Physiology of Labor

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Obstetrics and Gynecology
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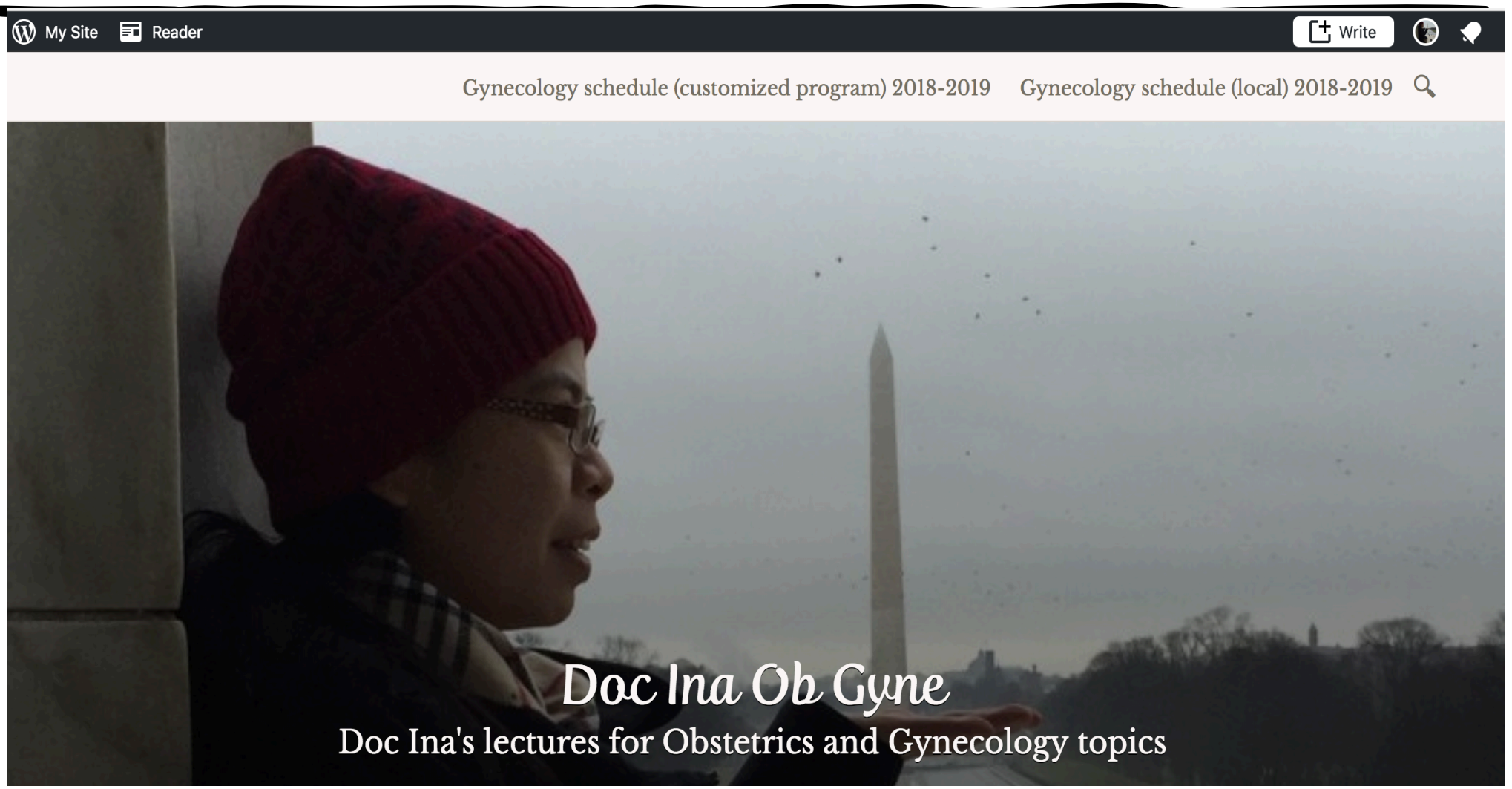

Reference

- Cunningham FG, Leveno KJ, Bloom SL, Spong CY, Dashe JS, Hoffman BL, Casey BM, Sheffield JS (eds).William's Obstetrics 25th edition; 2018; chapter 21 Physiology of Labor

Outline

- MATERNAL AND FETAL COMPARTMENTS
- SEX STEROID HORMONE ROLE
- PROSTAGLANDINS ROLE
- PHASE 1: UTERINE QUIESCENCE AND CERVICAL SOFTENING
- PHASE 2: PREPARATION FOR LABOR
- PHASE 3: LABOR
- UTEROTONINS IN PARTURITION PHASE 3
- PHASE 4: THE PUERPERIUM

Maternal and fetal compartments

Uterus: myometrium

- The myometrial layer of the uterus is composed of bundles of smooth muscle cells surrounded by connective tissue.
- the uterine smooth muscle cell is not terminally differentiated and therefore is readily adaptable to environmental changes.
- several smooth muscle qualities confer advantages for uterine contraction efficiency and fetal delivery:
    1. the degree of smooth muscle cell shortening with contractions is greater than in striated muscle cells.
    2. forces can be exerted in smooth muscle cells in multiple directions.
    3. Myometrial smooth muscle is not organized in the same manner as skeletal muscle (the thick and thin filaments are found in long, random bundles throughout the cells)
    4. greater multidirectional force generation in the uterine fundus compared with that of the lower uterine segment permits versatility in expulsive force directionality.

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Uterus: decidua

- term used for the endometrium that is transformed by pregnancy hormones
- Composed of stromal cells and maternal immune cells
- serves to maintain the pregnancy via unique immunoregulatory functions that suppress inflammatory signals during gestation.
- at the end of pregnancy, decidual activation ensues → decidua transitions to induce inflammatory signals and withdraw active immunosuppression, which contribute to parturition initiation.

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Uterus: cervix

- During pregnancy, the cervix has multiple functions:
    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
    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.

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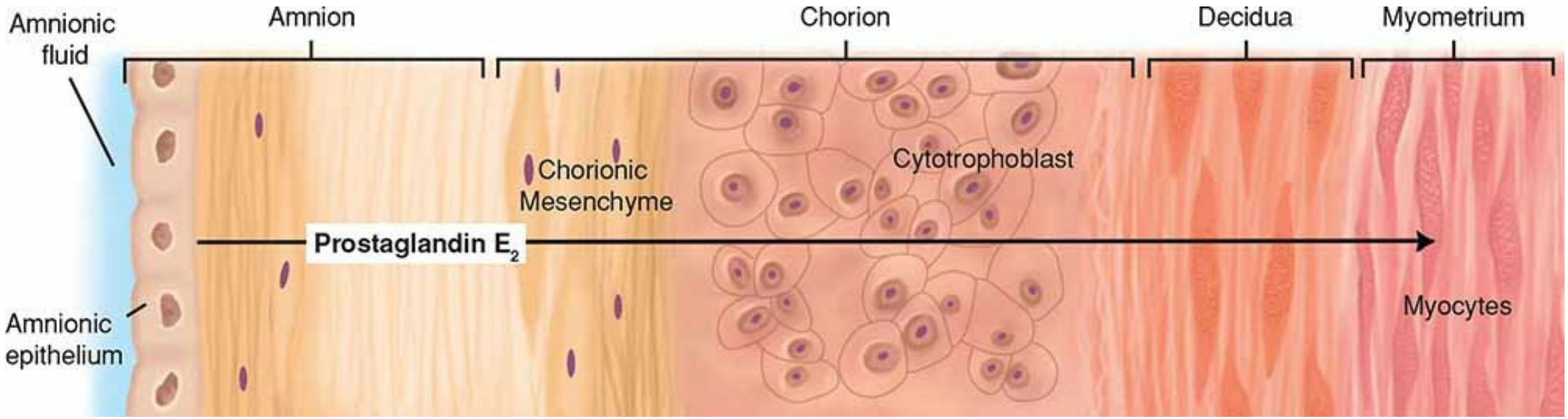
Placenta

- providing the exchange of nutrients and waste between mother and fetus
- 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.



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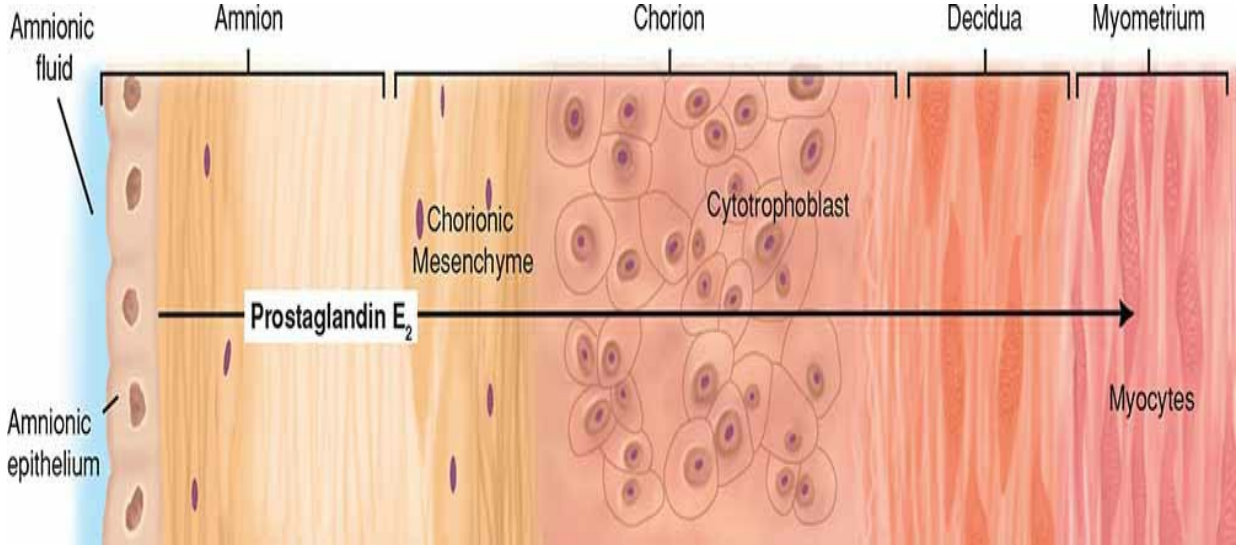
Placenta: amnion



- The amnion provides virtually all of the fetal membranes' tensile strength to resist membrane tearing and rupture
- This avascular tissue is highly resistant to penetration by leukocytes, microorganisms, and neoplastic cells
- It also constitutes a selective filter to prevent fetal particulate-bound lung and skin secretions from reaching the maternal compartment
    - 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.

