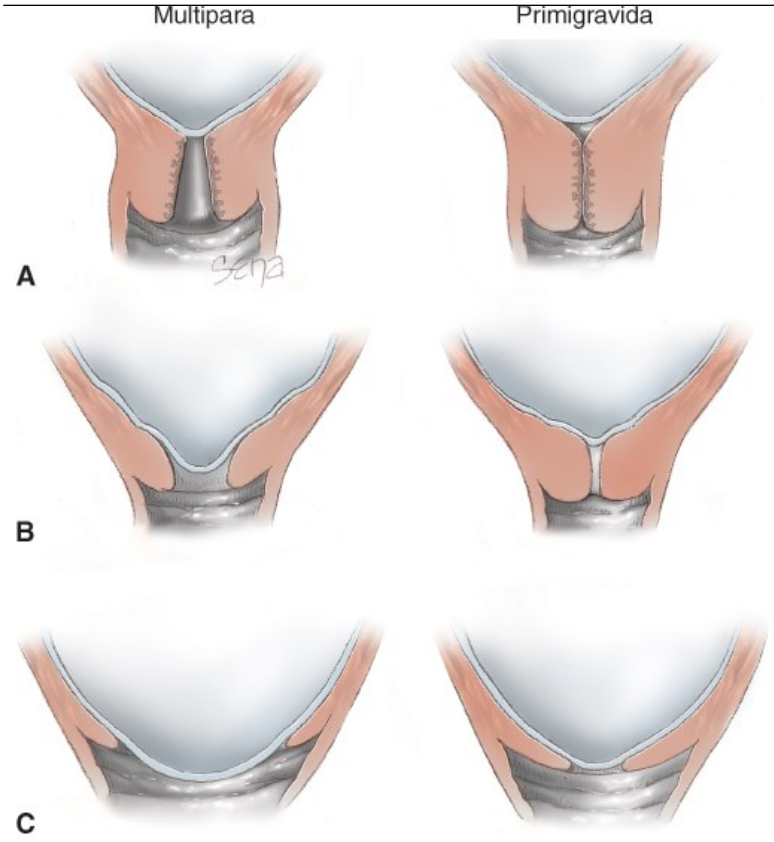
Cervical Changes

As the result of contraction forces, two fundamental changes—effacement and dilation—occur in the ripened cervix. For an average-sized fetal head to pass through the cervix, its canal must dilate to a diameter of approximately 10 cm. At this time, the cervix is said to be completely or fully dilated. Although there may be no fetal descent during cervical effacement, most commonly the presenting fetal part descends somewhat as the cervix dilates.

Cervical effacement is "obliteration" or "taking up" of the cervix. It is manifest clinically by shortening of the cervical canal from a length of approximately 3 cm to a mere circular orifice with almost paper-thin edges. The muscular fibers at the level of the internal cervical os are pulled upward, or "taken up," into the lower uterine segment. The condition of the external os remains temporarily unchanged (Fig. 21-13).

FIGURE 21-13

Schematic showing effacement and dilation. **A.** Before labor, the primigravid cervix is long and undilated in contrast to that of the multipara, which has dilation of the internal and external os. **B.** As effacement begins, the multiparous cervix shows dilation and funneling of the internal os. This is less apparent in the primigravid cervix. **C.** As complete effacement is achieved in the primigravid cervix, dilation is minimal. The reverse is true in the multipara.



