PHYSIOLOGY OF PARTURITION

EVALS 2

Dr. D Salvador

Trans Group: 1A

OUTLINE

REFERENCES:

Dr. D Salvador — PPT & Recorded Lecture

I. INTRODUCTION

- Labor is characterized by forceful and painful uterine contractions that effect **cervical dilation** and cause the fetus to **descend** through the birth canal

Professor's Notes:

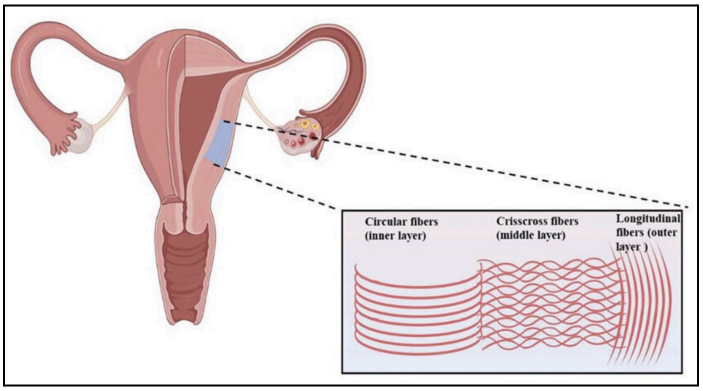
- Two pre-requisites in vaginal delivery: cervical dilation and fetus descend
- It is not required to be painful at all times, but vaginal delivery will not be pursued if there will be one missing in the pre-requisites

A. THEORIES OF LABOR INITIATION

- The physiological processes that regulate parturition and the onset of labor continue to be defined
- Three theories describe labor initiation:
  1. Functional loss of pregnancy maintenance factor
     - There are maintenance factors on-going during the quiescence phase of the pregnancy. However, during labor initiation, the factors responsible for maintaining uterine quiescence are no longer active
  2. Synthesis of factors that induce parturition
  3. Fetus as signal for parturition commencement
- Thus, labor onset represents the culmination of a series of biochemical changes in the uterus and cervix

II. MATERNAL & FETAL COMPARTMENTS

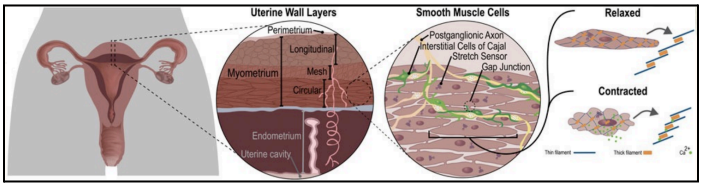
- Varied stimuli such as mechanical stretch, inflammation, and endocrine and paracrine signals modulate the transition of the smooth muscle cell into phenotypes that provide cell growth, proliferation, secretion, and contractility



- **STIMULI: Stretch, Inflammation, Endocrine and Paracrine signals**

A. UTERUS

- Additionally, several smooth muscle qualities confer advantages for uterine contraction efficiency and fetal delivery

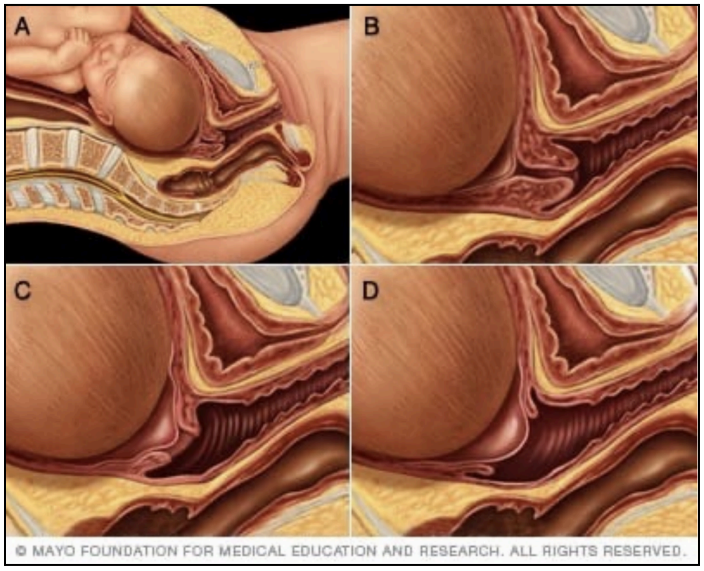


- **SMOOTH MUSCLE QUALITIES:**
  1. Degree of smooth muscle cell shortening > striated muscles
     - May be one order of magnitude greater than that attained in striated muscle cells
  2. Forces exerted in multiple directions
     - This differs from the contraction force generated by skeletal muscle, which is always aligned with the axis of the muscle fibers

3. Thick and thin filaments of smooth muscle are found in long, random bundles → aiding augmented shortening and increased force

B. CERVIX

- During pregnancy, the cervix has multiple functions that includes:
  1. Maintains the epithelial barrier
     - to protect the reproductive tract from infection
  2. Sustains cervical competence despite greater gravity
  3. Orchestrating extracellular matrix (ECM) 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**
- The cervix (in labor) has a ↑ **(high) ratio** of loose fibroblasts to smooth muscle cells and extracellular matrix