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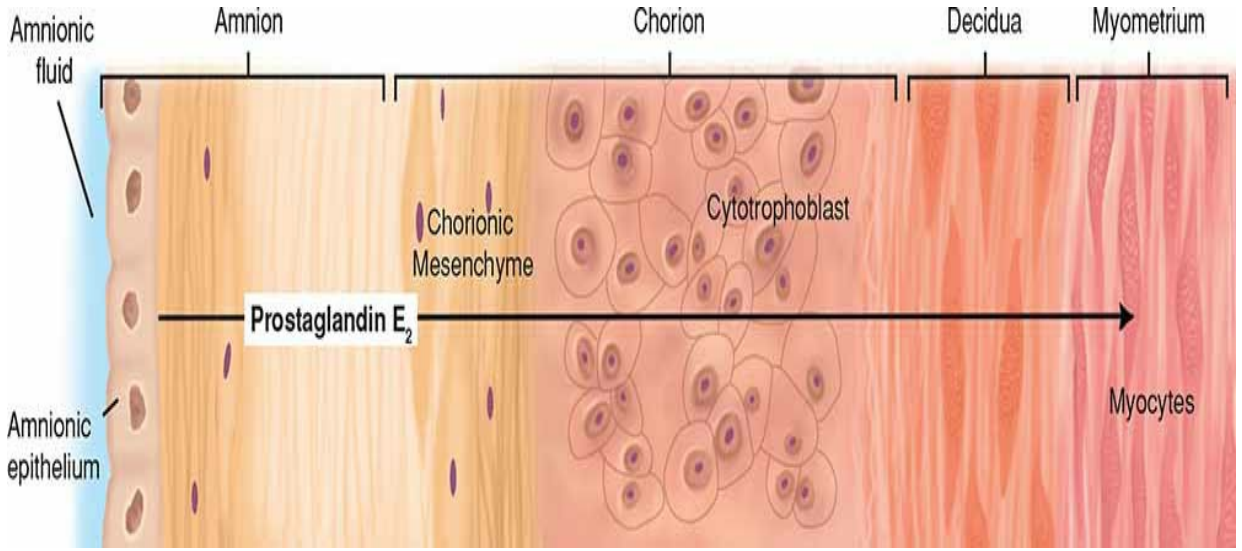
Placenta: chorion



- 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

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Sex steroids hormone role

Estrogen and Progesterone

- estrogen promotes and progesterone inhibits the events leading to parturition.
- Progesterone withdrawal directly precedes progression of parturition.
- Providing progesterone will delay parturition via a decline in myometrial activity and continued cervical competency
- 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.

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Prostaglandins

- Prostaglandins are lipid molecules with varied hormone-like actions
- During parturition, they play a prominent role in myometrial contractility, relaxation, and inflammation.
- Prostaglandins are produced using plasma membrane-derived arachidonic acid, which usually is released by the action of phospholipase A2 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 G2 and then to prostaglandin H2.
- These enzymes are the target of many nonsteroidal antiinflammatory drugs (NSAIDs).

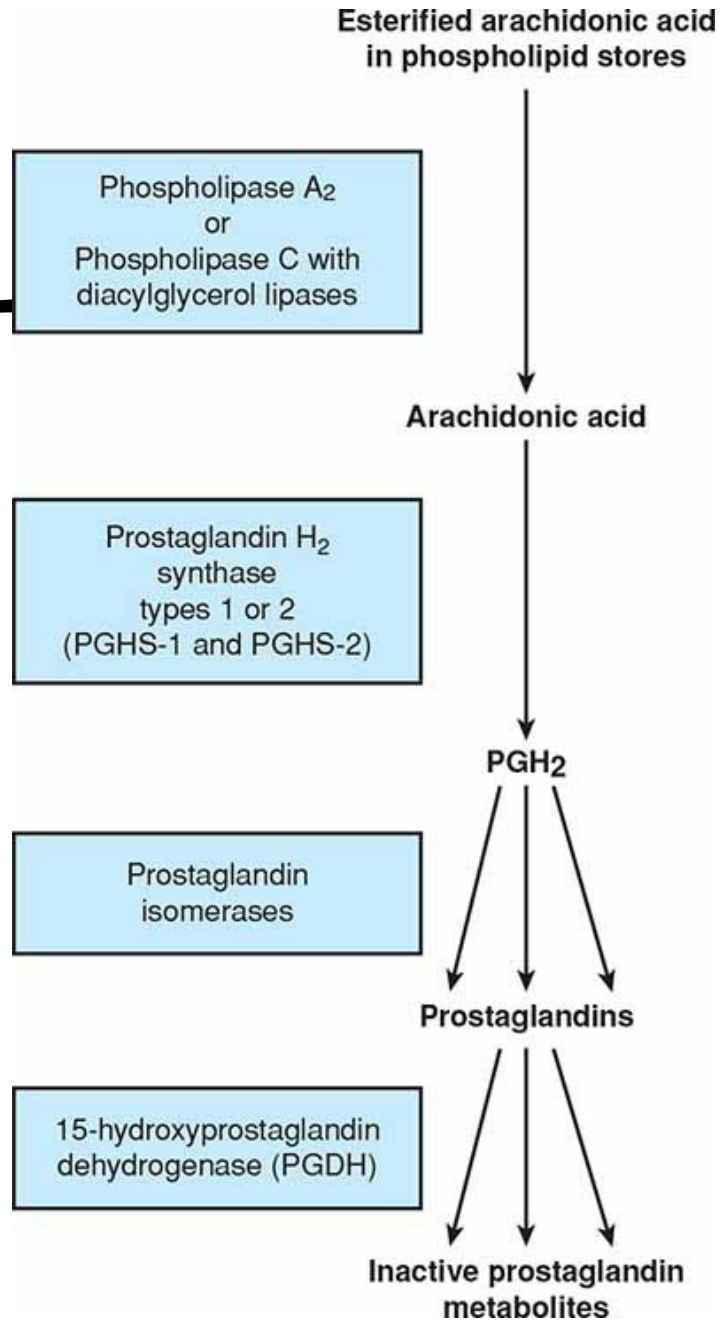

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FIGURE 21-2 Overview of the prostaglandin biosynthetic pathway.

Prostaglandins

- Through prostaglandin isomerases, prostaglandin H2 is converted to active prostaglandins. These include prostaglandins E2 (PGE2), F2α (PGF2α), and I2 (PGI2).
- 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
- 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.

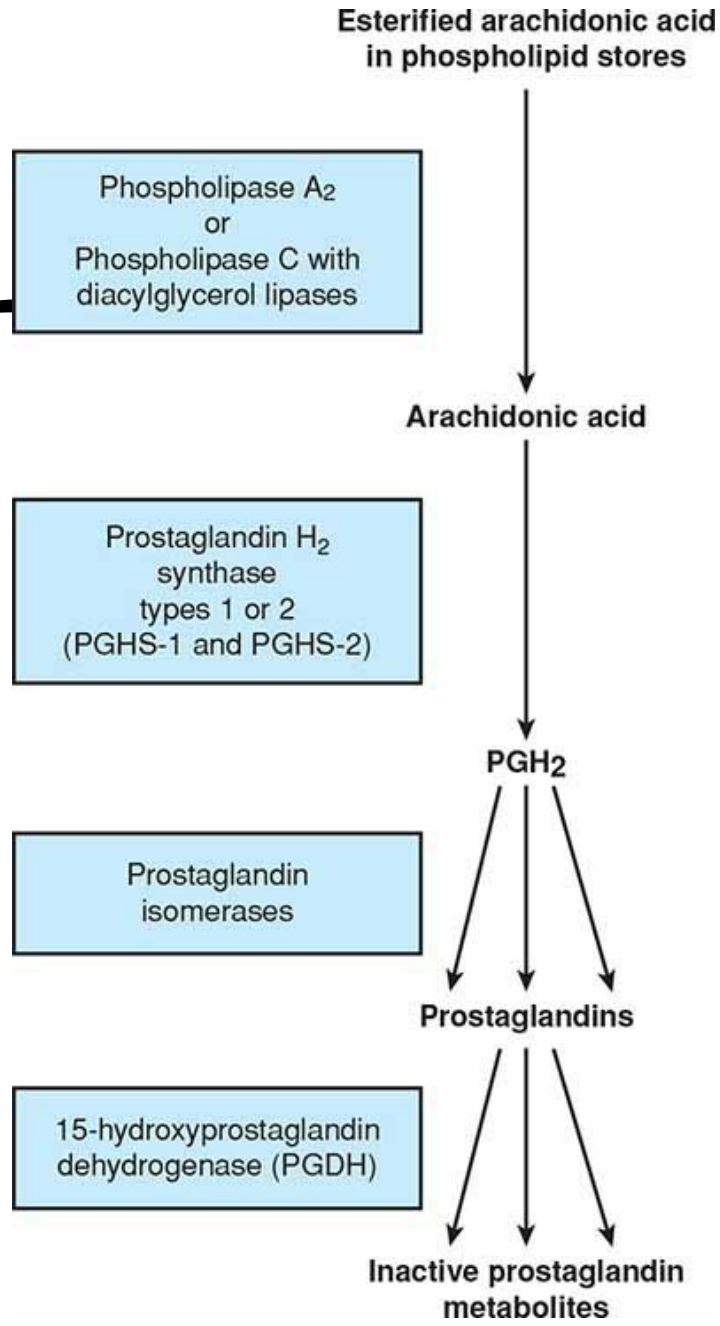

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FIGURE 21-2 Overview of the prostaglandin biosynthetic pathway.