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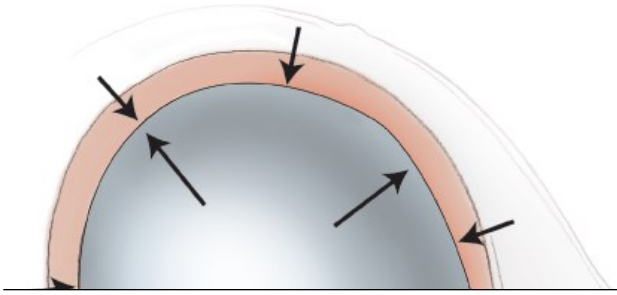
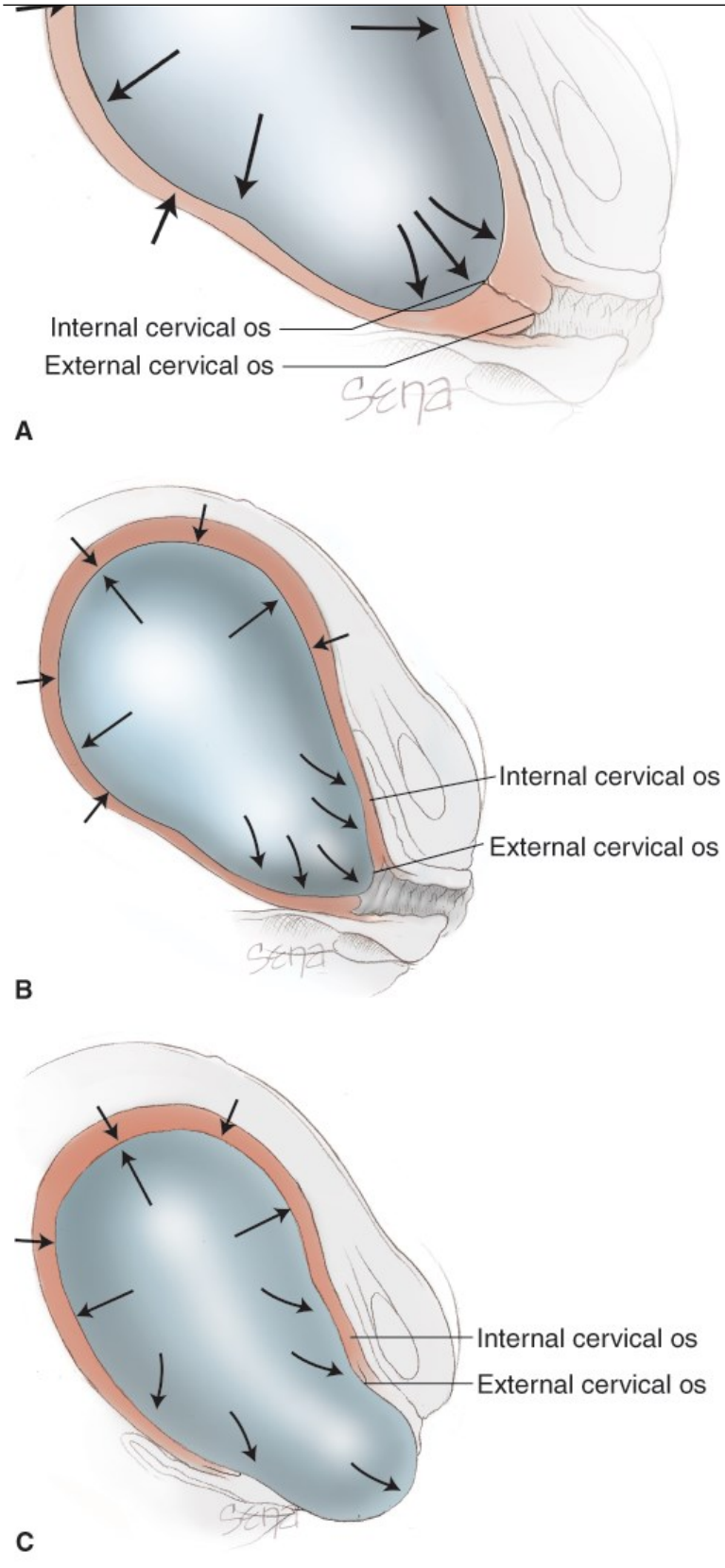
Effacement may be compared to a funneling process in which the whole length of a narrow cylinder is converted into a very obtuse, flaring funnel with a small distal circular opening. Because of growing myometrial activity during uterine preparedness for labor, appreciable effacement of a softened cervix sometimes is accomplished before active labor begins. Effacement causes expulsion of the mucous plug as the cervical canal is shortened.

