

# Normal Pregnancy

Jason Ryan, MD, MPH



# Obstetric History

- **Gravida:** number of pregnancies
  - Nulligravida: woman has never been pregnant
  - Multigravida: pregnant more than once
- **Para:** number of completed pregnancies (>20 weeks)
- G1P0: first pregnancy (1 pregnancy, 0 births)
- Multiple gestation count as a single birth
- Mother of triplets after first pregnancy: G1P1



# Obstetric History

- **TPAL**: expanded obstetric history
- T = term births: delivery at  $\geq 37$  weeks' gestation
- P = preterm birth: delivery at 20 to  $< 37$  weeks' gestation
- A = abortion
- L = living children
- Example: G3P1114
  - Pregnant 3 times
  - One term delivery (1 child)
  - One preterm delivery of triplets (3 children)
  - 1 miscarriage



# Gestational Age

- Weeks since last menstrual period
- Conception at time 2 weeks (15 days prior to missed period)
- Contrast with developmental or embryonic age (conception at 0 weeks)
- Term: 37 weeks or more
- Preterm: < 37 weeks
- Postterm: > 42 weeks
- **Naegele's Rule**
  - $\text{EDD} = \text{last menstrual period} + 7 \text{ days} - 3 \text{ months}$





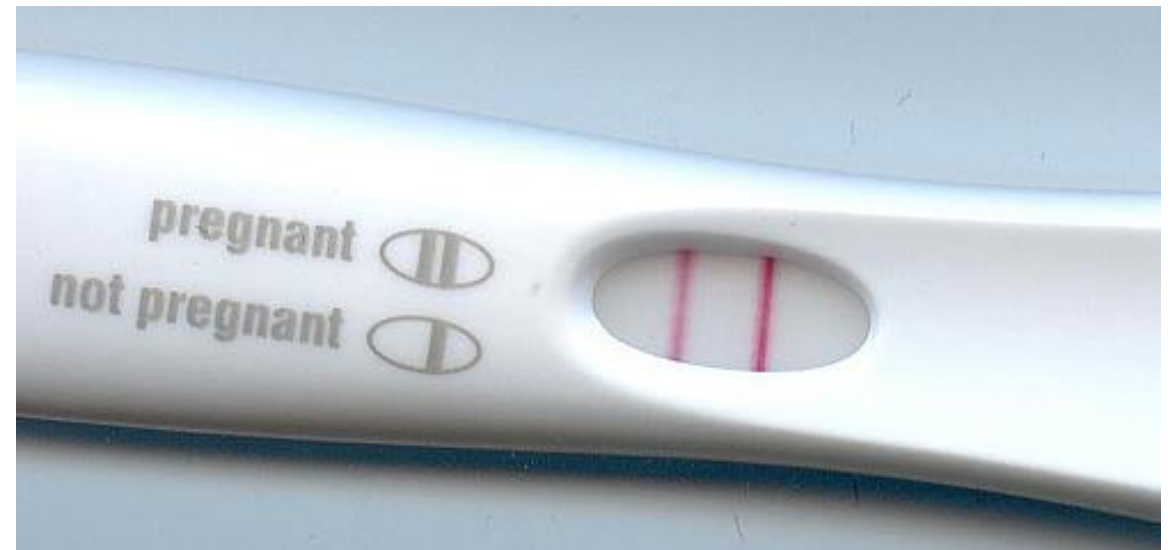
# Trimesters

- First: weeks 1 to 12
- Second: weeks 13 to 27
- Third: weeks 28 to birth



# Pregnancy Diagnosis

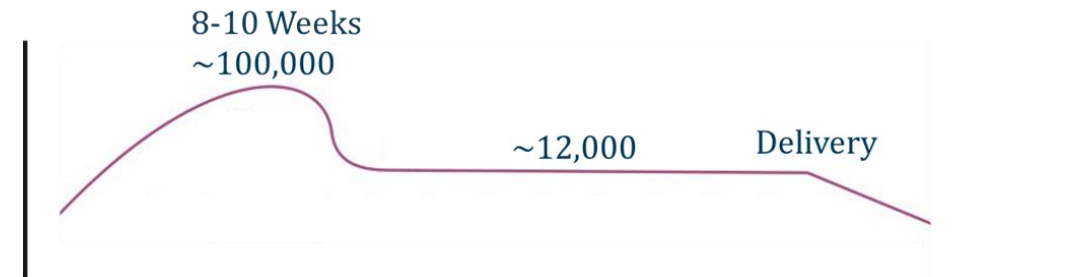
- **Human chorionic gonadotropin (hCG)**
- Usually antibody-based tests for  $\beta$  subunit of hCG
- Serum tests
  - Most sensitive method for detecting hCG
  - Can detect very low levels 1-2 mIU/mL
  - Can be positive within 1 week of conception
- Urine tests
  - hCG threshold 20 to 50 mIU/mL
  - May not be positive until 2 weeks or more



# $\beta$ -hCG

## Beta human chorionic gonadotropin

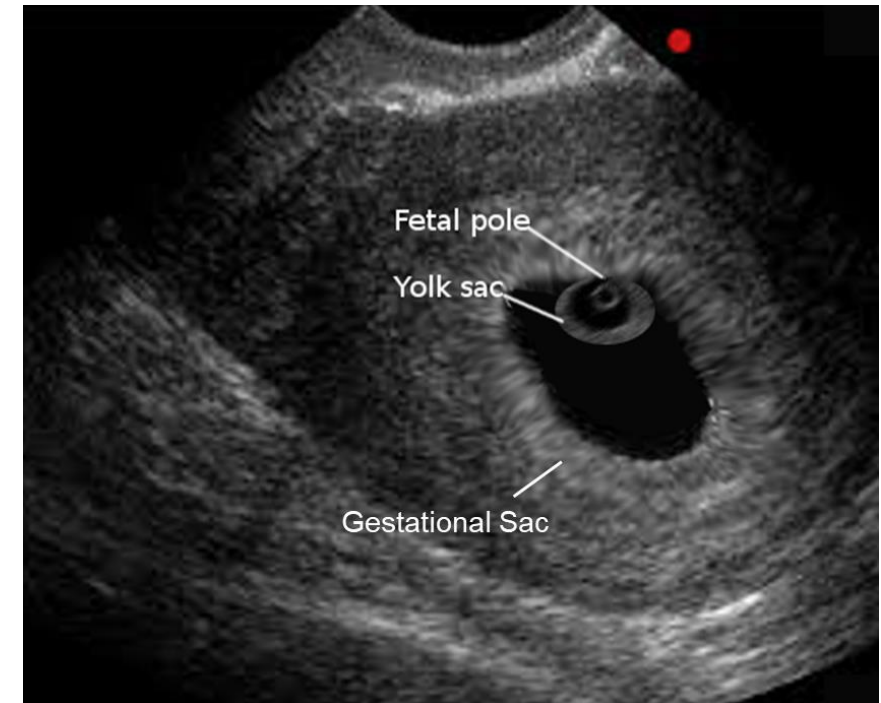
- Doubles about every 48 hours initially
- Should rise at least 60% over 48 hrs
- Peaks about 100,000 mIU/mL by 8 to 10 weeks
- Decline to about 12,000 mIU/mL at 20 weeks
- Wide range of peak and level values
- Cannot use level to determine gestational age
- Used clinically for **diagnosis only**
- Usually measured twice at onset of pregnancy
- Not routinely measured later in pregnancy



# Ultrasound

## Pregnancy Diagnosis

- Used after positive  $\beta$ -hCG testing
- Confirms intrauterine pregnancy
- **Most accurate method pregnancy dating (1<sup>st</sup> trimester)**
- Gestational landmarks by gestational age
  - Gestational sac: 4.5 to 5 weeks
  - Yolk sac: 5 to 6 weeks
  - Fetal pole: 5.5 to 6 weeks

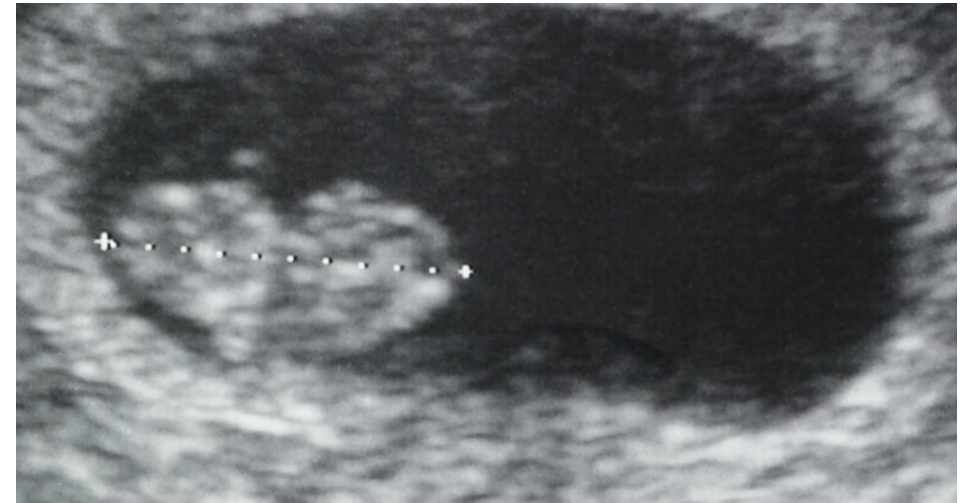


# Pregnancy Dating

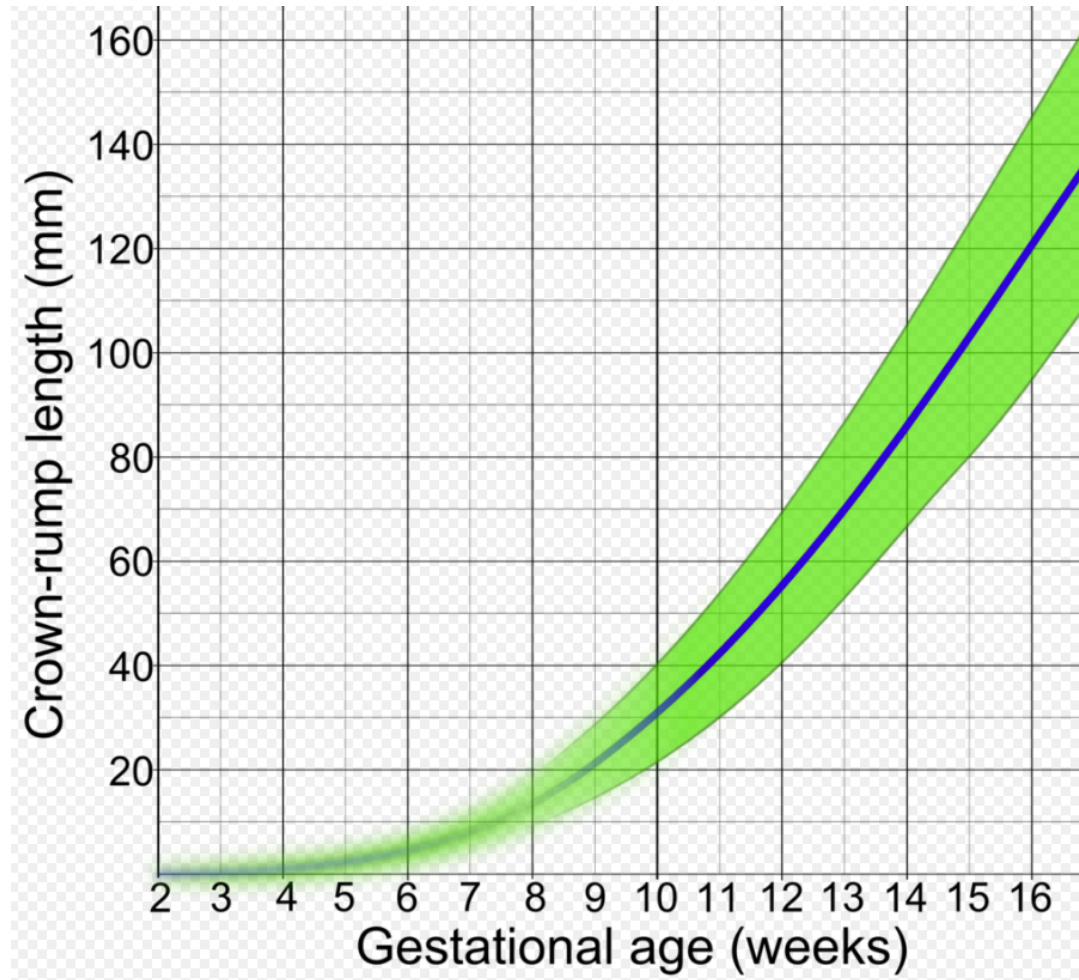
## Early Pregnancy

- **Crown-rump length**
- Used in first trimester (< 13 weeks)
- Correlates with gestational age
- Most accurate biometric parameter for pregnancy dating
  - If done before  $\leq 9$  weeks of gestation: dates to  $\pm 5$  days
  - Dates to  $\pm 7$  days from 9 to 13 weeks

Crown-Rump Length Measurement



# Pregnancy Dating

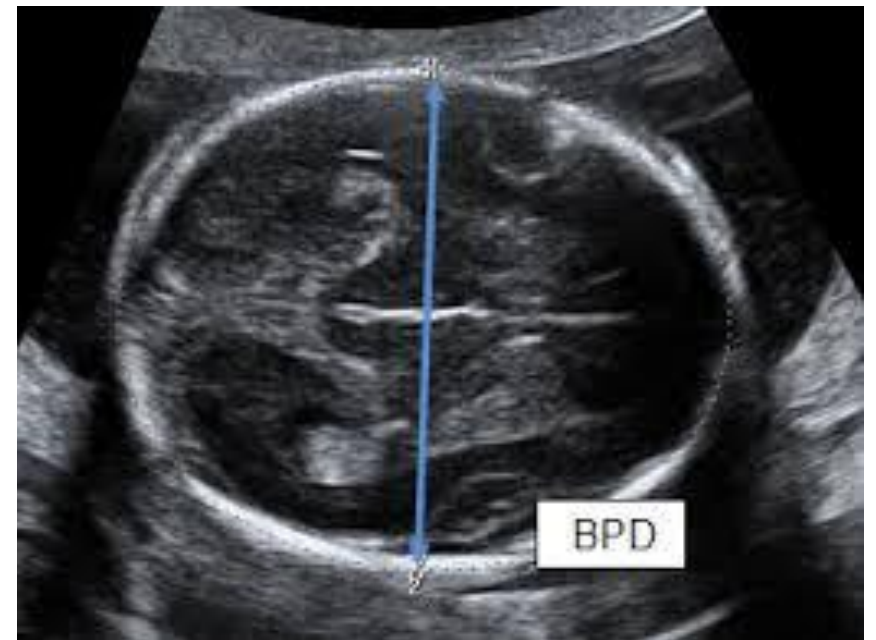


\*\* less accurate as pregnancy advances

# Ultrasound

## Second and Third Trimester

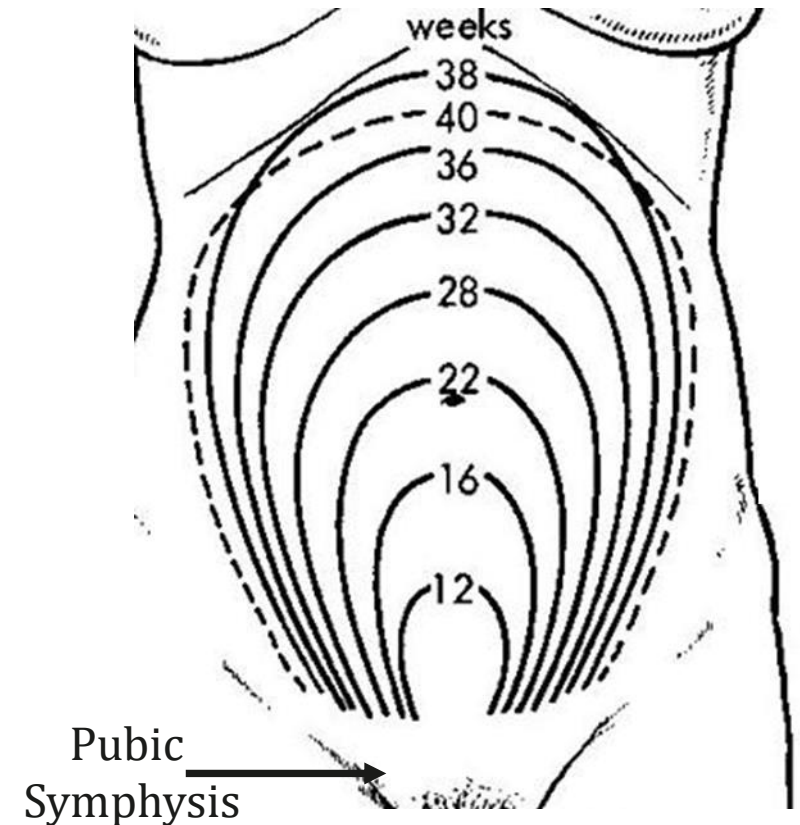
- US used to date pregnancy if no first trimester US
- Four standard **biometric markers** to estimate fetal weight
  - Biparietal diameter
  - Head Circumference
  - Abdominal circumference
  - Femur length
- Often used for growth assessment
  - Compared to expected size based on 1<sup>st</sup> trimester dating
  - Normal, restricted or accelerated





# Pregnancy Dating

- In vitro fertilization: add 266 days to date of conception
- Fundal height: 1 cm/week
- Fetal heart tones: 10 to 12 weeks
- Fetal movements (“quickening”)
  - 18-20 weeks nulligravida
  - 16-18 weeks multigravida





# Size-Date Discrepancy

- Fundal height mismatch with known pregnancy dating
- Can be due to incorrect dating
- Further assessment via **ultrasound**

Larger than Expected	Smaller than Expected
Multiple gestation Macrosomia Polyhydramnios Molar pregnancy	Fetal growth restriction Oligohydramnios Fetal demise

# Pregnancy

## Signs and Symptoms

<b>Clinical Symptoms</b>	<b>Examination Findings</b>
<ul style="list-style-type: none"><li>- Amenorrhea</li><li>- Nausea +/- vomiting</li><li>- General fatigue</li><li>- Breast enlargement</li><li>- Mild uterine cramping</li></ul>	<ul style="list-style-type: none"><li>- Telangiectasias, palmar erythema, linea nigra</li><li>- Softening of cervix (Goodell sign)</li><li>- Softening of uterus (Ladin sign)</li><li>- Blue discoloration of vagina/cervix (Chadwick sign)</li></ul>

# Pregnancy

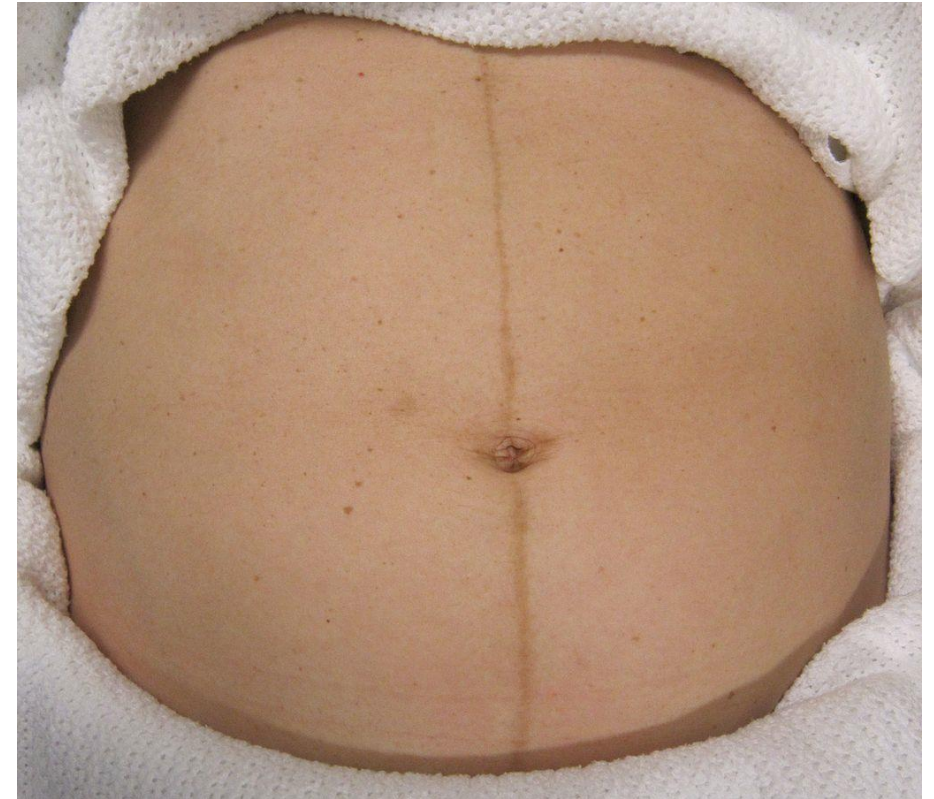
## Signs and Symptoms

Chadwick's Sign



<https://www.memorangapp.com/>

Linea Nigra

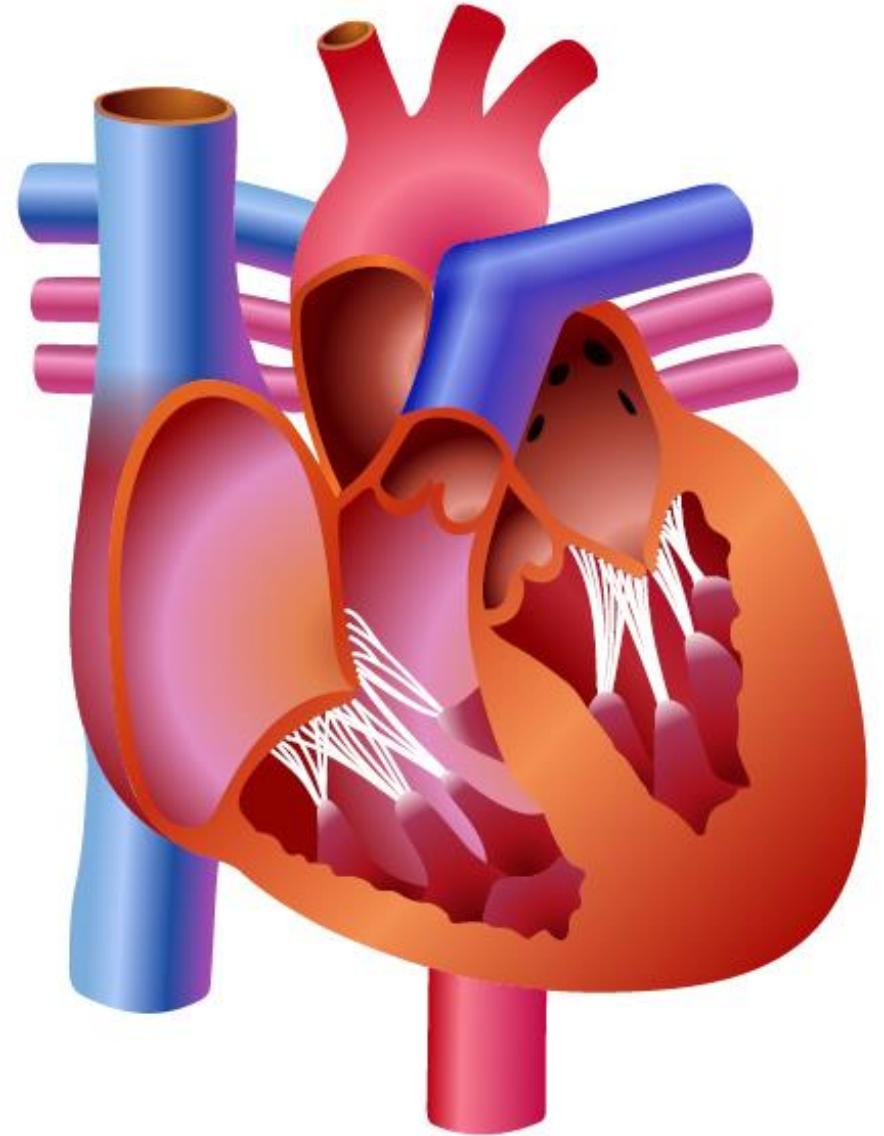


James Heilman, MD

# Physiologic Changes

## Cardiovascular

- **Fall in systemic vascular resistance**
  - Fall in afterload
  - Decrease in blood pressure
- Preload increased by rise in blood volume
- Cardiac output rises
- Maternal heart rate rises slightly
- Regurgitation (aortic/mitral): well-tolerated
- Stenosis (aortic/mitral): poorly-tolerated



# Physiologic Changes

## Pulmonary

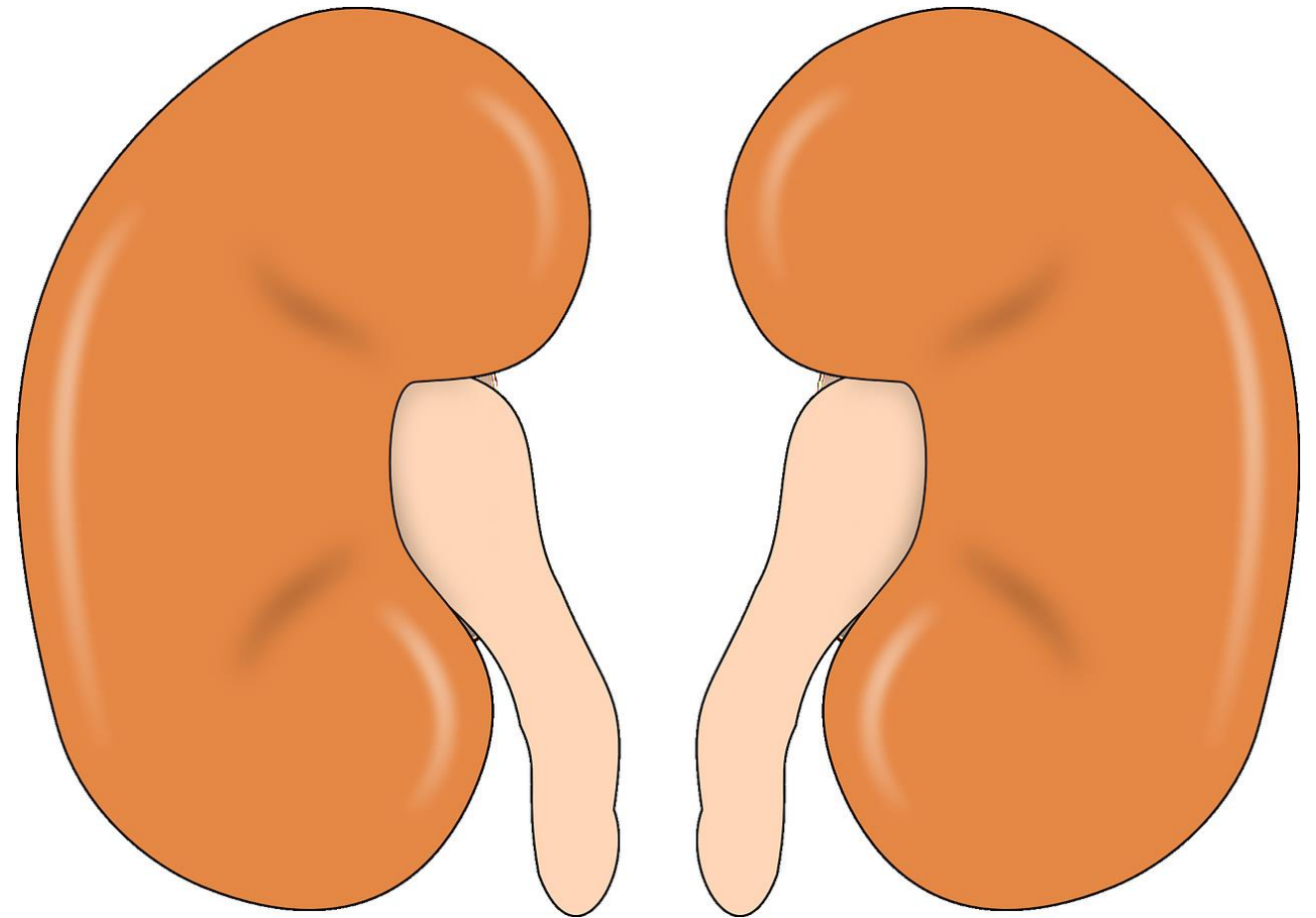
- **Minute ventilation increases**
  - More CO<sub>2</sub> to exhale
  - Triggered by progesterone
- Mostly due to **increased tidal volume**
- Respiratory rate minimally increased
- PCO<sub>2</sub> falls to about 30 mm Hg
- Respiratory alkalosis
- Renal compensation: ↓ HCO<sub>3</sub>
- Normal to slightly increased pH



# Physiologic Changes

## Renal

- **Total body volume expands**
  - Blood fills placenta
  - Diverted from maternal circulation
  - $\uparrow$  renin  $\rightarrow$  salt/water retention
- **Increased GFR**
  - Increased renal plasma flow
  - $\downarrow$  BUN and Cr





# Physiologic Changes

## Red Cell Mass

- **Red cell mass expands**
- Increased maternal EPO
- **Dilutional anemia**
  - Rise in volume > rise in red cells
  - Result: ↓ hematocrit
- Vital to treat mild anemia early
- Blood volume peaks 32 weeks
- As pregnancy progresses: ↓ hematocrit



# Supine Hypotension

- Occurs in later stages of pregnancy
- Large baby compresses IVC when lying flat
- Decreased venous return (preload)
- Fall in cardiac output
- Reflex tachycardia may produce symptoms
- Can cause fainting when lying flat



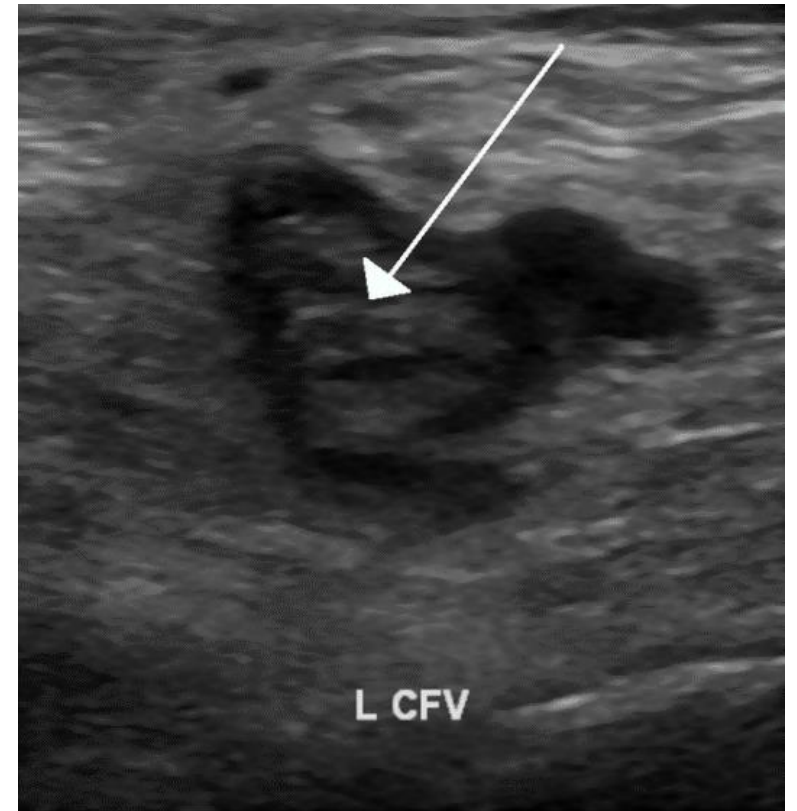


# Physiologic Changes

## Coagulation

- Pregnancy is a **hypercoagulable state**
  - Probably evolved to protect against blood loss at delivery
  - Many clotting factor levels change
  - Increased fibrinogen
  - Decreased protein S
- Fetus also obstructs venous return → DVTs common