PHASE 1: UTERINE QUIESCENCE AND CERVICAL SOFTENING

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- parturition can be arbitrarily divided into four overlapping phases that correspond to the major physiological transitions of the myometrium and cervix during pregnancy
- These phases of parturition include: (1) a prelude to it, (2) the preparation for it, (3) the process itself, and (4) recovery.

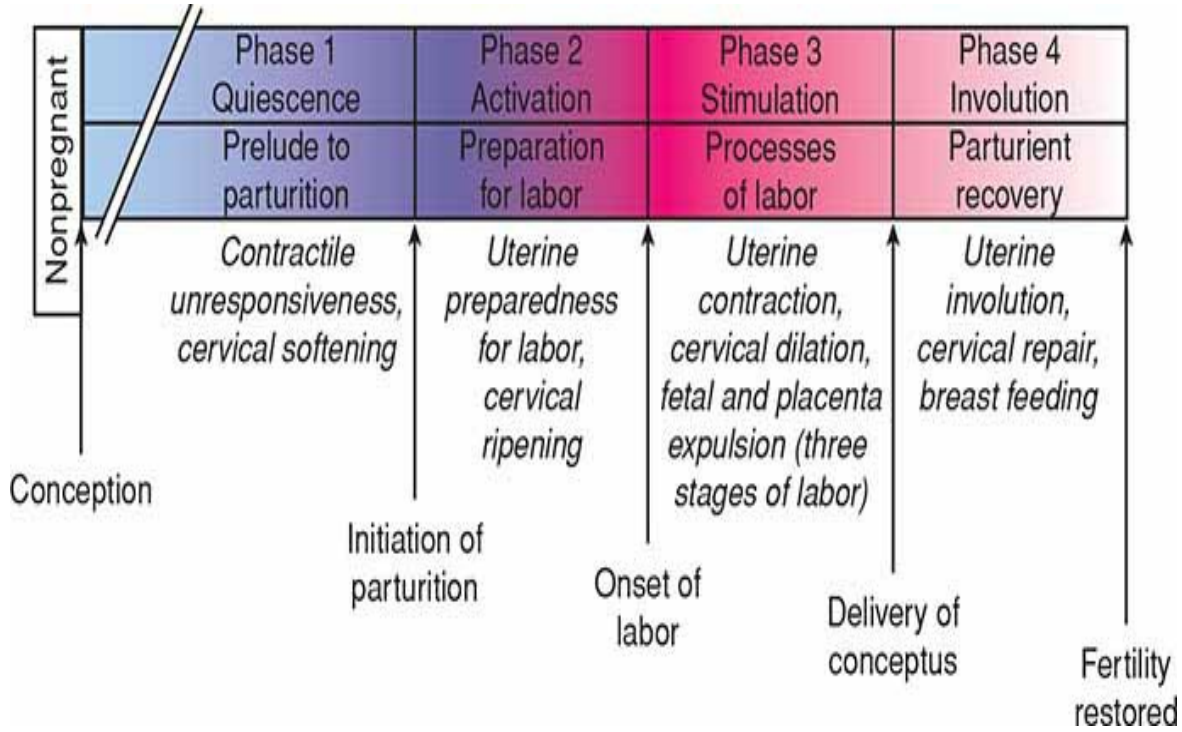

FIGURE 21-3 The phases of parturition.

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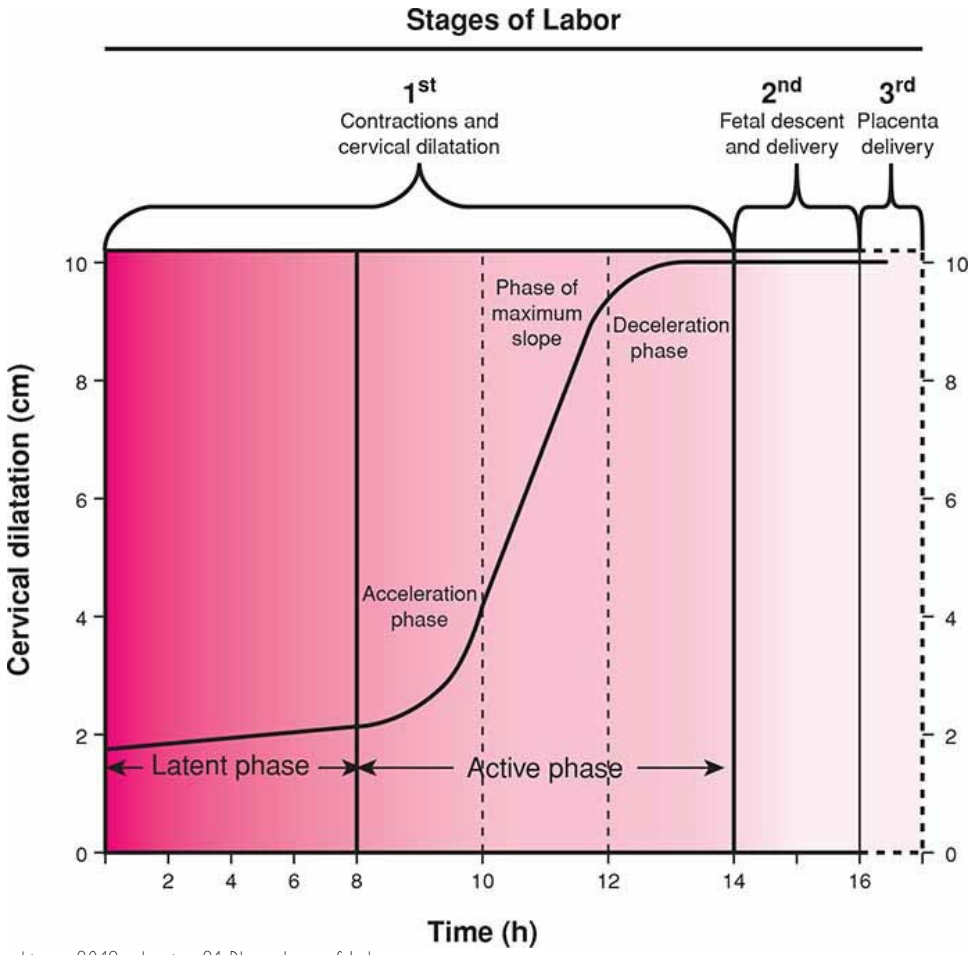
PHASE 1: UTERINE QUIESCENCE AND CERVICAL SOFTENING

- 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
- 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.



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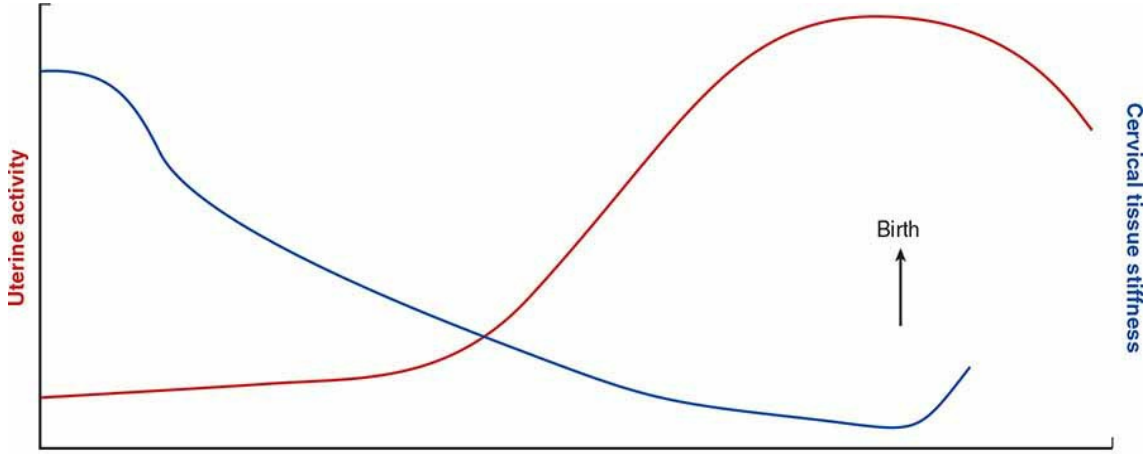
PHASE 1: UTERINE QUIESCENCE AND CERVICAL SOFTENING

- 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
- 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.



Phase 1	Phase 2	Phase 3	Phase 4
Prostacyclin Nitric oxide hCG CRH Caspase 3 Progesterone PGDH	Uterine stretch Gap junction receptors Fetal signals (SPA, PAF, CRH) Fetal membrane senescence Prostaglandins Cortisol? Progesterone (nonclassic withdrawal) Estrogen Relaxin Hyaluronan	Prostaglandins Oxytocin CRH? Inflammatory cell activation Estrogen Relaxin	Oxytocin Inflammatory cell activation

Myometrium is major site of action | Cervix is major site | Both are sites of action

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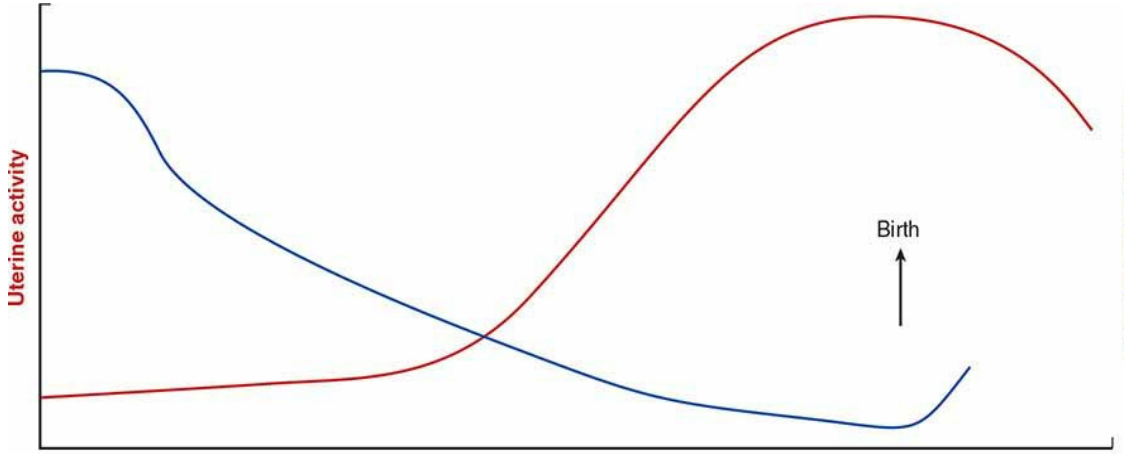
PHASE 1: UTERINE QUIESCENCE AND CERVICAL SOFTENING

- During phase 1, the myometrial cells undergo a noncontractile state, and uterine muscle is rendered unresponsive to natural stimuli → continues until near the end of pregnancy.
- some low-intensity myometrial contractions are felt during the quiescent phase, but they do not normally cause cervical dilation → common toward the end of pregnancy, (Braxton Hicks contractions or false labor)
- 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.