Because the lower segment and cervix have less resistance during a contraction, a centrifugal pull is exerted on the cervix and creates *cervical dilation* (Fig. 21-14). As uterine contractions cause pressure on the membranes, the hydrostatic action of the amnionic sac in turn dilates the cervical canal like a wedge. The process of cervical effacement and dilation causes formation of the *forebag* of amnionic fluid. This is the leading portion of fluid and amnionic sac located in front of the presenting part. In the absence of intact membranes, the pressure of the presenting fetal part against the cervix and lower uterine segment is similarly effective. Early rupture of the membranes does not retard cervical dilation so long as the presenting fetal part is positioned to exert pressure against the cervix and lower segment.

FIGURE 21-14

Hydrostatic action of membranes in effecting cervical effacement and dilation. With labor progression, note the changing relations of the internal and external os in **(A)**, **(B)**, and **(C)**. Although not shown in this diagram, with membrane rupture, the presenting part, applied to the cervix and the forming lower uterine segment, acts similarly.





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Referring back to Figure 21-4, recall that cervical dilation is divided into latent and active phases. The active phase is subdivided further into the

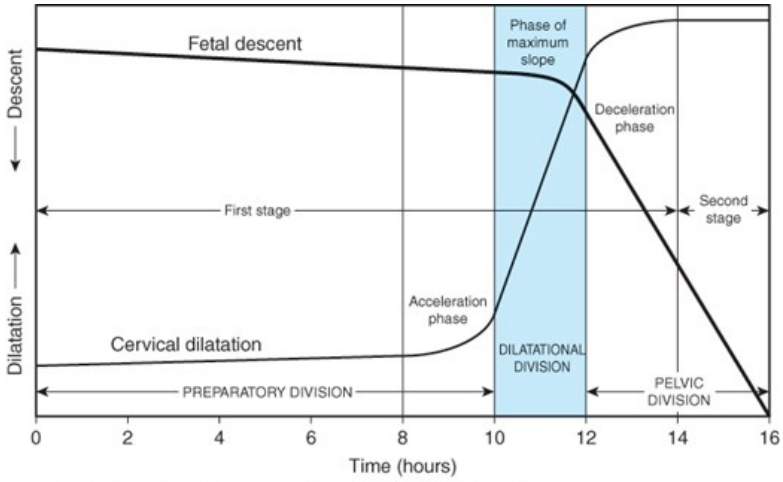
acceleration phase, the phase of maximum slope, and the deceleration phase (Friedman, 1978). The duration of the latent phase is more variable and sensitive to extraneous factors. For example, sedation may prolong the latent phase, and myometrial stimulation shortens it. The latent phase duration has little bearing on the subsequent course of labor, whereas the characteristics of the accelerated phase are usually predictive of labor outcome. The first stage ends when cervical dilation is complete.

Second Stage: Fetal Descent

In many nulliparas, engagement of the head is accomplished before labor begins. That said, the head may not descend further until late in labor. In the descent pattern of normal labor, a typical hyperbolic curve is formed when the station of the fetal head is plotted as a function of labor duration. *Station* describes descent of the fetal biparietal diameter in relation to a line drawn between maternal ischial spines (Chap. 22, Management of First-Stage Labor). Active descent usually takes place after dilation has progressed for some time (Fig. 21-15). During second-stage labor, the speed of descent is maximal and is maintained until the presenting part reaches the perineal floor (Friedman, 1978). In nulliparas, the presenting part typically descends slowly and steadily. In multiparas, however, particularly those of high parity, descent may be rapid.

FIGURE 21-15

Labor course divided on the basis of expected evolution of the dilatation and descent curves into three functional divisions. The preparatory division includes the latent and acceleration phases. The dilatational division is the phase of maximum slope of dilatation. The pelvic division encompasses both the deceleration phase and the second stage, which is concurrent with the phase of maximum slope of fetal descent. (Redrawm from Friedman EA: Labor: Clinical Evaluation and Management, 2nd ed. New York, Appleton-Century-Crofts, 1978.)