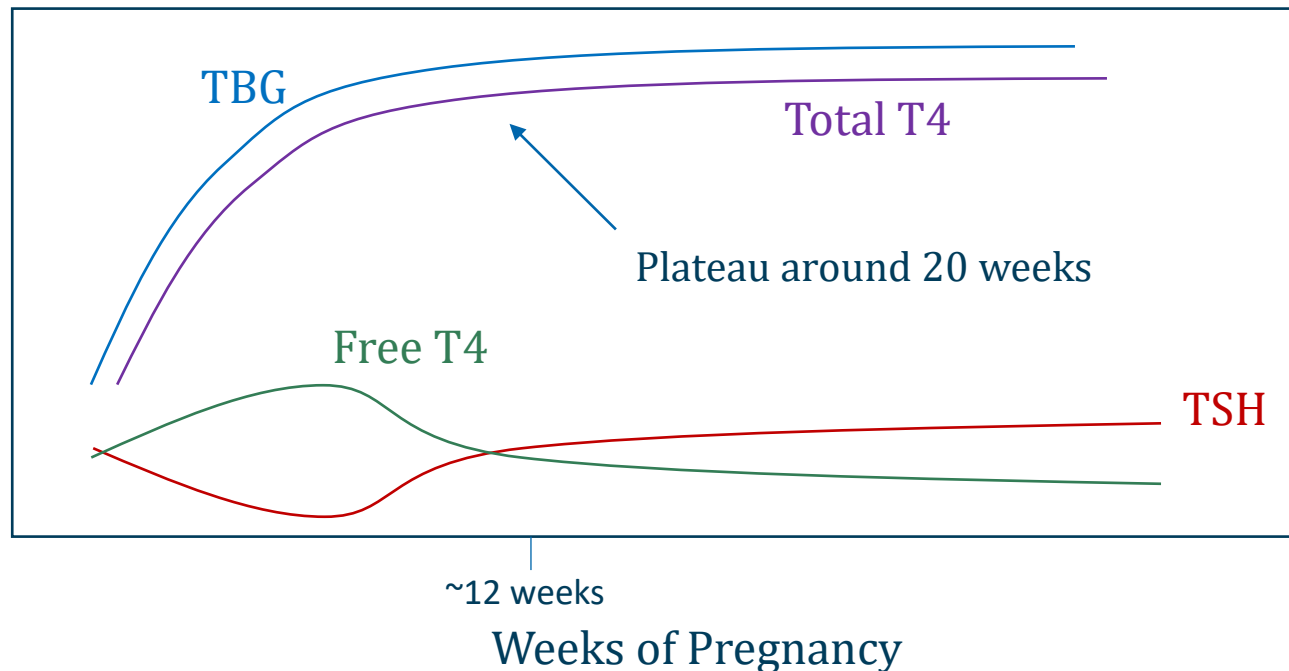
DVT by Ultrasound



# Physiologic Changes

## Thyroid Gland

- Rise in TBG levels (estrogen)
- Rise in total plasma T4/T3 levels
- hCG stimulates thyroid (same alpha unit as TSH)
- Raises free T4 → lower TSH



# Pregnancy

## Weight Gain

- Normal weight gain during pregnancy approximately 25 lbs
- Excess weight gain associated with increased risk
  - Fetal macrosomia
  - Large for gestational age baby
  - Cesarean delivery
  - Pregnancy-related hypertension
  - Gestational diabetes
- Below average weight gain associated with increased risk
  - Lower birth weight
  - Small for gestational age baby
  - Preterm delivery



# Pregnancy

## Weight Gain

- **Pre-pregnancy BMI:** predicts pregnancy outcomes
  - More predictive than gestational weight gain
  - Underweight ( $< 18.5 \text{ kg/m}^2$ ) or overweight ( $\geq 30 \text{ kg/m}^2$ ) women have more risk
- Encourage normal BMI prior to pregnancy



# Pregnancy

## Weight Gain

- More weight gain recommended for underweight women

< 18.5:	1 lb/wk (28-40 lbs total)
18.5-25:	0.75 lb/wk (25-35 lbs total)
25-30:	0.5 lb/wk (15-25 lbs total)
> 30:	0.25 lb/wk (10-20 lbs total)

# Pregnancy

## Exercise

- Generally safe
- Lowers risk of gestational diabetes, preeclampsia and cesarean delivery
- Low-impact, non-contact activities with little fall risk
- Avoid raising core temperature: hot tubs, exercising too hard
- Contraindicated in some **high-risk patients**:
  - Cervical insufficiency
  - Placenta previa
  - Hypertension in pregnancy (e.g., preeclampsia)
  - Multiple gestation
  - Amniotic fluid leak

# Common Pregnancy Problems

Back Pain	<ul style="list-style-type: none"><li>- Most common in 3rd trimester, as enlarged uterus exaggerates lordosis and changes center of gravity</li><li>- Tx: Supportive (stretch, heat, massage, Acetaminophen)</li></ul>
Constipation	<ul style="list-style-type: none"><li>- Tx: Increased PO fluids, bulking agents, laxatives</li></ul>
Edema	<ul style="list-style-type: none"><li>- Lower extremity edema from IVC compression</li><li>- Tx: Positional change (avoid IVC compression), elevated LE</li></ul>
GERD	<ul style="list-style-type: none"><li>- Increased relaxation of sphincters</li><li>- Tx: Antacids</li></ul>
Hemorrhoids	<ul style="list-style-type: none"><li>- From venous congestion/IVC compression</li><li>- Tx: Topical anesthetics/steroids</li></ul>
Round Ligament Pain	<ul style="list-style-type: none"><li>- Adnexal pain from stretching of uterus/ligament attachments</li><li>- Tx: Self-limited</li></ul>
Urinary Frequency	<ul style="list-style-type: none"><li>- From increased circulating volume/GFR</li><li>- Tx: Rule-out UTI</li></ul>

# Common Pregnancy Problems

## Medical Therapy

- **NSAIDs**

- Generally avoided during pregnancy
- May close DA, especially in late 2<sup>nd</sup> or 3<sup>rd</sup> trimester
- Low-dose aspirin (81mg) given for prevention of preeclampsia

- **Antacids**

- Generally safe during pregnancy
- Avoid sodium bicarbonate (increases fluid retention; causes alkalosis)
- Avoid magnesium antacids (inhibits uterine contractions)
- Sucralfate often used if antacids fail
- H2RAs and PPIs can be used if antacids fail



# Prenatal Care

Jason Ryan, MD, MPH



# First Trimester Screening

- ACOG guidelines for standard panel of **laboratory testing**
- Complete blood count (CBC)
- Blood type and Rh factor
- Urinalysis
- Urine culture
- Infectious disease screening



# Complete Blood Count

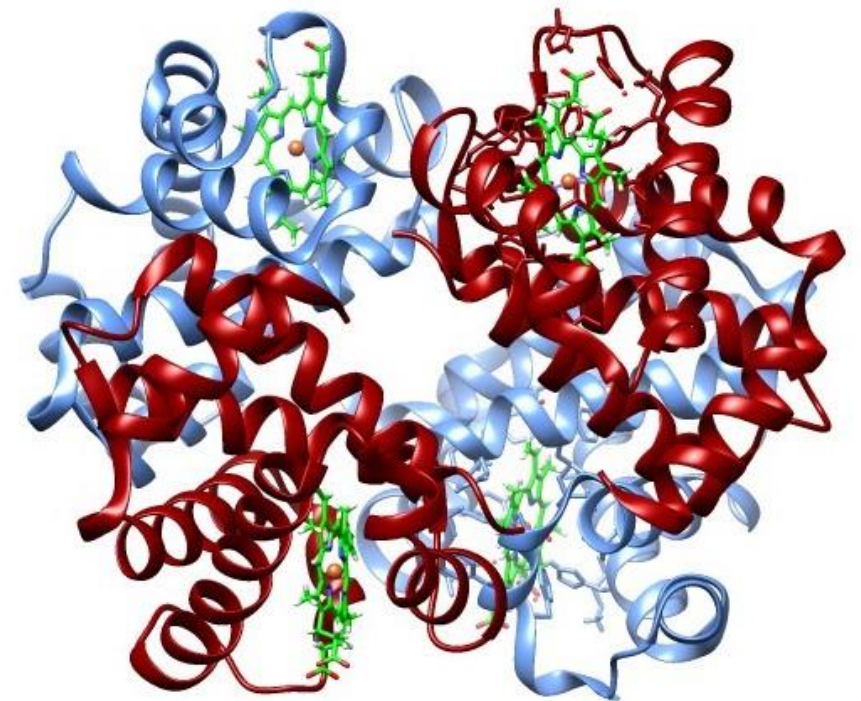
- Hematocrit
- Hemoglobin
- Platelets
- Mean corpuscular volume
- Establish baseline
- Exclude anemia
- Exclude iron deficiency/thalassemia (low MCV)



# Hemoglobinopathy Screening

- Low MCV ( $< 80$ ) and normal iron = possible thalassemia
- Next best test: **maternal hemoglobin analysis**
  - High-performance liquid chromatography (HPLC)
  - Isoelectric focusing (IEF)
  - Gel electrophoresis
- Test father if mother has hemoglobinopathy
- Fetal testing if both parents carry mutations

Hemoglobin



# Blood Type and Rh Factor

- Determine ABO type
- Determine Rh factor positive or negative
- Screen for anti-Rh alloantibodies – indirect Coombs test
- Rh positive: no risk of newborn hemolytic disease
- Rh negative: next steps based on alloantibody status



# Blood Type and Rh Factor

- **Rh-negative mother** with **negative antibody screen**
  - At risk of developing anti-Rh antibodies (alloimmunization)
  - Alloimmunization may lead to newborn hemolytic disease
  - Prophylactic anti(Rh)-immune globulin at 28 weeks (RhoGAM)
  - Effective as late as 72 hours after delivery if not given early
  - Given for any event that may sensitize mother
  - Amniocentesis, SAB, trauma



# RhD Alloimmunization

## Diagnosis and Management

- **Rh-negative mother** with **positive antibody screen**
- Mother has alloimmunization
- Next step: determine **Rh status of baby**
  - Rh- baby not at risk
  - Rh+ baby at risk for hemolytic disease



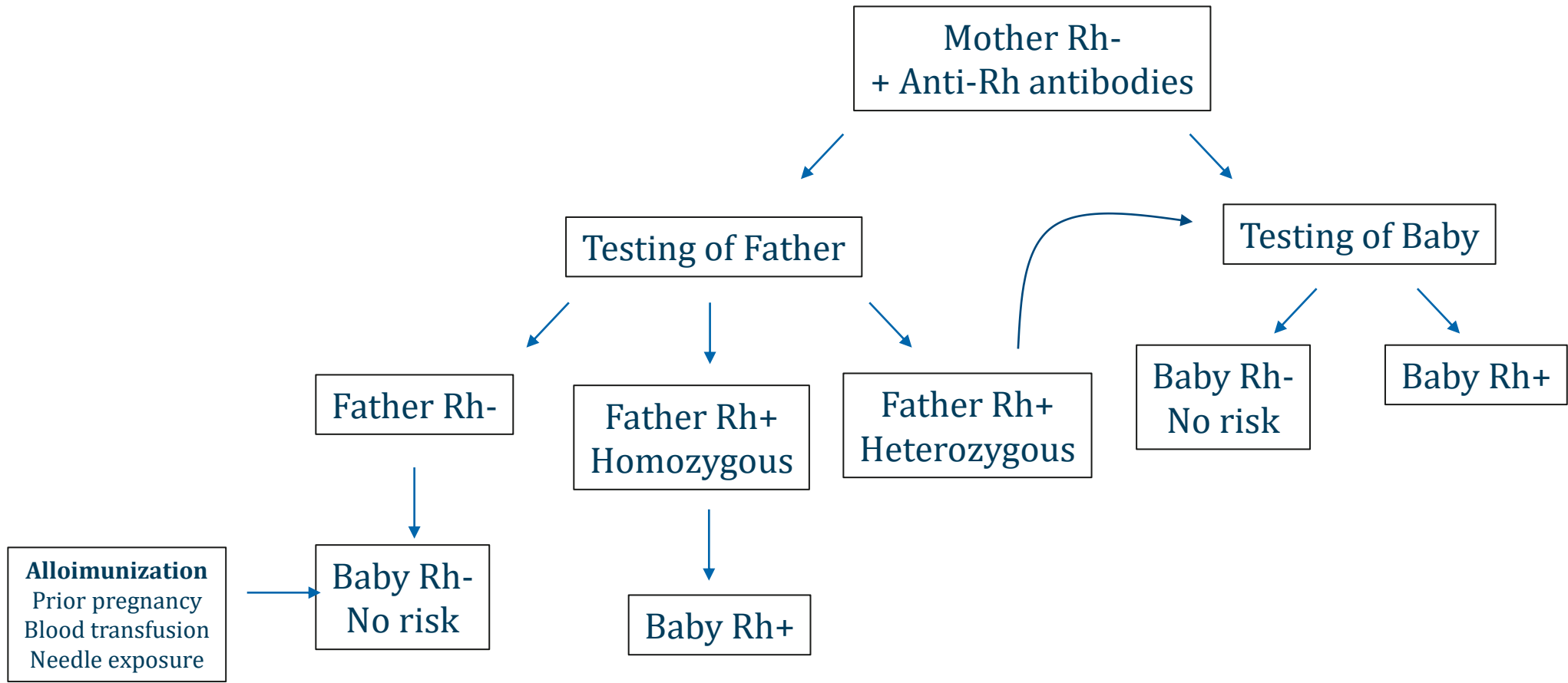
# RhD Alloimmunization

## Diagnosis and Management

- **Paternal testing**
  - If father is Rh-, baby must be Rh- and not at risk
  - If father is homozygous Rh+ baby is Rh+
  - If father is heterozygous Rh+ → testing of fetus
- **Fetal testing**
  - Cell free DNA testing
  - Amniocentesis



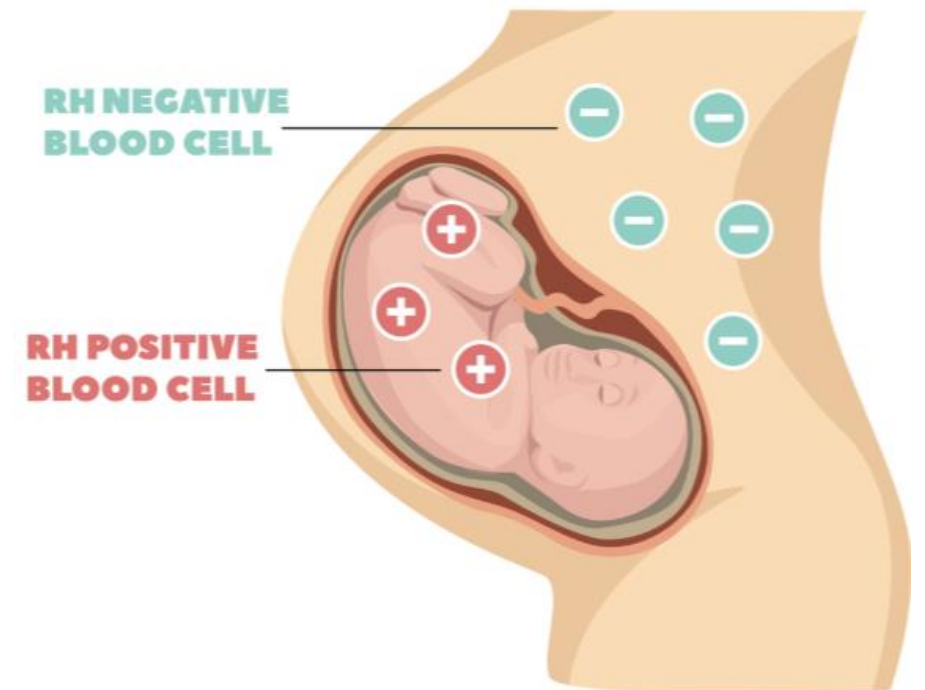




# RhD Alloimmunization

## Diagnosis and Management

- **Mother with anti-Rh antibodies** and **Rh+ fetus**
  - Serial maternal antibody titers
  - Fetal transcranial MCA Doppler: high flow occurs in anemia
  - Fetal H/H via umbilical cord sampling
- Severe anemia interventions
  - Fetal transfusions
  - Delivery at > 35 weeks



# Urinalysis and Urine Culture

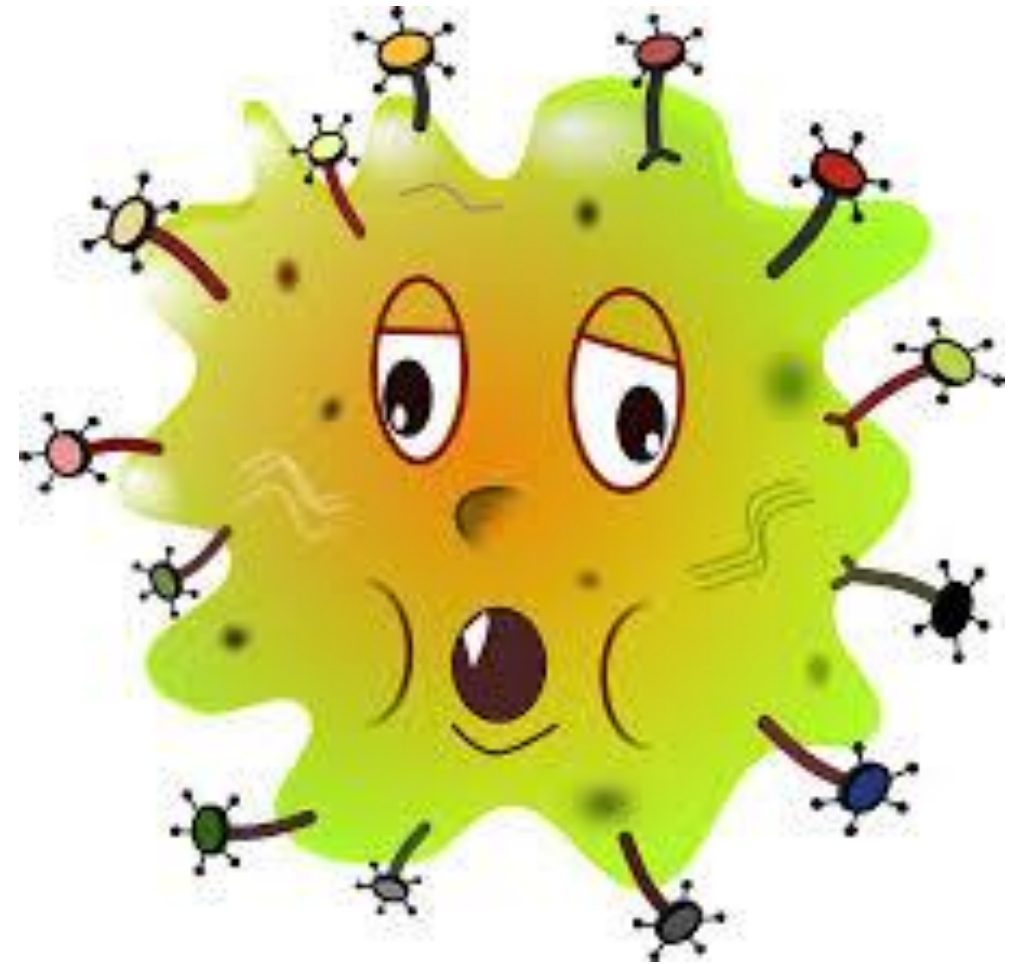
- Exclude proteinuria and establish baseline
- **Asymptomatic bacteriuria**
  - High risk of pyelonephritis and preterm birth
  - Treat positive culture with antibiotics
  - Up to 30% do not clear bacteriuria after antibiotics
  - Repeat culture is usually done for test of cure



# Infectious Disease Screening

## First Trimester

- Rubella and varicella
- Human immunodeficiency virus
- Syphilis
- Chlamydia and Gonorrhea
- Pap smear
- Hepatitis B



# Infectious Disease Screening

## Rubella and Varicella

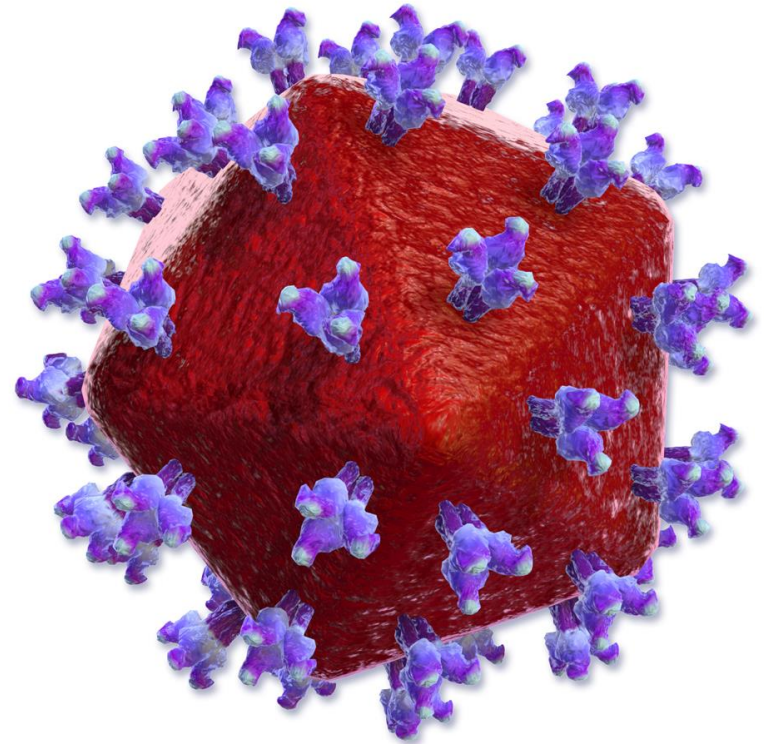
- Screen for antibodies
- If non-immune:
  - Avoid exposure
  - Postpartum immunization
- **Do not immunize in pregnancy**
  - Both vaccines are live vaccines



# Infectious Disease Screening

## HIV Testing

- ACOG guidelines: **“opt out” approach**
- Screening should be done unless patient opts out

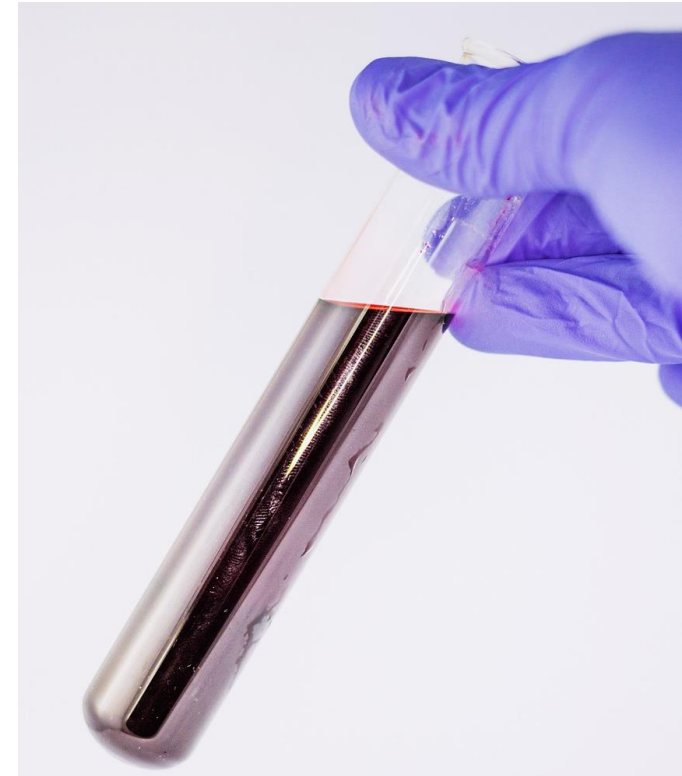


**Human Immunodeficiency Virus (HIV)**

# Other Standard Tests

## First Trimester

- Syphilis: VRDL/RPR
- Chlamydia: NAAT test (urine)
- Pap smear (unless done within past 6 months)
- Hepatitis B surface antigen (HBSAg)
  - If non-immune: vaccinate
  - Chronic HepB: HBIG + HBV vaccine at birth





# Selective Screening

## First Trimester

- TSH
- Hemoglobin A1c
- Genetic screening (cystic fibrosis, Tay-Sachs)

# Gestational Diabetes Screening

- **Screening:** 50-gram, one-hour glucose challenge test (GCT)
  - Performed 24 to 28 weeks
  - 50-gram oral glucose load given any time of day (fasting no required)
  - Plasma glucose measured one hour later
  - Positive screen:  $\geq 130$  mg/dL,  $\geq 135$  mg/dL, or  $\geq 140$  mg/dL (varies by practice/lab)
- **Diagnostic test:** 100-gram, three-hour oral glucose tolerance test (GTT)
  - Fasting for 6 hours
  - Baseline, one-hour, two-hour, and three-hour glucose testing
  - Any two elevated measurements is diagnostic of gestational diabetes

DIABETES



# Gestational Diabetes Screening

## Diagnostic Criteria 100-gram 3-hour GTT

Time	Cutoff (mg/dL)
Fasting	95
One hour	180
Two hours	155
Three hours	140

# Vaccinations

- Tetanus, reduced diphtheria, acellular pertussis (Tdap)
  - Given even if previously immunized
  - Usually single dose given 27 to 36 weeks
  - If not previously immunized: complete series of three vaccinations given
- Inactivated influenza vaccine (injection)
  - Preferred 2nd or 3rd trimester to protect baby after birth
- Others only if not immunized
- Live vaccines: **MMR**, **Varicella**, **Rotavirus**
  - Also live influenza
- HPV avoided in pregnancy (limited safety data)



# Nutrition

- Pregnancy requires extra ~ 300 kcal/day
- Iron: 27 mg/day
- Calcium: 1000 mg/day
- Vitamin D: 200 to 600 IU/day
- Iodine – 150 mcg/day
- Folate
  - Normal-risk mothers: 400 mcg/day 1<sup>st</sup> trimester
  - High-risk mothers: 4 mg/day



# Group B Streptococcus

- May cause newborn infections
- Screening: **rectovaginal cultures** 3<sup>rd</sup> trimester (36 to 37 weeks)
- **Intrapartum antibiotic prophylaxis** if positive screen

Group B Streptococcus



# Aneuploidy Screening

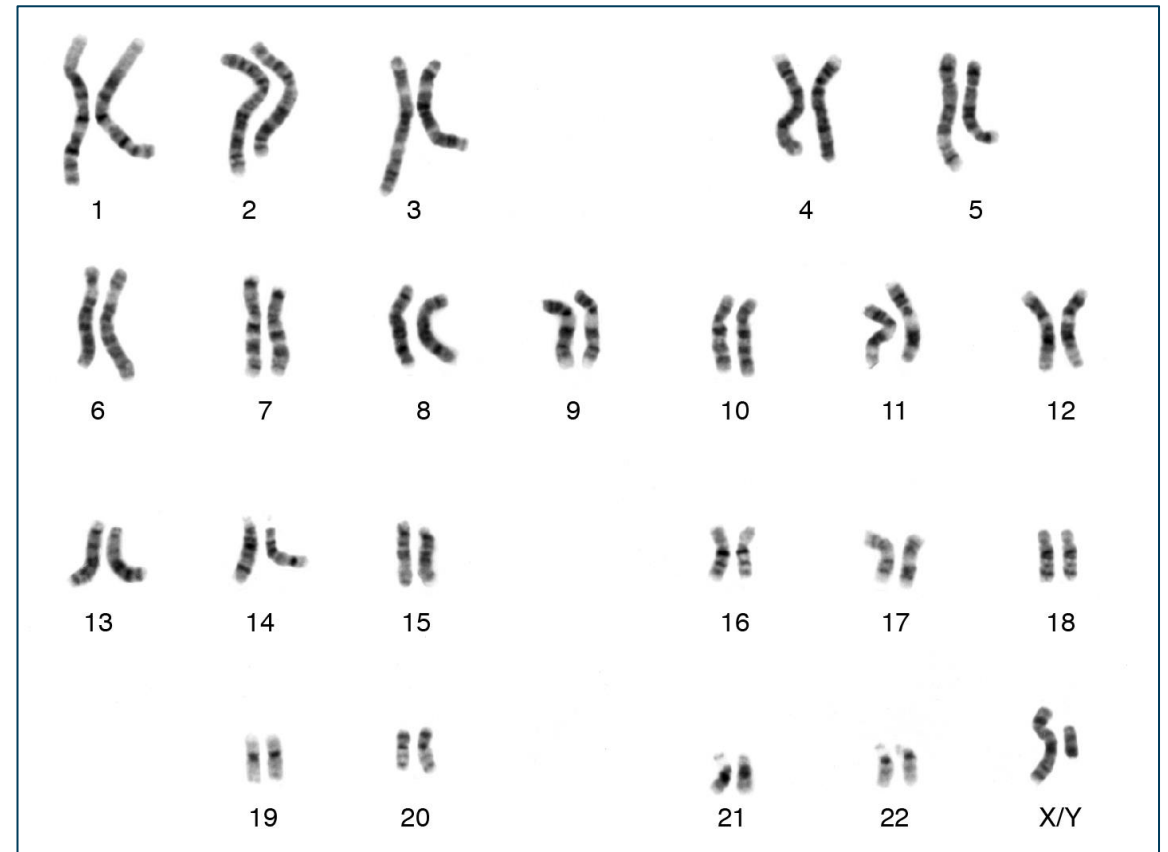
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# Aneuploidy Screening

- Down syndrome (trisomy 21)
- Edward syndrome (trisomy 18)
- Patau syndrome (trisomy 13)
- Several screening methods
  - Maternal serum markers
  - Fetal ultrasound findings
  - Cell free DNA
- Positive screen requires confirmation

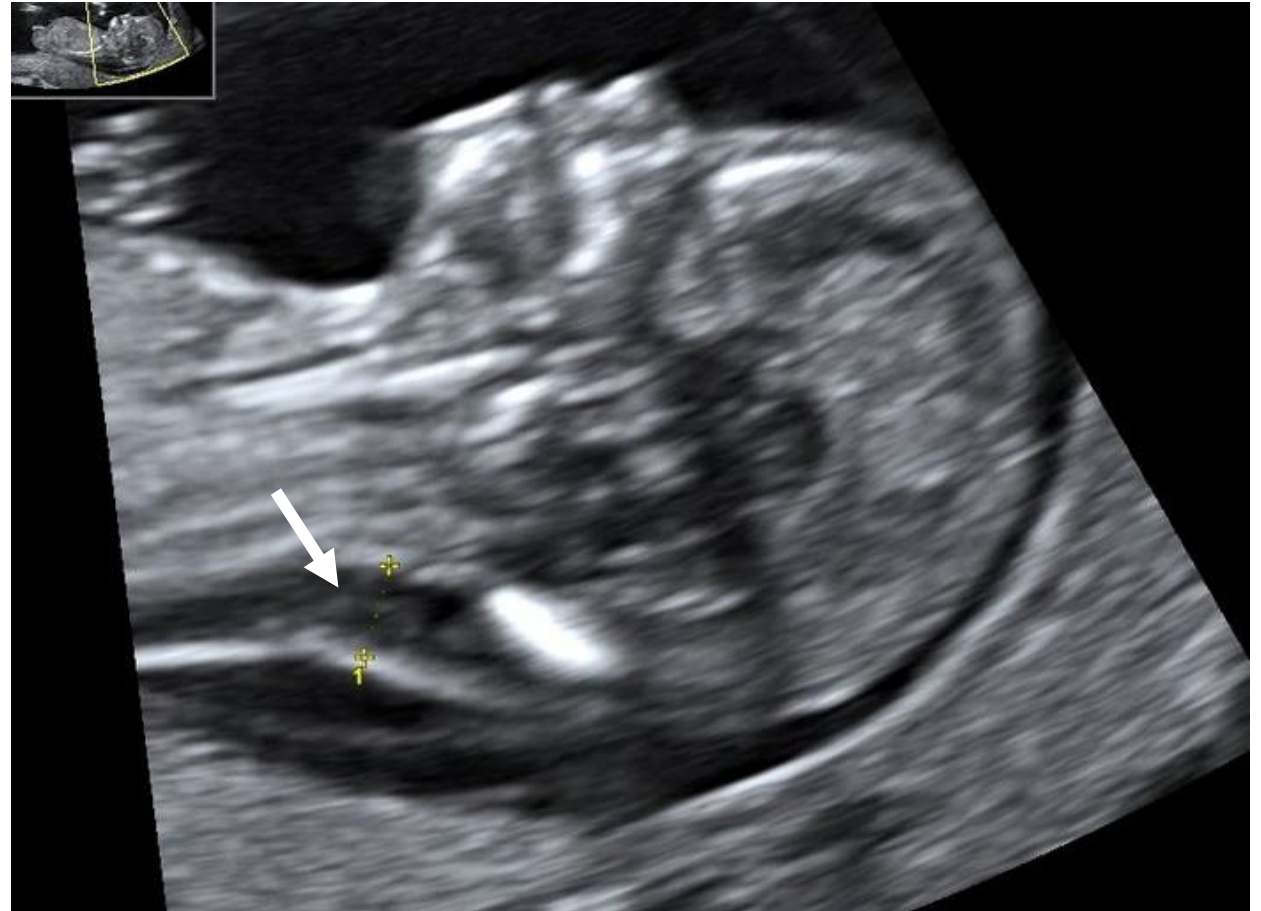


# Maternal Serum Markers

- Abnormal levels associated with aneuploidy
- Alpha-fetoprotein (AFP)
- Free  $\beta$ -human chorionic gonadotrophin (free  $\beta$ -hCG)
- Unconjugated estriol
- Inhibin A
- Pregnancy-associated plasma protein-A (PAPP-A)