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Myometrial Relaxation and Contraction

- Quiescence is achieved in part by:
    1. diminished intracellular crosstalk and reduced intracellular Ca2+ ([Ca2+]i) levels;
    2. ion-channel regulation of cell membrane potential
    3. activation of the uterine endoplasmic reticulum stress-unfolded protein response
    4. uterotonin degradation.
- contractility results from:
    1. enhanced interactions between the actin and myosin proteins
    2. heightened excitability of individual myometrial cells
    3. promotion of intracellular crosstalk that allows synchronous contractions to develop.

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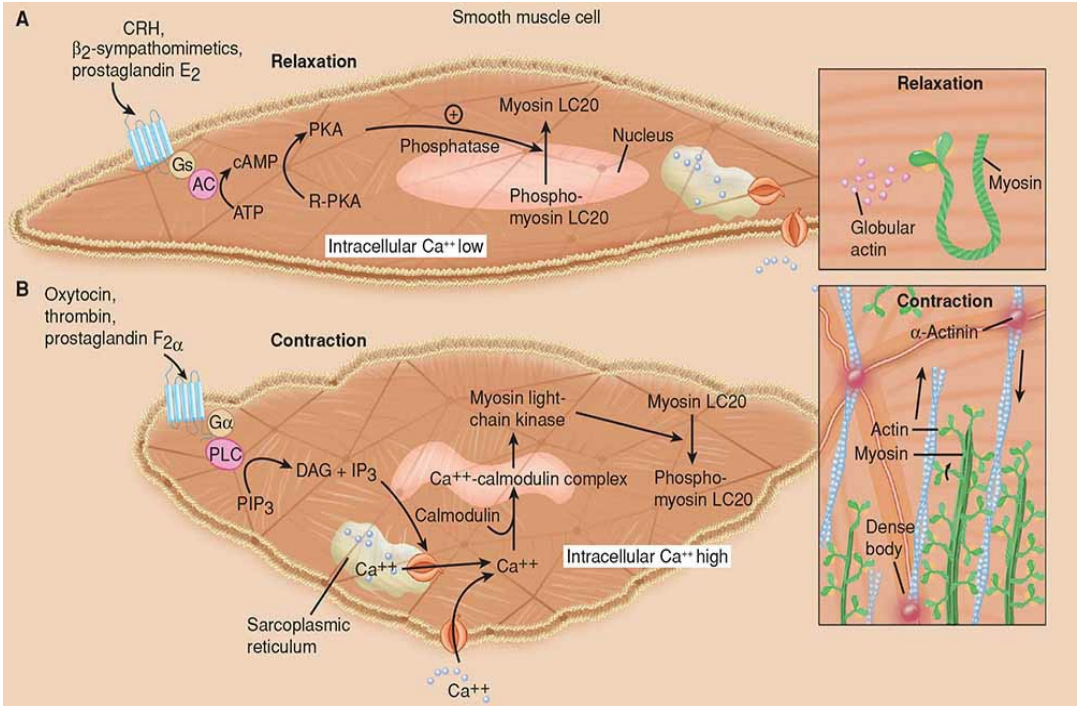
Actin-Myosin Interactions

- Actin and myosin proteins are essential to muscle contraction.
- Actin must be converted from a globular to a filamentous form → 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
- Actin must be attached to the cytoskeleton at focal points in the cell membrane to allow tension to develop.
- 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 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.



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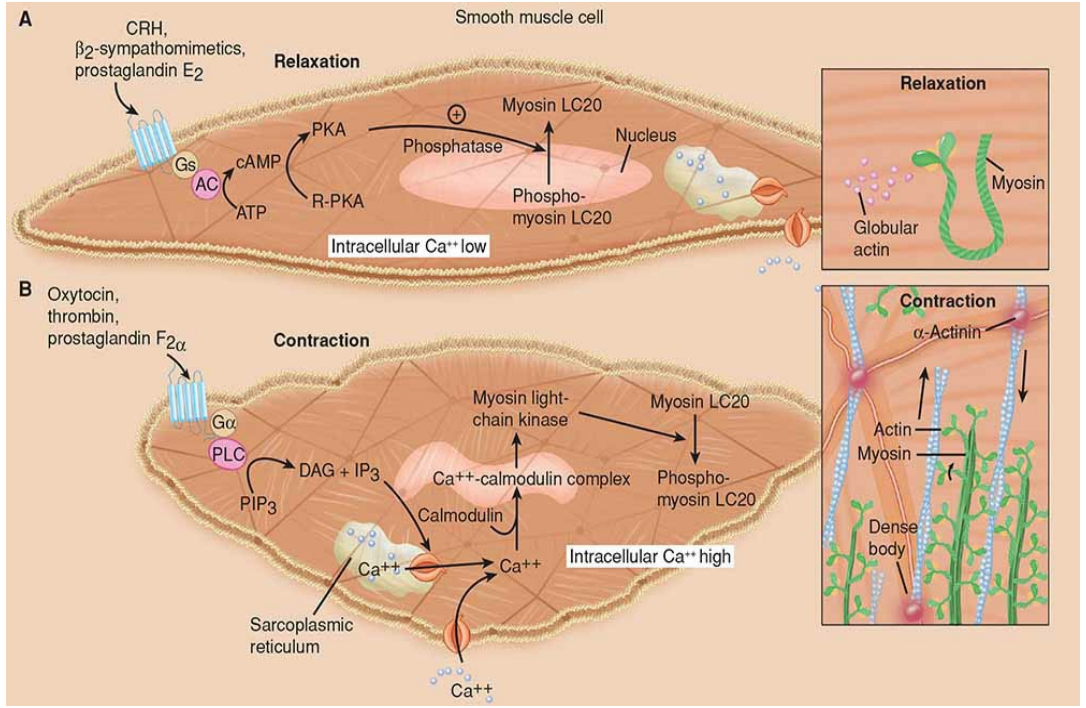
Actin-Myosin Interactions

- Uterine relaxation ordinarily is promoted by conditions that lower concentrations of (Ca2+)i.
- In contrast, agents that prompt contraction act on myometrial cells to augment (Ca2+)i levels. Or, they allow an influx of extracellular calcium through ligand- or voltage-regulated calcium channels
- Voltage-gated ion channels open, additional calcium ions move into the cell, and cellular depolarization follows.
- For example, prostaglandin F2α 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 Ca2+ entry The rise in (Ca2+)i levels is often transient.
- But, contractions can be prolonged by inhibition of myosin phosphatase, an enzyme which dephosphorylates myosin.



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Regulation of Membrane Potentials

- Numerous potassium channels control membrane potential. One key regulator is the large-conductance voltage- and Ca^{2+}-activated K channel (BK_{Ca})
- In normal physiology, the myometrial BK_{Ca} channel plays dual and opposing roles to maintain a balance between uterine quiescence and contractility.
- 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.

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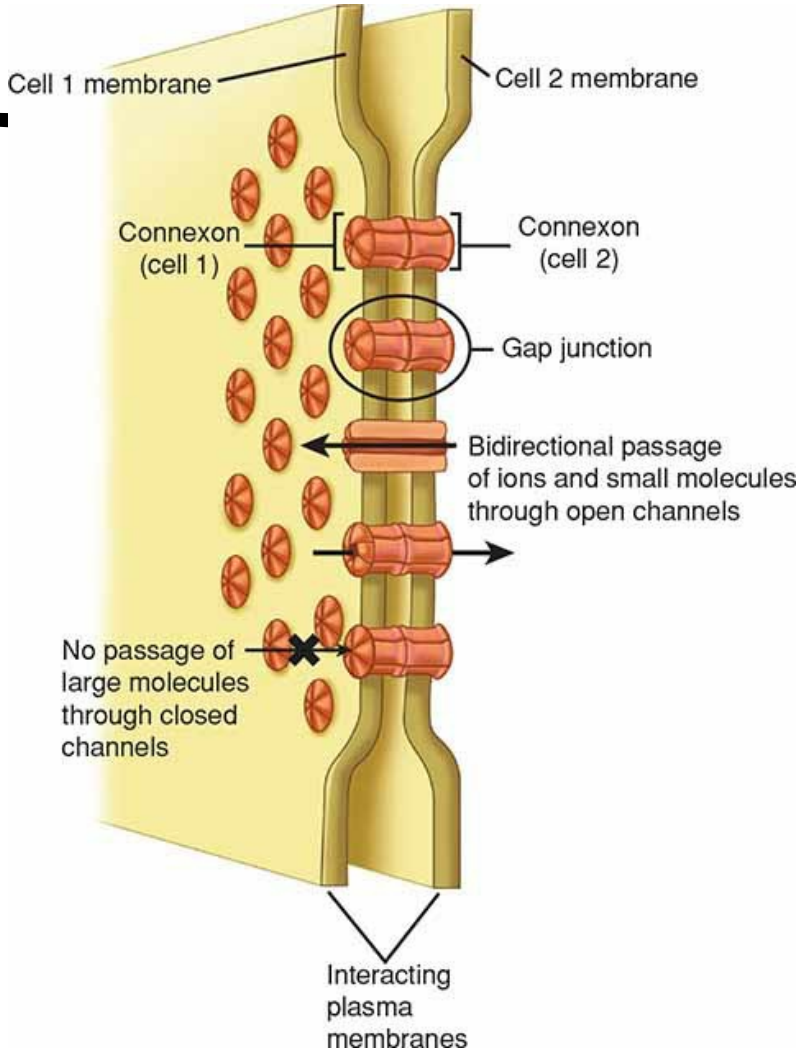
Myometrial Gap Junctions

- 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"
- These connexons are each composed of six connexin subunit proteins → Of these, connexin-43 is expressed in myometrium, and concentrations rise near labor onset.