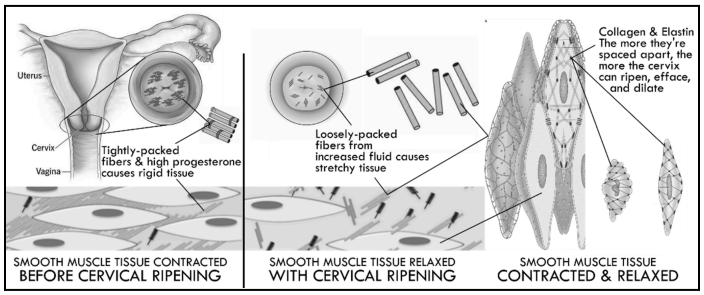


Figure 4. Changes in the Smooth Muscles of the Cervix

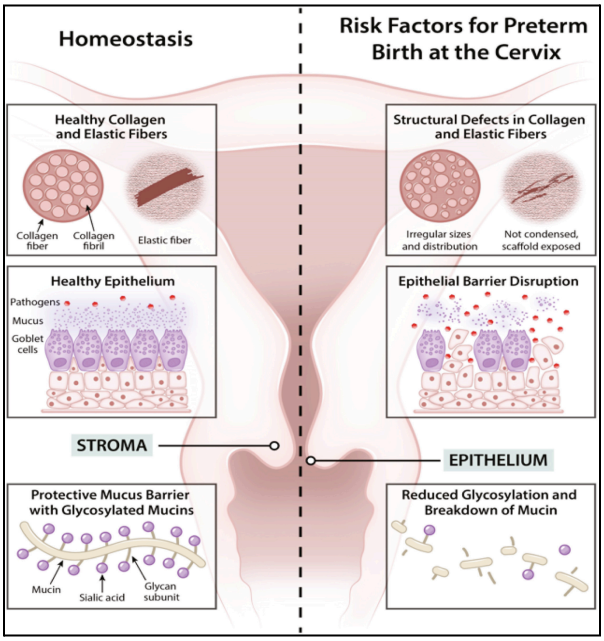


Figure 5. Changes During Normal Labor or Pre-term Labor

Professor's Notes:

- Some events occurring during pre-term labor may also happen during normal labor, such as those in Figure 5

	Homeostasis	Changes during Normal Labor or Pre-term Labor
Collagen and Elastic Fibers	Equally spaced and sized, arranged in an organized manner	Irregular sizes and distribution Fibers are not condensed, scaffold exposed
Epithelium	Goblet cells arranged side-by-side, leaving no space for pathogens to enter the basement membrane Thick mucus	Epithelial barrier disruption; areas without goblet cells, allowing pathogens to pass through the barrier Mucin is not as thick
Mucin	Protective Mucus Barrier with Glycosylated Mucins	Reduced Glycosylation and Breakdown of Mucin

C. PLACENTA

AMNION

- Tensile strength
- Resist membrane tear and rupture
- Synthesize prostaglandins (PGs)

William's Obstetrics Chapter 21; pg. 399

- 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 amniotic fluid constituents that could prematurely accelerate decidual or myometrial activation or could promote adverse events such as amniotic fluid embolism

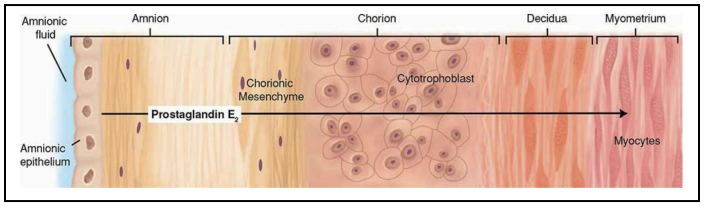


Figure 6. Synthesis of Prostaglandins in the Amnion

CHORION

- **Inactivate uterotonins**
- Inactivating enzymes:
  - Prostaglandin Dehydrogenase
  - Oxytocinase
  - Enkephalinase

Professor's Notes:

- The chorion is a **primarily protective tissue layer** and provides immunological acceptance
- It is also enriched with enzymes that inactivate labor uterotonins
  - **Uterotonins**: Agents that stimulate contractions

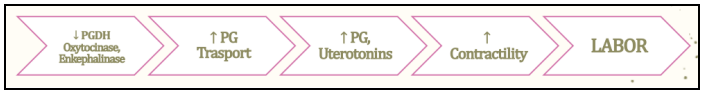


Figure 7. Decreased Inactivating Enzymes Resulting to Labor

III. SEX STEROID HORMONE

- **Estrogen:** Promotes labor
- **Progesterone**: Inhibits labor, provides cervical competency, delays myometrial contractility
  - Maintains uterine **quiescence or tranquility**
- **Progesterone:Estrogen** (Progesterone to Estrogen Ratio)
- **P-receptor antagonists (Mifepristone or Onapristone)**: Induce labor