# Nuchal Translucency

- Normal fluid at back of neck
- Identified by fetal ultrasound
- Measured **12 to 13.5 weeks**
- Larger with aneuploidy



# Aneuploidy Screening

## 1<sup>st</sup> Trimester

- **Combined screening test**
- Ultrasound plus lab findings
- Performed 12 to 13 weeks (late 1<sup>st</sup> trimester)
- Determines a risk estimate for trisomy (1 in 200; 1 in 100)

	Nuchal Translucency	PAPP-A	β-HCG
T21	↑	↓	↑
T18	↑	↓	↓
T13	↑	↓	↓

# Aneuploidy Screening

## 2<sup>nd</sup> Trimester

- **Quad screening test**
- Maternal lab findings only
- Determines a risk estimate for trisomy (1 in 200; 1 in 100)

	AFP	$\beta$ -HCG	Estriol	Inhibin
T21	↓	↑	↓	↑
T18	↓	↓	↓	Variable
T13	Variable – US findings often used			

# Aneuploidy Screening

## 2<sup>nd</sup> Trimester

- **Fully integrated test**
- Ultrasound plus lab findings from **1<sup>st</sup> and 2<sup>nd</sup> trimesters**
  - 1<sup>st</sup> trimester: PAPP-A and nuchal translucency (US)
  - 2<sup>nd</sup> trimester: AFP, estriol, inhibin A, and  $\beta$ -hCG
- Determines a risk estimate for trisomy 21 or 18

# Cell Free DNA

## cfDNA

- Some fetal DNA detectable in maternal circulation
- Can be used to screen for aneuploidy
- Maternal plasma must have adequate fetal cfDNA
  - Test may find “no result” in inadequate cases
- Not used before **10 weeks gestation** (cfDNA levels low)
- Low fetal cfDNA in **obese women**



DNA



# Cell Free DNA

## cfDNA

- Not diagnostic: used only for aneuploidy **screening**
  - Positive test indicates high likelihood of trisomy
  - Rare false positives and false negatives
  - Requires follow-up like other screening tests
- Not universally available and can be costly
- Most sensitive and specific testing method
- Used to follow-up abnormal serum/US testing
- Increasingly used as **primary screening**
  - ACOG recommendation September 2020
  - When available and not limited by cost



DNA

# AFP

## Alpha-fetoprotein

- Varies during pregnancy
- Reports as multiple of median for gestational age (MoM)

Reduced AFP (< 0.5 MoM)	Increased AFP (> 2.5 MoM)
Trisomy 21 or 18 Fetal demise Incorrect gestational dating	Neural tube defects Abdominal wall defects (e.g., gastroschisis) Multiple gestation Incorrect gestational dating

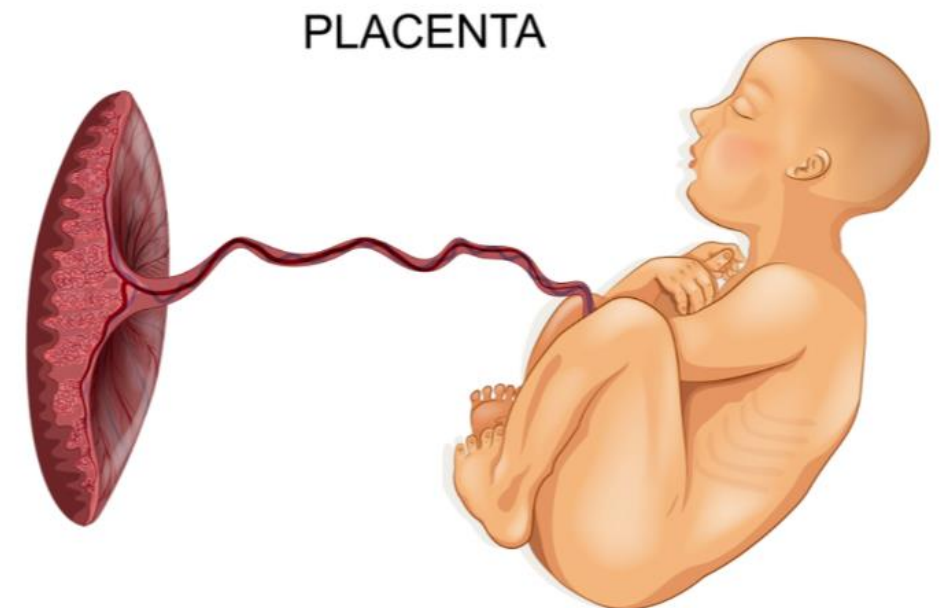
# Invasive Diagnostic Tests

- Used to obtain fetal DNA
- Definitive diagnosis of fetal aneuploidy
- Chorionic villus sampling
- Amniocentesis

# Chorionic Villus Sampling

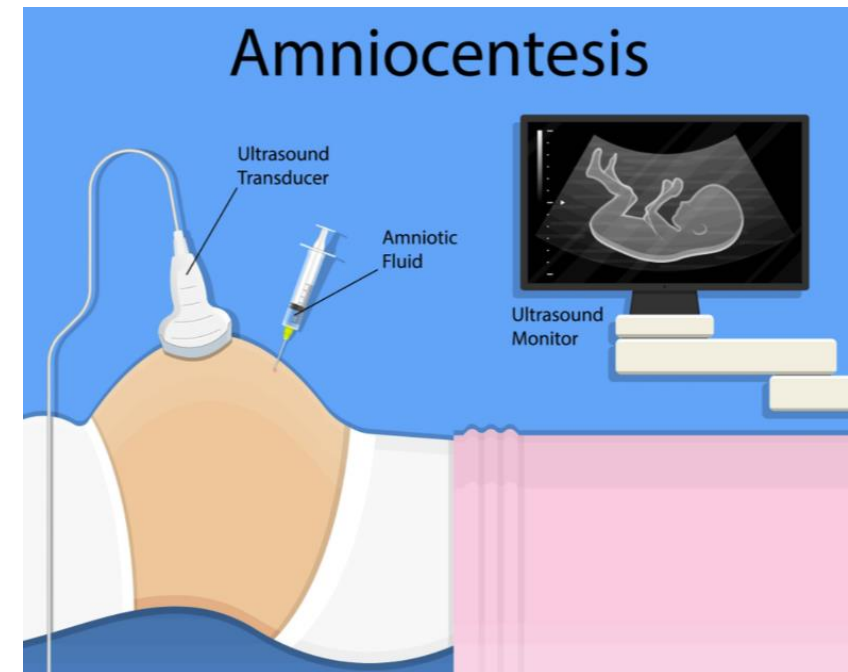
## CVS

- Obtains sample of the **placenta**
- Transabdominal or transcervical approaches
  - Approach varies by operator preference and anatomy
  - Transcervical associated with higher fetal loss
- Performed 10 to 13 weeks
- Risk of fetal loss ~1:100
- May cause maternal bleeding or infection
- May cause bands or limb amputation



# Amniocentesis

- Obtains fetal cells in **amniotic fluid**
- Transabdominal aspiration
- Performed 15 to 20 weeks
- Risk of fetal loss 0.1% to 0.3% (~1:500)
- Sample should be clear
- Green/brown fluid associated with adverse outcomes
  - Indicates intra-amniotic hemorrhage
  - Increased risk of spontaneous abortion or fetal death



# Antepartum Fetal Surveillance

Jason Ryan, MD, MPH



# Antepartum Fetal Surveillance

- Performed to evaluate health of developing fetus
- Identifies risk of intrauterine death or evidence of fetal hypoxia
- May guide intervention to avoid poor outcomes
- May prompt **early delivery**
- May guide vaginal versus cesarean delivery





# Nonstress Test

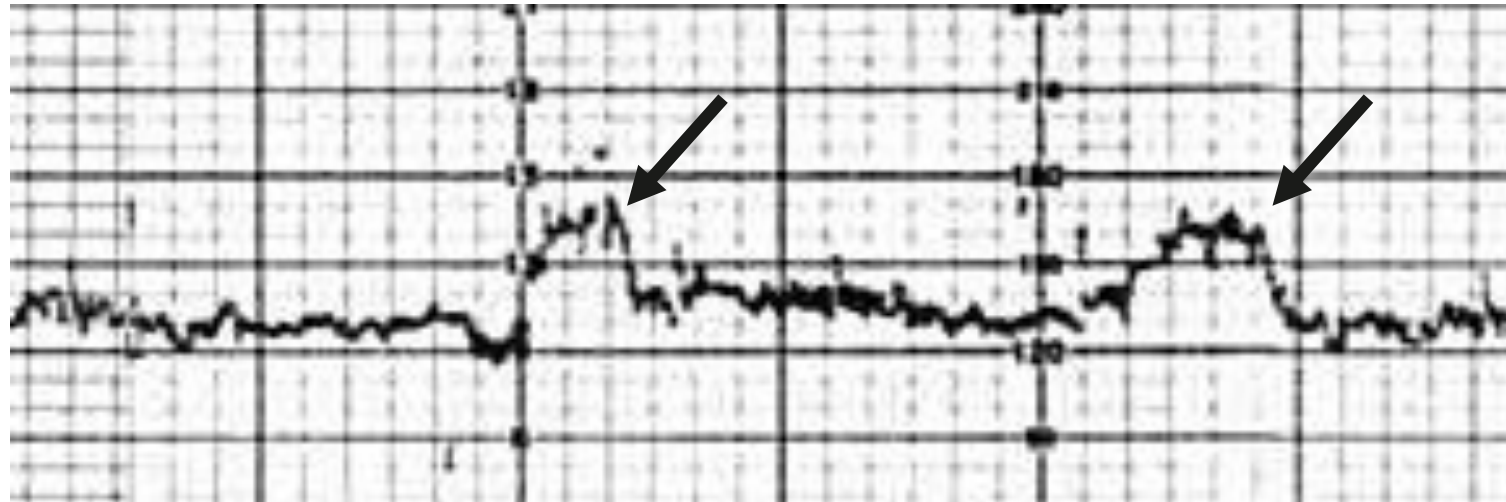
## NST

- Continuous fetal heart rate monitoring
- Fetal movements → increased heart rate
- Used **after 32 weeks gestation**
- Requires intact autonomic nervous system
  - Parasympathetic and sympathetic



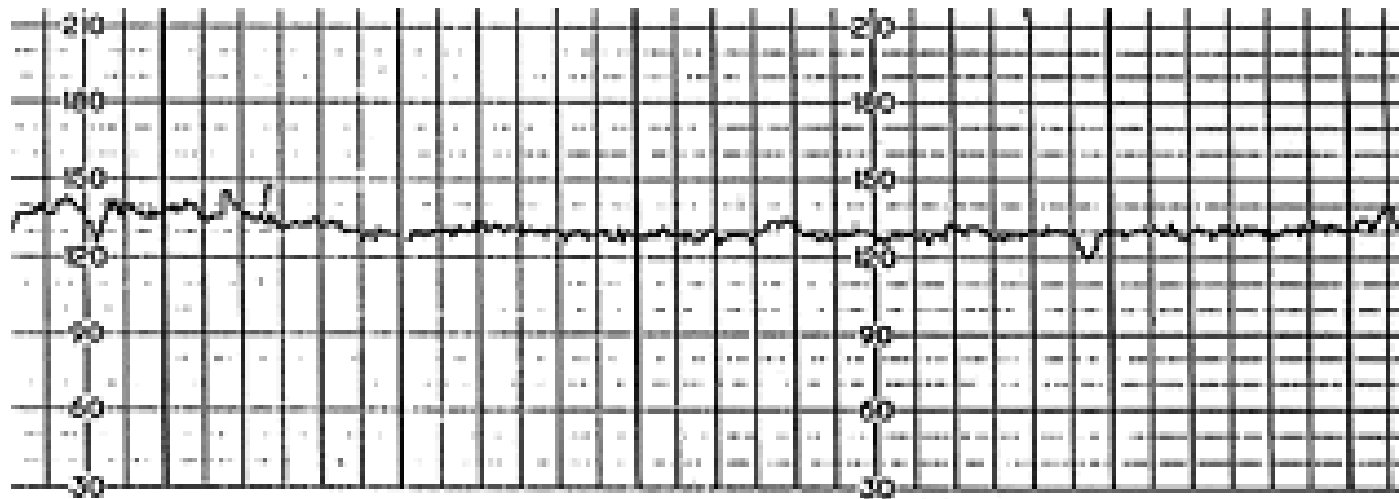
# Reactive NST

- **Two accelerations in 20 minutes**
  - Increase of **15 beats/min** over baseline
  - Lasting at least **15 seconds**
- Reassuring of fetal well-being
- Usually indicates no need for urgent delivery



# Nonreactive NST

- Insufficient accelerations after 40 minutes of monitoring
- Often due to **baby sleeping**
- Potential next steps in evaluation:
  - Repeat test in 30 minutes
  - Vibroacoustic stimulation
  - Additional testing (biophysical profile)



# Biophysical Profile

- **Ultrasound** test of five parameters
- Nonstress test plus 4 ultrasound parameters
- Each given score of 2 (normal) or 0 (abnormal)



# Biophysical Profile

## Ultrasound Parameters

- **Fetal movement:** 3 distinct movements in 30 minutes
- **Fetal tone:** 1 extension of extremity or spine with return to flexion
- **Fetal breathing:** 1 episode of chest expansion  $\geq$  30 seconds
- **Amniotic fluid volume:** single deepest fluid pocket  $\geq$  2 cm

# Biophysical Profile

- Maximum score = 10 out of 10
- 8 to 10 normal
  - 2 points deduction allowed for movement, tone, or breathing
  - Not amniotic fluid
- 6 = equivocal (usually repeated 24 hours)
- 0 – 4 = abnormal (consider delivery)



# Modified Biophysical Profile

- Nonstress test and amniotic fluid volume assessment only
- Parameters most predictive of outcome
- Saves time if both parameters normal
- If abnormal → proceed with additional assessments

# Amniotic Fluid Index

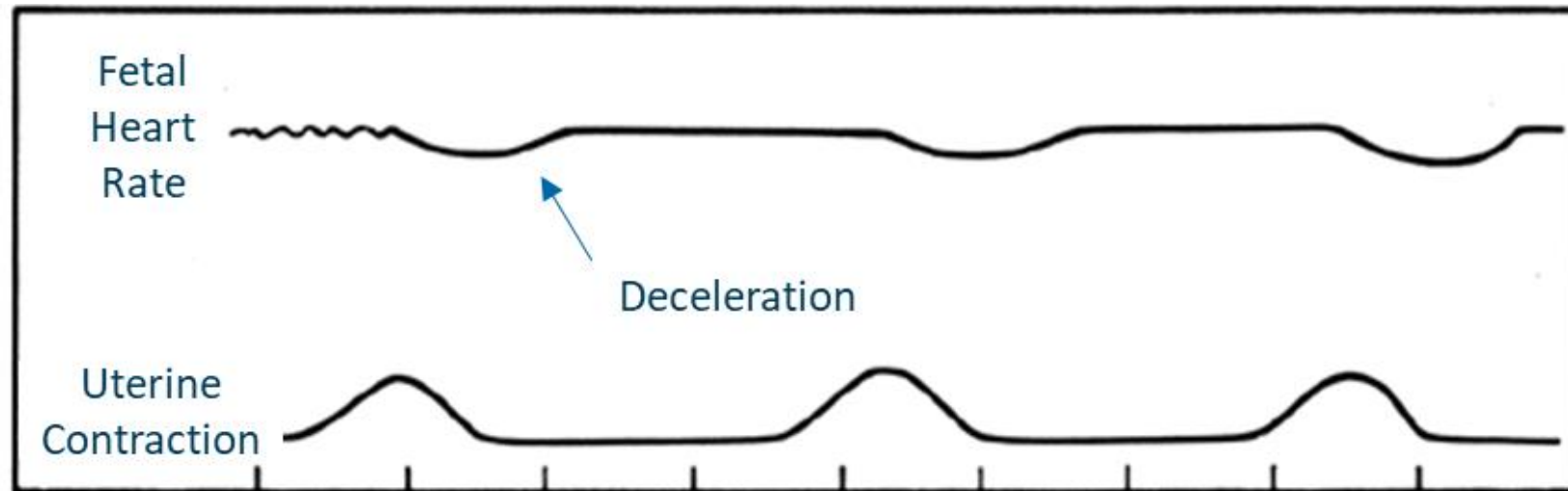
- Determined from depth of fluid pocket (cm)
- Measured in each of four abdominal quadrants
- Normal = usually 10 to 15 cm
- Oligohydramnios < 5 cm
- Polyhydramnios > 24 cm





# Contraction Stress Test

- Rarely used test to determine safety of vaginal delivery
- Fetal heart rate monitoring after oxytocin or nipple stimulation
- Late heart rate decelerations indicate hypoxia → inability to tolerate labor
- Abnormal result indicates need for caesarean section

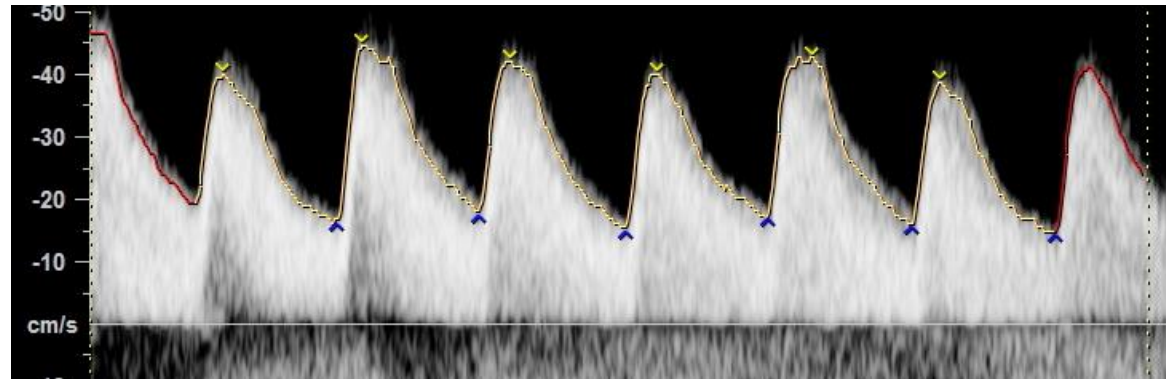


# Umbilical Artery Doppler

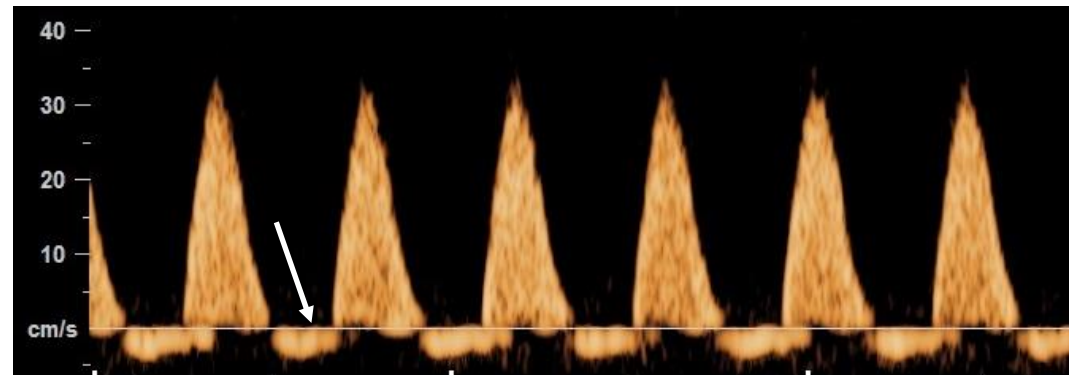
- Uses Doppler ultrasound
- Determines flow velocity and direction
- Flow should not stop and always be forward
- Absent or backward diastolic flow = abnormal
  - Absence of end-diastolic flow velocity (AEDV)
  - Reversal of end-diastolic flow velocity (REDV) - fetal demise imminent
- Usually indicate need for urgent delivery

# Umbilical Artery Doppler

Normal Umbilical Artery Doppler



Flow Reversal - Umbilical Artery Doppler



# Teratogens

Jason Ryan, MD, MPH



# Teratogens

- Substances that cause **abnormal fetal development**
  - Fetal loss
  - Growth restriction
  - Birth defects
  - Impaired neurologic function
- Greatest risk of fetal exposure **1<sup>st</sup> trimester**
  - Embryonic period
  - Formation of organs



# Teratogen Timing

- First two weeks after fertilization
  - “All or none” period – spontaneous abortion or no effect
- Embryonic period: 8 weeks from conception (10 weeks from LMP)
  - Organogenesis
  - Structural defects
- After week 8
  - Decreased growth
  - Central nervous system dysfunction
  - Usually no birth defects

# Teratogens

- Drugs
- Substances of abuse (alcohol, cocaine, smoking)
- Radiation
- Chemicals (mercury)

# Drug Testing

- Animals
  - FDA requires all drugs be tested in animal models
  - Often rodents (rats)
- Case reports



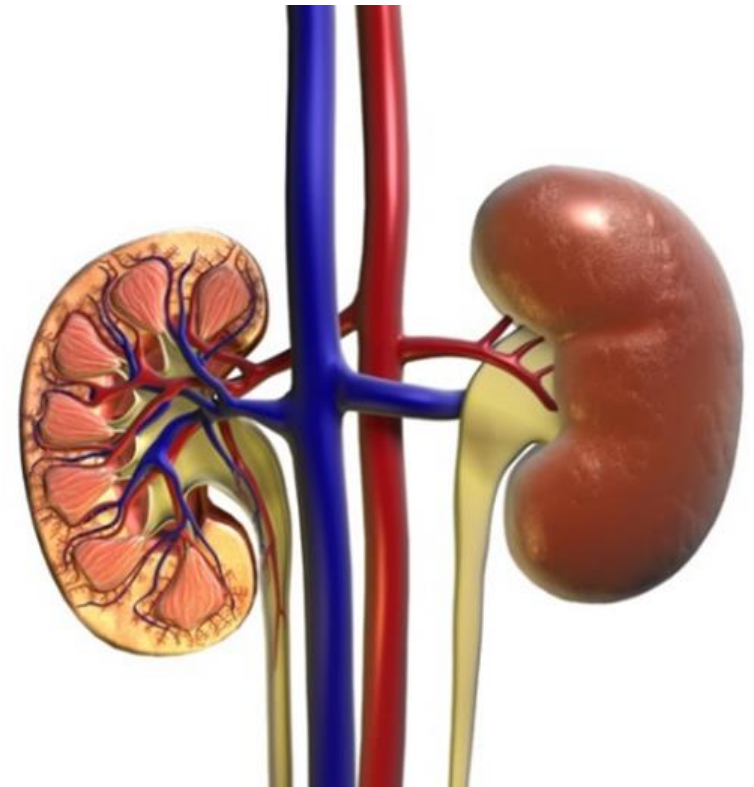


# Drug Categories

- FDA labels drugs during pregnancy in categories
- Category A: no risk to fetus in human studies (very few drugs)
- Category B: no risk to fetus in other studies
- Category C: risk cannot be ruled out
- Category D: positive evidence of risk
- Category X: contraindicated in pregnancy
  - Drugs known to be teratogenic in animals and humans
  - Risks clearly outweigh benefits

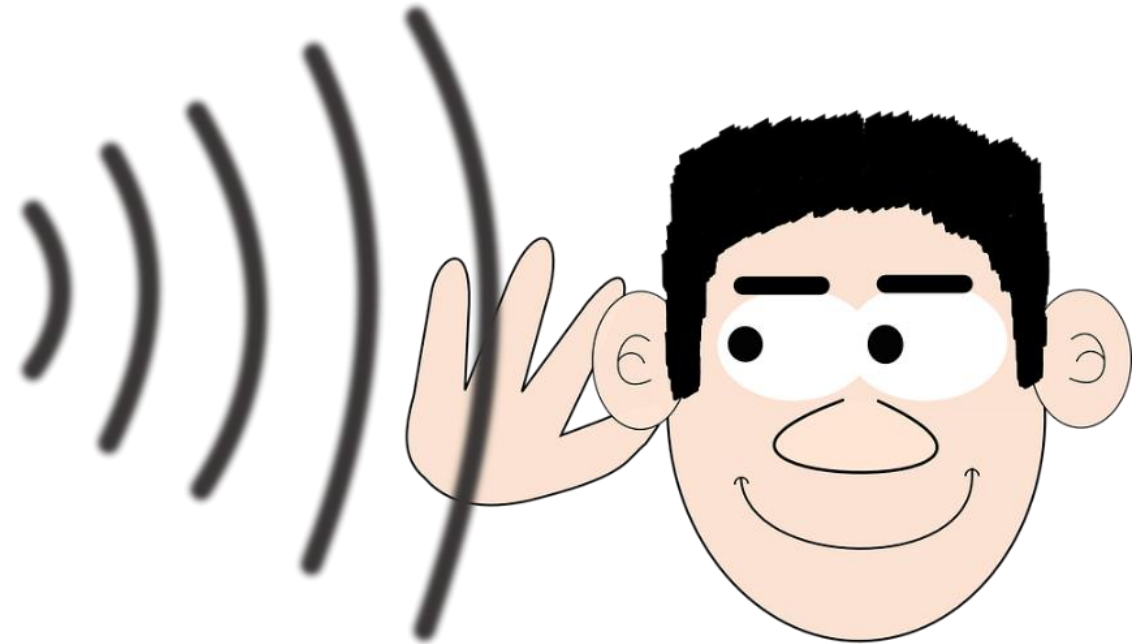
# ACE Inhibitors and ARBs

- Pregnancy class D
- 1<sup>st</sup> trimester: numerous congenital malformations
- 2<sup>nd</sup>/3<sup>rd</sup> trimester: **oligohydramnios**
  - Decreased fetal kidney function
  - Fetal renal failure
  - Can lead to Potter's syndrome
  - Pulmonary hypoplasia, limb/skeletal deformities



# Antibiotics

- **Aminoglycosides**
  - Reports of permanent deafness in fetus
- **Tetracycline**
  - Accumulate in fetal teeth and long bones
  - May permanently discolor fetal teeth
- **Fluoroquinolones**
  - Fetal cartilage damage



# Antibiotics

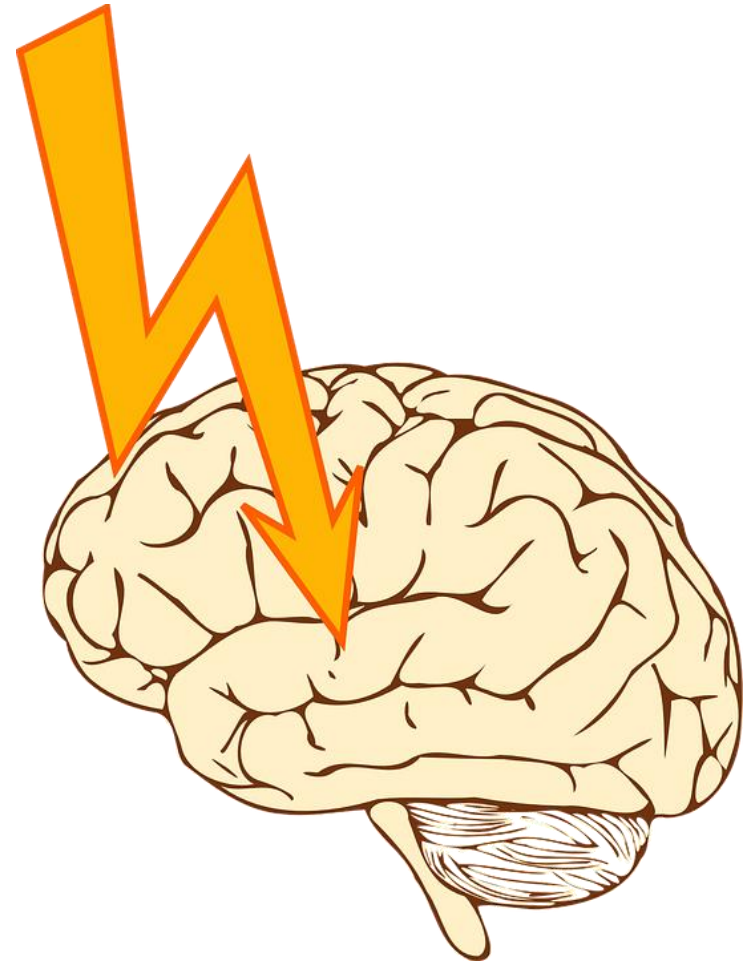
- **Trimethoprim**
  - May disrupt folate metabolism in fetus
  - Associated with neural tube defects
- **Sulfonamides**
  - Displace bilirubin from albumin
  - Can cause kernicterus

**TMP-SMX**

# Antiepileptic Drugs

## AEDs

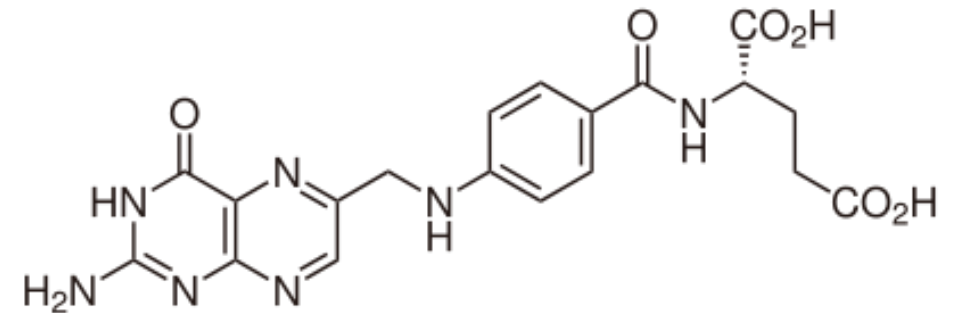
- Women with epilepsy may require drugs in pregnancy
- All anti-seizure drugs may affect fetus
  - **Neural tube defects**
  - Congenital heart disease
  - Cleft palate
  - Short fingers
  - Abnormal facial features
- Most are pregnancy class D



# Antiepileptic Drugs

## AEDs

- High risk drugs
  - **Valproic acid** (↑↑ neural tube defects)
  - Phenytoin
  - Phenobarbital
  - Carbamazepine
- Many anti-seizure drugs associated with ↓ folic acid
- ↓ folic acid → neural tube defects
- **High dose folic acid supplementation**
  - Normal recommendation: 400 mcg/day
  - High risk mothers: 4mg/day

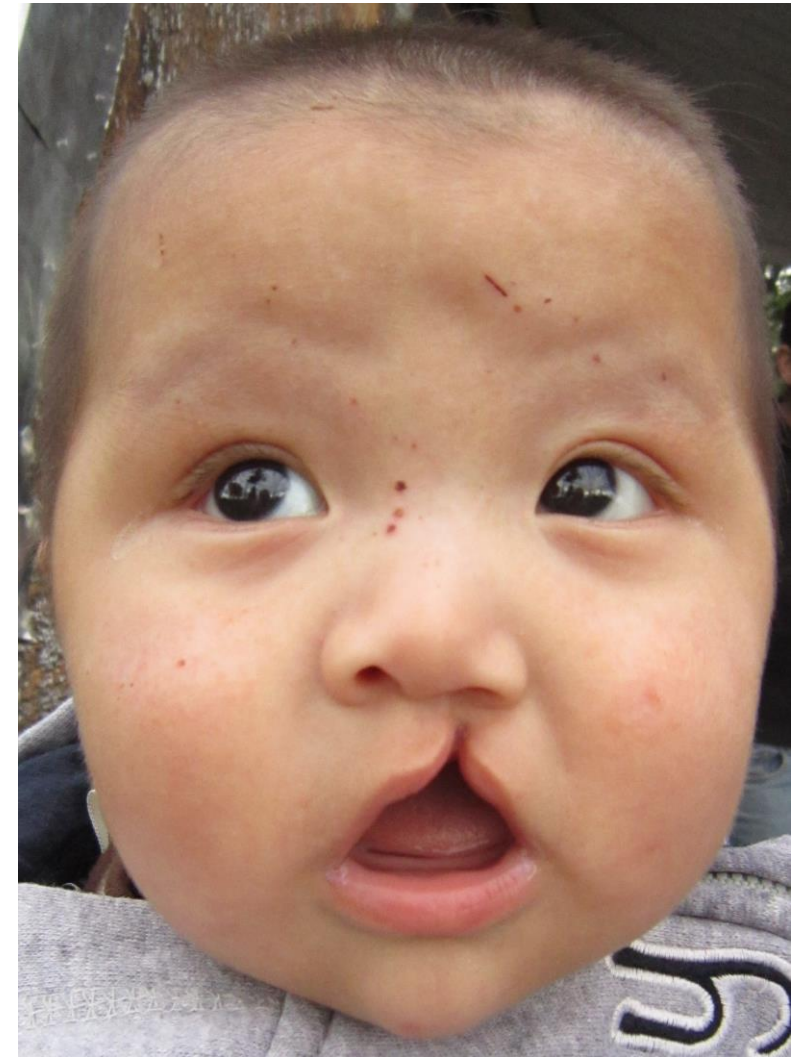


Folate

# Fetal Hydantoin Syndrome

- Associated with **phenytoin** use in pregnancy
- Growth deficiency
- Abnormal facial features
  - Broad, short nose
  - Wide-spaced eyes
  - Malformed ears
  - Classically **cleft lip and cleft palate**