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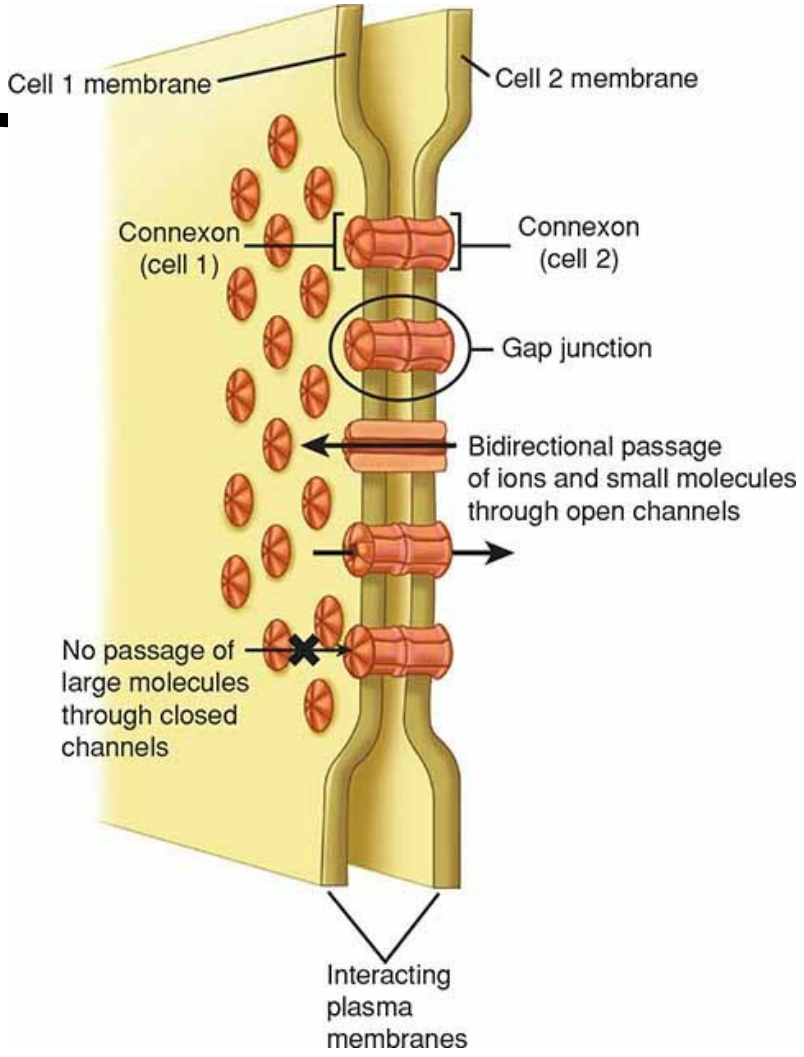
Myometrial Gap Junctions

- 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.
- 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



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Endoplasmic Reticulum Stress Response

- progesterone maintains uterine quiescence through support of myometrial caspase 3, which is an anticontractile agent
  - This protein degrades both actin and the specific gap junction protein, connexin-43
- In mice, myometrial caspase 3 activation is regulated by a pregnancy-induced endoplasmic reticulum stress response (ERSR)
- 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.

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G-Protein-Coupled Receptors

- numerous G-protein-coupled receptors appear to be modified during the phases of parturition. Several of these are present in myometrium and associated with Gαs-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

  Examples are the LH receptor and corticotropin-releasing hormone receptor 1 (CRHR1)
- Other G- protein-coupled myometrial receptors, instead, are associated with G-protein- mediated activation of phospholipase C, which releases arachidonic acid.
- Many of these are available to the myometrium during pregnancy in high concentration via endocrine or autocrine mechanisms.

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G-Protein-Coupled Receptors

- β-Adrenoreceptors are prototypical examples of cAMP signaling causing myometrium relaxation. β-Adrenergic receptors mediate Gαs-stimulated increases in adenylyl cyclase, elevated levels of cAMP, and myometrial cell relaxation. T
- he 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

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G-Protein-Coupled Receptors

- LH and hCG hormones share the same receptor, and this G-protein-coupled receptor has been found in myometrial smooth muscle and blood vessels
- 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 Gαs-linked system.
- This lessens contraction frequency and force and lowers the number of tissue-specific myometrial cell gap junctions
    - Thus, high circulating levels of hCG may be one mechanism of uterine quiescence.

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G-Protein-Coupled Receptors

- Corticotropin-releasing hormone (CRH) is synthesized in the placenta and hypothalamus.
- 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
- CRH appears to promote myometrial quiescence during most of pregnancy but then aids myometrial contractions with parturition onset.
- 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 (IP3) and stabilization of (Ca2+)i levels
    - However, in term laboring myometrium, $(Ca^{2+})i$ concentrations are augmented by CRH activation of G proteins Gq and Gi and prompts stimulation of IP3 production and greater contractility.

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Decidua

- To ensure uterine quiescence, the synthesis in the decidua of prostaglandins, in particular PGF2α, is markedly suppressed.
- Suppression of prostaglandin production persists throughout most of pregnancy, and suppression withdrawal is a prerequisite for parturition
- Phase 1 of parturition also promotes an environment of immune tolerance to protect the fetus.
  - 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.

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Cervical Softening

- The initial stage of cervical remodeling (cervical softening)–begins in phase 1 of parturition.
- It is characterized by greater tissue compliance, yet the cervix remains firm and unyielding.
- Cervical softening results from increased vascularity, cellular hypertrophy and hyperplasia, and slow, progressive compositional and structural changes in the extracellular matrix
- collagen, which is the main structural protein in the cervix, undergoes conformational changes that alter tissue stiffness and flexibility
    - Specifically, collagen processing and the number or type of stable covalent cross- links between collagen triple helices is altered.
    - activity of the cross-link-forming enzymes beginning in early pregnancy (lysyl hydroxylase and lysyl oxidase).

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PHASE 2: PREPARATION FOR LABOR

"uterine awakening" or "activation"

progression of uterine changes during the last few weeks of pregnancy.

Progesterone Withdrawal

- Parturition progression to labor can be blocked by administering progesterone to the mother.
- 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.
- The diverse mechanisms by which functional progesterone withdrawal or antagonism is achieved may be through the following:
    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
    5. microRNA regulation of progesterone-metabolizing enzymes and transcription factors that modulate uterine quiescence

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Myometrial Changes

- Phase 2 myometrial changes prepare it for labor contractions → results from a shift in the expression of key proteins that control uterine quiescence to an expression of contraction-associated proteins.
- 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 → 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."

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Oxytocin Receptors

- Myometrial oxytocin receptor levels 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
- 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.
- Progesterone also may act within the myometrial cell to enhance oxytocin receptor degradation and inhibit oxytocin activation of its receptor at the cell surface

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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.

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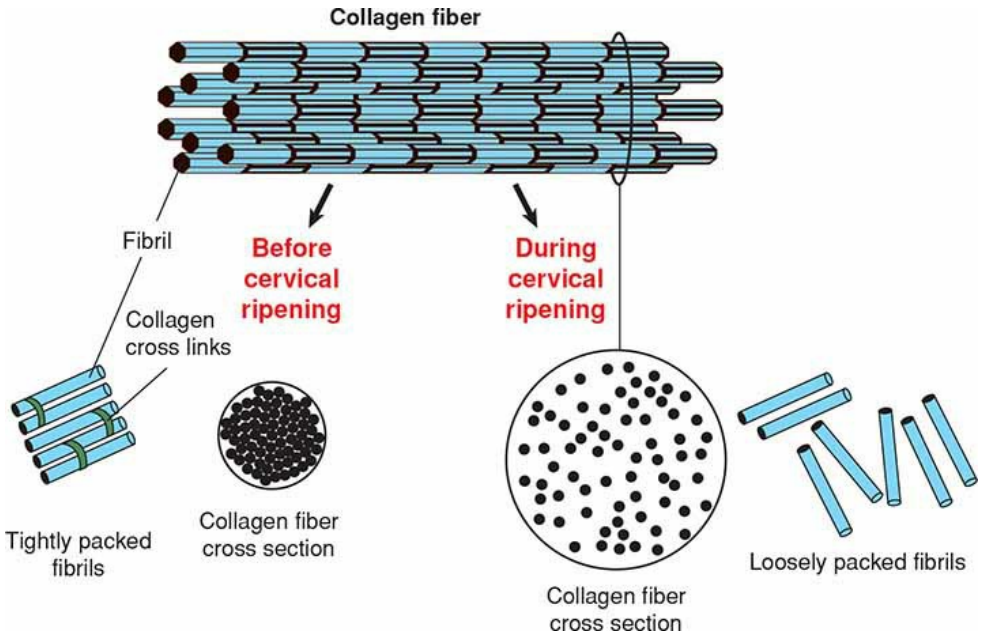
Cervical ripening: Cervical Connective Tissue



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.
- collagen is largely responsible for the structural disposition of the cervix.
- 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.

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Cervical ripening: Cervical Connective Tissue

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
- changes in proteoglycan composition are also suggested to accompany cervical ripening.