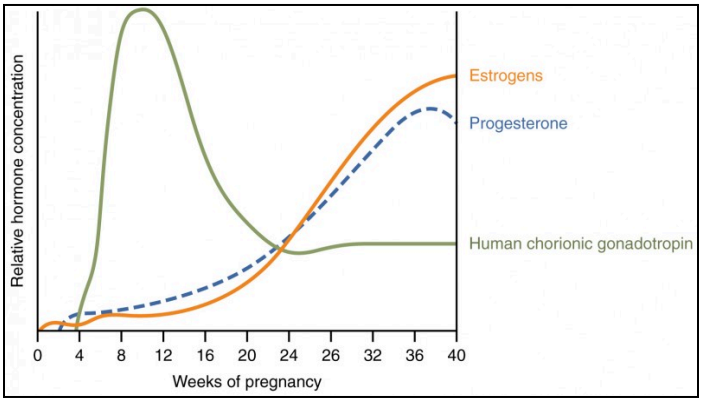


Figure 8. Relative Hormone Concentration During the Different Weeks of Pregnancy

Professor's Notes:

- As a general rule, there are 2 predominant hormones during pregnancy, similar to hormones of non-pregnancy women: **Estrogen and Progesterone**
- Sometimes, more importance is given to the ratio between the 2 hormones, rather than their individual levels
  - Term pregnancy (37 weeks AOG): Increased estrogen and progesterone; almost the same levels
  - During labor: Estrogen plateaus and decreased progesterone or **progesterone withdrawal**, which is a signal for labor
  - Whenever progesterone decreases, it is a signal to deliver the baby
    - Also happens during pre-term labor, abortion, and miscarriage

IV. PROSTAGLANDINS

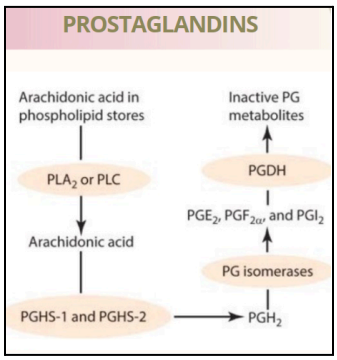


Figure 8. Prostaglandin Biosynthesis

- Produced using plasma membrane-derived arachidonic acid, which is released by the action of PLA_2 or PLC

- Type 1 and 2 prostaglandin synthase (PGHS-1 and -2), *a.k.a COX 1 and 2*, convert arachidonic acid to PGH2
  - These enzymes are the target of many non-steroidal anti-inflammatory drugs (NSAIDs)
    - Though, NSAIDs cause congenital malformations if given as a medication to the mother for the maintenance of pregnancy

V. PHASES OF LABOR

A. PHASE I: QUIESCENCE AND CERVICAL SOFTENING

- 95% of pregnancy is allocated for this phase
- Marked by uterine smooth muscle tranquility with maintenance of cervical structural integrity
- Uterus must be in a non-contractile state and unresponsive to natural stimuli
- **Braxton-Hicks contractions (false labor)**
  - Low-intensity myometrial contractions that are felt during quiescent phase
  - Sometimes experienced during or after vigorous fetal movement
- Likely stem from: Estrogen, Progesterone, cAMP, cGMP, myometrial ion channels

1. MYOMETRIAL RELAXATION & CONTRACTION

- **Quiescence**
  - **Tranquility**
  - Diminished intracellular crosstalk and reduced iCa2+ levels
  - Ion-channel regulation of cell membrane potential
  - Activation of the stress unfolded protein response by the uterine endoplasmic reticulum
  - Uterotonin degradation
- **Contractility**
  - Enhanced interactions between the actin and myosin proteins
  - Heightened excitability of individual myometrial cells
  - Promotion of intracellular crosstalk that allows synchronous contractions to develop

Professor's Notes:

- Relaxation = calcium efflux
- Uterotonin is a factor that promotes labor, hence degrading it will entail quiescence.

ACTIN-MYOSIN INTERACTIONS

- **Relaxation**
  - ↓ Ca2 → ↑ cAMP → activates PKA → promote PDE and MLCK de-P04 → **globular** actin
  - Nifedipine
    - a calcium-channel blocker, further decreasing the intracellular Ca2+
- **Contraction**
  - Reversal
  - ↑ Ca2+ enters cell → forms Ca-Calmodulin complex → activate MLCK → P04 → ATP activity → **fibrillar** actin