Pelvic Floor Changes

The birth canal is supported and functionally closed by the pelvic floor (Chap. 2, Pelvic Diaphragm). The most important component of the floor is the levator ani muscle and the fibromuscular connective tissue that covers its upper and lower surfaces. The biomechanical properties of these structures and of the vaginal wall change markedly during parturition. These result from altered extracellular matrix structure or composition (Alperin, 2015; Rahn, 2008; Lowder, 2007).

The levator ani muscle closes the lower end of the pelvic cavity as a diaphragm. Thereby, a concave upper and a convex lower surface are presented. The posterior and lateral portions of the pelvic floor, which are not spanned by the levator ani muscle, are occupied bilaterally by the piriformis and coccygeus muscles.

The levator ani muscle varies in thickness from 3 to 5 mm, although its margins encircling the rectum and vagina are somewhat thicker. During pregnancy, the levator ani usually undergoes hypertrophy, forming a thick band that extends backward from the pubis and encircles the vagina about 2 cm above the plane of the hymen. On contraction, the levator ani draws both the rectum and the vagina forward and upward in the direction of the

symphysis pubis and thereby acts to close the vagina.

In the first stage of labor, the membranes, when intact, and the fetal presenting part serve to dilate the upper vagina. The most marked change consists of stretching levator ani muscle fibers. This is accompanied by thinning of the central portion of the perineum, which becomes transformed from a wedge-shaped, 5-cm-thick tissue mass to a thin, almost transparent membranous structure less than 1 cm thick. When the perineum is distended maximally, the anus becomes markedly dilated and presents an opening that varies from 2 to 3 cm in diameter and through which the anterior wall of the rectum bulges.

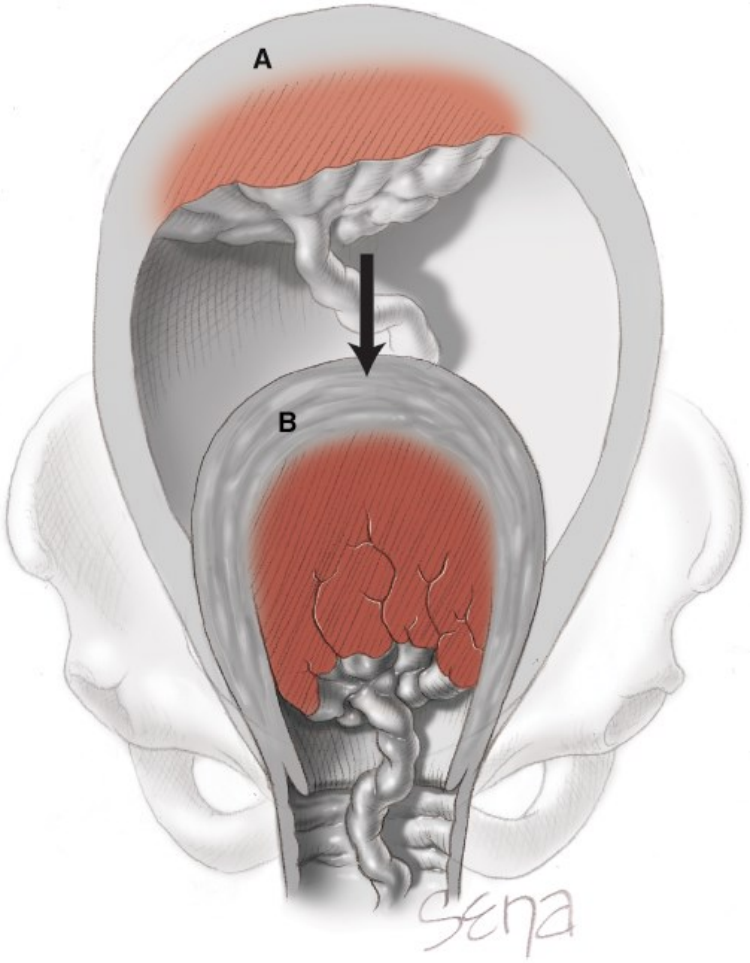
Third Stage: Delivery of Placenta and Membranes

This stage begins immediately after fetal delivery and involves separation and expulsion of the placenta and membranes. As the neonate is born, the uterus spontaneously contracts around its diminishing contents. Normally, by the time the newborn is completely delivered, the uterine cavity is nearly obliterated. The organ consists of an almost solid mass of muscle, several centimeters thick, above the thinner lower segment. The uterine fundus now lies just below the level of the umbilicus.