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Fetal Contributions to Parturition: 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.
- 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
- Due to "over"stretching, multifetal pregnancies carry a much greater risk for preterm labor than singleton ones.

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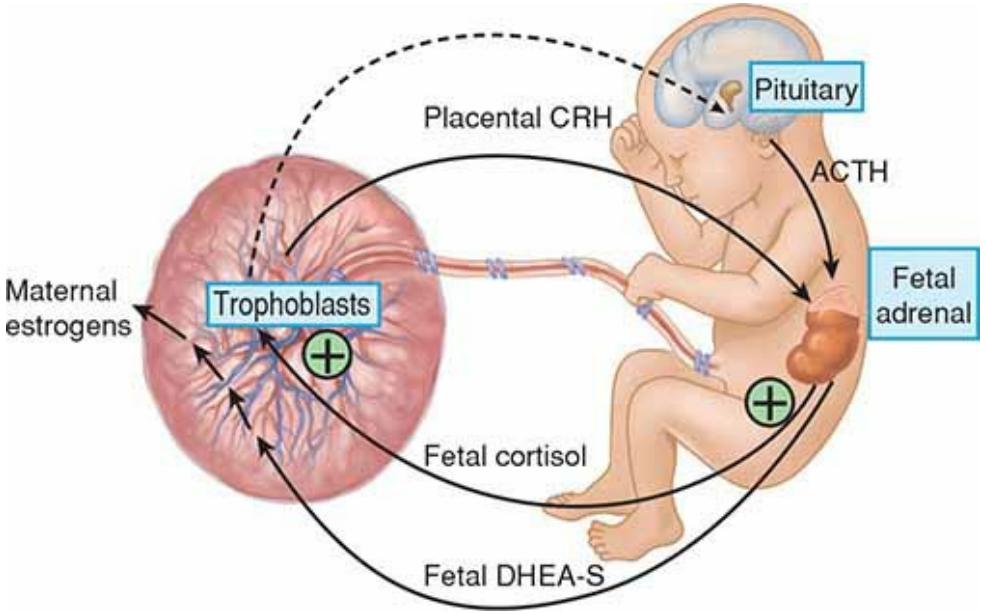
Fetal Contributions to Parturition: Fetal Endocrine Cascades

- 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
- 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



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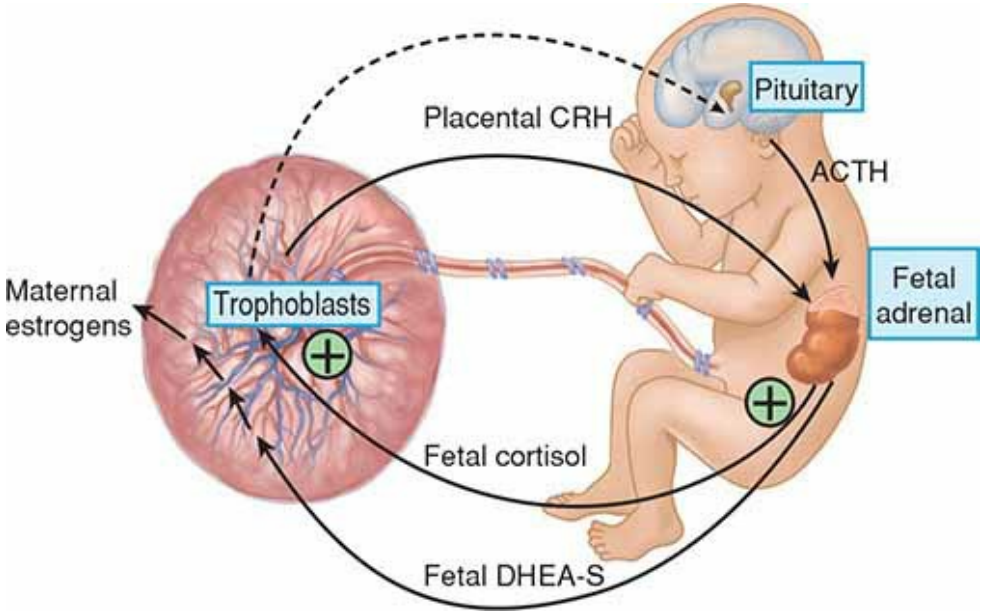
Fetal Contributions to Parturition: Fetal Endocrine Cascades

- A CRH hormone that is identical to maternal and fetal hypothalamic CRH is synthesized by the placenta in relatively large amounts
- 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.
- In the last 12 weeks, of pregnancy CRH plasma levels rise exponentially, peak during labor, and then fall precipitously after delivery
- 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 → The placenta is the likely source of this elevated CRH concentration.



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PHASE 3: LABOR

First Stage: Clinical Onset of Labor Uterine Labor Contractions

- 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.
- contractions, of uterine smooth muscle during labor are painful due to:
    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
    4. stretching of the peritoneum overlying the fundus.
- 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.
    - myometrial contractions in paraplegic women and in women after bilateral lumbar sympathectomy are normal but painless.

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First Stage: Clinical Onset of Labor Uterine Labor Contractions

- Mechanical stretching of the cervix enhances uterine activity → This phenomenon is the Ferguson reflex
- Manipulation of the cervix and "stripping" the fetal membranes is associated with a rise in blood levels of prostaglandin F2α 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.
  - amnionic fluid pressures generated by contractions during spontaneous labor average 40 mm Hg, but vary from 20 to 60 mm Hg

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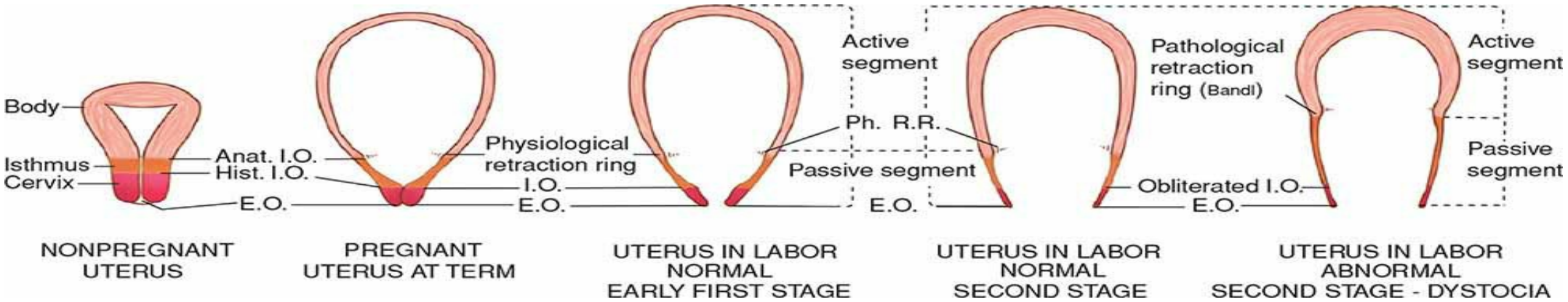
Distinct Lower and Upper Uterine Segments

- 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.



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Distinct Lower and Upper Uterine Segments

- 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.
- 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 → This process continues and results in a tremendously thickened upper uterine segment immediately after delivery.

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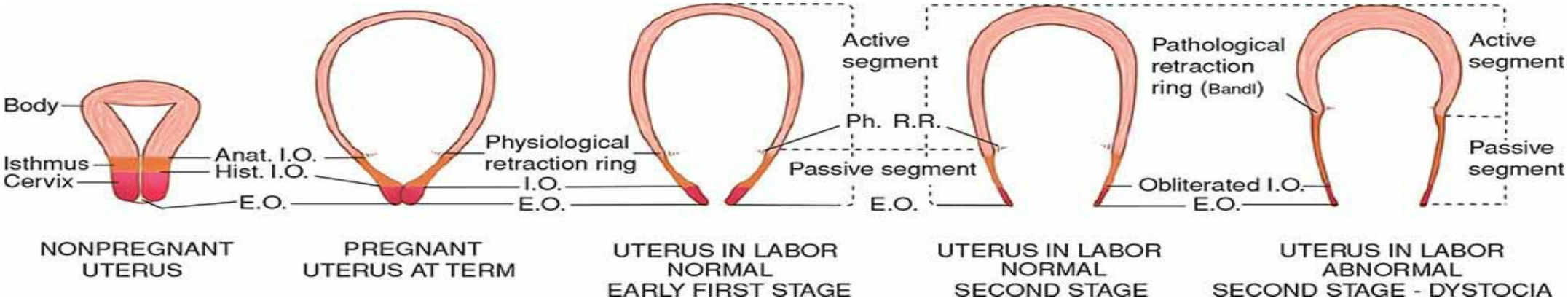
Distinct Lower and Upper Uterine Segments

- 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 → also known as the Bandl ring



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Changes in Uterine Shape

- Each contraction gradually elongates the ovoid uterine shape and thereby narrows the horizontal diameter which has important effects on the labor process.
  - 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.
  - With lengthening of the uterus, the longitudinal muscle fibers are drawn taut → 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.

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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.
- pushing accomplishes little in the first stage → exhausts the mother, and its associated elevated intrauterine pressures may be harmful to the fetus.