Cleft Lip



# Caffeine

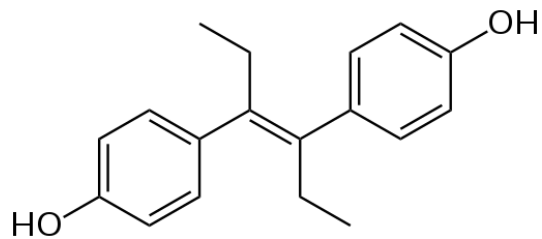
- Crosses the placenta
- May increase wakefulness in baby
- Few well-conducted studies of fetal effects
- Typical levels (up to 300 mg/day) no evidence of harm
- Some studies show high intake associated with SAB





# Diethylstilbestrol

- Nonsteroidal estrogen
- Used to prevent miscarriage, premature birth
- Removed from US market 1971
- Slightly increased risk of breast cancer for mothers
- **Female babies: reproductive tract abnormalities**

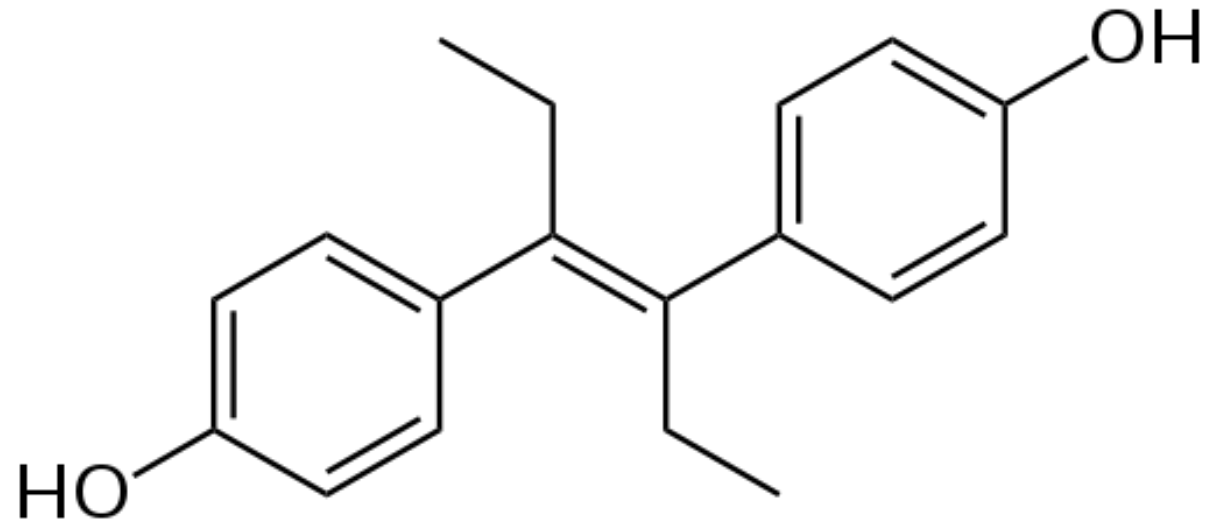


Diethylstilbestrol



# Diethylstilbestrol

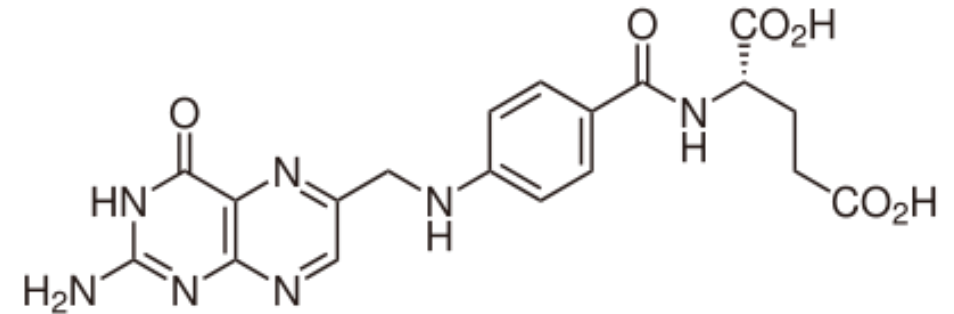
- Hypoplastic uterus
- Cervical hypoplasia
- High rate of **infertility**
- Vaginal adenosis (red spots)
- **Vaginal clear cell adenocarcinoma**



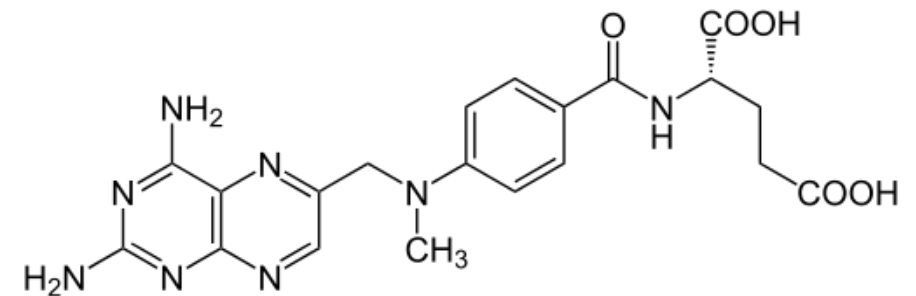
Diethylstilbestrol

# Methotrexate

- Inhibits folate metabolism
- Used as anti-inflammatory
- Pregnancy class X
- Used to induce abortion in ectopic pregnancy
- May cause **neural tube defects**
- Associated with numerous other anomalies
  - Microcephaly
  - Growth restriction
  - Limb and cranial malformations



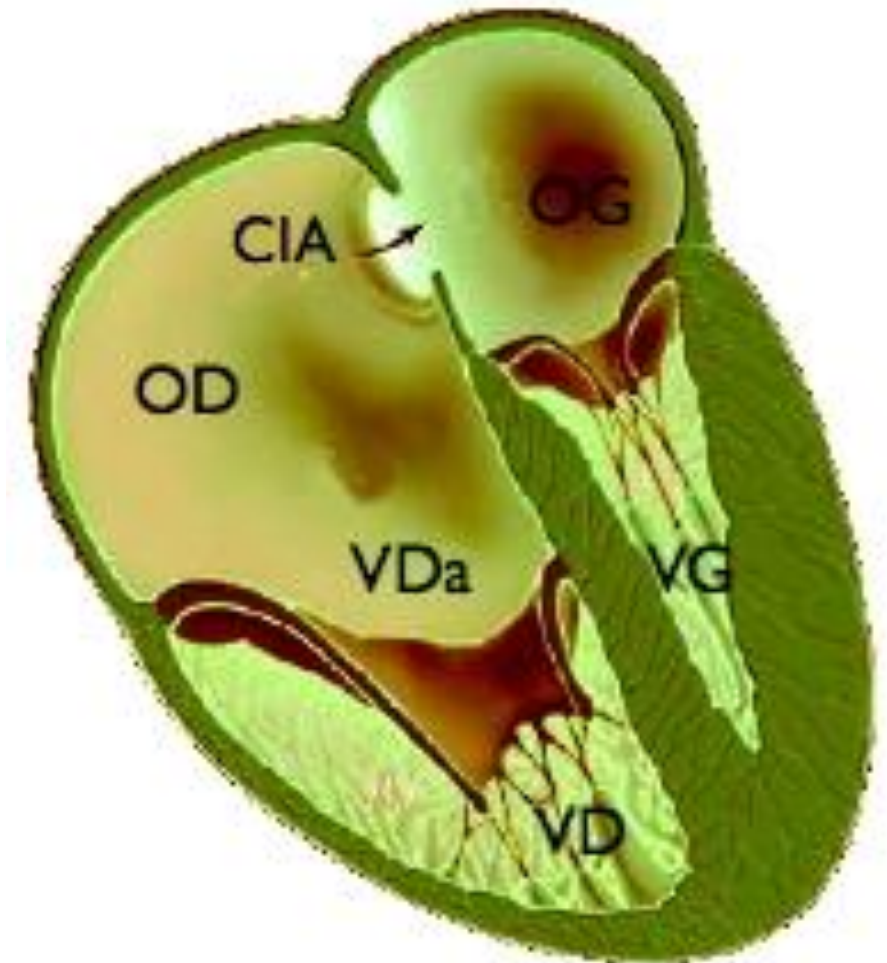
Folate



Methotrexate

# Lithium

- Mood stabilizer
- Pregnancy class D
- Teratogenic effects primarily involve heart
- **Ebstein's anomaly** most common



**Ebstein**

# Methimazole

- Treatment for hyperthyroidism in pregnancy
- Pregnancy class D
- May cause fetal and neonatal hypothyroidism
- **Aplasia cutis**: absence of epidermis on scalp
  - Solitary defect on scalp ~ 70% of cases
  - Missing patch skin/hair
- Propylthiouracil (PTU) used in 1<sup>st</sup> trimester
  - Less effective but fewer associated adverse effects

## Aplasia Cutis



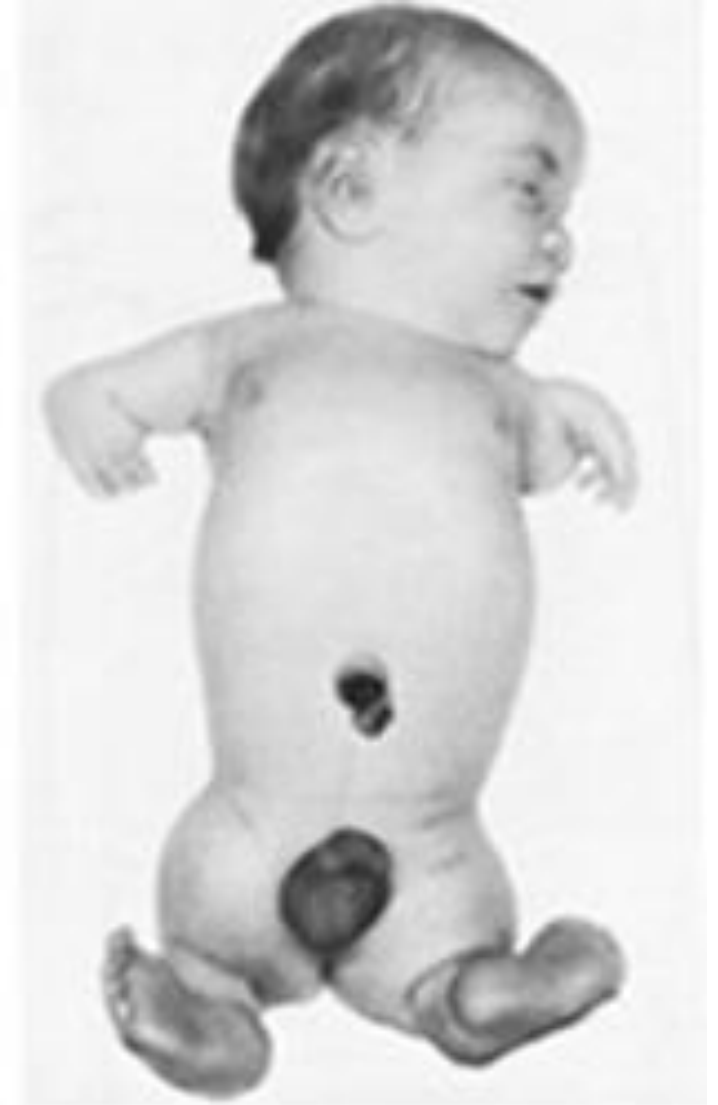
# Statins

- **Pregnancy category X**
- Should be discontinued prior to pregnancy
- Animal studies: adverse fetal outcomes
- Mostly central nervous system and limb defects
- Limited human data shows no major adverse effects
- Due to conflicting data → avoid statins
- Inadvertent exposure probably low risk to fetus



# Thalidomide

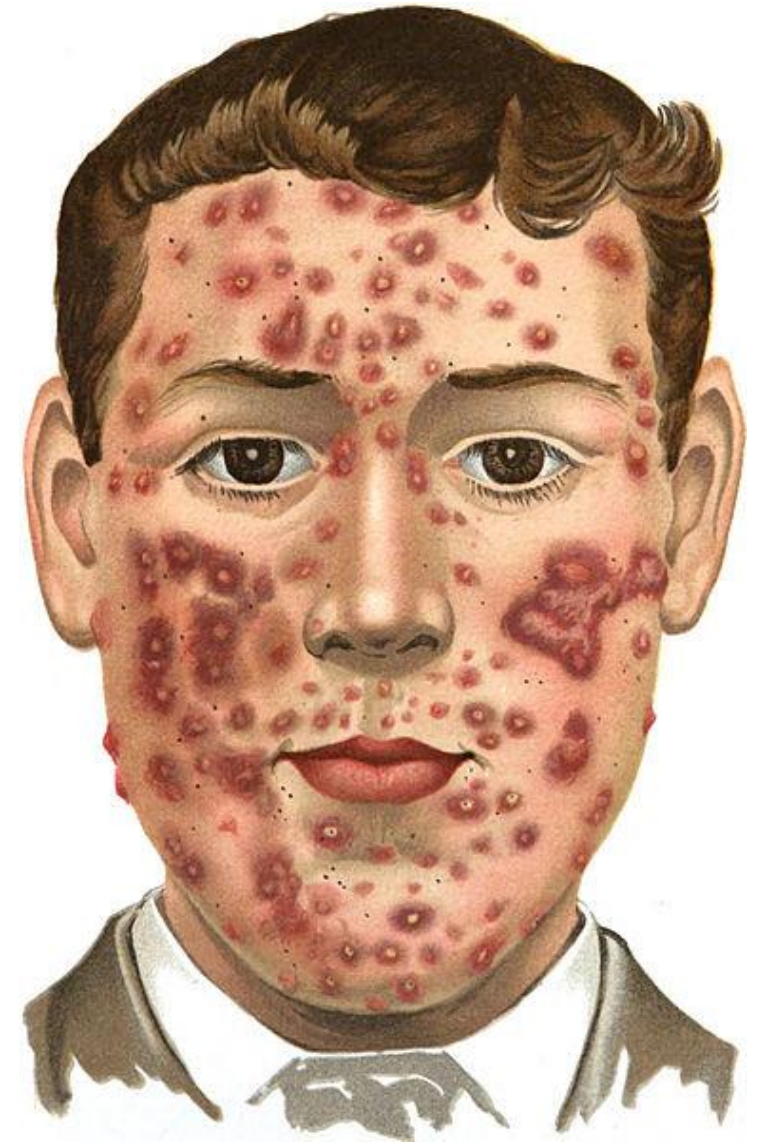
- Pregnancy class X
- Used as treatment of **multiple myeloma**
- Used in 1950s as sedative in pregnancy
- **Limb deformities**
  - Amelia: absence of limb
  - Micromelia: short limbs
  - Phocomelia: abnormal limb





# Isotretinoin

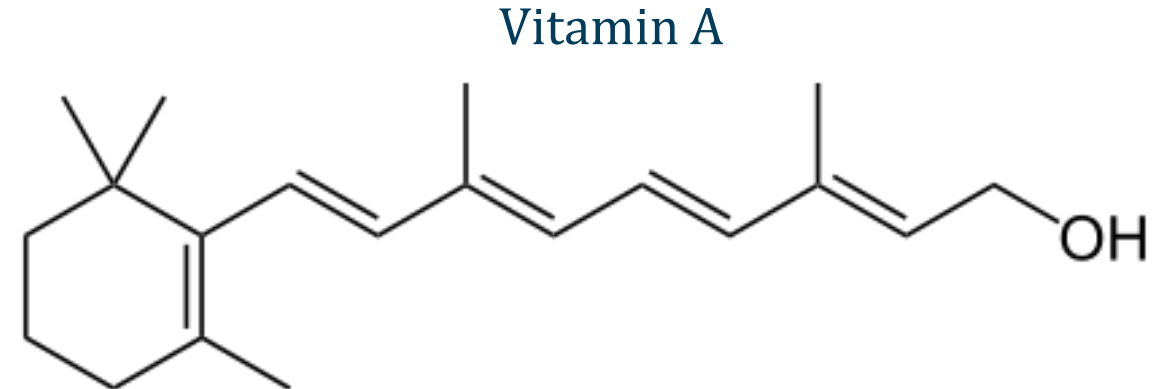
- Derivative of vitamin A
- Used to treat acne
- Pregnancy class X
- Spontaneous abortions (~ 20%)
- “Embryopathy”: 20 to 30% of live births
  - Abnormal facial features (low ears, wide-spaced eyes)
  - Congenital heart disease
  - Hydrocephalus
- **Birth control mandatory**





# Vitamin A Excess

- Teratogenic in first trimester
- Spontaneous abortions
- Microcephaly
- Cardiac anomalies
- Occurs at doses several times RDA
- Difficult to develop from regular diet
- Can be seen with excessive supplements



# Warfarin

- Anticoagulant
- Pregnancy class D
- Fetal hemorrhage, spontaneous abortion
- Optic atrophy (vision loss)
- **Warfarin embryopathy**
  - Bone and cartilage abnormalities
  - Stippled epiphyses: small, round densities on X-ray
  - Nasal hypoplasia
  - Limb hypoplasia
- LMW heparin used for anticoagulation



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# Alcohol

- Neurotoxin
- May cause fetal alcohol spectrum disorder (FASD)



# FASD

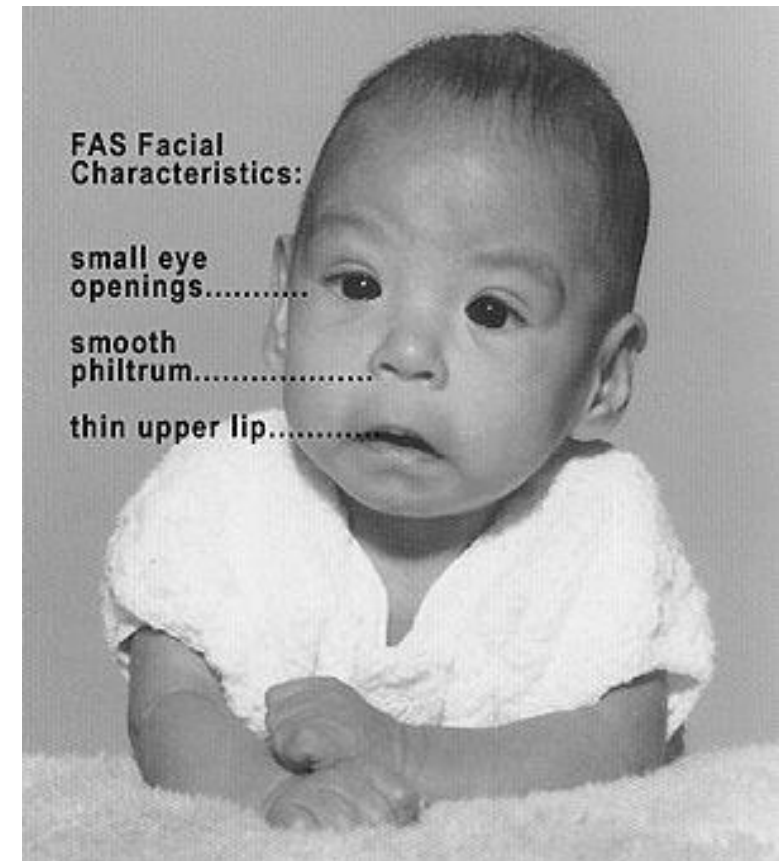
## Fetal Alcohol Spectrum Disorder

- Group of alcohol-related developmental disorders
- Fetal alcohol syndrome (FAS)
- Partial fetal alcohol syndrome (pFAS)
- Alcohol-related neurodevelopmental disorder (ARND)
- Neurobehavioral disorder associated with prenatal alcohol exposure (ND-PAE)
- Alcohol-related birth defects (ARBD)

# Fetal Alcohol Syndrome

## Clinical Features

- **Characteristic facial features** plus **intellectual impairment**
- Smooth philtrum
  - Groove from base of nose to upper lip
- Short palpebral fissures
  - Small opening of eyes
- Thin vermilion border
  - Upper lip
- Cognitive, memory, and behavioral problems



# Fetal Alcohol Syndrome

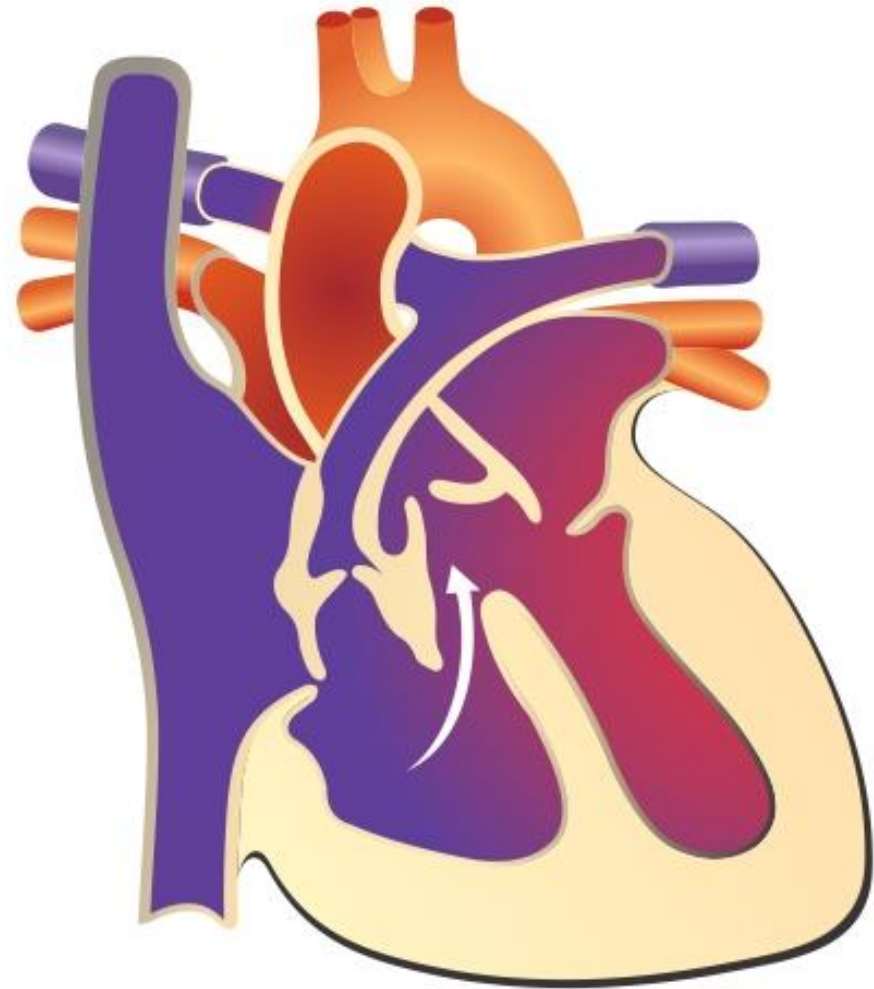
## Diagnostic Criteria

- At least 2 characteristic facial features
- Evidence of brain involvement
  - Decreased cranial size at birth
  - Structural brain abnormalities (e.g., microcephaly, cerebellar hypoplasia)
  - Neurologic signs (e.g., impaired motor skills, hearing loss, abnormal gait)
- Growth retardation
  - Low birth weight
  - Decelerating weight gain over time

# Alcohol

## Heart Defects

- Atrial septal defect
- Ventricular septal defect
- Tetralogy of Fallot

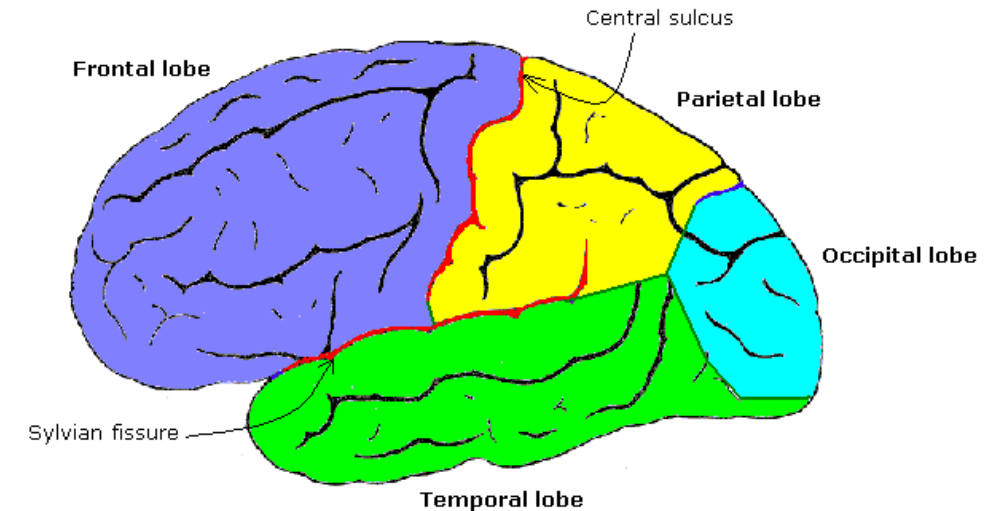


# Alcohol

## CNS

- **Neurobehavioral impairment**
- Reduced IQ
- Developmental delay
- Intellectual disability
- Behavioral abnormalities

Lobes of the brain





# Smoking

- Two toxins: **nicotine and carbon monoxide**
- Impaired oxygen delivery to the fetus
  - Nicotine-induced vasoconstriction → ↓ placental blood flow
  - CO competes with O<sub>2</sub> → ↓ oxyhemoglobin



# Smoking

- **IUGR/Low birthweight**
  - 20% cases associated with smoking
- **Placental anomalies**
  - Abruption
  - Previa
- Premature rupture of membranes
- Preterm labor
- Well-documented association with **SIDS**



# Cocaine and Amphetamines

- **Stimulants**
- Vasoconstriction
- IUGR/low birthweight
- Placental abruption
- Preterm birth
- Miscarriage



# Marijuana

- Use discourage during pregnancy
- Potential neurodevelopmental effects
- Data regarding safety and risks is limited



# Mercury

- Methylmercury ( $\text{CH}_3\text{-Hg}$ ) found in **fish/seafood**
- Not removed by cooking
- Mother not usually affected
- Fetal brain highly sensitive to mercury
- Delayed milestones
- Rarely blindness, deafness, or cerebral palsy
- **Canned tuna safe** - mercury levels tested



# Radiation

- X-rays, CT scan
- No evidence of harm at small doses
- Threshold for harm not definitively determined
- Higher dosages at 8 to 15 weeks may cause:
  - Microcephaly
  - Growth restriction
  - Intellectual disability
- Lead shielding used to protect fetus



# TORCH Infections

Jason Ryan, MD, MPH



# TORCH Infections

- Maternal infections → poor fetal outcomes
  - Miscarriage or stillbirth
  - Fetal abnormalities at birth
- **TORCH**
  - Toxoplasmosis
  - **O**ther (syphilis, varicella-zoster, parvovirus B19)
  - **R**ubella
  - **C**MV
  - **H**erpes



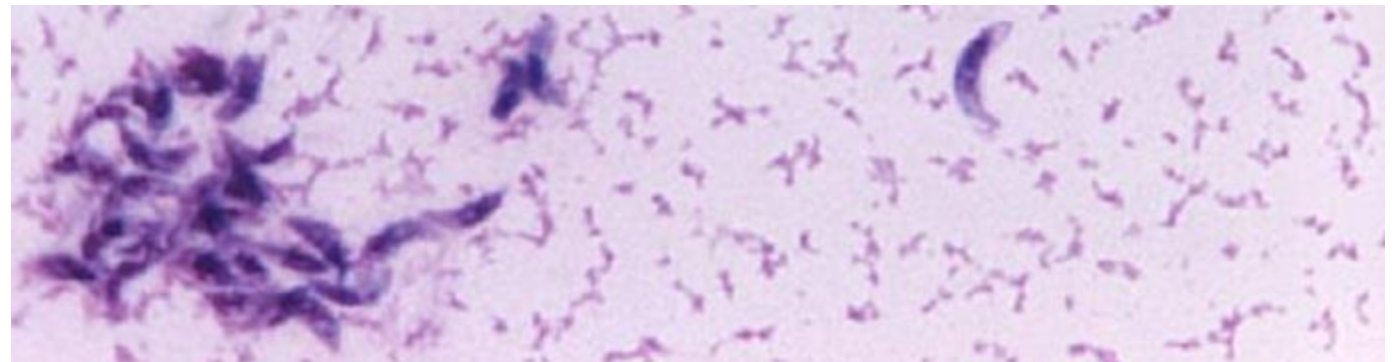


# Toxoplasma gondii

## Toxoplasmosis

- Protozoa
- Commonly lives in cats (felines)
- Oocysts shed in stool
- Infection from ingested oocysts (soil)
- Found in meat from contaminated animal
- Found in raw shellfish

## Toxoplasma



# Toxoplasma gondii

## Toxoplasmosis

- Maternal 1° infection usually **asymptomatic**
  - Immunocompetent mothers
  - 80 to 90% of infections asymptomatic
  - Lymphadenopathy
  - Fever, chills, sweats
- Latent infection usually does not infect fetus

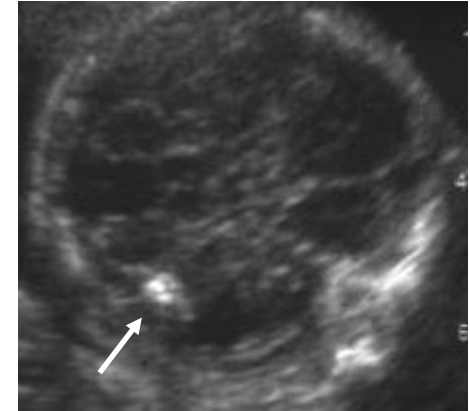


# Toxoplasma gondii

## Toxoplasmosis

- Most newborns appear normal
- May develop symptoms later
- Classic triad:
  - Hydrocephalus
  - Chorioretinitis (inflammation of choroid in eye)
  - Intracranial calcifications (often on prenatal US imaging)

## Intracranial Calcifications Fetal US



## Chorioretinitis



Wikipedia/Public Domain

# Toxoplasma gondii

## Prevention

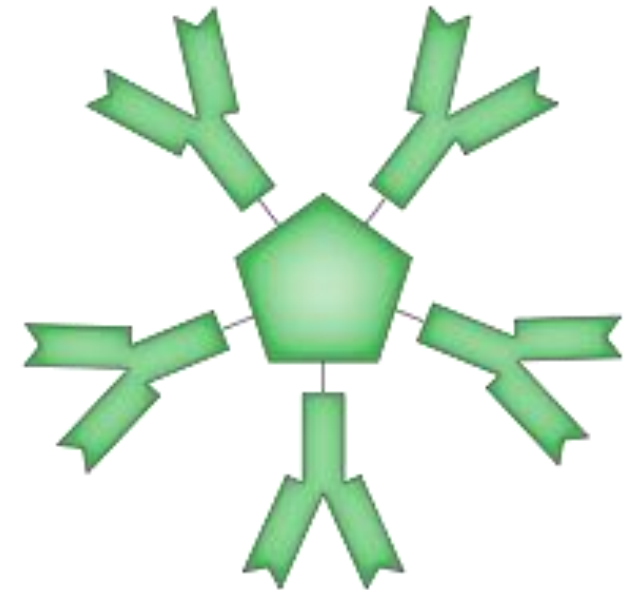
- Avoid raw or uncooked meat
- Avoid raw shellfish
- Wash or cook fruits/vegetables
- Avoid changing cat litter