This sudden diminution in uterine size is inevitably accompanied by a decrease in the area of the placental implantation site (Fig. 21-16). For the placenta to accommodate itself to this reduced area, it thickens, but because of limited placental elasticity, it is forced to buckle. The resulting tension pulls the weakest layer—decidua spongiosa—from that site. Thus, placental separation follows the disproportion created between the relatively unchanged placental size and the reduced implantation site size.

FIGURE 21-16

Diminution in size of the placental site after birth of the newborn. **A.** Spatial relations before birth. **B.** Placental spatial relations after birth.



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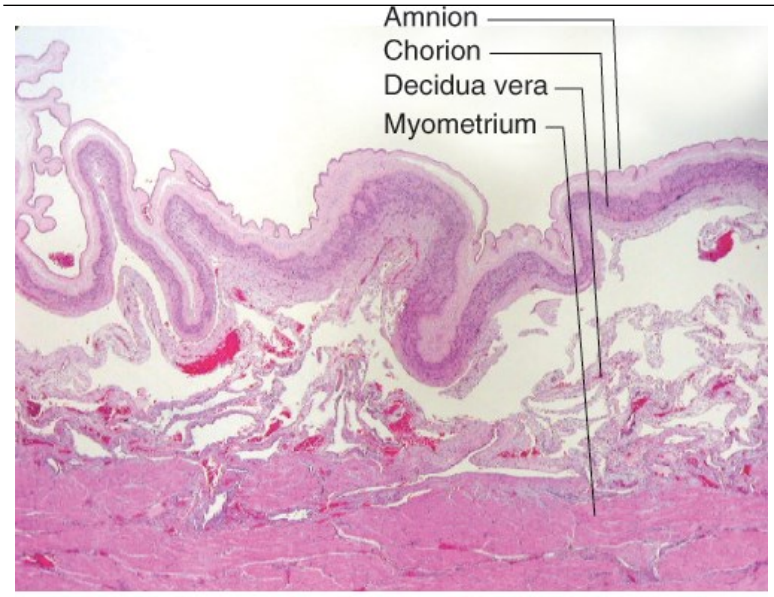
Cleavage of the placenta is aided greatly by the loose structure of the spongy decidua. As detachment proceeds, a hematoma forms between the separating placenta and the adjacent decidua, which remains attached to the myometrium. The hematoma is usually the result rather than the cause of the separation, because in some cases bleeding is negligible.

The great decline in uterine cavity surface area simultaneously throws the fetal membranes—the amniochorion and the parietal decidua—into innumerable folds (Fig. 21-17). Membranes usually remain in situ until placental separation is nearly completed. These are then peeled off the uterine wall, partly by further contraction of the myometrium and partly by traction that is exerted by the separated placenta as it descends during expulsion.

FIGURE 21-17

Postpartum, membranes are thrown up into folds as the uterine cavity decreases in size. (Used with permission from Dr. Kelley S. Carrick.)



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After the placenta has detached, it can be expelled by increased abdominal pressure. Completion of the third stage is also accomplished by alternately compressing and elevating the fundus, while exerting minimal traction on the umbilical cord. The retroplacental hematoma either follows the placenta or is found within the inverted sac formed by the membranes. In this process, known as the *Schultze mechanism* of placental expulsion, blood from the placental site pours into the membrane sac and does not escape externally until after extrusion of the placenta. In the other form of placental extrusion, known as the *Duncan mechanism,* the placenta separates first at the periphery and blood collects between the membranes and the uterine wall and escapes from the vagina. In this circumstance, the placenta descends sideways, and its maternal surface appears first.