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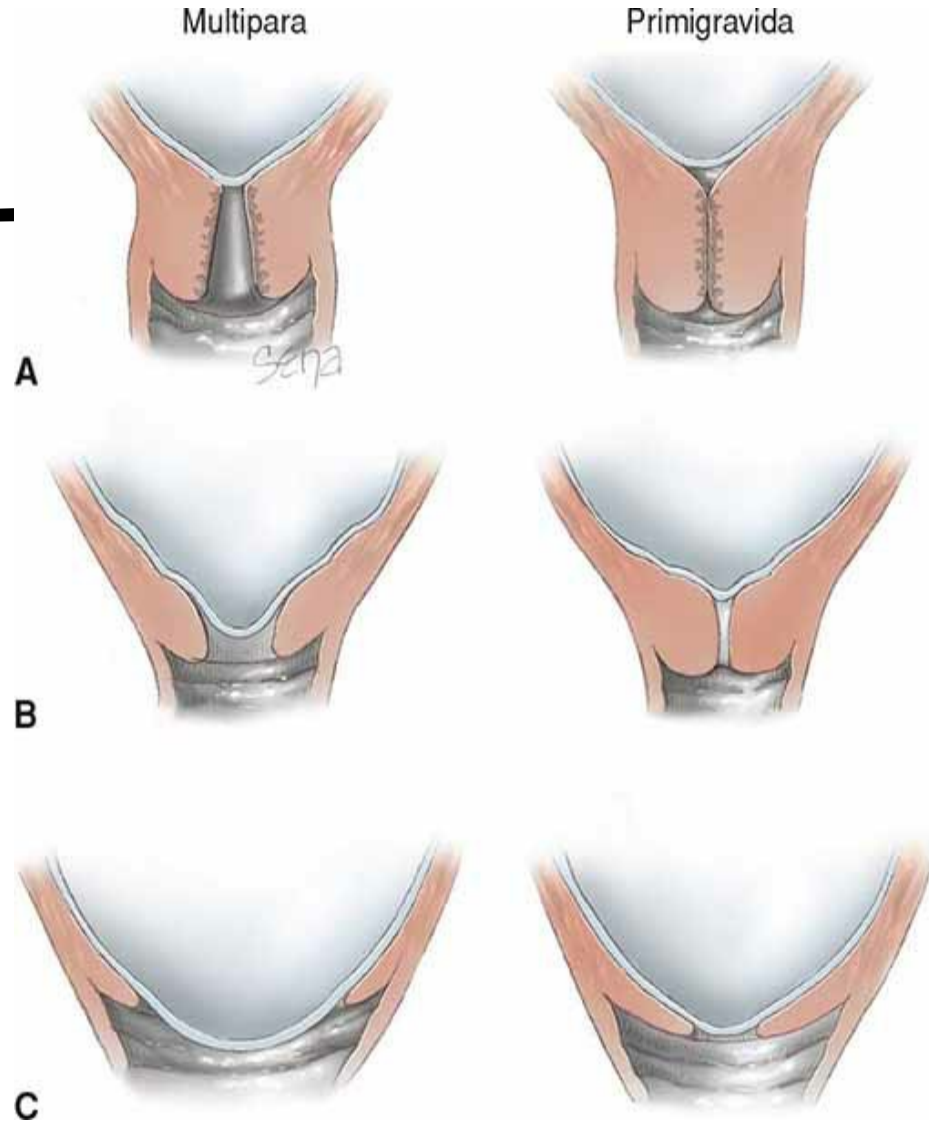
Cervical Changes: dilatation and effacement

- For an average-sized fetal head to pass through the cervix, its canal must dilate to a diameter of approximately 10 cm (completely or fully dilated)
- 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



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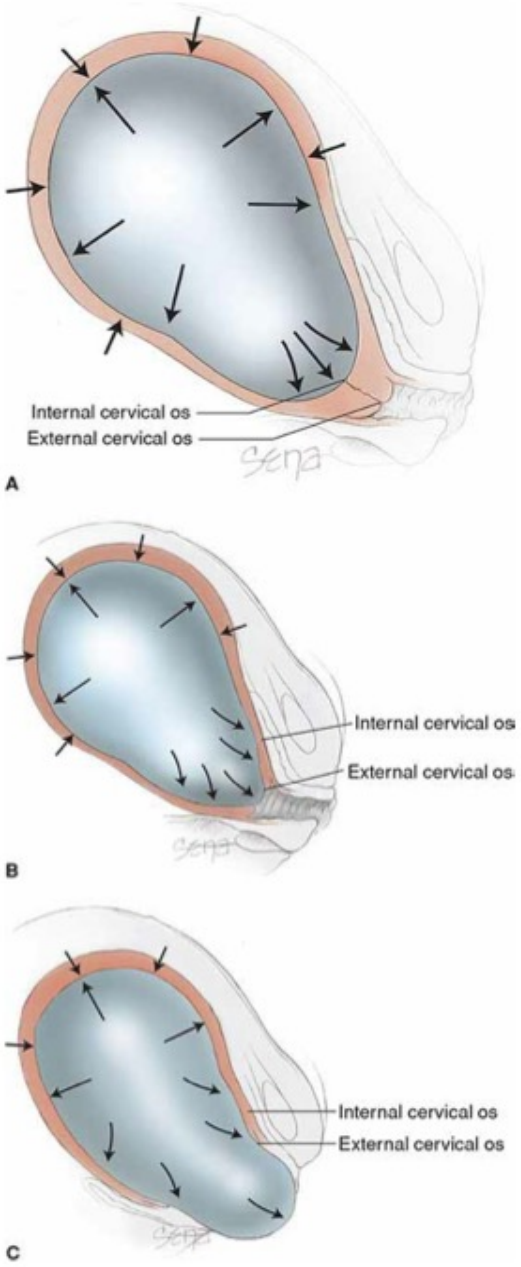
Cervical Changes: dilatation and effacement

- 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.



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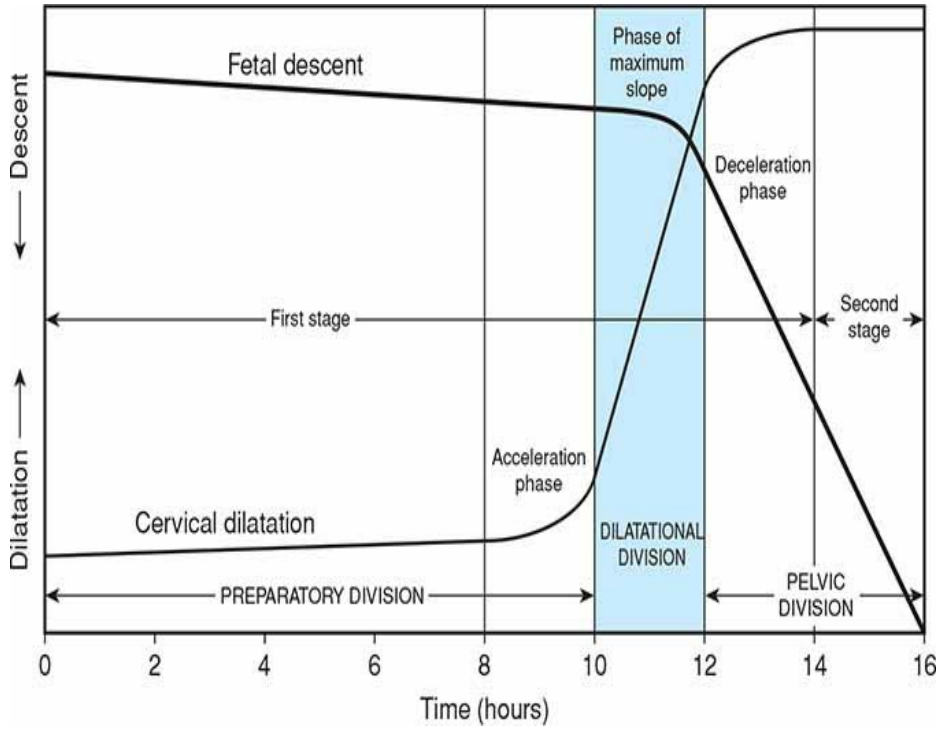
Second Stage: Fetal Descent

- In many nulliparas, engagement of the head is accomplished before labor begins.
- 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
- Active descent usually takes place after dilation has progressed for some time
- During second-stage labor, the speed of descent is maximal and is maintained until the presenting part reaches the perineal floor



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Pelvic Floor Changes

- The birth canal is supported and functionally closed by the pelvic floor
- 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 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.

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Pelvic Floor Changes

- In the first stage of labor, the intact membranes 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.

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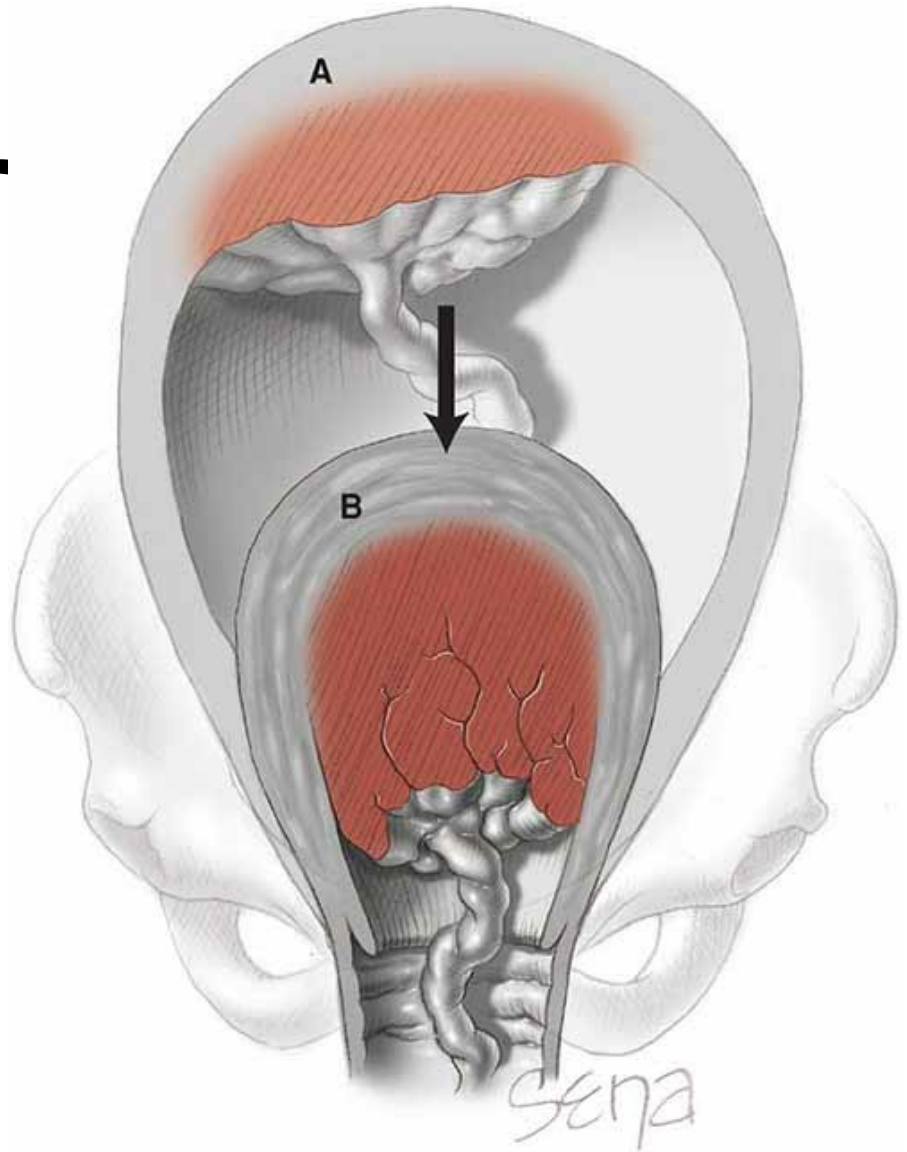
Third Stage: Delivery of Placenta and Membranes

- 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.
    - 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
- 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. → placental separation follows the disproportion created between the relatively unchanged placental size and the reduced implantation site size.