# Toxoplasma gondii

## Screening and Diagnosis

- Usually no screening (low prevalence)
- Consider with maternal febrile illness or abnormal fetal US findings
- Diagnosis: **antibody testing**
  - IgM antibodies in first week
  - IgG antibodies peak 6 to 8 weeks, fall over next two years



# Toxoplasma gondii

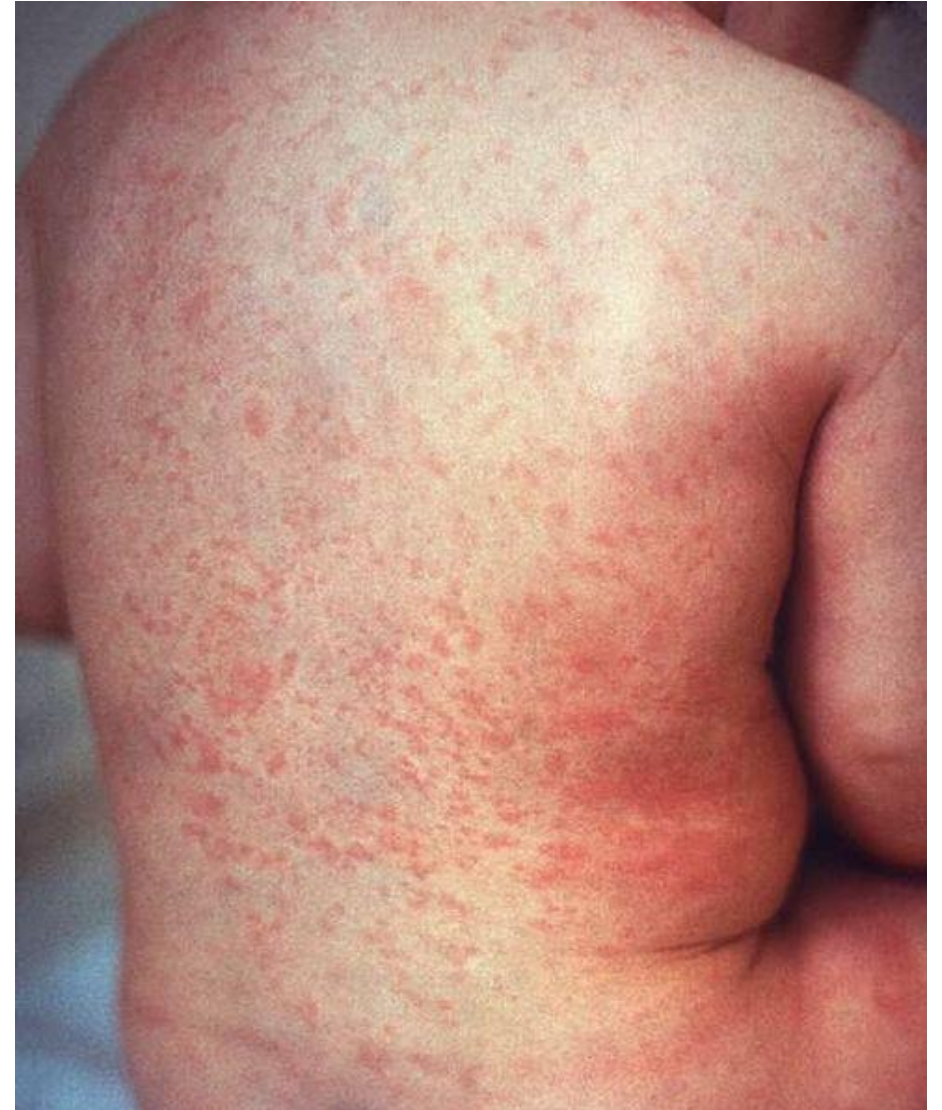
## Screening and Diagnosis

- Treatment (mother): antibiotics
  - Pyrimethamine-sulfadiazine
  - Spiramycin
- Treatment (baby at birth): antibiotics
  - Pyrimethamine-sulfadiazine plus leucovorin



# Rubella

- RNA virus
- Mild, self-limited illness in mother
  - Maculopapular rash
  - Lymphadenopathy
  - Joint pain
- May cause IUGR or fetal demise
- First trimester infection: 80% transmission
- Major fetal effects rare if infected after 20 weeks



# Congenital Rubella Syndrome

- Sensorineural deafness
- Congenital cataracts
- Cardiac malformations (classically PDA)
- Purpuric skin lesions (blueberry muffin baby)
- Microcephaly
- Intellectual disability
- Autism

Congenital Cataracts

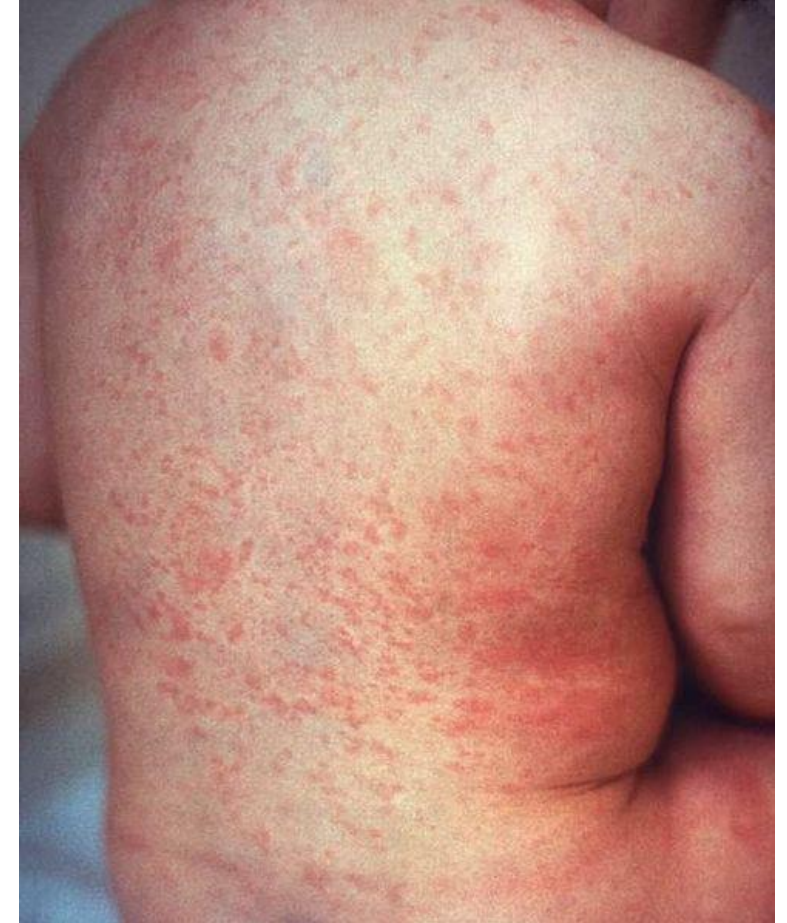




# Rubella

## Diagnosis and Management

- Diagnosis: rubella IgM/IgG or viral culture
- Treatment: supportive
- Termination may be offered if 1<sup>st</sup> trimester infection
- Prevention: **vaccinate prior to pregnancy**
  - MMR: live, attenuated vaccine
  - Not given during pregnancy
- Screen for Rubella antibodies at first prenatal visit



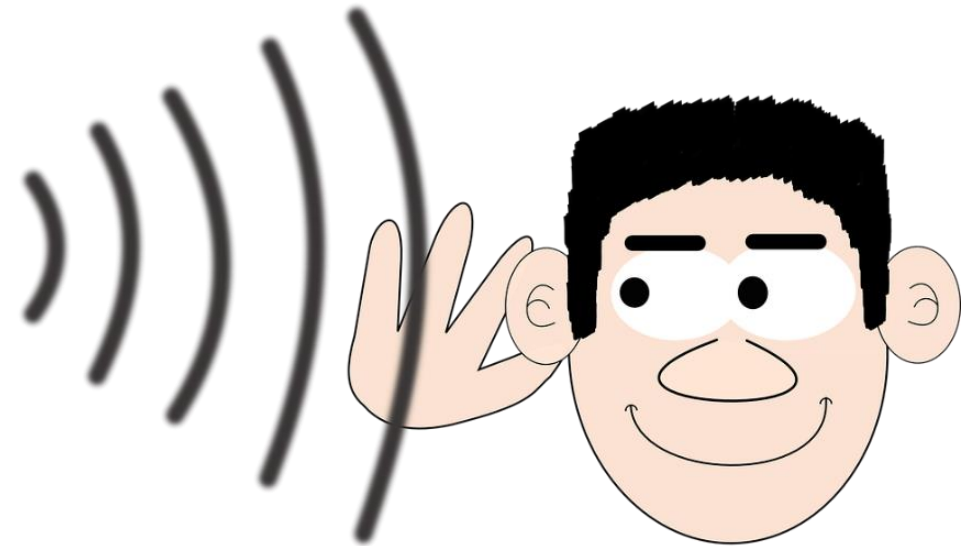
# Cytomegalovirus

- Herpes virus (DNA)
- Several modes of maternal infection:
  - Sexual contact
  - Close contact of infected individual (family member)
  - Blood/tissue exposure (transfusion)
- Primary CMV infection asymptomatic 90% cases
- May cause mild febrile illness (“mononucleosis-like”)
- Rhinitis, pharyngitis, headache, myalgia, arthralgia
- Latent infection and reactivation may occur



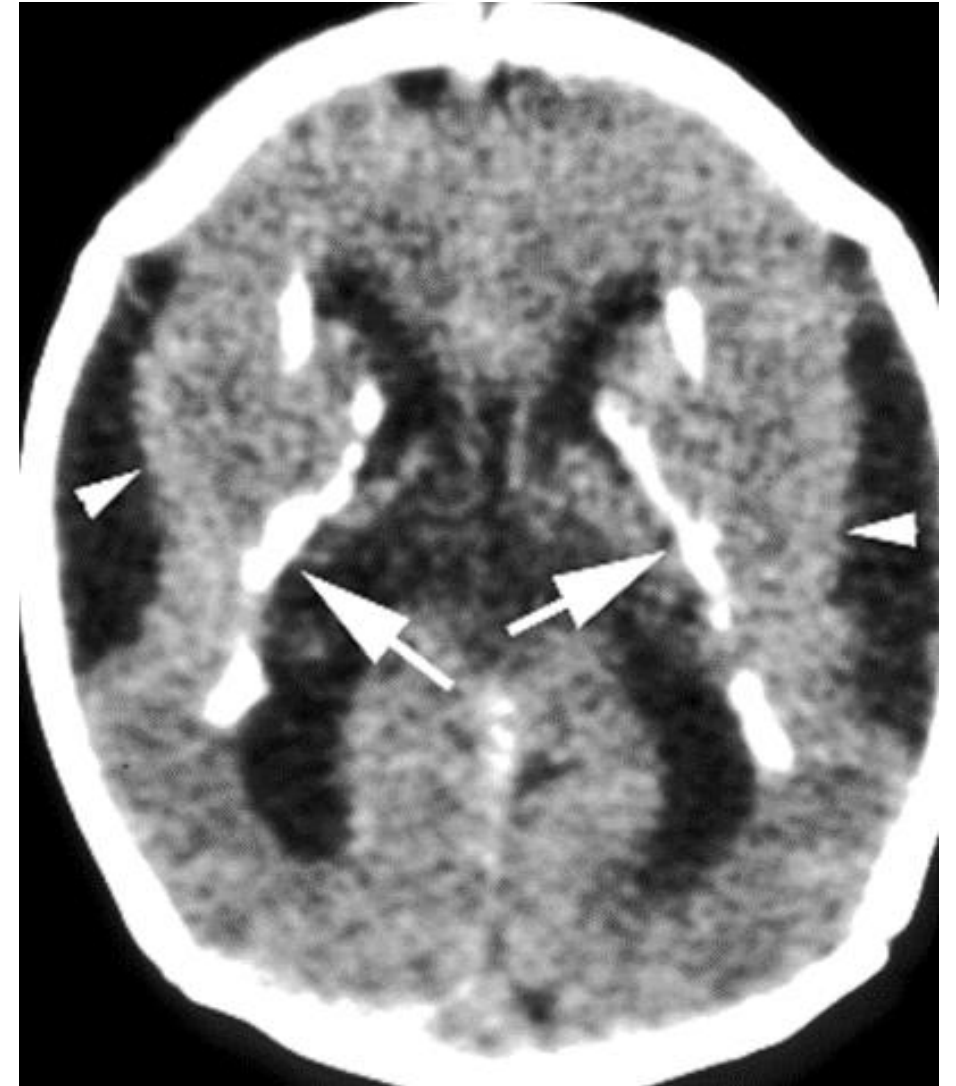
# Cytomegalovirus

- Most infected newborns are asymptomatic
- Major consequence: **sensorineural hearing loss**
  - Most common consequence of congenital CMV
  - Many babies diagnosed based only on failed hearing screen
  - Most common ID cause of congenital sensorineural deafness



# Cytomegalovirus

- Other potential findings
  - Small for gestational age
  - Microcephaly
  - Hepatosplenomegaly
  - Blueberry muffin baby
  - Seizures
- **Intracranial periventricular calcifications**
  - Classic neuroimaging finding



Daniel J Bonthius, Stanley Perlman. Congenital Viral Infections of the Brain: Lessons Learned from Lymphocytic Choriomeningitis Virus in the Neonatal Rat. PLOS Pathogens

# Cytomegalovirus

## Diagnosis

- Screening not routinely done
- Mother tested if mono-like illness or CMV-related fetal US findings
- Maternal diagnosis: **CMV IgM and IgG**
  - IgG = past infection
  - IgM = recent infection (usually < 4 months but can be longer)
  - IgG avidity index = low avidity indicates infection within past 4 months
- Fetal diagnosis: amniocentesis for PCR or viral culture
- Newborn diagnosis: blood or saliva for **PCR or viral culture**

# Cytomegalovirus

## Management

- No proven maternal treatment
- Newborns: **ganciclovir** and **valganciclovir**





# Herpes Simplex Virus

- HSV-1 and HSV-2
- Genital HSV → transmission at birth via genital tract lesions
  - Usually NOT transplacental
- Maternal infection may be primary or secondary
  - Primary infection: HSV antibodies negative
  - Secondary infection: HSV antibodies positive
- Highest risk transmission with primary infection

Genital Herpes



# Herpes Simplex Virus

## Newborn Findings

- Vesicles: skin, near eyes, in mouth
- May spread to CNS
- May disseminate to multiple organs





# Herpes Simplex Virus

## Diagnosis and Management

- Antibody screening often done at 1<sup>st</sup> prenatal visit
- Clinical diagnosis based vesicular or ulcerated lesions
- Confirmation with vesicle swab for **viral DNA testing by PCR**
  - Alternative: viral culture or direct fluorescent antibody testing
  - HSV antibodies negative if primary infection
- Treatment: **acyclovir for 7 to 10 days**
  - Alternative: valacyclovir (more expensive but easier compliance)

# Herpes Simplex Virus

## Diagnosis and Management

- After 36 weeks: **suppressive acyclovir therapy**
  - Acyclovir for any woman with history of genital HSV infection
  - Continue until onset of labor
- **Cesarean delivery** often recommended
  - CDC and ACOG guidelines
  - If active genital lesions
  - Or prodromal symptoms (vulvar pain or burning)
  - After onset of labor before rupture of membranes

## Cesarean Delivery



# Syphilis

*Treponema pallidum*

- Spirochete (bacteria)
- Transmitted by sexual contact
- Maternal symptoms
  - Primary syphilis: chancre
  - Secondary syphilis: maculopapular rash
- Findings in baby can be early or late
  - Early (< 2 yrs); Late (> 2 yrs)

## Syphilis on Palms



# Congenital Syphilis

## Early Findings

- **Maculopapular rash**
- **Runny nose**
- Abnormal long-bones
  - More common in legs
  - Many, many abnormalities reported





# Congenital Syphilis

## Late Findings

- Ears/nose
  - Saddle nose (no nasal bridge)
  - Hearing loss/deafness
- Teeth
  - Hutchinson teeth (notched, peg-shaped teeth)
  - Mulberry molars (maldevelopment of the molars)
- Legs
  - Saber shins (bowed legs)
- Caused by scarring and gumma formation

Syphilis Saddle Nose



# Congenital Syphilis

## Diagnosis and Treatment

- **Universal screening in first trimester**
- Diagnosis: **serologic testing**
  - Nontreponemal tests: RPR/VDRL
  - Treponemal tests: FTA-ABS
- Treatment (mother): **penicillin**
  - Primary or secondary: single dose penicillin G 2.4M units IM
  - Tertiary: three doses penicillin G 2.4M units IM



# Parvovirus B19

- Found in respiratory secretions of infected persons
- Classic infection: **Fifth disease in children**
  - “Slapped cheek” appearance of face
- Adults often develop **arthritis**
  - Hands, wrists, knees, and ankles
- Infects red cell progenitors
  - Mild anemia in normal individuals
  - Severe in chronic anemia (sickle cell)



# Parvovirus B19

- Fetus especially vulnerable to B19
  - Shortened RBC half-life
  - Expanding RBC volume
  - Immature immune system
- Miscarriage, fetal death





# Parvovirus B19

- Most intrauterine parvovirus infections cause no harm
- May cause fetal loss in early pregnancy
- After 20 weeks: **hydrops fetalis**
  - Fluid accumulation in fetus
  - Ascites, pleural, etc.
  - Often diagnosed on ultrasound
  - “Immune hydrops” from Rh mismatch
  - Many non-immune causes including B19

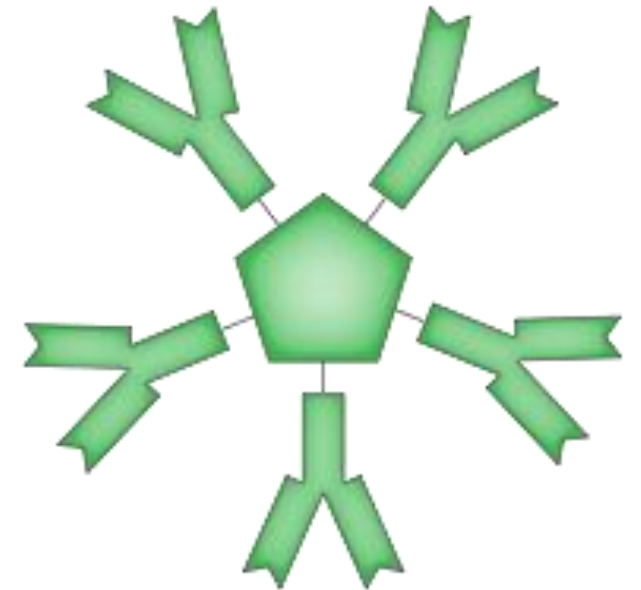


Toni Kasole Lubala, Nina Lubala, Arthur Ndundula Munkana.  
Adonis Muganza Nyenga, Augustin Mulangu MutomboT

# Parvovirus B19

## Diagnosis and Management

- Diagnosis: **antibody testing**
  - Maternal parvovirus IgM antibodies indicate acute infection
  - Positive 10 days after exposure, prior to onset of symptoms
- Most sensitive test: amniocentesis for B19 DNA
- Management in first half of pregnancy: reassurance
  - No proven risk of anomalies
  - Small risk for fetal loss



# Parvovirus B19

## Diagnosis and Management

- After 20 week: **weekly ultrasounds**
  - Monitor for evidence of fetal hydrops
  - Doppler assessment middle cerebral artery peak systolic velocity
  - High velocity seen with anemia
- Treatment (baby): **intrauterine RBC transfusion**



# Varicella Zoster Virus

- Herpes virus infection
- Primary: **chickenpox**
- Reactivation: herpes zoster (shingles)
- Maternal **first trimester chickenpox** → fetal infection
  - Rare due to vaccination
  - Risk only with chickenpox; zoster does not impact baby

# Varicella Zoster Virus

## Newborn Clinical Features

- Seen with maternal infection during 1<sup>st</sup> trimester
- Vesicular rash or scarring
- Microcephaly, hydrocephalus, seizures
- Ocular abnormalities (cataracts, nystagmus)
- Limb atrophy and hypoplasia
- Long term: learning disabilities or intellectual impairment

Chickenpox



# Varicella Zoster Virus

## Diagnosis and Treatment

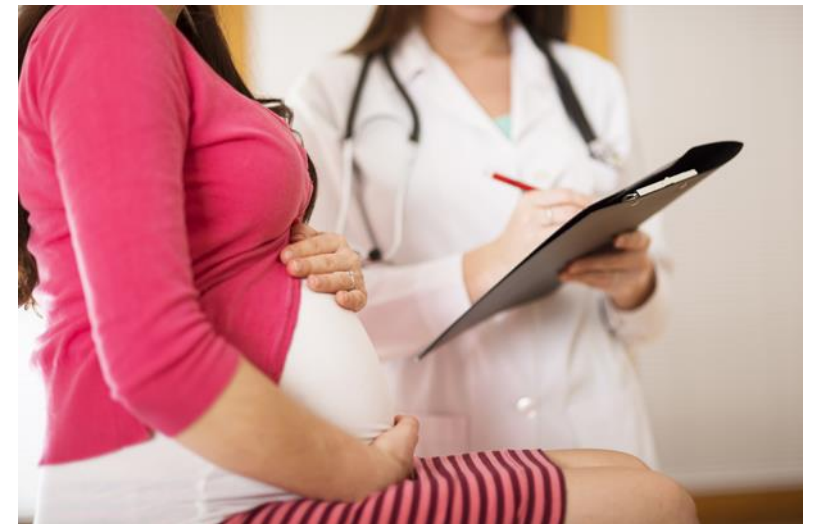
- Clinical diagnosis in mother
- Treatment: **acyclovir**
- Exposure in nonimmune woman: **Varizig**
  - Varicella-zoster immune globulin
  - Not indicated if prior vaccination





# TORCH Screening

- Standard first prenatal visit: **rubella, varicella and syphilis**
  - Rubella: antibodies
  - Varicella: antibodies
  - Syphilis: RPR/VDRL
- Additional testing varies by practice
  - Toxoplasmosis, HSV, B19, CMV
- Rubella and varicella: live vaccines
- Immunization not done during pregnancy



# Perinatal Infections

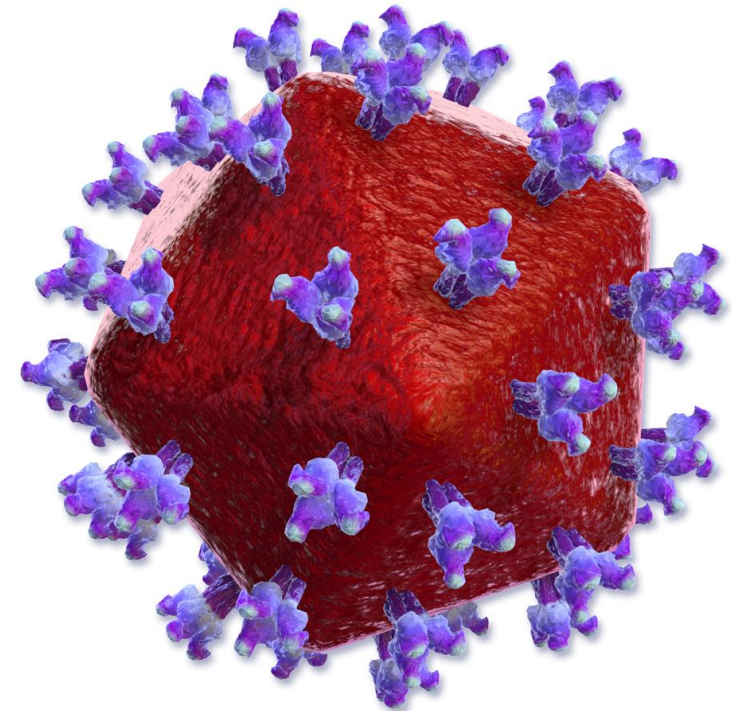
Jason Ryan, MD, MPH





# Maternal HIV

- Placental transmission to baby may occur
- HIV+ mothers treated for prevention
- Prenatal HIV testing: “opt out” approach per CDC
- Unless women decline, HIV testing performed



**Human Immunodeficiency Virus (HIV)**

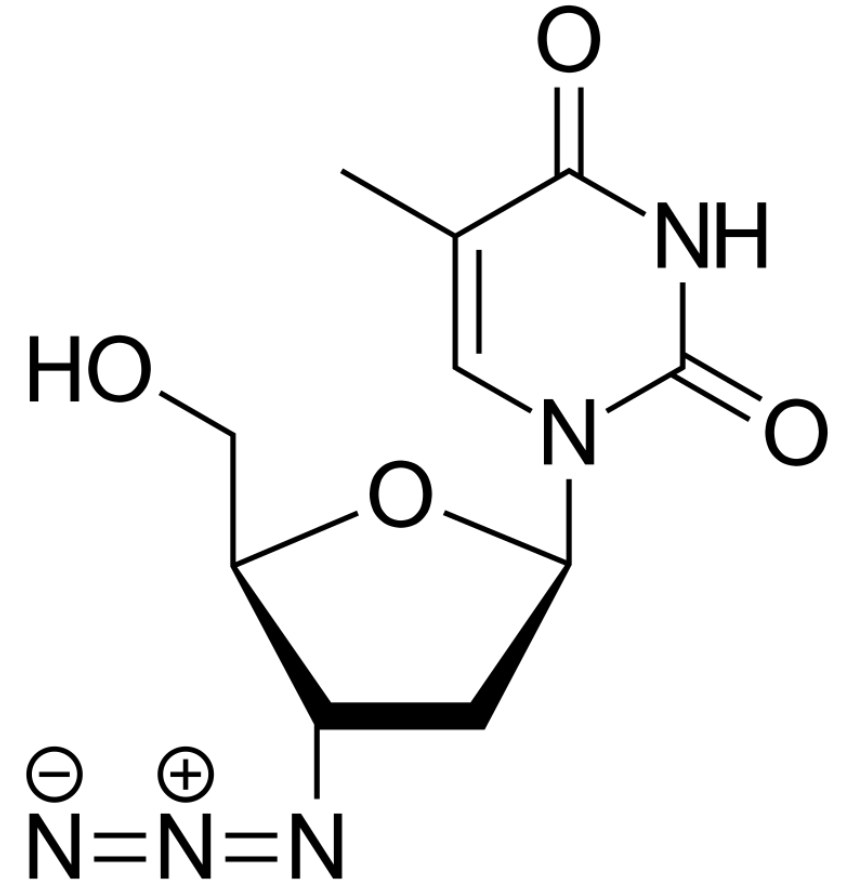
# Maternal HIV

- **All HIV+ mothers** should receive **antiretroviral therapy (ART)**
- Mothers already on ART with low viral load: continue ART
- Treatment naïve mothers: **initiate ART**
  - NRTI backbone (abacavir/lamivudine or tenofovir/emtricitabine)
  - Plus protease inhibitor (atazanavir or darunavir) or integrase inhibitor (raltegravir)
- Continue ART through the postpartum period

# Zidovudine

## Azidothymidine (AZT)

- Crosses the placenta
- Provides prophylaxis to the fetus
- Intravenous zidovudine used intrapartum
- ↓ transmission when HIV RNA  $\geq 1000$  copies/mL



# Maternal HIV

## Delivery

- Viral load  $\leq$  1000 copies/mL on ART: vaginal delivery low risk
  - C-section usually not recommended
  - IV zidovudine not routinely administered
- **Viral load > 1000 copies/mL at time of delivery**
  - Schedule C-section
  - Administer IV zidovudine during delivery
- Newborn therapy
  - Maternal viral load < 50: **zidovudine for 4 to 6 weeks after birth**
  - Maternal viral load > 50: combined ART therapy (two or three drug regimen)

# Hepatitis B

- Transplacental infection may occur
- HBsAg testing performed at first prenatal visit
- Infection at birth often leads to chronic disease
- All babies receive hepatitis B vaccine at birth
- Babies born to hepatitis B + mothers:
  - **HBIG**
  - **HBV vaccine**



# Hepatitis C

- Transplacental infection may occur
- Less common than hepatitis B
- Only occurs in women with detectable HCV RNA during pregnancy
- No interventions shown to reduce vertical transmission
- Only prevention is **pre-pregnancy treatment** for chronic hepatitis C

# Chlamydia

- Maternal infection associated with adverse outcomes
  - PPRM, preterm delivery, low-birthweight
- Most women with are asymptomatic
- All patients screened at first visit
- Cervical swab for nucleic acid amplification testing (NAAT)
- Treatment: **azithromycin** (1 gram orally as single dose)
- Treat all partners
- Test of cure two weeks after treatment



# Chlamydia

- Maternal infection transmitted to baby during vaginal delivery
- May cause newborn **conjunctivitis** or **pneumonia**
- Conjunctivitis occurs 5 to 14 days after birth
  - Prophylactic erythromycin eye ointment not effective for prevention
- Pneumonia occurs 4 to 12 weeks after birth
  - About half have history of conjunctivitis
  - Cough and nasal congestion may begin 2 weeks after birth



# Chlamydia

- Diagnosis (newborn): conjunctival and nasopharyngeal swabs
  - Sent for nucleic acid amplification testing (NAAT)
- Treatment: **oral erythromycin**

# Gonorrhea

- Most women (70%) are asymptomatic
- May cause vaginal pruritus, discharge, or dysuria
- Maternal infection in pregnancy associated with adverse outcomes
  - Chorioamnionitis
  - Premature rupture of membranes
  - Preterm birth
  - Low birth weight
  - Spontaneous abortions

# Gonorrhea

- Diagnosis: cervical swab for **nucleic acid amplification testing (NAAT)**
- Treatment: **ceftriaxone** plus **azithromycin**
- Resistance common to single agent therapy
- Treat all partners
- Test of cure two weeks after treatment

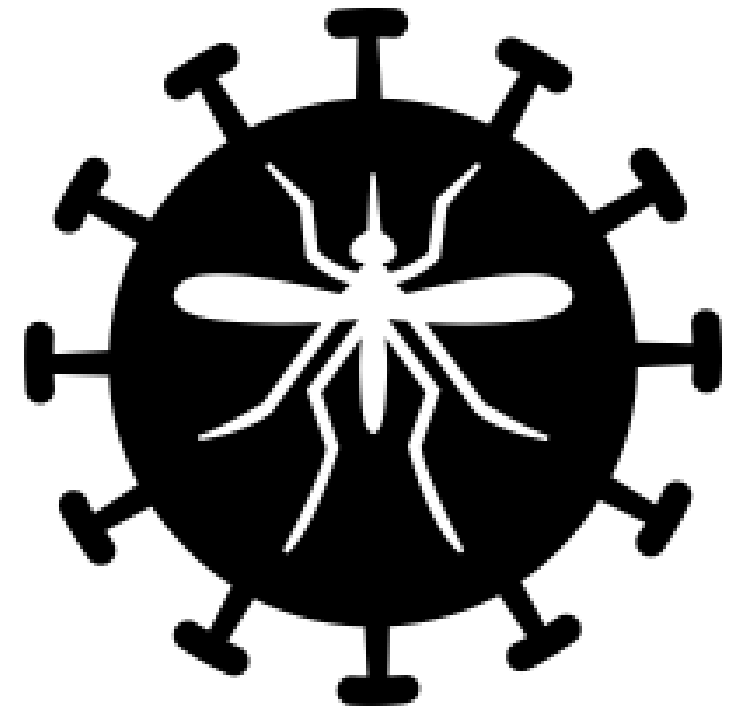
# Gonorrhea

- Newborn infection causes **conjunctivitis**
- Occurs days 2 to 5
- Prophylaxis: erythromycin eye ointment at birth
- Treatment: **ceftriaxone** (single dose IM or IV)