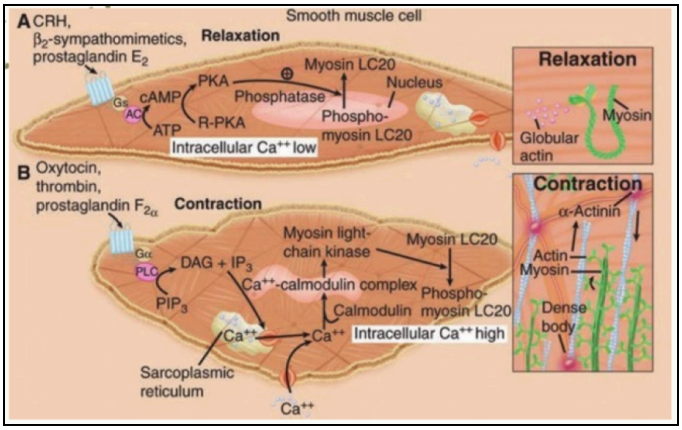


Figure 9. Actin-Myosin Interactions

REGULATION OF MEMBRANE POTENTIAL

- **Myocyte Excitability**
  - Regulated by changes in the electrochemical potential gradient across 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
  - BK_{Ca} allows K+ efflux to maintain high interior **e-** → prevents voltage gated Ca2+ influx and contraction
  - Inhibition of the BK_{Ca} channel augments myometrial contractility

Professor's Notes:

- Na+, Ca2+ influx
- K+ efflux
- Large conductance voltage
- Ca2+ activated K+ channel (BK_{Ca})

MYOMETRIAL GAP JUNCTIONS

- Communication between myocytes
- Aid passage of electrical or ionic coupling currents, metabolite coupling
- Connexin-43 is expressed in the myometrium, and has high concentrations near labor
- 6 connexin subunits form a connexon
- 2 adjacent connexons establish a conduit between communicating cells
- Believed to be important for electrical myometrial synchrony

Professor's Notes:

- ↓ Connexin-43
- ↓ Contraction-Associated Protein
- ↑ Caspase 3 (anticontractile agent)

G-PROTEIN COUPLED RECEPTORS

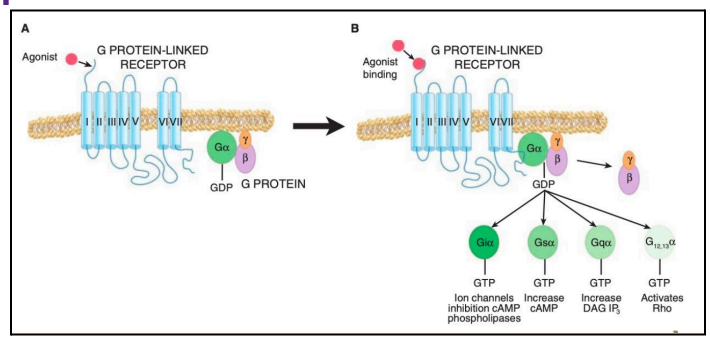


Figure 10. G-Protein Coupled Receptors

- **Relaxation:** G protein subunits (α,β,γ) are stuck together, there is no linkage
- **Contraction:** There is dissociation of the α-subunit from the β-γ, producing GTP ion channels, cAMP, DAG & IP_3, and Rho.
- **LH** and **hCG** (shares same receptor) have high concentrations before labor
- **hCG** → activate adenylyl cyclase → lessen contraction freqency → **uterine quiescence**
- **PGE2** maintains pregnancy during quiescence but switches to $G_{\alpha}q/11$ Calcium-activating pathway during labor
- **Relaxin + Relaxin Family Peptide Receptor 1 (RXFP1)**
  - Another important GPCR
  - Binding activates adenylyl cyclase → prevents iCa^{2+} → promotes **uterine quiescence**

cGMP

- Activation of guanylyl cyclase → increase intracellular cGMP → promoting **relaxation**
- During promotion of relaxation, there is an **increase** in:
  - Atrial Natriuretic Peptide (ANP)
  - Brain Natriuretic Peptide (BNP)
  - Nitric Oxide

ACCELERATED UTEROTONIN DEGRADATION

- There is an **increase** in the activity of the following enzymes:
  - PGDH - Prostaglandin (PG)
  - Enkephalinase - Endothelins (specifically, Endothelin 1)
  - Oxytocinase - Oxytocin

Professor's Notes:

- Oxytocin promotes labor so an increase in the activity of oxytocinase, which degrades oxytocin, will remove the oxytocin thus promoting relaxation.

2. DECIDUA

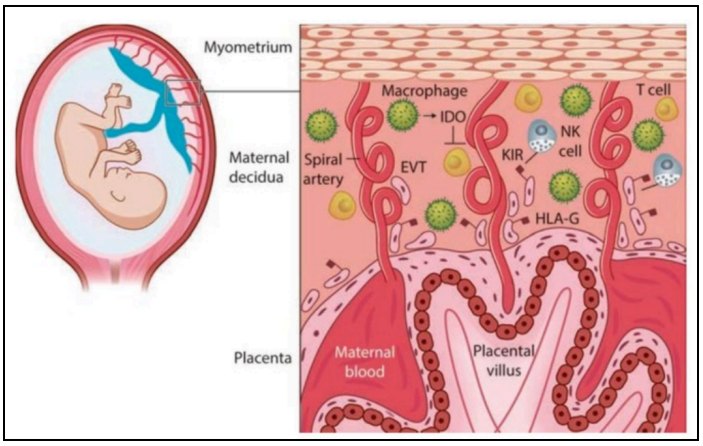


Figure 11. Decidua

- Decidua synthesizes PGF2α but is suppressed during quiescence
- **Phase 1** of parturition: promotes immune tolerance to protect the fetus
- **Phase 2:** undergo cellular senescence → leads to synthesis of proinflammatory cytokines, prostaglandin production, and increased protease expression → break down fetal membranes

Professor's Notes:

- The mother and the fetus come in direct contact at the decidua basalis and decidua parietalis
- At this interface, myeloid and lymphoid immune cells (NK cells, macrophages, dendritic cells, T cells, and all inflammatory cells) are **inactivated during Phase 1**
- During **Phase 2, all are activated**
- This is because these cells break down fetal membranes when they are activated.