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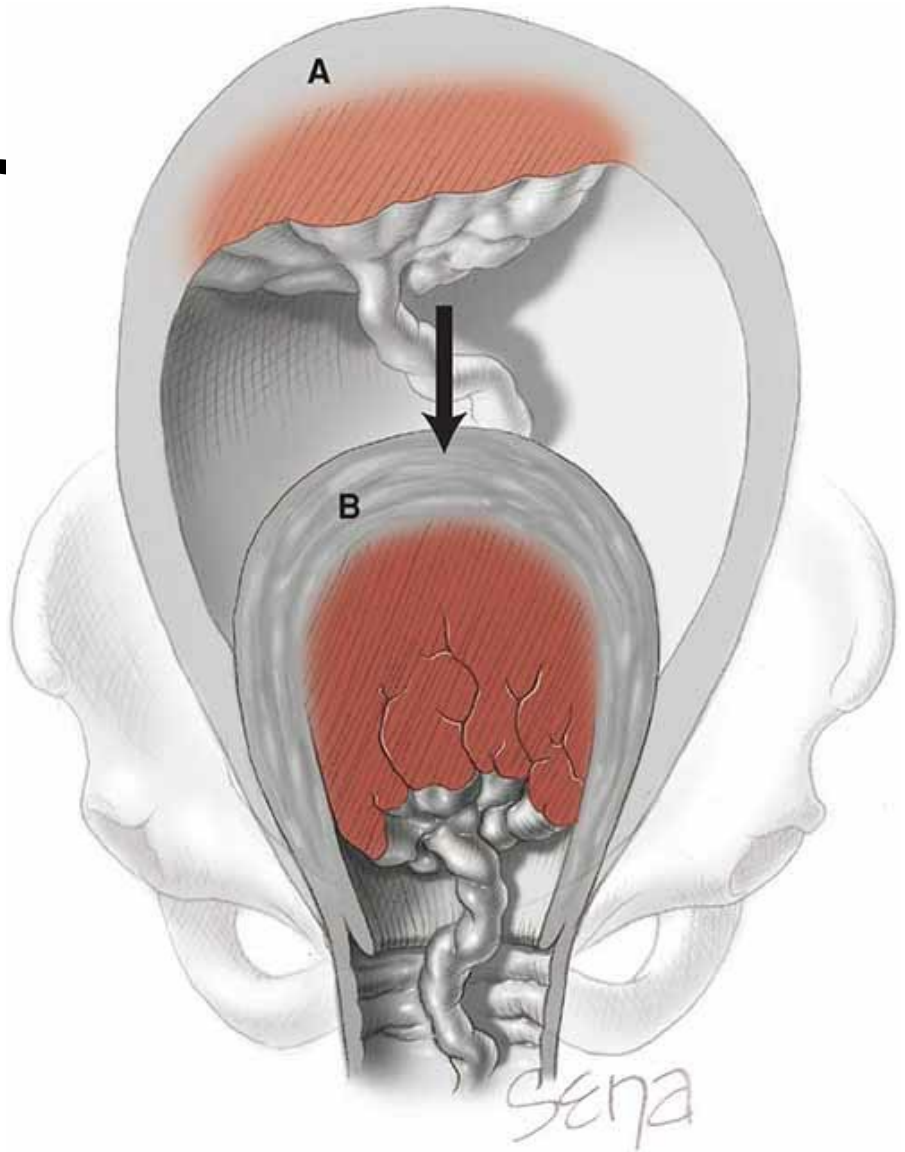
Third Stage: Delivery of Placenta and Membranes

- 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
- 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



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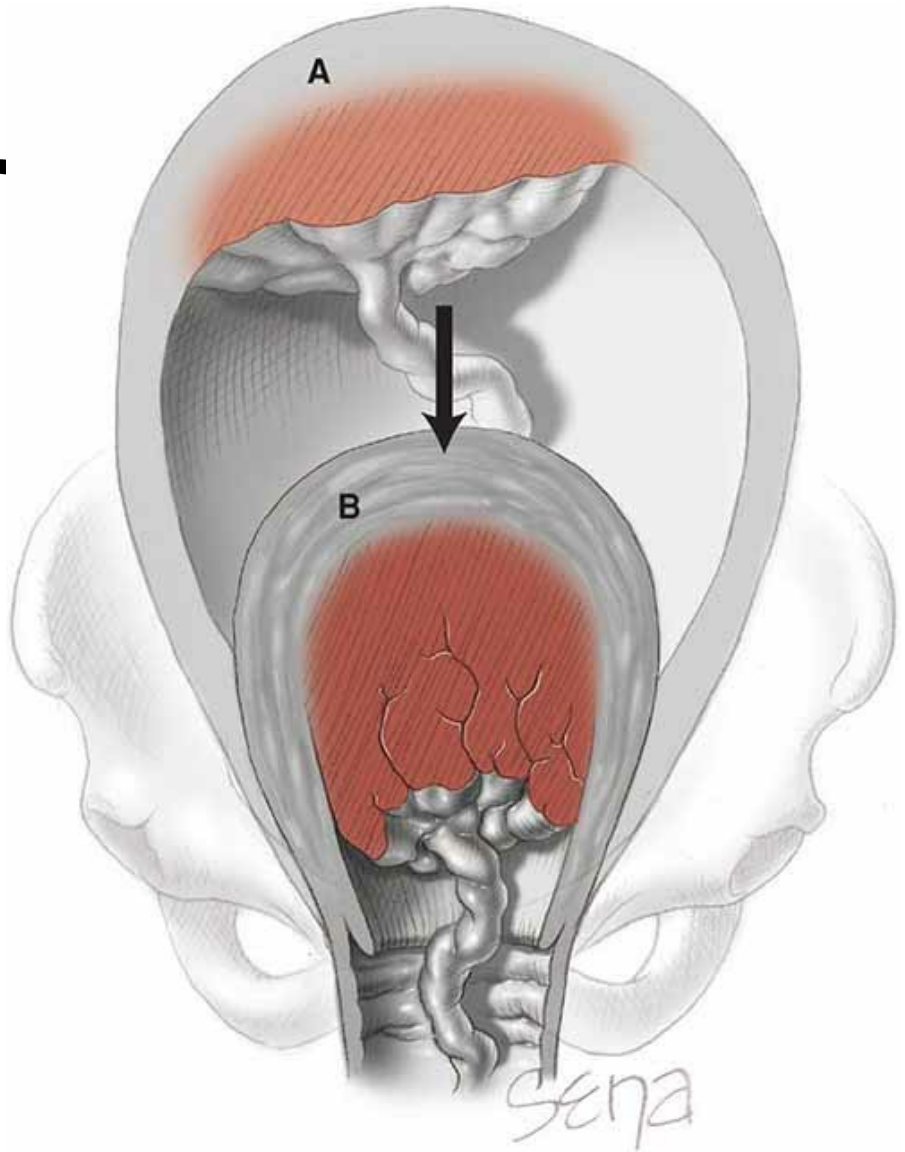
Third Stage: Delivery of Placenta and Membranes

- 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 (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.
- 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.
    - , the placenta descends sideways, and its maternal surface appears first.



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UTEROTONINS IN PARTURITION PHASE 3

Oxytocin

- Late in pregnancy, during phase 2 of parturition, the number of myometrial oxytocin receptors grows appreciably → This increase coincides with a greater uterine contractile responsiveness to oxytocin.
- Stored and released by the posterior pituitary gland
- 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
- 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.

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Prostaglandins

- During labor, prostaglandin production within the myometrium and decidua is an efficient mechanism of activating contractions.
- The fetal membranes and placenta also produce prostaglandins. Primarily PGE2, but also PGF2α, are detected in amnionic fluid at all gestational ages.
- prostaglandin levels in the amnionic fluid are at its highest after labor begins → These higher levels likely result as the cervix dilates and exposes decidual tissue
- 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.

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Endothelin-1

- The endothelins are a family of 21-amino-acid peptides that powerfully induce myometrial contraction
- 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

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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
- 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

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PHASE 4: THE PUERPERIUM

The Perperium

- 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. → typically augmented by endogenous and pharmacological uterotonic agents
- Uterine involution and cervical repair are prompt remodeling processes that restore these organs to the nonpregnant state. → 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
- 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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Summary

- MATERNAL AND FETAL COMPARTMENTS
- SEX STEROID HORMONE ROLE
- PROSTAGLANDINS ROLE
- PHASE 1: UTERINE QUIESCENCE AND CERVICAL SOFTENING
- PHASE 2: PREPARATION FOR LABOR
- PHASE 3: LABOR
- UTEROTONINS IN PARTURITION PHASE 3
- PHASE 4: THE PUERPERIUM

Thank you!

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