UTEROTONINS IN PARTURITION PHASE 3

Oxytocin

Late in pregnancy, during phase 2 of parturition, the number of myometrial oxytocin receptors grows appreciably (Fuchs, 1982; Kimura, 1996). This increase coincides with a greater uterine contractile responsiveness to oxytocin. Prolonged gestation is associated with a delay in the rise of these receptor levels (Fuchs, 1984).

Oxytocin—literally, *quick birth*—was the first uterotonin to be implicated in parturition initiation. This nanopeptide is synthesized in the magnocellular neurons of the supraoptic and paraventricular neurons. The prohormone is transported with its carrier protein, *neurophysin*, along the axons to the neural lobe of the posterior pituitary gland in membrane-bound vesicles for storage and later release. The prohormone is converted enzymatically to oxytocin during transport (Gainer, 1988; Leake, 1990).

In addition to its effectiveness in pharmacologically inducing labor at term, oxytocin is a potent uterotonin and occurs naturally in humans. Subsequent observations provide additional support for this theory: (1) the number of oxytocin receptors strikingly rises in myometrial and decidual tissues near the end of gestation; (2) oxytocin acts on decidual tissue to promote prostaglandin release; and (3) oxytocin is synthesized directly in decidual and extraembryonic fetal tissues and in the placenta (Chibbar, 1993; Zingg, 1995).

Although little evidence suggests a role for oxytocin in phase 2 of parturition, abundant data support its important role during second-stage labor and in the puerperium—phase 4 of parturition. Specifically, maternal serum oxytocin levels are elevated: (1) during second-stage labor, which is the end of phase 3 of parturition; (2) in the early puerperium; and (3) during breastfeeding (Nissen, 1995). Immediately after delivery of the fetus, placenta, and membranes, which completes parturition phase 3, firm and persistent uterine contractions are essential to prevent postpartum hemorrhage. Oxytocin likely causes persistent contractions.

Prostaglandins

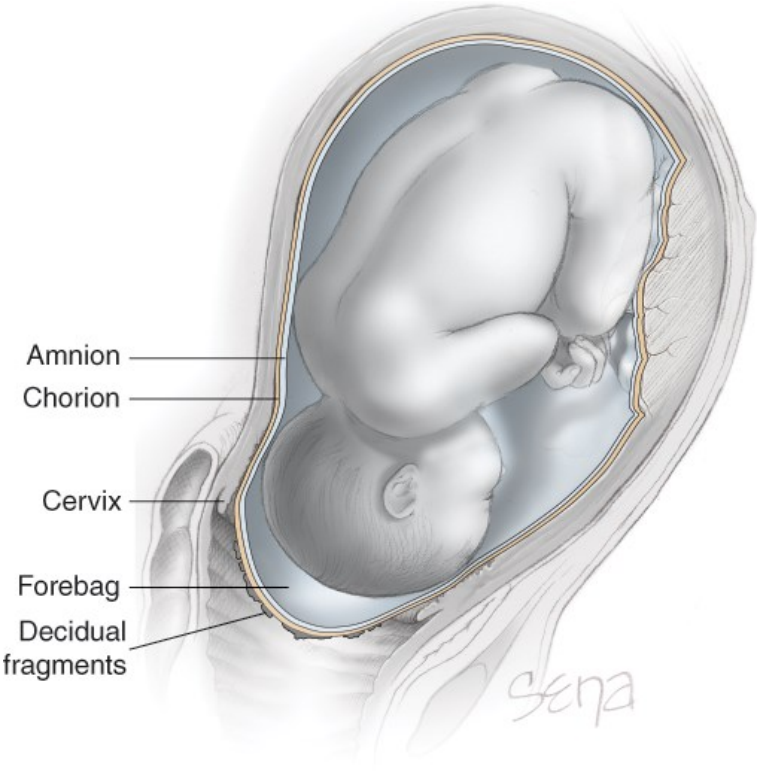
Although their role in phase 2 of parturition in uncomplicated pregnancies is less well defined, a critical role for prostaglandins in phase 3 of parturition is clear (MacDonald, 1993). First, levels of prostaglandins—or their metabolites—in amniotic fluid, maternal plasma, and maternal urine are increased during labor. Second, receptors for PGE_2 and $PGF_{2\alpha}$ are expressed in the uterus and cervix. Thus, if these tissues are exposed to prostaglandins, they will respond. Third, treatment of pregnant women with prostaglandins, by any of several administration routes, causes abortion or labor at all gestational ages. Moreover, administration of prostaglandin H synthase type 2 (PGHS-2) inhibitors to pregnant women will delay spontaneous labor onset and sometimes arrest preterm labor (Loudon, 2003). Last, prostaglandin treatment of myometrial tissue in vitro sometimes causes contraction, dependent on the prostanoid tested and the physiological status of the tissue treated.