3. CERVICAL SOFTENING

- This is the initial stage of cervical remodeling or what is called **"softening"**
- It is characterized by greater tissue compliance
- **Hegar Sign:** palpable softening of the cervix
  - Occurs during from **4-6 weeks**
- Maintenance of cervical anatomical and structural integrity
  - Essential for term pregnancy
- Preterm cervical dilation, structural insufficiency, or both may forecast early delivery or delivery

4. CERVICAL CONNECTIVE TISSUE

- **Cervical Softening** is an active molecular process that balances tissue competence against slow, progressive compositional and structural changes in the ECM to increase compliance
- Constituents of ECM:
  - Fibrillar Collagen I and III

- Glycosaminoglycans (GAGs)
- Matricellular proteins
- Proteoglycans
- Elastic Fibers

- Collagen undergoes conformational changes → alter stiffness and flexibility
- Thus, in **early pregnancy:** ↓ mature cross-links between newly synthesized collagen monomers due to diminished expression of **lysyl hydroxylase** and **lysyl oxidase**
  - !! Remember these 2 enzymes
- Gradual turnover of collagen replaces mature cross-linked collagen fibrils with poorly-linked fibrils → **poor stiffness**

B. PHASE II: LABOR PREPARATION

- ***"Uterine Awakening or Activation"***
- Suspension of myometrial tranquility of phase 1

1. PROGESTERONE WITHDRAWAL

- Expected at 37 weeks AOG or at term

DIVERSE MECHANISMS	
1	Changes in the relative expression of the nuclear progesterone-receptor (PR) isoforms
2	Differential interaction of PR isoforms A and B with enhancers and inhibitors of gene expression
3	Altered PR activity through changes in the expression of coactivators or corepressors of receptor function
4	Local progesterone inactivation by steroid metabolizing enzymes or synthesis of a natural antagonist
5	MicroRNA regulation of progesterone-metabolizing enzymes and transcription factors that modulate uterine quiescence

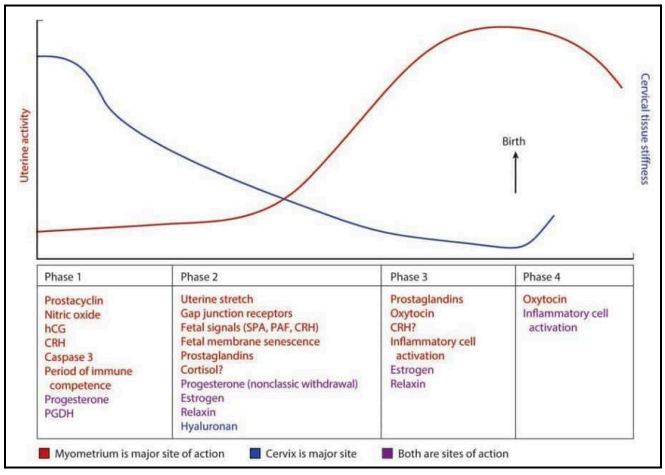


Figure 12. Key factors thought to regulate the phases of human parturition

Professor's Notes:

- All those in red are about uterine activity:
  - Major site of action: Myometrium/Uterus
  - Increased as the labor progresses
- Those in blue (Hyaluronan):
  - Major site of action: Cervix
- Those in purple:
  - Major site of action: Myometrium & Cervix (Both are sites of action)

2. MYOMETRIAL CHANGES AND OXYTOCIN RECEPTOR

- Changes result from a shift in the expression of proteins that control uterine quiescence to an expression of CAPs,
- CAP's increases uterine responsiveness to uterotonins
- Formation of lower uterine segment — causes "lightening" or descent of fetal head to the inlet

OXYTOCIN RECEPTORS

- 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.

3. CERVICAL RIPENING

- Cervical state shifting from ***competence*** ***to*** ***compliance***.
  - *"Ayaw then pumapayag na sya"*

Factors	Changes
1. GAGs & PG's	• **Hyaluronan** ~ HMW Polysaccharide ○ *only factor happening in Cervix* • Hydrophilic, space filling molecule that increases viscoelasticity, hydration, and matrix disorganization. • Synthesized by ***hyaluronan synthase isoenzyme***
2. Inflammatory Changes	• Activation of: **Neutrophils**, **M1** Macrophages, and tissue repair **M2** Macrophages in the cervix are augmented
3. Induction of Cervical Ripening	• Labor induction using PGE2 and PGFα modify ECM structure
4. Endocervical Epithelia	• Mucosal Epithelium recognizes pathogen invasion via expression of toll-like receptors that identify pathogens and via antimicrobial peptides and protease inhibitors • Express signals to underlying immune cells when a pathogenic

	challenge exceeds their protective capacity

Professor's Notes:

- Prostaglandins = ECM and Placental membranes

4. FETAL CONTRIBUTIONS

THEORIES	CHANGES
1. Uterine Stretch	• Stretch increases connexin-43, oxytocin receptors, gastrin-releasing peptide. • Explained by multifetal pregnancies and cases of hydramnios are at risk of preterm labor. • Cell signaling systems influenced by stretch regulating the myometrial cell ***~Mechanotransduction***.
2. Fetal endocrine cascades - fetus also sends signals to promote labor	• Premature activation of fetal hypothalamic-pituitary-adrenal-placental axis • Large production of maternal CRH (identical to fetal CRH) → stimulates placental CRH → reflects placental clock → stimulates fetal DHEA-S + Cortisol → Labor • Seen in "fetus under stress"

Professor's Notes:

- **Uterine Stretch - Connexin 3**
  - seen in Gap junctions
    - The main function is communication between myocytes
  - As the uterus is stretched, the Gap Junctions become more prominent and numerous.
  - Ex: 37 y/o G1P0 pregnancy uterine 30 weeks AOG with multifetal pregnancy now having regular contractions every 5 minutes.
    - Preterm labor due to multifetal pregnancy as the uterine size is bigger. The fundic height is bigger than the AOG of the fetus.
    - Fundic height: From the symphysis pubis to the fundic area
    - If the fundic height is 35 cm, and the AOG is 30 weeks —the fundic height is bigger than the AOG

C. PHASE 3: LABOR

1. 1ST STAGE: CLINICAL ONSET OF LABOR

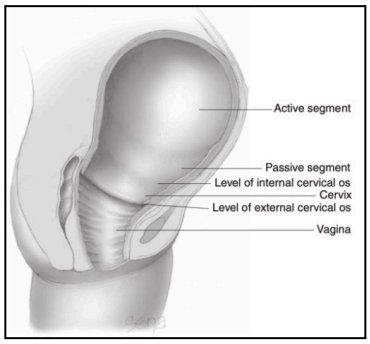
UTERINE LABOR CONTRACTIONS

Professor's Notes:

- In normal delivery, we have what we call Cardiotocogram (CTG) that monitors both the fetal heart rate and uterine contractions

- Uterine contractions now become painful due to:
  - Hypoxia of the contracted myometrium-such as that with angina pectoris and with dysmenorrhea
    - Due to the heavy and persistent contraction, the myometrial cells loses oxygen supply causing pain
  - Cervical stretching during dilation
    - Cervix do not normally feel pain only pressure but during cervical dilatation, there will now be pain
      - ➢ Same theory with menstruation wherein in the absence of menstruation, cervix is partially closed however, during the time of menstruation, it will now be painful due to cervical stretching and dilatation
  - Stretching of the peritoneum overlying the fundus
    - Peritoneum is sensitive
  - Compression of the nerve ganglia in the cervix and lower uterus by contracted interlocking muscle bundles
    - Paracervical infiltration with local anesthetic produces appreciable belief
    - Neural blockade from epidural analgesia

DISTINCT LOWER & UPPER UTERINE SEGMENT



- During active labor, the anatomical uterine divisions are evident
- The **Upper Uterine Segment (UUS)** is firm during contractions
- The **Lower Uterine Segment (LUS)** should relax and is softer so that fetus can pass

Professor's Notes:

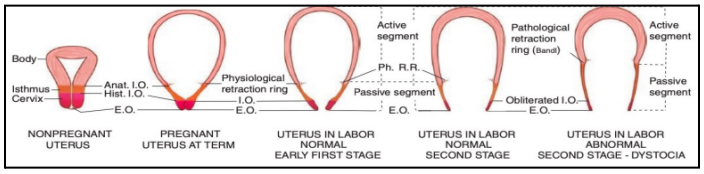
If we compare the **uterus to a balloon**, the **cervix is at the end of the balloon.**

- If there is cerclage (tinatahi ang cervix), meaning the cervix is stitched closed, even if the contractions are frequent and the area where the cervix is being stretched is under pressure, it will not dilate
  - If the cervix does not dilate, will there be vaginal delivery? **No.**

- Now, during cervical dilatation, the lower part (like the lower balloon) must open. It should be open and steady, without hyper contraction.
  - If there is no proper cervical dilatation, will there be vaginal delivery? **No.**

So again, **during the first cycle**, to have **normal delivery,** there is a prerequisite:

- Cervical dilatation
- Fetal dilatation (or descent)



- Myometrium of the upper segment does not relax to its original length after contractions. They become relatively **short**. Meaning, if it is short, there is a **lot of contraction**
  - They become shorter and thicker as the labor progresses "***US retraction"***
- Physiologic retraction ring — UUS thickens, LUS thins out

Professor's Notes:

Changes in the Upper and Lower Uterine Segments During Labor

In the illustration, you can see the body of the upper uterine segment, followed by the isthmus, and then the cervix, which is colored pink.