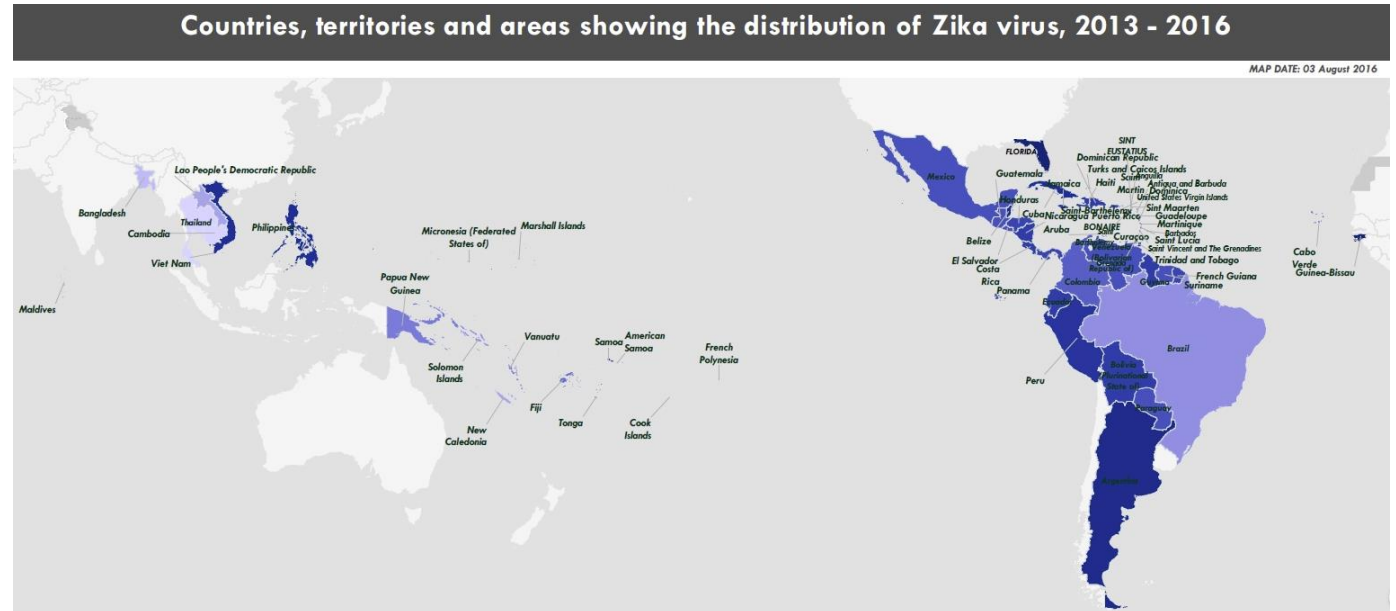
# Zika Virus

- Usually transmitted via mosquito bite
- Most dangerous in 1<sup>st</sup> trimester
- Infected mothers usually asymptomatic
- Virus infects **fetal brain**
  - Microcephaly
  - Thin cerebral cortices
  - Intracranial calcifications
- Classically baby will have **closed anterior fontanelle**



# Zika Virus

- Diagnosis: PCR testing of newborn serum, urine or CSF
- Treatment: supportive
- Prevention: **avoid travel to endemic areas**
- Central and South America





# Abortion

Jason Ryan, MD, MPH



# Spontaneous Abortion

## Miscarriage, SAB

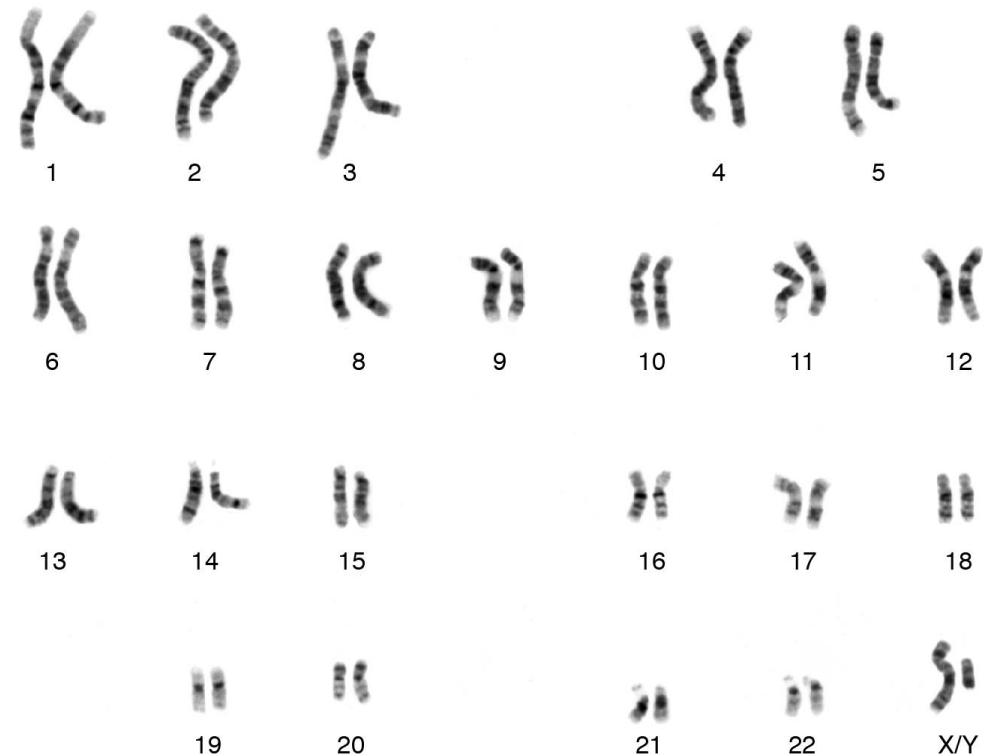
- Loss of viable uterine pregnancy prior to 20 weeks
- Occurs most commonly in first trimester (before 12 weeks)
- Often identified by falling serial hCG levels or ultrasound findings
- Presents clinically as **vaginal bleeding** and **pelvic cramping**



# Spontaneous Abortion

## Etiology

- **Fetal chromosomal anomalies**
  - Found in ~ 70% pregnancy losses
- Maternal anatomic anomalies
  - Uterine fibroids
  - Uterine polyps or septa
- Abnormal implantation
- Corpus luteum failure
- TORCH infections
- Trauma



# Spontaneous Abortion

## Risk Factors

- Maternal age > 35 years
- Prior pregnancy loss
- Smoking and alcohol consumption
- Maternal disease
  - Infection
  - Diabetes
  - Obesity
  - Thyroid
  - Thrombophilias



# Spontaneous Abortion

## Workup

- **Pelvic exam**
  - Confirm bleeding from cervix
  - Assess cervical os
  - Open os = loss of pregnancy likely
- **Transvaginal ultrasound**
  - Assess for products of conception
  - Assess fetal heartbeat
- Serial hCG and progesterone level
  - HCG should  $\uparrow$  at least 60% over 48 hrs
  - $\downarrow$  progesterone associated with failed gestation or ectopic

## Transvaginal Ultrasound



# Complete Spontaneous Abortion

- Documented intrauterine pregnancy
- Bleeding and cramping
- **Closed cervical OS**
- **No products of conception (POC) evident**
- No evidence of ectopic pregnancy
- Management: supportive
  - Antibiotics in some cases
  - Methylergonovine may be used: ↓ retained tissue and infection risk

# Other Abortion Types

Type	Findings	
Threatened	Bleeding and cramping <b>Closed os</b> Fetal heartbeat if older than 6 weeks	Supportive care May stop or progress
Inevitable	Bleeding and cramping Open os Fetal heartbeat present	Surgery Medical Expectant
Incomplete	Bleeding and cramping Open os No fetal heartbeat; POC partially expelled	
Missed	Bleeding and Cramping Closed os No fetal heart beat; POC retained	

# Threatened Abortion

- Bleeding in early pregnancy (< 20 weeks)
- **Cervical os closed**
- **Pregnancy still viable**
- May resolve or progress to spontaneous abortion
- Weekly ultrasounds and serial hCGs until bleeding resolves
- Increased risk of preterm labor or IUGR
- Common causes of bleeding that resolves:
  - Implantation at time menses
  - Cervical trauma during intercourse
  - Subchorionic hemorrhage



# Spontaneous Abortion

Inevitable, Incomplete, Missed

- Surgical evacuation: **dilation and suction curettage**
- Medical evacuation: **mifepristone and misoprostol**
- Mifepristone: progesterone antagonist
  - Causes endometrial degeneration
  - Only dispensed to limited facilities that perform terminations
- Misoprostol: prostaglandin E1 analog
  - Causes uterine contractions
  - Must be hemodynamically stable
  - Must have no evidence of hemorrhage or infection
- Expectant management: allow natural passage of POC

# Septic Abortion

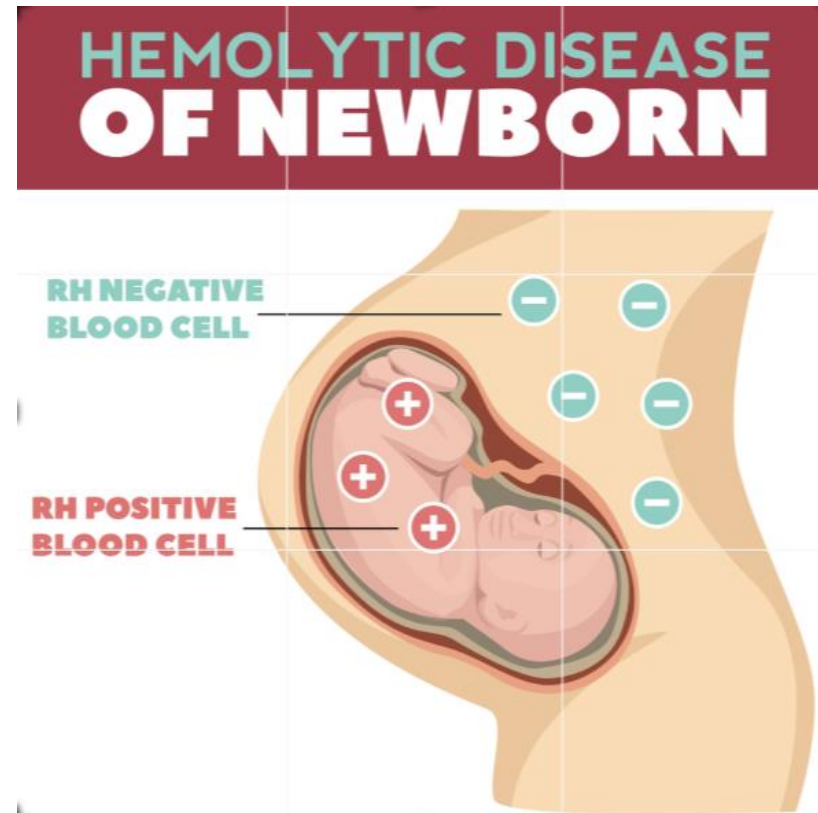
- Spontaneous abortion with **intrauterine infection**
- May occur with attempted self-abortion
- Vaginal bleeding and pelvic cramping
- **Fever and foul-smelling discharge**
- Treated with broad-spectrum antibiotics
- Surgical evacuation with **suction curettage**
  - Increased risk of uterine perforation
  - Suction less traumatic than sharp curettage



# Spontaneous Abortion

## Alloimmunization prevention

- Rh negative mothers administered Rh (D) immune globulin



# Intrauterine Fetal Demise

## Stillbirth or Fetal Death

- Pregnancy loss **after 20 weeks**
- Death before delivery
  - During delivery: intrapartum demise
- Mother may note lack of movement
- Uterus may be small for gestational age
- Suspected by absence of fetal heart sounds
- Diagnosis: **ultrasound**
  - Will show absence of fetal heartbeat

# Intrauterine Fetal Demise

## Selected Risk Factors

- Most cases have no identifiable etiology
- Congenital anomalies
- Fetal growth restriction
- Maternal infection – systemic or in utero
- Placental abruption
- Maternal chronic disease
- Cord accidents
- Drugs, especially crack cocaine

# Intrauterine Fetal Demise

## Management

- Before 24 weeks: **dilation and evacuation (D&E)**
- After 24 weeks: **induction of labor**
  - Preferred route even if baby is breech
- Traumatic for families
- May allow **delay until patient is ready**
- Prolonged retention of fetus **over weeks** may cause DIC

# Intrauterine Fetal Demise

## Further Workup

- Fetal autopsy
- Placental examination
- Drug screen
- Fetal chromosome testing
- Testing for antiphospholipid syndrome
- Testing for fetomaternal hemorrhage

# Fetomaternal Hemorrhage

- Bleeding without trauma or abruption
- Large hemorrhage can present as fetal death
- Diagnosis: **Kleihauer-Betke acid elution assay**
  - Test of red cells in maternal circulation
  - Detects hemoglobin F in fetal red cells
  - Reports percentage fetal red cells in circulation
- Alternative: flow cytometry
  - Uses monoclonal antibody to hemoglobin F



# Recurrent Pregnancy Loss

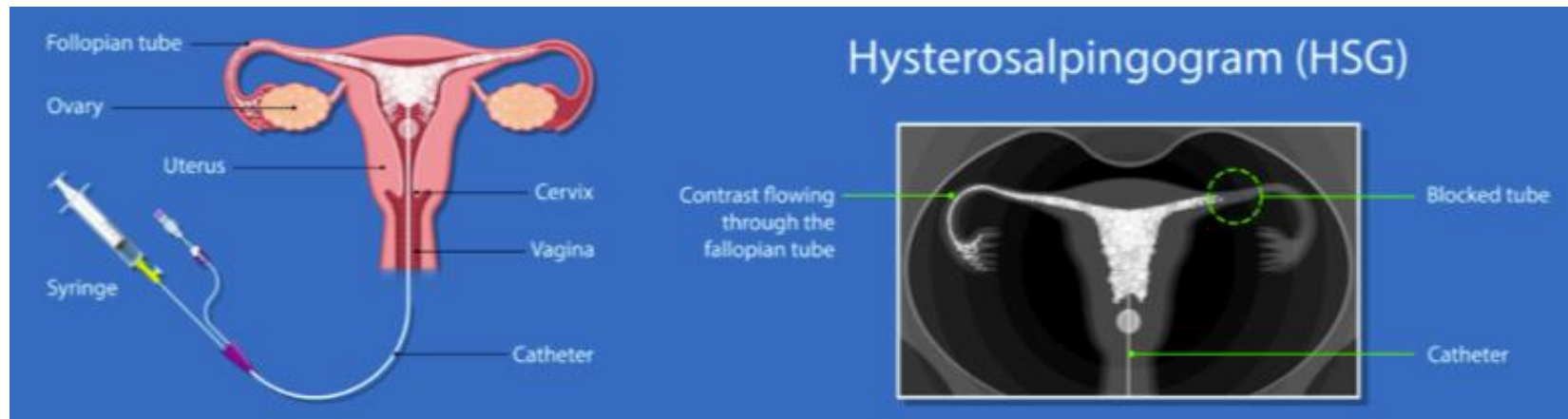
- Three or more consecutive pregnancy losses
- Many potential causes

Uterine	- Polyps/fibroids/adhesions - Cervical insufficiency
Genetic	- Aneuploidy - Parents with balanced or Robertsonian translocations
Immunologic	- Antiphospholipid syndrome
Endocrine	- Uncontrolled diabetes - Hypothyroidism
Hematologic	- Inherited or acquired hypercoagulable states

# Recurrent Pregnancy Loss

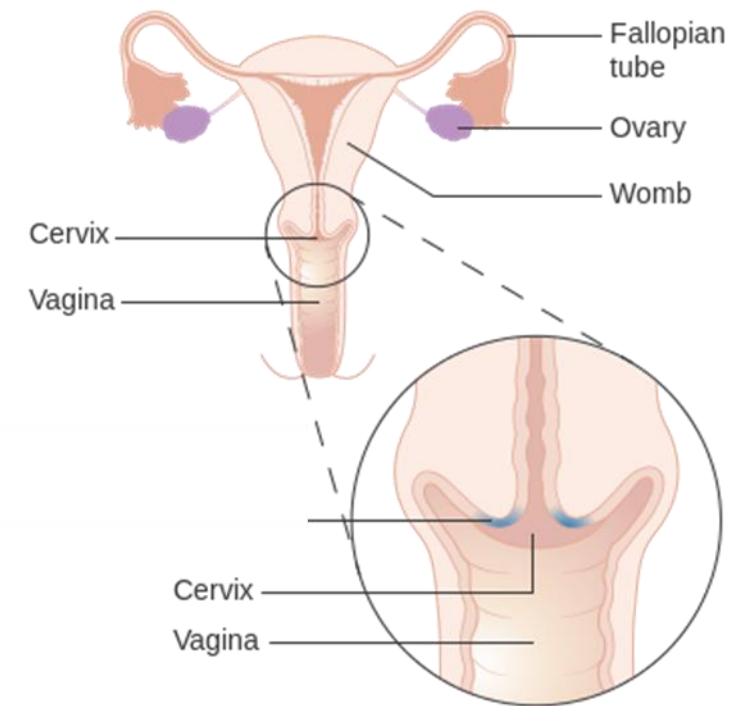
## Selected Common Testing

- Uterine **hysterosalpingography** or **sonohysterography**
  - Hysterosalpingography: fluoroscopy of uterus and fallopian tubes
  - Sonohysterography: ultrasound of uterus filled with saline contrast
- Karyotype of parents
- Anticardiolipin antibodies and lupus anticoagulant
- TSH



# Cervical Insufficiency

- Inability of cervix to retain pregnancy in second trimester
- Recurrent **second-trimester pregnancy losses**
- **Mild symptoms** with pregnancy loss
- Absence of significant bleeding, cramping or contractions
- Contrast with spontaneous abortion
  - Often < 20 weeks
  - Often associated with cramping and contractions



# Cervical Insufficiency

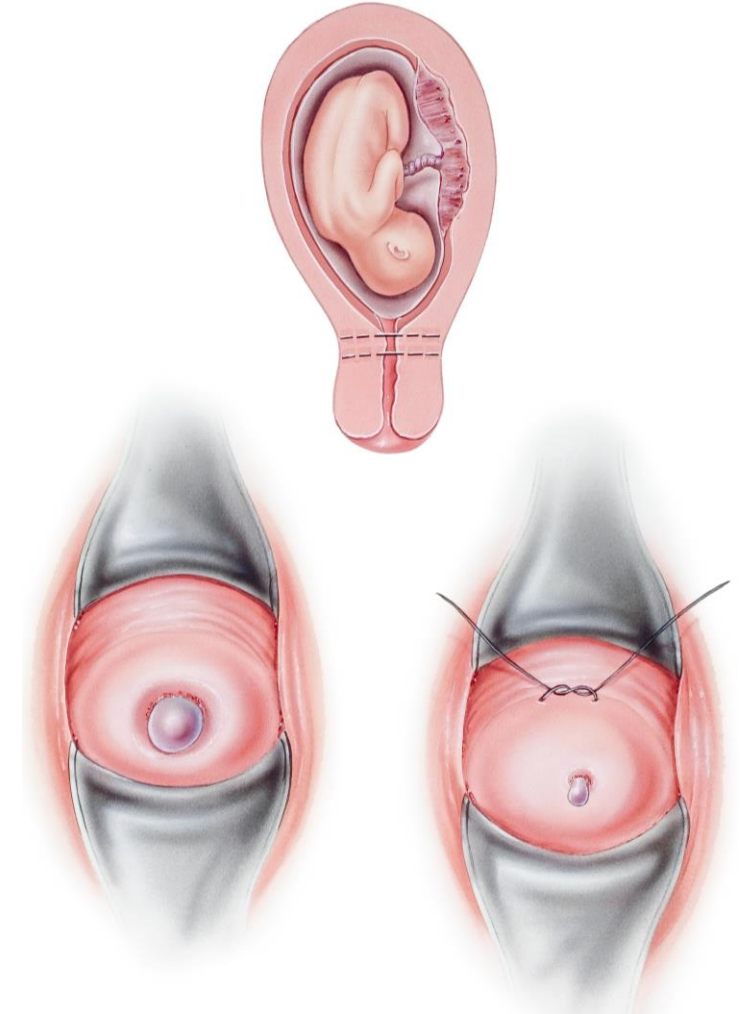
## Diagnostic Criteria

Method	Criteria
Obstetric History	≥2 consecutive second-trimester losses No or mild symptoms
Ultrasound	Second-trimester cervical length < 25mm Plus prior loss or preterm delivery
Physical Exam	Dilated and effaced cervix in early pregnancy

# Cervical Insufficiency

- Treatments: **cerclage** and **vaginal progesterone**
- Cerclage: cervical stabilization with stitching
- **Avoid exercise during pregnancy**

Cervical Cerclage



# Elective Abortion

- Legalized in the U.S. in 1973 case Roe v. Wade
- Performed before 24 weeks (fetal viability)
  - Extra-uterine survival before 24 weeks less likely
  - After 24 weeks survival more likely
  - “Late-term” abortions occur 21 to 24 weeks
- Medical and surgical options
- Medical abortion (less than 10 weeks): mifepristone/misoprostol

# Ectopic Pregnancy

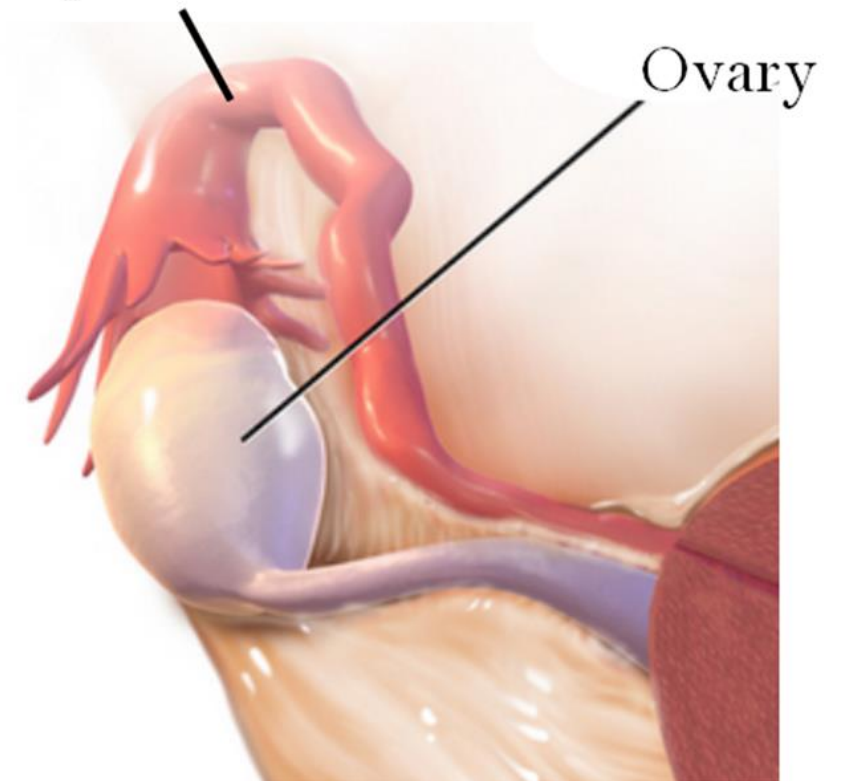
Jason Ryan, MD, MPH



# Ectopic Pregnancy

- Pregnancy outside the endometrium and uterus
- Most common location (98%): **fallopian tube**
  - 80% ampulla (mid portion)
  - 10% isthmus
  - 5% fimbriae
- Rarely abdominal, cervical or cesarean scar

Fallopian tube





# Ectopic Pregnancy

- Symptoms in 1<sup>st</sup> trimester
- Vaginal bleeding
- Abdominal pain (may mimic appendicitis)
- Abnormal  $\uparrow$  hCG based on dates
  - Smaller than expected increase with ectopic
  - Should double every 72 hours
  - $\uparrow$  less than 35% in 48 hours suggests ectopic

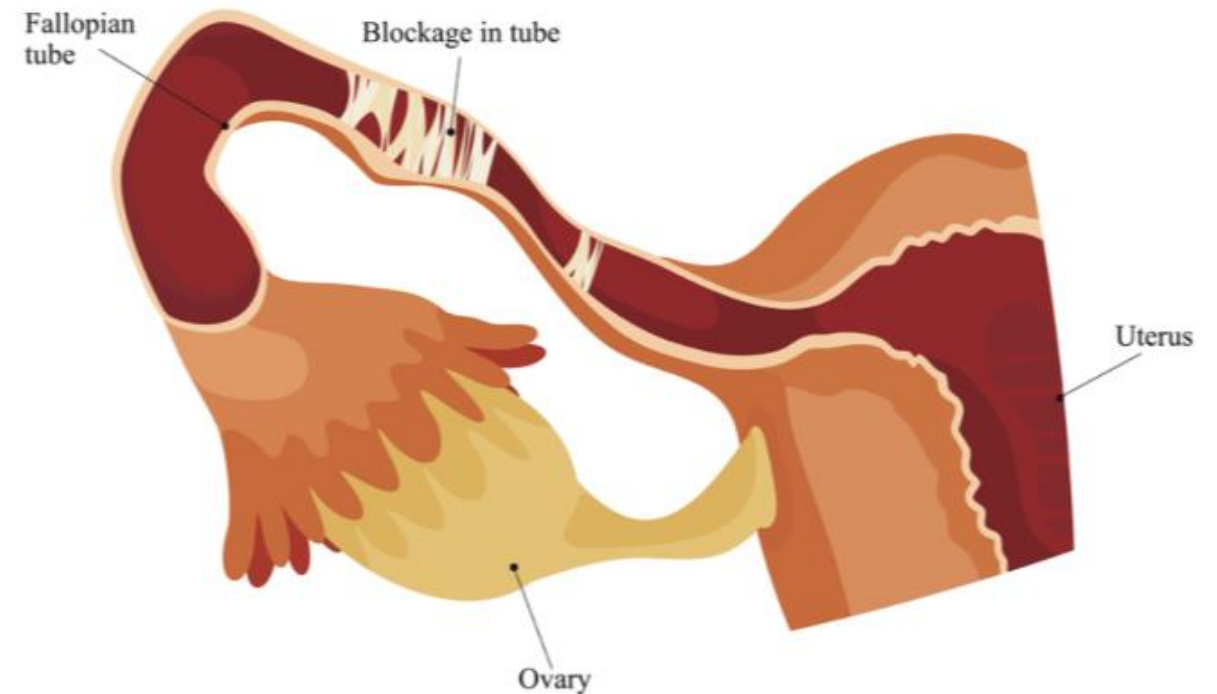


# Ectopic Pregnancy

## Risk Factors

- Damage to fallopian tube
- Prior ectopic pregnancy
- Tubal obstruction
  - Tubal ligation (rarely pregnancy occurs)
  - Tubal surgery (tumor)
  - Pelvic inflammatory disease
- Intrauterine device
  - Lower risk for pregnancy overall
  - If pregnancy occurs, higher risk ectopic

FALLOPIAN TUBE OBSTRUCTION



# Ectopic Pregnancy

## Diagnosis

- Suspected based on + hCG, abdominal pain and bleeding
- Best first test: **transvaginal ultrasound**
  - Classic finding: adnexal mass
  - Excludes intrauterine pregnancy
  - No IUP plus hCG > 1,500 = ↑ likelihood of ectopic pregnancy
  - Note: *transabdominal* ultrasound unreliable



# Ectopic Pregnancy

## Diagnosis

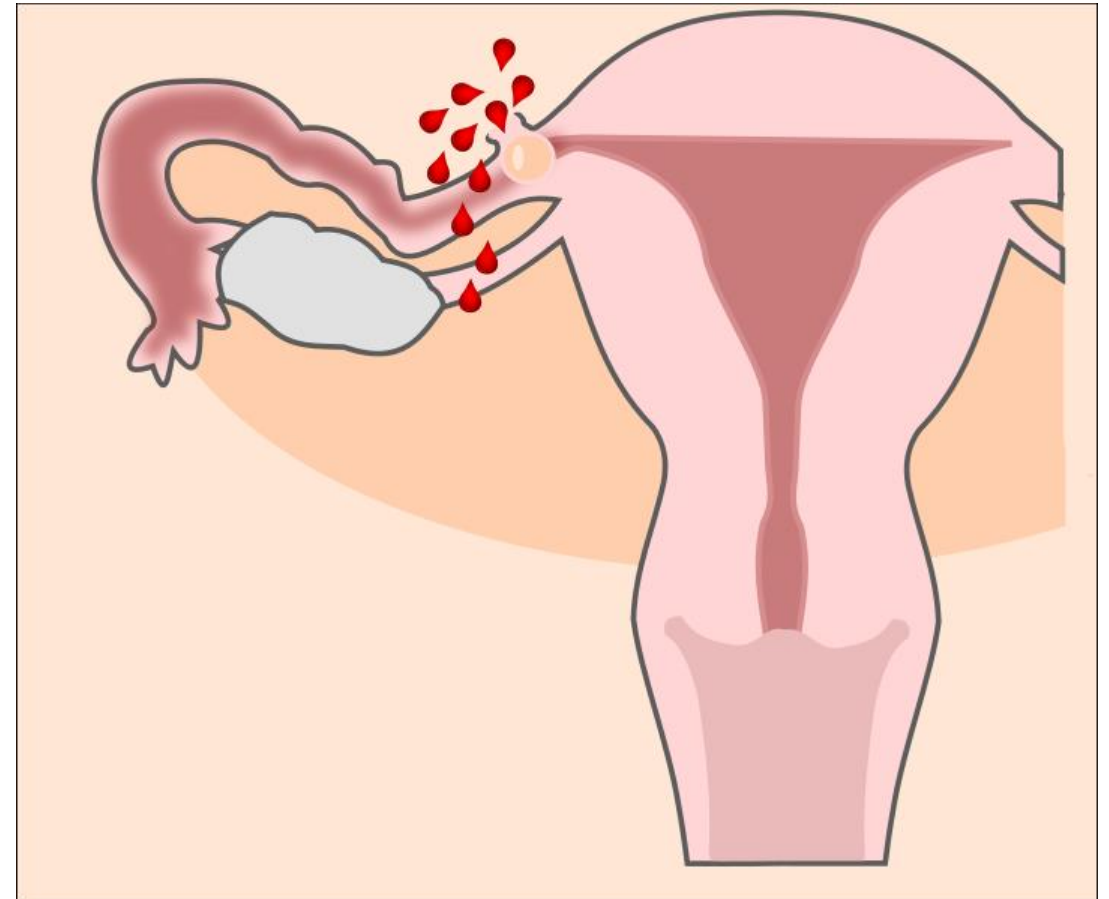
- TVUS may be **non-diagnostic**
  - Pregnancy may be too small to localize
  - Or spontaneous abortion may have occurred
- **Follow hCG levels**
  - Usually measured every 48 hours
  - Falling levels indicate nonviable pregnancy
  - Slowly rising levels suggest ectopic
- **Repeat TVUS**
  - Identify intrauterine or ectopic

## Transvaginal Ultrasound



# Tubal Rupture

- Feared complication of ectopic pregnancy
- May cause life-threatening **hemorrhage**
- Severe abdominal pain
- Rebound tenderness and guarding
- Hypotension





# Ectopic Pregnancy

## Treatment

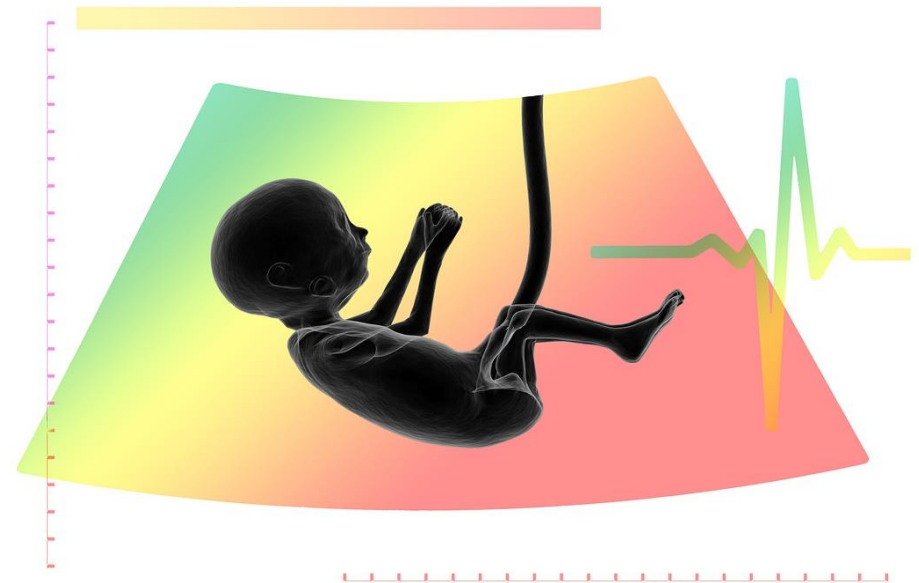
- Definitive treatment: **surgery**
  - Hemodynamically unstable
- Medical therapy: **methotrexate**
  - Stable patients in early pregnancy