During labor, prostaglandin production within the myometrium and decidua is an efficient mechanism of activating contractions. For example, prostaglandin synthesis is high and unchanging in the decidua during phase 2 and 3 of parturition. Moreover, the receptor level for $PGF_{2\alpha}$ is augmented in the decidua at term, and this increase most likely is the regulatory step in prostaglandin action in the uterus.

The fetal membranes and placenta also produce prostaglandins. Primarily PGE_2, but also $PGF_{2\alpha}$, are detected in amniotic fluid at all gestational ages. As the fetus grows, prostaglandin levels in the amniotic fluid rise gradually. Their greatest elevation in concentration within amniotic fluid, however, is demonstrable after labor begins. These higher levels likely result as the cervix dilates and exposes decidual tissue (Fig. 21-18). These higher levels in the forebag, compared with those in the upper compartment, are believed to follow an inflammatory response that signals the events leading to active labor. Together, the rise in cytokine and prostaglandin concentrations further degrade the extracellular matrix, thus weakening fetal membranes.

FIGURE 21-18

Sagittal view of the exposed forebag and attached decidual fragments after cervical dilation during labor. (Redrawn from MacDonald PC, Casey ML: Preterm birth. Sci Am 3:42, 1996.)



Endothelin-1

The endothelins are a family of 21-amino-acid peptides that powerfully induce myometrial contraction (Word, 1990). The endothelin A receptor is preferentially expressed in smooth muscle, and when activated, it effects a rise in intracellular calcium. Endothelin-1 is produced in myometrium of term gestations and is able to induce synthesis of other contractile mediators such as prostaglandins and inflammatory mediators (Momohara, 2004; Sutcliffe, 2009). The requirement of endothelin-1 in normal parturition physiology remains to be established.

Angiotensin II

Two G-protein-linked angiotensin II receptors are expressed in the uterus—AT1 and AT2. In nonpregnant women, the AT2 receptor predominates, but the AT1 receptor is preferentially expressed in gravidas (Cox, 1993). Angiotensin II binding to the plasma-membrane receptor evokes contraction. During pregnancy, the vascular smooth muscle that expresses the AT2 receptor is refractory to the pressor effects of infused angiotensin II (Chap. 4, Renin, Angiotensin II, and Plasma Volume).

PHASE 4: THE PUERPERIUM

Immediately and for about an hour after delivery, the myometrium remains persistently contracted. This directly compresses large uterine vessels and allows thrombosis of their lumens to prevent hemorrhage. This is typically augmented by endogenous and pharmacological uterotonic agents (Chap. 27, Management of the Third Stage).

Uterine involution and cervical repair are prompt remodeling processes that restore these organs to the nonpregnant state. These protect the reproductive tract from invasion by commensal microorganisms and restore endometrial responsiveness to normal hormonal cyclicity.

During the early puerperium, lactogenesis and milk let-down begin in mammary glands (Chap. 36, Lactation and Breastfeeding). Reinstitution of ovulation signals preparation for the next pregnancy. Ovulation generally occurs within 4 to 6 weeks after birth. However, it is dependent on the duration of breastfeeding and lactation-induced, prolactin-mediated anovulation and amenorrhea.

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