As labor progresses (moving toward the right side of the illustration), the upper uterine segment becomes thicker and thicker.

- At term, the uterus already has a certain thickness
- During normal labor, it thickens even more
- **REMEMBER: It is thicker during the second stage of labor compared to the first stage**

This thickening happens because the upper uterine segment **actively contracts.**

- Pathologic retraction **"Bandl ring"**

Professor's Notes:

Pathologic Retraction (Bandl Ring)

In pathologic retraction (Bandl's ring), the active segment (upper uterine segment) becomes excessively thick compared to the lower uterine segment, which is the passive segment. Normally, the lower uterine segment should gradually thin out to allow the baby to descend.

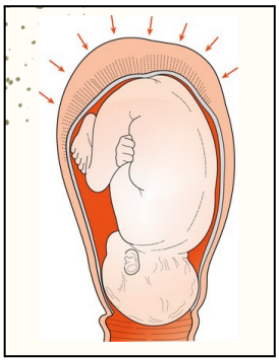
However, if:

- The upper segment continues to contract strongly, and
- The lower segment becomes excessively thin and weak (manipis na),

Then what can happen? Instead of the baby coming out through the vagina, the uterus may rupture. The baby can come out into the peritoneal cavity.

This is uterine rupture (puputok ang matres), and it is a dangerous complication.

CHANGES IN UTERINE SHAPE



- Each contraction gradually elongates the ovoid uterine shape an estimated 5 to 10 cm, and thereby narrows the horizontal diameter.
- Fetal axis pressure straightens the fetal vertebral column preparing for expulsion.

ANCILLARY FORCES

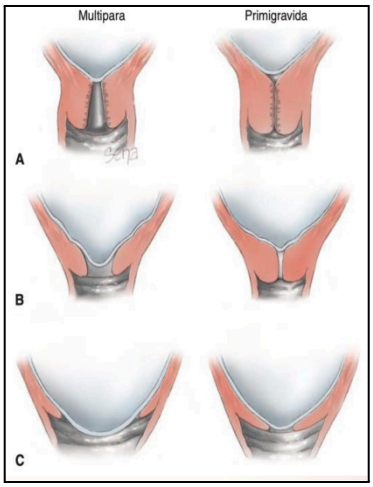
- **Maternal Pushing Effort -** force in fetal expulsion produced by maternal intraabdominal pressure.
- Contractions of maternal abdominal muscles.

Professor's Notes:

- It is not just the uterus working. The mother also contributes through active pushing.
- However, pushing does not simply come from inhaling. When you inhale, what expands? The lungs. When the lungs expand, the diaphragm moves downward. This affects intra-abdominal pressure.
- For effective pushing, the **abdominal muscles must tighten or contract**. This increases intra-abdominal pressure and helps push the baby downward during labor.

- So, proper maternal pushing involves coordinated contraction of the abdominal muscles together with uterine contractions.

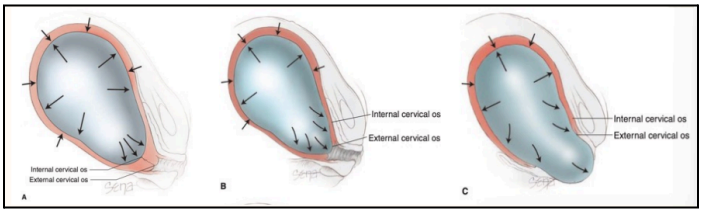
CERVICAL CHANGES



- Cervical effacement refers to the **"obliteration" or "taking up" of the cervix**. This means the cervix becomes shorter and thinner as labor progresses.
- Shortening from ~3 cm to a almost paper-thin edges
- Muscular fibers at the level of the internal cervical os are pulled upward
- Causes expulsion of the mucous plug as the cervical canal is shortened
- LUS and cervix have lesser resistance which causes cervical dilation.

Professor's Notes:

- In a **multipara**, the cervix may already appear slightly open at baseline. However, this does not mean she will give birth right away. Because she has delivered before, the cervix does not return completely to its original closed state.
- In a **primigravida**, the cervix is usually tighter and more closed at the start. As labor progresses, the cervix gradually effaces—until it becomes very thin. Eventually, it becomes almost completely obliterated.
- If effacement does not occur, labor will not progress properly, and vaginal delivery cannot happen.



- LUS and cervix have lesser resistance → centrifugal pull towards cervix → **DILATATION**

Professor's Notes:

- There is also a **centrifugal pull** exerted on the cervix during labor, which contributes to further effacement and dilatation.
- Because of this natural pressure and pulling effect, it is **not always necessary to rupture the bag of water (amniotic sac) immediately**.
- If the bag of water is not ruptured right away, it does not automatically delay delivery. The pressure from the intact membranes can actually help in cervical dilatation.