# Surgery

## Ectopic pregnancy treatment

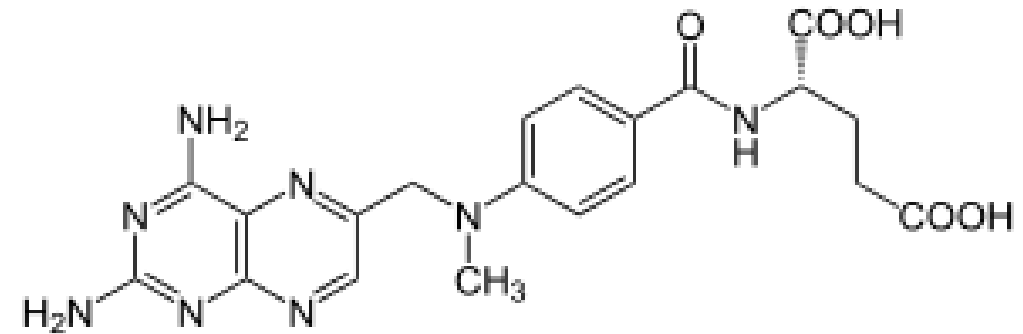
- Salpingectomy: removal of fallopian tube
- Salpingotomy: creation of opening in fallopian tube
- Indications:
  - **Hemodynamic instability**
  - hCG > 5000
  - Fetal cardiac activity on TVUS
  - Evidence of rupture (severe pain, free fluid on US)
  - Intolerance to MTX
  - Patient unreliable to follow-up



# Methotrexate

## Ectopic pregnancy treatment

- **Stable patients with hCG < 5,000**
- No contraindications to methotrexate
  - Immunodeficiency
  - Hematologic disease
- No liver or kidney disease
- No co-existing intrauterine pregnancy (heterotopic)
- Patient must be able to comply with follow-up
- hCG and ectopic size increase for up to 4 days
- Begin to decrease after 4 days
- Follow hCG twice weekly to zero



Methotrexate



# Methotrexate

## Ectopic pregnancy treatment

- Single IM 50 mg/m<sup>2</sup> dose given day 1
  - Lower dose than for chemotherapy
  - Leucovorin may be given in some cases
- hCG checked days 4 and 7
- hCG should decline until undetectable
- Inadequate decline: 2<sup>nd</sup> dose given



# Gestational Trophoblastic Disease

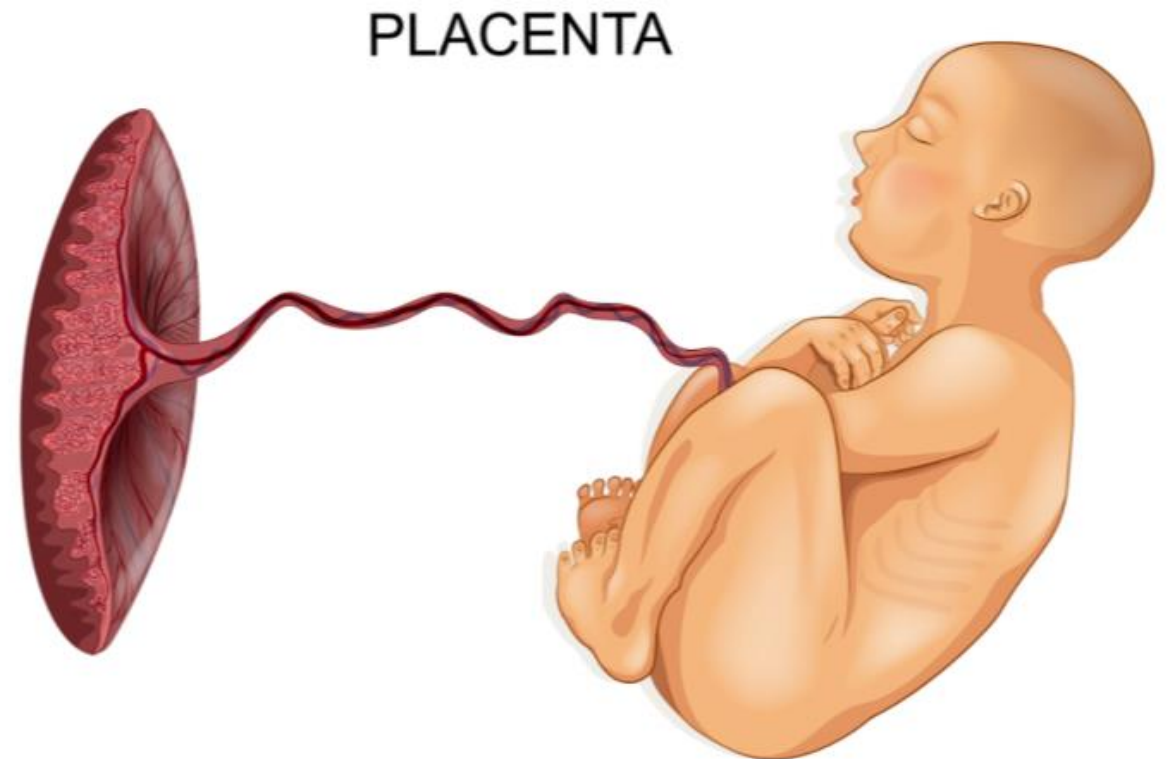
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# GTD

## Gestational Trophoblastic Disease

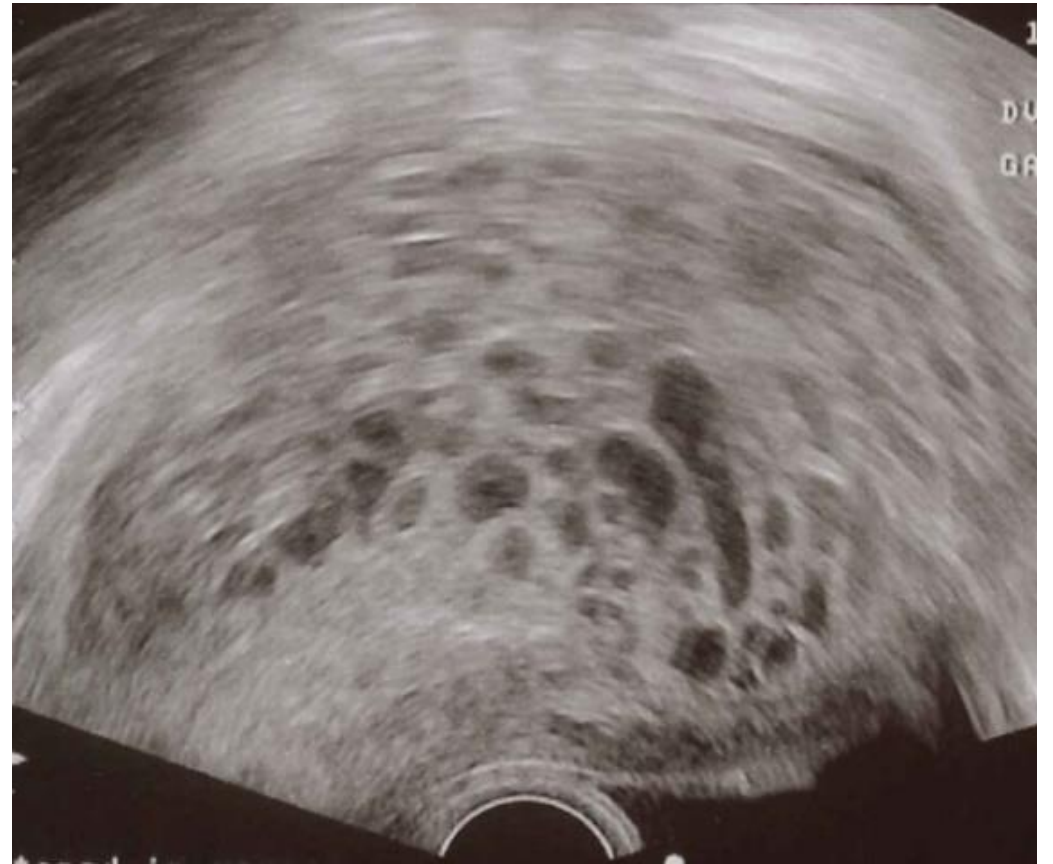
- Rare variant of pregnancy
- Neoplasms of trophoblast (placenta)
- Usually benign (molar pregnancy)
- Rarely malignant



# Hydatidiform Mole

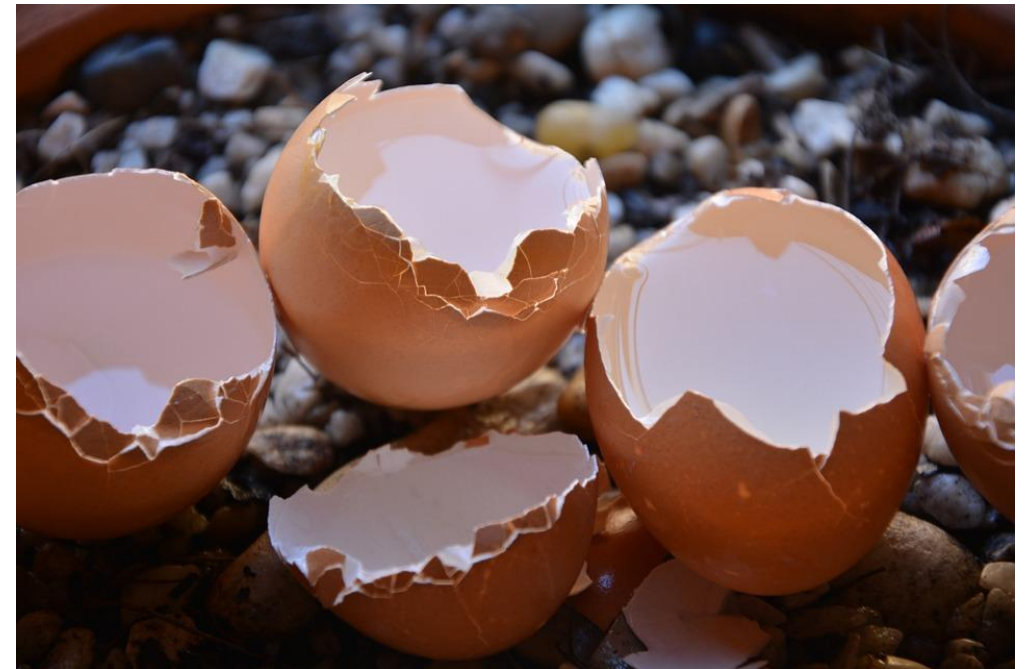
## Molar Pregnancy

- Most common form of GTD
- Hydatid = fluid filled cyst
- Mola = Greek for “false pregnancy”
- Growth of trophoblast tissue
- Swollen chorionic villi
- Villi form clusters - “clusters of grapes”
- Ultrasound: “snowstorm appearance”



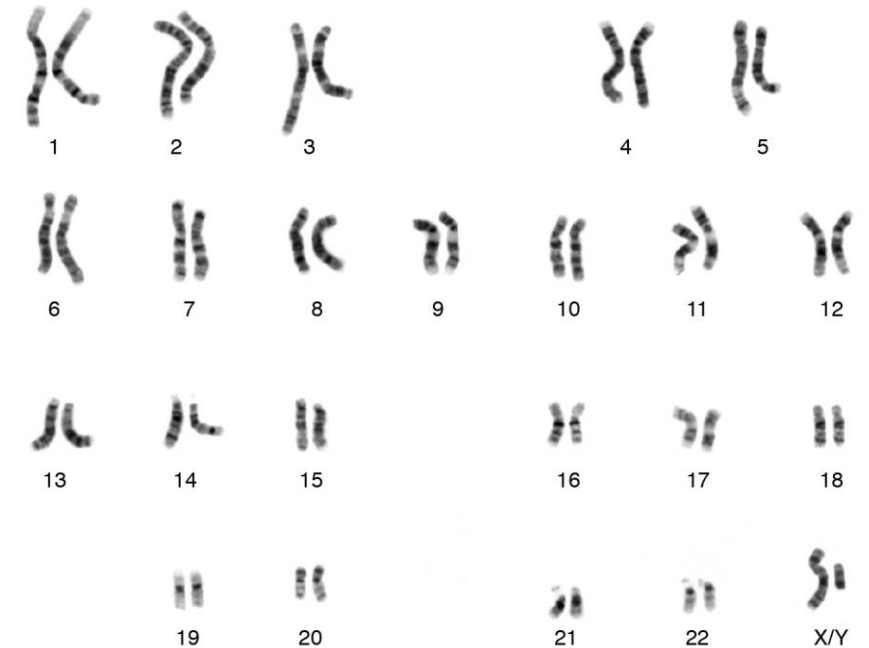
# Complete Mole

- Most common form of molar pregnancy
- Fertilization of “empty” egg
- All chromosomes of paternal origin
- No maternal chromosomes
- No fetal tissue
- Maternal chromosomes needed for fetal tissue
- No fetus to drain villi = massively swollen villi



# Complete Mole

- Cells usually **46, XX karyotype**
- Haploid sperm that duplicates
- 23 X → 46 XX
- 46,YY does not occur → lethal
- Rarely 46,XY moles occur
  - Empty egg fertilized by two sperm
- **p57-negative** on immunostaining
  - Cyclin dependent kinase
  - Only expressed by maternal chromosomes

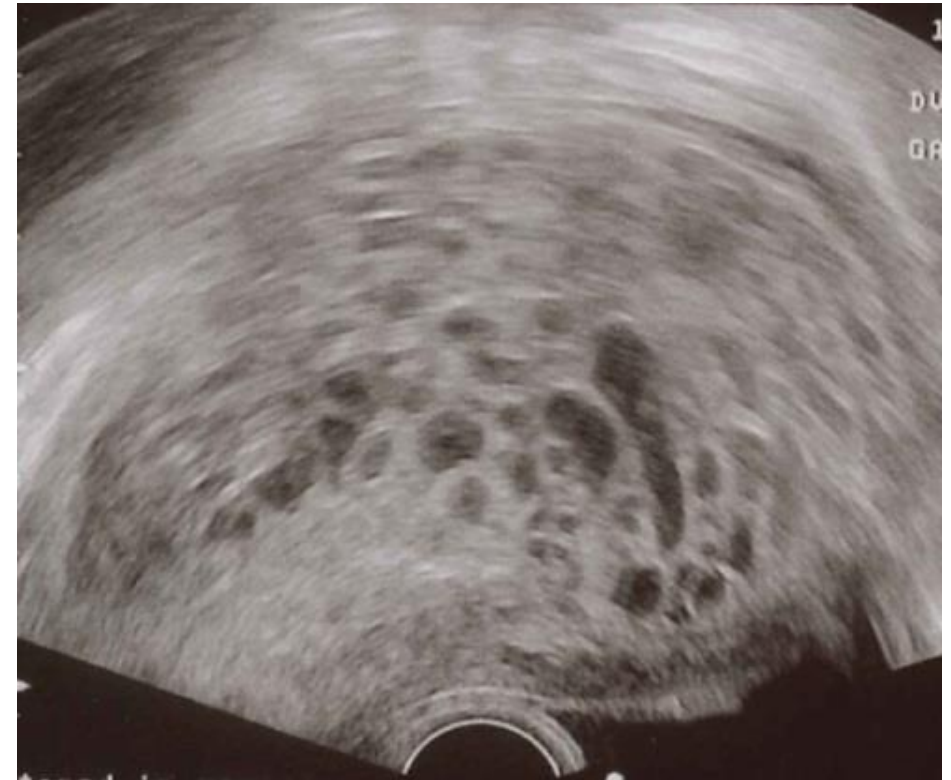




# Complete Molar Pregnancy

## Clinical Features

- Initially may appear to be normal pregnancy
  - Positive pregnancy test; uterine enlargement
- **Size/date discrepancy of uterus**
  - Uterus too big for stage of pregnancy
- Painless uterine bleeding
  - Separation of molar villi from decidua
- These findings often lead to **ultrasound**
  - Cluster of grapes
  - Snowstorm appearance



# Complete Molar Pregnancy

## Clinical Features

- Maternal serum hCG
  - Higher than normal for gestational age
  - May be very high ( $>100,000$ ) early in pregnancy
- **Hyperemesis gravidarum**
  - Severe nausea and vomiting with weight loss
- Ovarian theca lutein cysts
  - Ovarian stimulation by hCG
  - Often bilateral



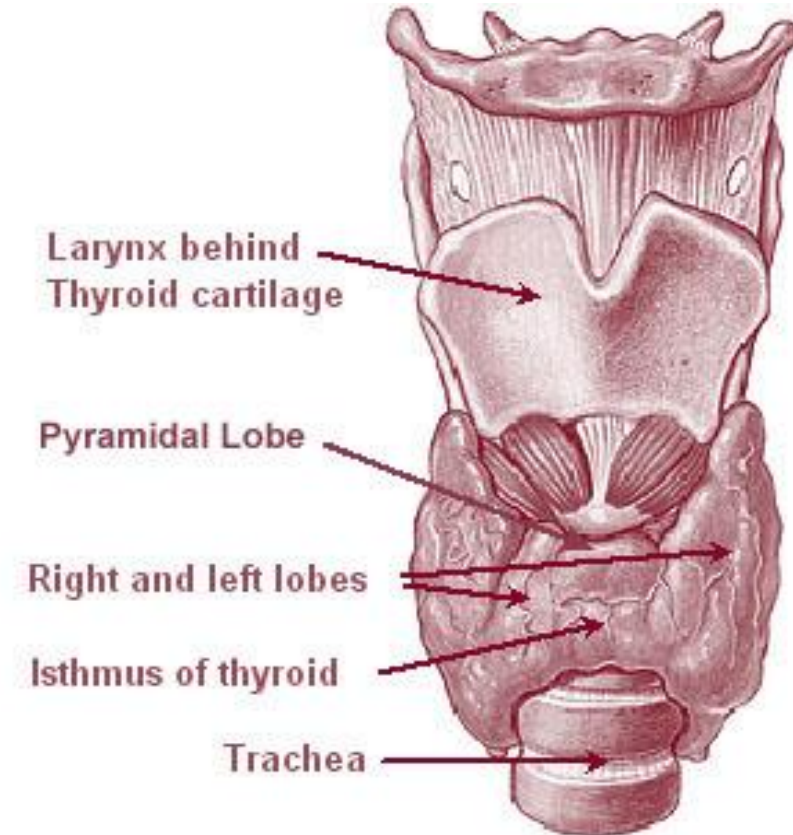


# Complete Molar Pregnancy

## Clinical Features

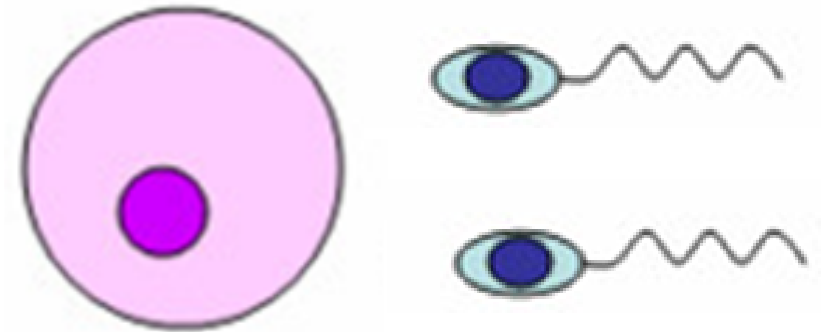
- **Hyperthyroidism**
  - Requires very high hCG
  - Rare in modern era due to early US
  - hCG stimulation of TSH receptor
  - Low TSH
  - High T3/T4
- **Preeclampsia**
  - Early development before 20 weeks

Thyroid Gland



# Partial Mole

- Less common form
- Fertilization of normal egg by two sperm
- Some fetal tissue (maternal chromosomes)
- Some villi drainage = less swollen villi
- Cells usually triploid
  - 69, XXX
  - 69, XXY
  - Rarely 69, XYY
- **p57-positive** from maternal genetic material



# Partial Molar Pregnancy

## Clinical Features

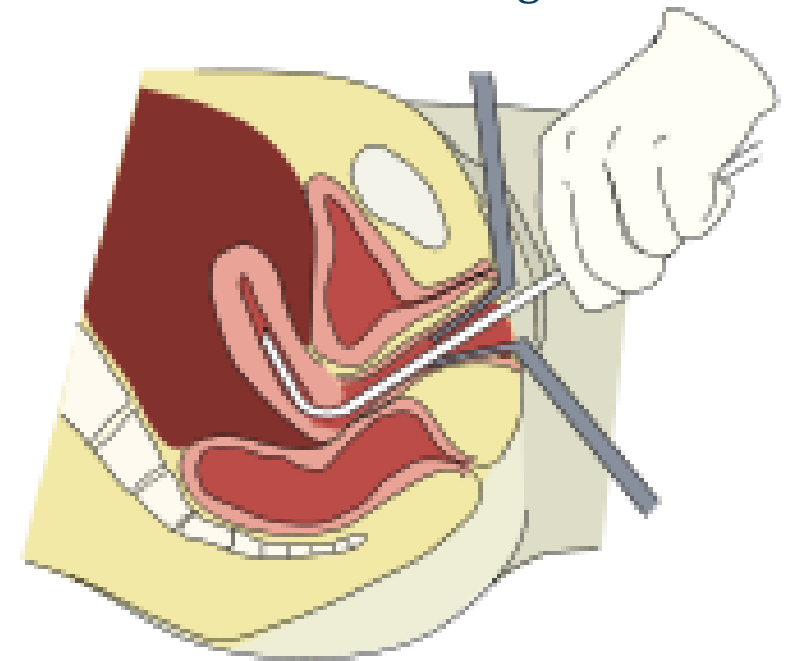
- Uterine size
  - May be normal (some villi drainage to fetus)
  - May be small for gestational age (slow growth of fetus)
- Marked ↑ hCG less common
- Diagnosis: ultrasound
  - A fetus may be identified but often small
  - Low volume of amniotic fluid
  - Abnormal placenta often with cystic spaces
  - Often diagnosed as missed or incomplete abortion

# Molar Pregnancy

## Treatment

- **Uterine suction curettage**
- Rarely hysterectomy
- Most cases do not require chemotherapy
- Chemotherapy for high-risk patients only
  - Features suggesting high likelihood of choriocarcinoma
  - Methotrexate or actinomycin D

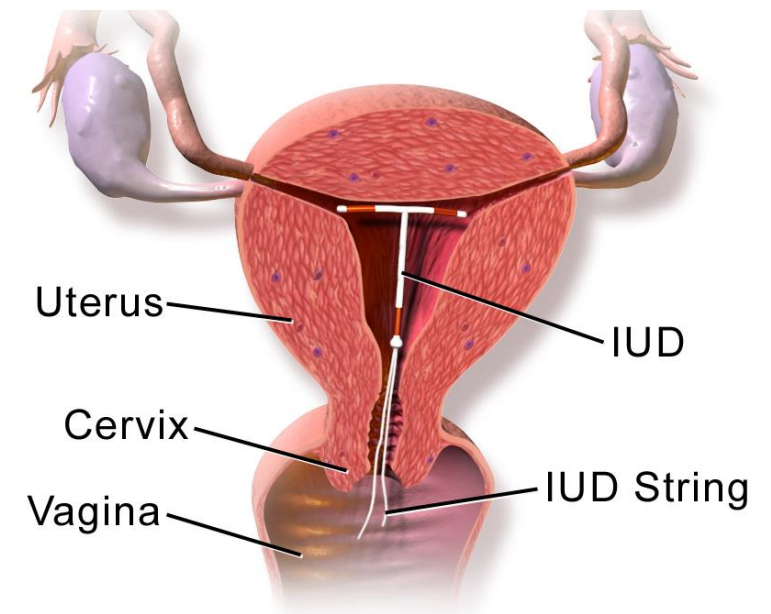
Uterine Curettage



# Molar Pregnancy

## Treatment

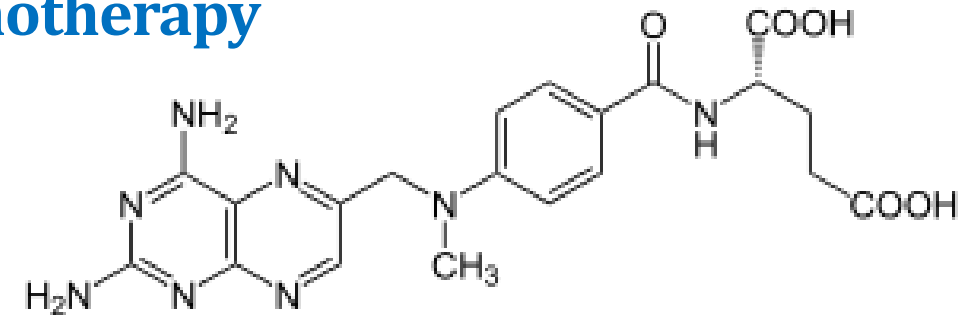
- Follow hCG until normalized - can take 6 months
- Plateau in hCG level: invasive mole or choriocarcinoma
- **Contraception**
  - New pregnancy will raise hCG
  - Unable to determine if molar pregnancy has resolved
  - Usual recommendation: no pregnancies for 1 year



**Intrauterine Device (IUD)**

# Gestational Trophoblastic Neoplasia

- Malignant trophoblastic neoplasms
- Invasive mole, choriocarcinoma and placental site trophoblastic tumor
- Present as **vaginal bleeding** and/or **↑ hCG**
- Diagnosis: **pelvic ultrasound**
  - Each has characteristic features
- Can metastasize to lung
  - Key test in workup: **chest x-ray**
- Low-risk cases respond well to **single agent chemotherapy**
  - Methotrexate or actinomycin D



Methotrexate

# Invasive Mole

- Usually occurs after a **molar pregnancy**
  - Occurs in up to 20% of patients with complete mole
  - Rarely follows partial mole, abortion or normal pregnancy
- **Swollen chorionic villi that invade the myometrium**
- May cause vaginal bleeding
- About 5% metastasize

# Invasive Mole

- Suggested by **hCG level**
  - Plateauing hCG following molar pregnancy
- Diagnosis: **pelvic ultrasound**
  - Poorly-defined mass in uterus
  - Invasion into the myometrium
- Treatment: **methotrexate or actinomycin D**
  - For women who desire additional pregnancies
- Alternative: hysterectomy



# Choriocarcinoma

- Rare malignant gestational neoplasm
- Syncytiotrophoblast and cytotrophoblast cells
- No formation of villi
- Most common after **complete molar pregnancy**
  - Rarely occurs after partial mole or normal pregnancy

Choriocarcinoma



# Choriocarcinoma

- Often identified due to **plateau in hCG trend** after molar pregnancy
- Early spread with extensive metastases
- Hematogenous spread
- 80% of case metastasize to **lungs**



# Choriocarcinoma

## Clinical Features

- **Vaginal bleeding**
- Cough, hemoptysis
- Elevated hCG level
- Possible ovarian cysts, hyperthyroidism (hCG)

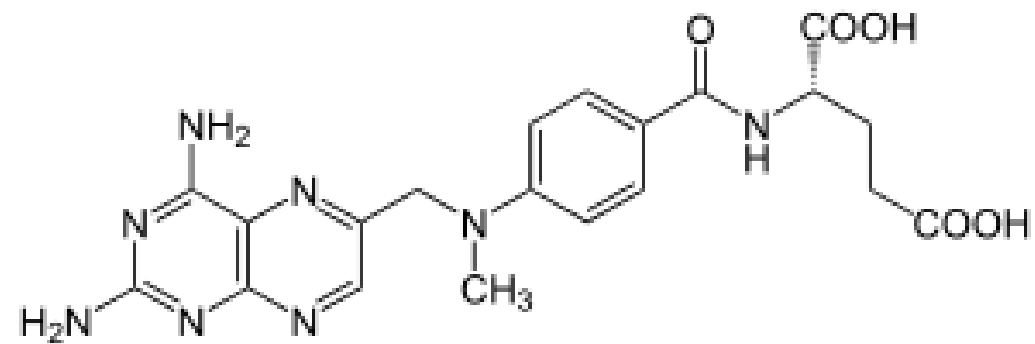
### Hemoptysis



# Choriocarcinoma

## Treatment

- Low-risk forms highly sensitive to single-agent chemotherapy
- Methotrexate or actinomycin D
- Most patients (>90%) cured with chemotherapy



Methotrexate

# Non-Gestational Choriocarcinoma

- Rare germ cell tumor
- May arise in the ovary or testes
- Germ cells differentiate into trophoblasts
- Histologically same as gestational choriocarcinoma
- Produces  $\beta$ -hCG
- Often lethal
- Difficult to treat or cure

# Placental site trophoblastic tumor

- Trophoblast proliferation without formation of villi
- Usually occurs after a **non-molar abortion or pregnancy**
- May occur months or years after pregnancy
- Secretes **low levels of hCG**
  - No syncytiotrophoblast proliferation
  - Contrast with other forms of GTD
  - Human placental lactogen (hPL) will be high

# Placental site trophoblastic tumor

- Presents as vaginal bleeding and increased **human placental lactogen**
- Normal or slightly elevated hCG
- Diagnosis: **pelvic ultrasound**
  - Intrauterine mass
  - Cystic and solid regions
- Poorly responsive to chemotherapy
- Often requires hysterectomy

# Placental Pathology

Jason Ryan, MD, MPH

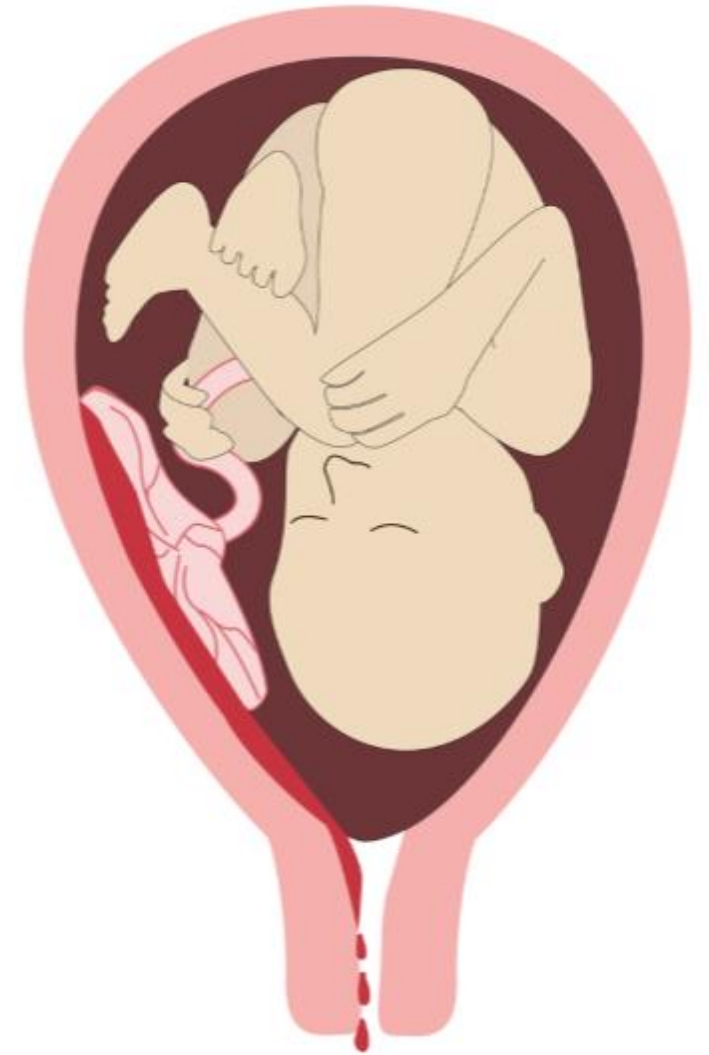




# Placental Abruption

## Abruptio Placentae

- **Placental detachment**
- Prior to delivery of baby
- Blood loss from maternal vessels
- Loss of gas and nutrient exchange
- Blood causes uterine contractions
- Life-threatening to mother and fetus



# Placental Abruption

## Risk Factors

- Previous abruption – strongest risk factor
- Chronic placental disease
  - Maternal hypertension or preeclampsia
  - Smoking
  - Cocaine
- Abnormal uterus
  - Bicornuate uterus
  - Prior C-section
- Trauma (motor vehicle accident)
- Rapid decompression (delivery of twin)