2. 2ND STAGE: FETAL DESCENT

- Takes place after some time after full cervical dilatation
- **Station** describes descent of the fetal biparietal diameter in relation to a line drawn between maternal ischial spines
  - Nulliparas- descends slowly and steadily
  - Multiparas- rapid

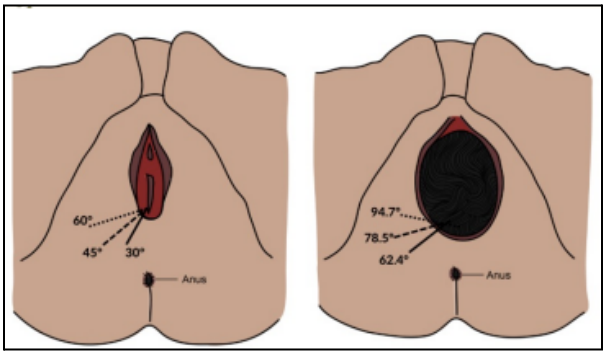
Professor's Notes:

If ever we have a patient that is 37 y.o. G1P0, 39 weeks AOG at 6 cm compared to a 29 y.o. G5P4 (4-0-0-4) all term deliveries who is currently pregnant and is 8 cm dilated, which one do you think will give birth first?

- The 29 y.o who is multigravid because she can give birth anytime. All it will take is a small push.

PELVIC FLOOR CHANGES

- Levator ani muscle and the fibromuscular connective tissues
- Perineum: a wedge-shaped, 5cm-thick tissue mass→ thin, almost transparent membranous < 1 cm thick

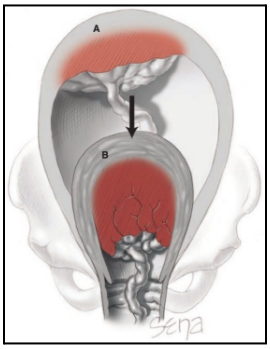


Professor's Notes:

- The distance between the anus and the posterior portion of the perineum is shorter due the expansion making it easier to cut with less to suture and has less bleeding.

3. 3RD STAGE: PLACENTA AND MEMBRANE DELIVERIES

- Stage begins after delivery
- Diminution in uterine size ≠ placental size
- Placental will accommodate to this reduced area → placental thickening (not elastic) → buckles
- Pulls the weakest layer –decidua spongiosa
- Formation or retroplacental hematoma

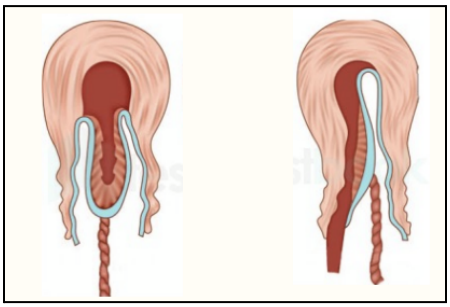


Professor's Notes:

- Remember, the mother already gave birth and the baby has been delivered. Previously, the uterine size was big and has now shrunk. The placenta is attached to the area superior to it (label A). Now that the baby is gone, how will the space taken up by the baby be accommodated?
  - The placenta will shrink and detach
  - There will be formation of retroplacental hematoma and eventually will be exposed

DIFFERENT MECHANISMS OF PLACENTAL DELIVERY

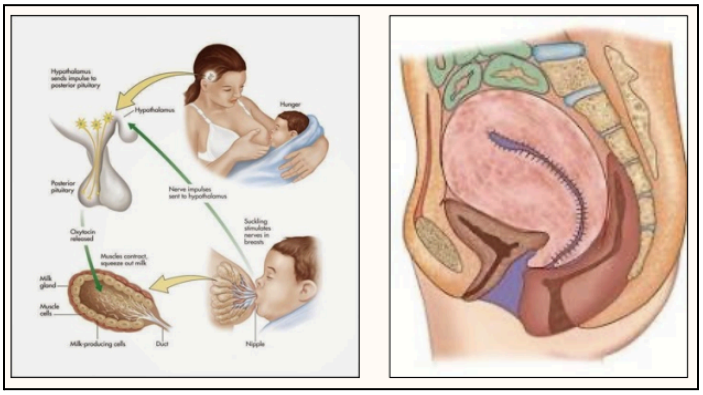
SCHULTZE	DUNCAN
Central detachment	Peripheral detachment
Lengthening of cord → bleeding	Bleeding → Lengthening of cord
Fetal side first	Maternal side first



UTEROTONINS

- **Oxytocin** - synthesized in magnocellular neurons of supraoptic and paraventricular neurons → carried by neurophysin → posterior pituitary → converted to oxytocin
- **Prostaglandin** - produced by fetal membranes and placenta → degrade ECM → weakening fetal membranes
- **Endothelin-1** - 21-amino-acid peptides, expressed in smooth muscles, and when activated, it effects a rise in iCa2+
- **Angiotensin II** - potent vasoconstrictor, AT1R in non-pregnant, AT2R in gravidas

D. PHASE IV: PUERPERIUM



- Immediately about an hour after delivery
- Myometrium remains contracted → directly compresses vessels
- Lactogenesis and milk let-down begins
- Reinstitution of ovulation within 4-6 weeks after birth