# Placental Abruption

## Clinical Presentation

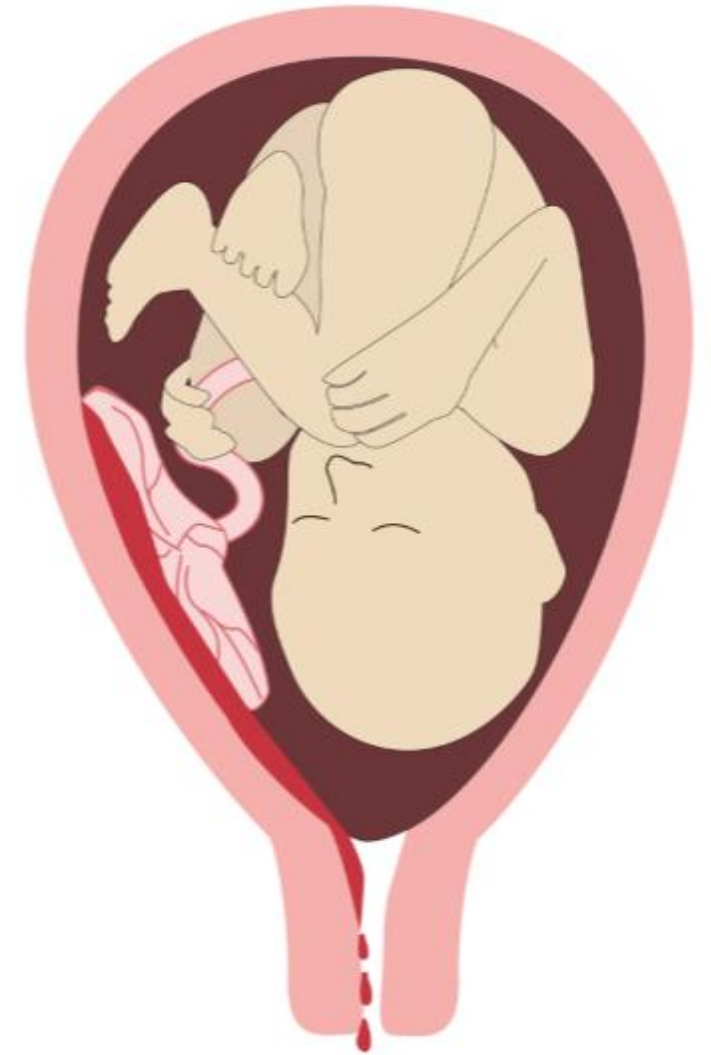
- Usually occurs in 3<sup>rd</sup> trimester
- Abrupt onset of **painful vaginal bleeding**
- Abdominal or back pain
- Uterine contractions
- Often diagnosed clinically
- Ultrasound not reliable
- Classic finding: **retroplacental hematoma**
- MRI used for imaging in some cases



# Concealed Placental Abruption

## Clinical Presentation

- **No bleeding**
- Blood trapped between membranes and decidua
- Occurs in ~20% of patients
- Presents as **preterm labor**
- Severe focal pain at site of placenta
- Uterine tenderness and rigidity



# Placental Abruption

## Complications

- Maternal shock
- Fetal distress/demise
- Disseminated intravascular coagulation (DIC)

# Placental Abruption

## Management

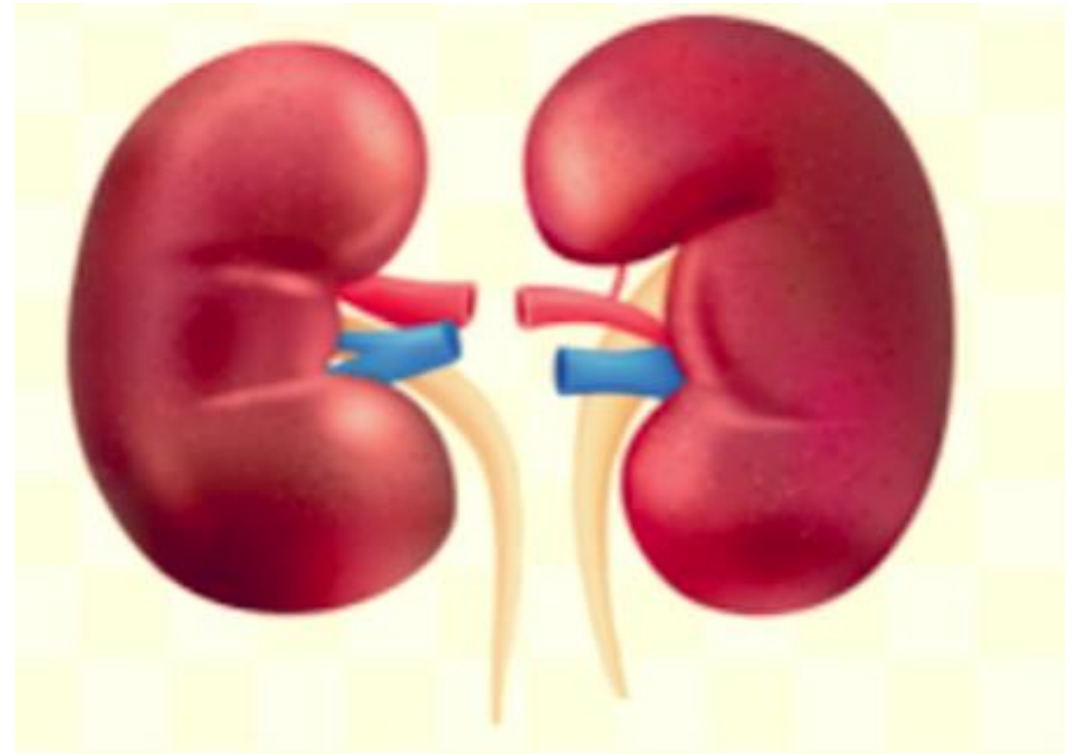
- Initiate fetal heart rate monitoring
- Maternal intravenous access
  - IV fluids
  - May require blood transfusion
- Unstable mother: **cesarean delivery**
  - Hypotension
  - Coagulopathy
- Stable mother: vaginal or cesarean delivery
  - Depends on multiple factors
  - Consider fetal status, weeks of gestation

Cesarean Delivery



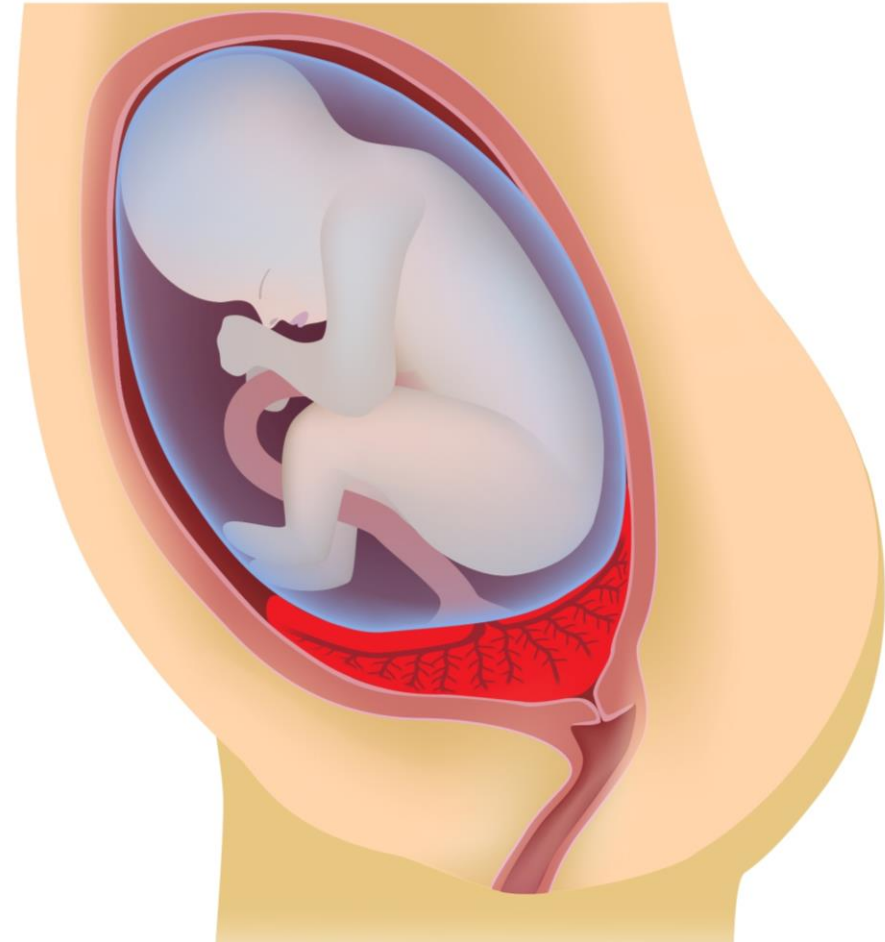
# Cortical Necrosis

- Ischemic necrosis of renal cortex
- Rare cause of **acute renal failure**
- Related to ischemia and DIC
- Often associated with placental abruption
- Clinical presentation
  - Acute renal failure
  - Anuria
  - Hematuria (may be gross)
  - Flank pain



# Placenta Previa

- Previa = “going before”
- Placenta before baby
- Placenta attached to lower uterus
- Over or close to cervical os





# Placenta Previa

## Subtypes

- Normal placenta: **> 2 cm from cervix**
- Complete or total: covers cervix
- Partial: partially covers cervix
- Marginal: extends to margin
- Low-lying: edge < 2 cm os



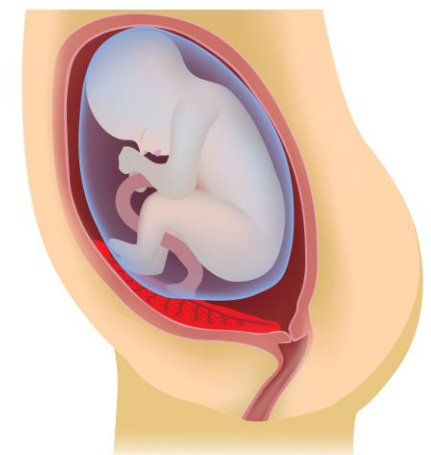
Normal



Total placenta previa



Partial placenta previa

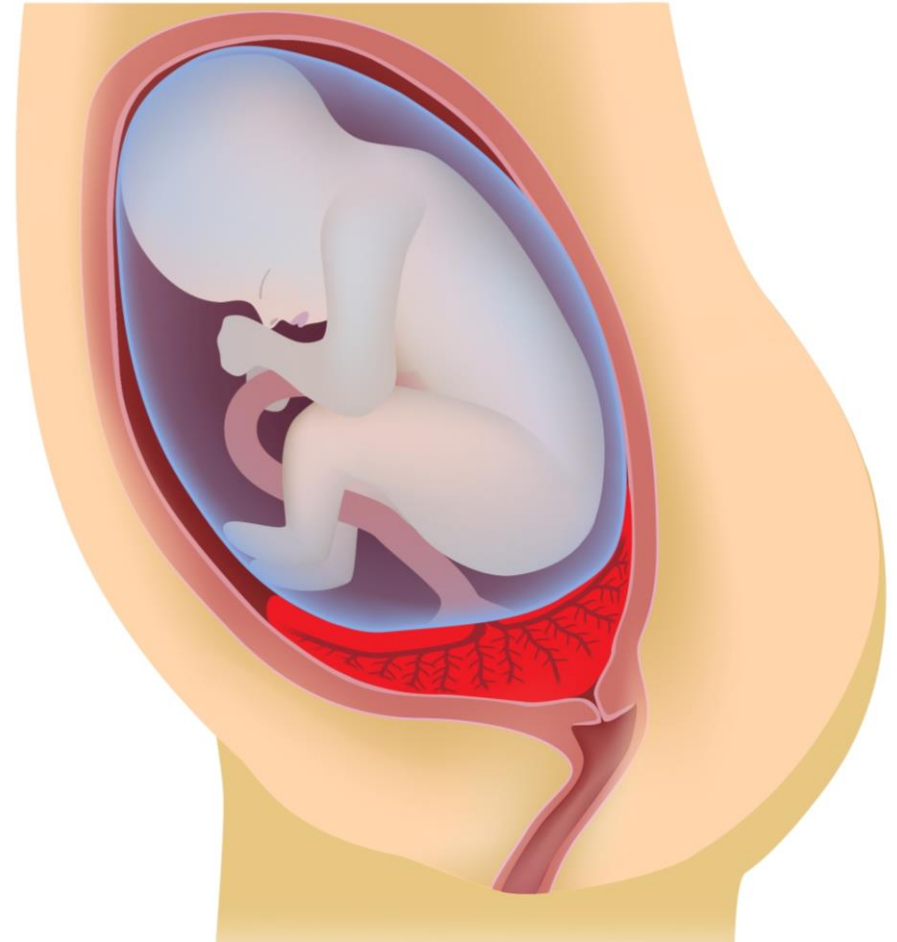


Marginal placenta previa

# Placenta Previa

## Risk Factors

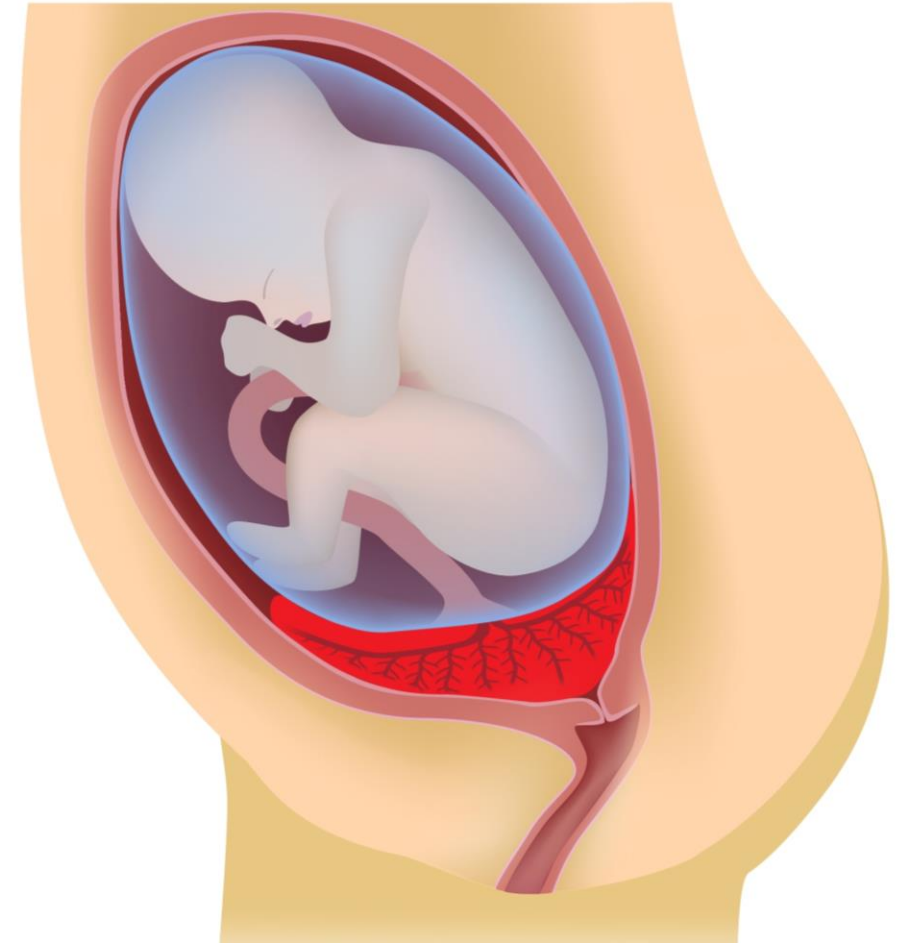
- Prior placenta previa
- Prior C-section
- Multiple prior pregnancies
- Previous uterine surgeries (myomectomy)



# Placenta Previa

## Clinical Features and Diagnosis

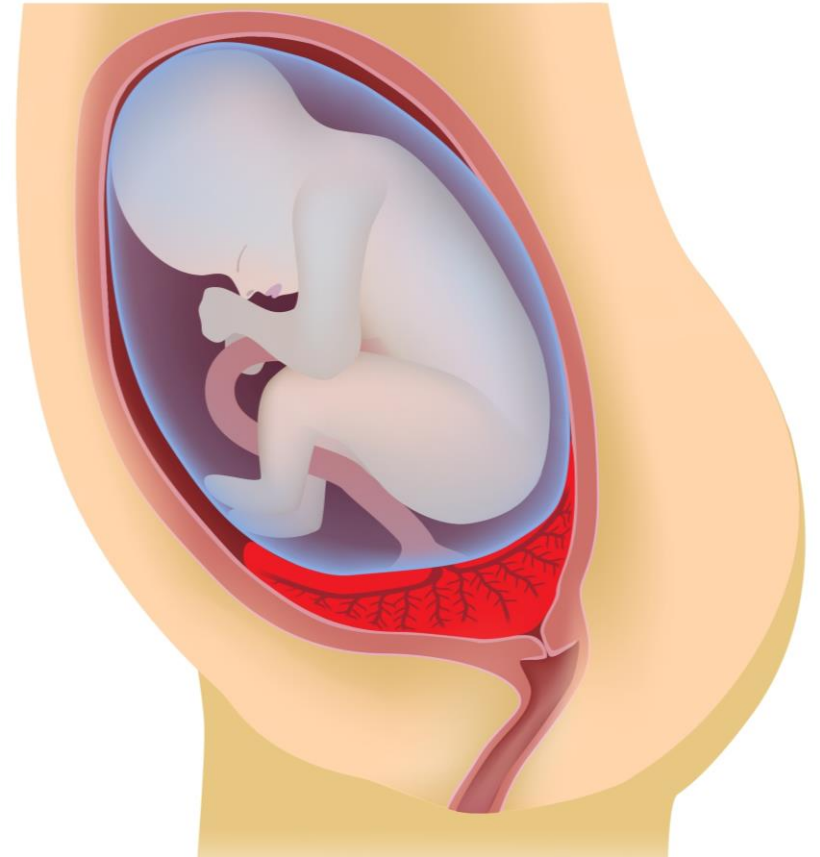
- Often detected on **prenatal ultrasound**
  - Most (90%) resolve spontaneously
  - When detected early in pregnancy, continue routine care
- May cause **painless bleeding** during pregnancy
- Associated with preterm delivery
- Diagnosis: ultrasound
  - Performed with any 2<sup>nd</sup> or 3<sup>rd</sup> trimester bleeding
  - Performed **before manual exam**
  - Evaluate for co-existing placenta accreta



# Placenta Previa

## Management

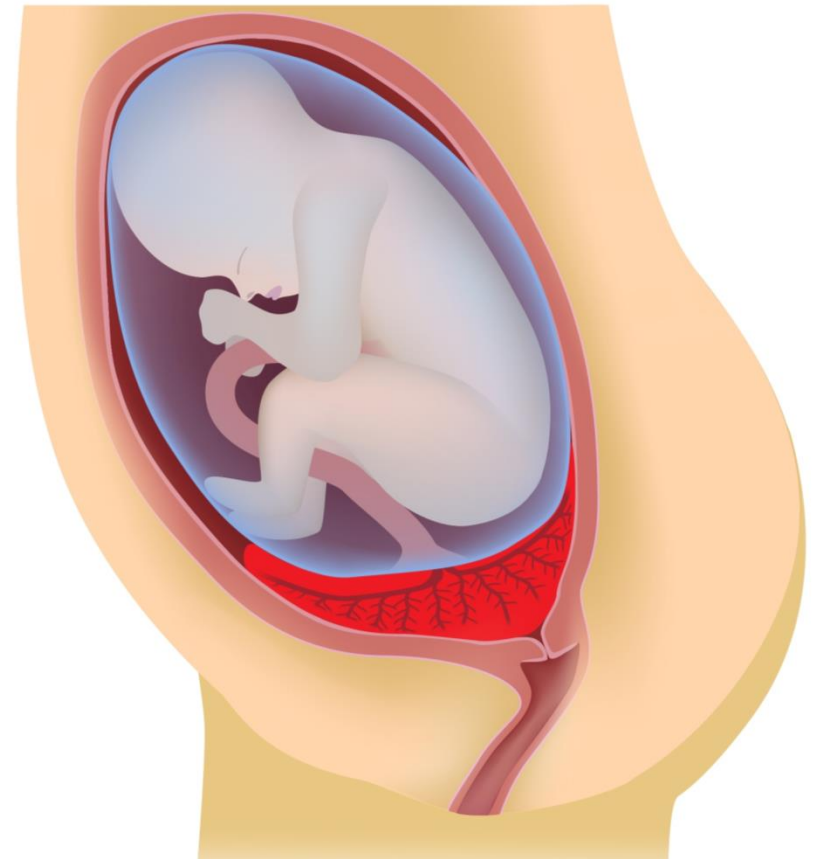
- Follow with ultrasound
- Previa may resolve with time
- Anterior wall expands more in pregnancy
- Anterior previa more likely to resolve



# Placenta Previa

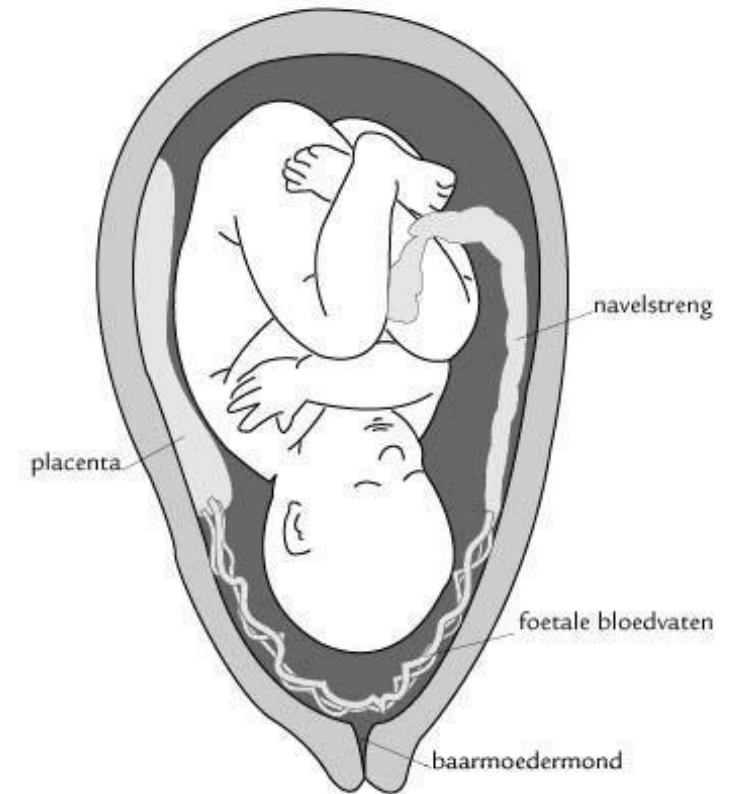
## Management

- Reduce bleeding risk
  - Avoid sexual activity
  - Also strenuous activity or prolonged standing
- Acute bleeding episodes: fluids or blood transfusion
- Significant bleed usually hospitalized until delivery
- **Scheduled cesarean delivery**
  - Usually 36 to 37 weeks
  - C-section also if patient enters labor



# Vasa Previa

- Fetal blood vessels near cervical os
- Rupture of membranes at birth → bleeding
- Usually requires C-section delivery
- Associated with **velamentous umbilical cord**

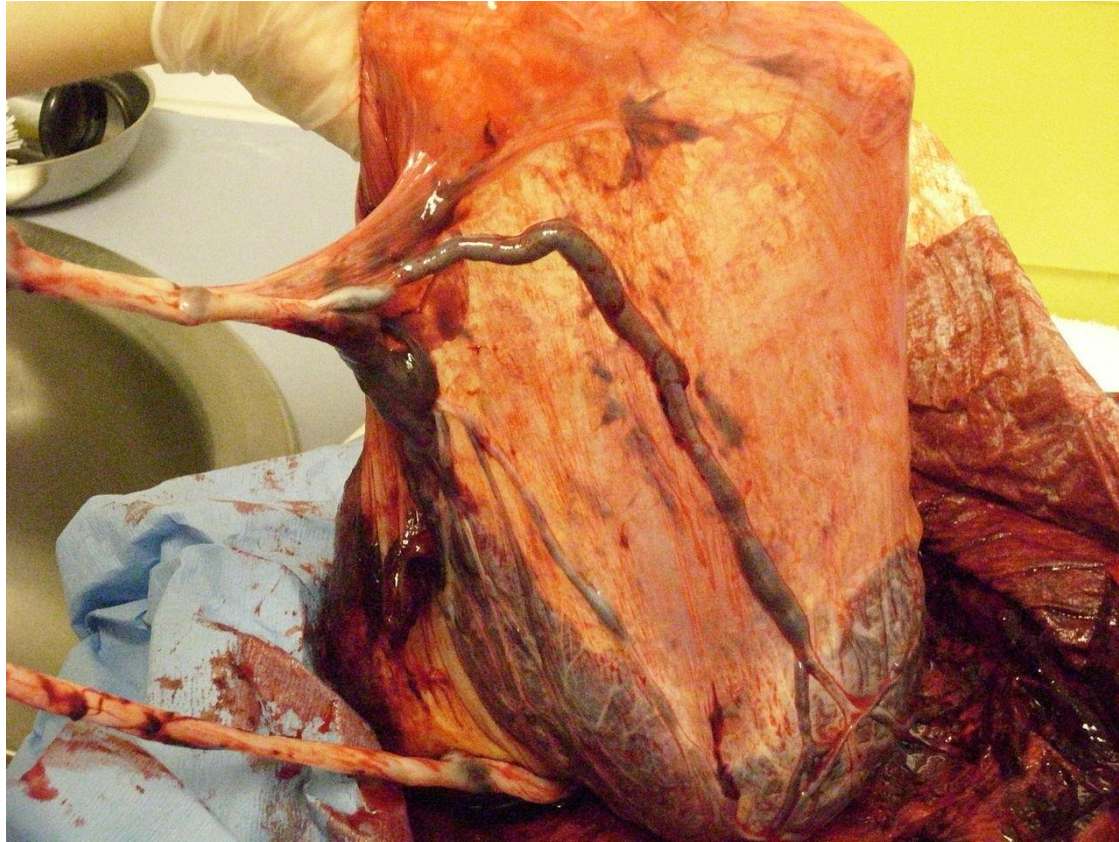


# Velamentous Umbilical Cord

- Normal umbilical cord inserts into central placenta
- Velamentous cord: inserts into fetal membranes
- Fetal vessels travel with membranes to placenta
- Vessels exposed with no protection from Wharton's jelly
- Risk of rupture and bleeding
- Fetus can exsanguinate in minutes once ROM tears vessels



# Velamentous Umbilical Cord

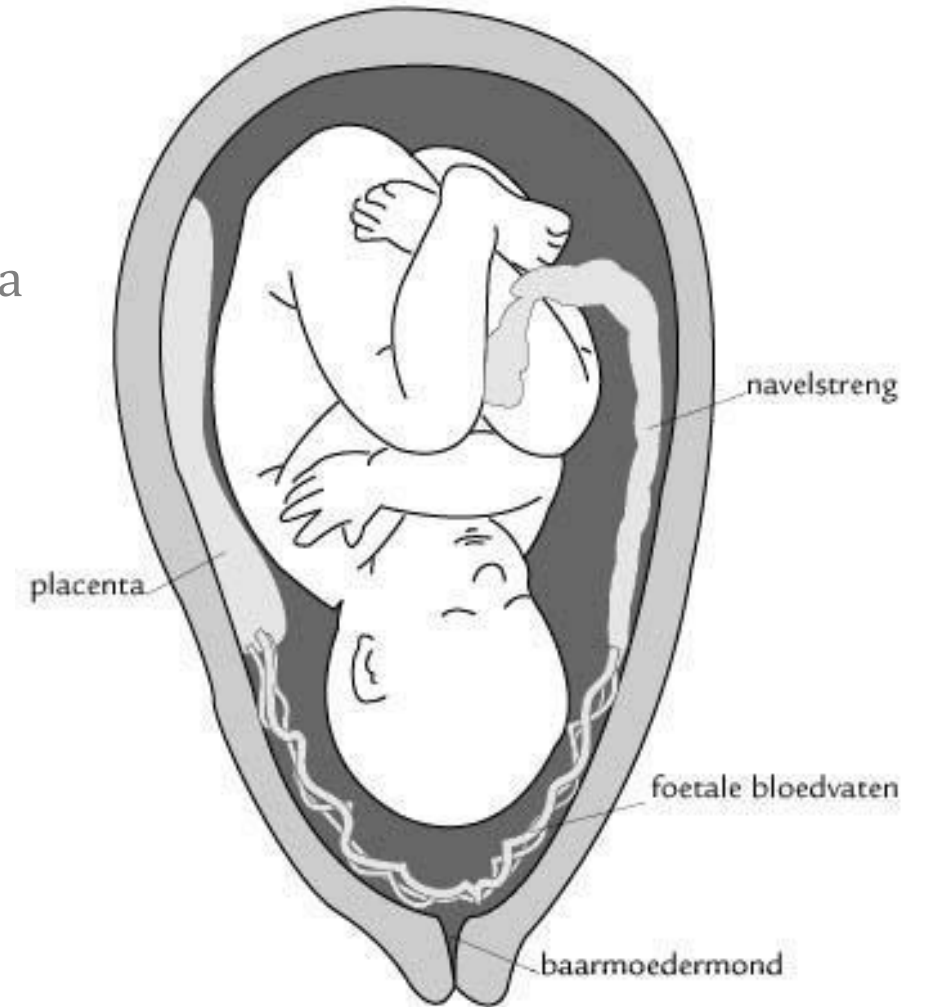




# Vasa Previa

## Diagnosis

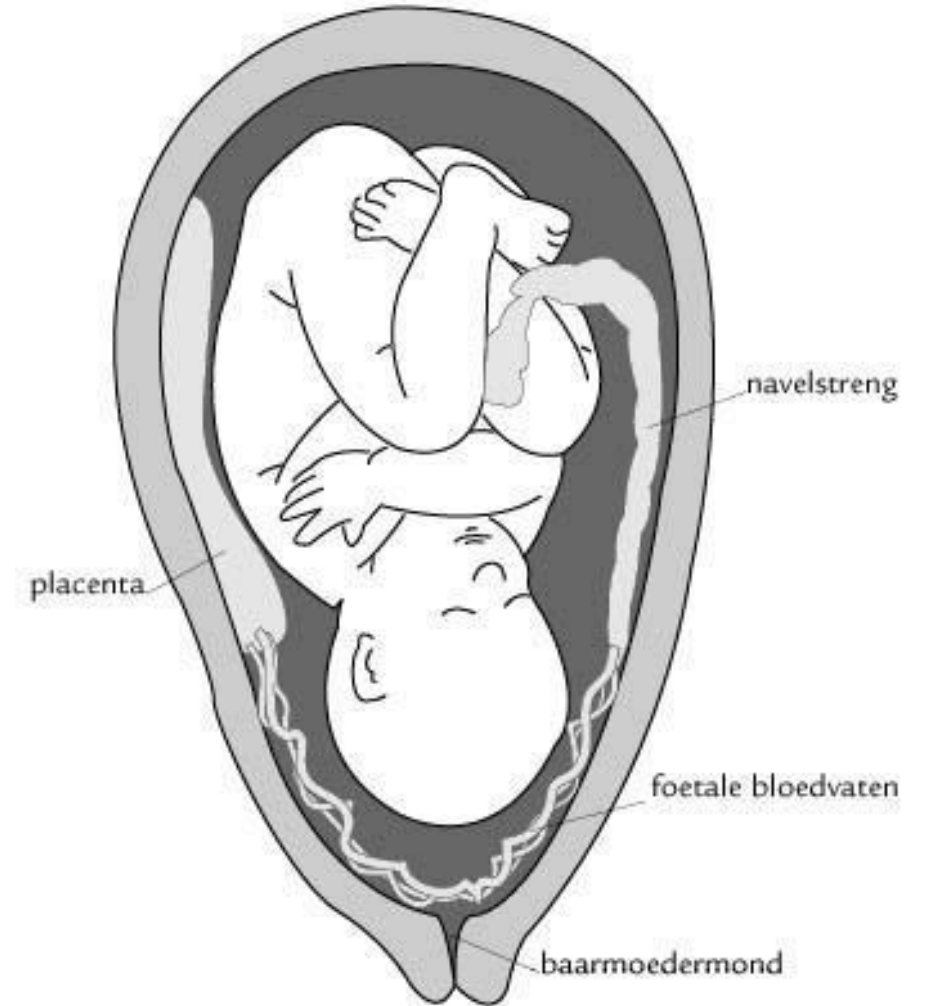
- **Prenatal ultrasound**
  - Fetal vessels within 2cm of os
  - Most cases also have velamentous cord or placenta previa
- If undetected prior to labor:
  - Painless bleeding with membrane rupture
  - Fetal distress at delivery
  - May lead to fetal demise
  - Detection of fetal blood (apt test; Kleihauer-Betke test)
- Classic case:
  - No prenatal care
  - Mother with bloody ROM and fetal demise



# Vasa Previa

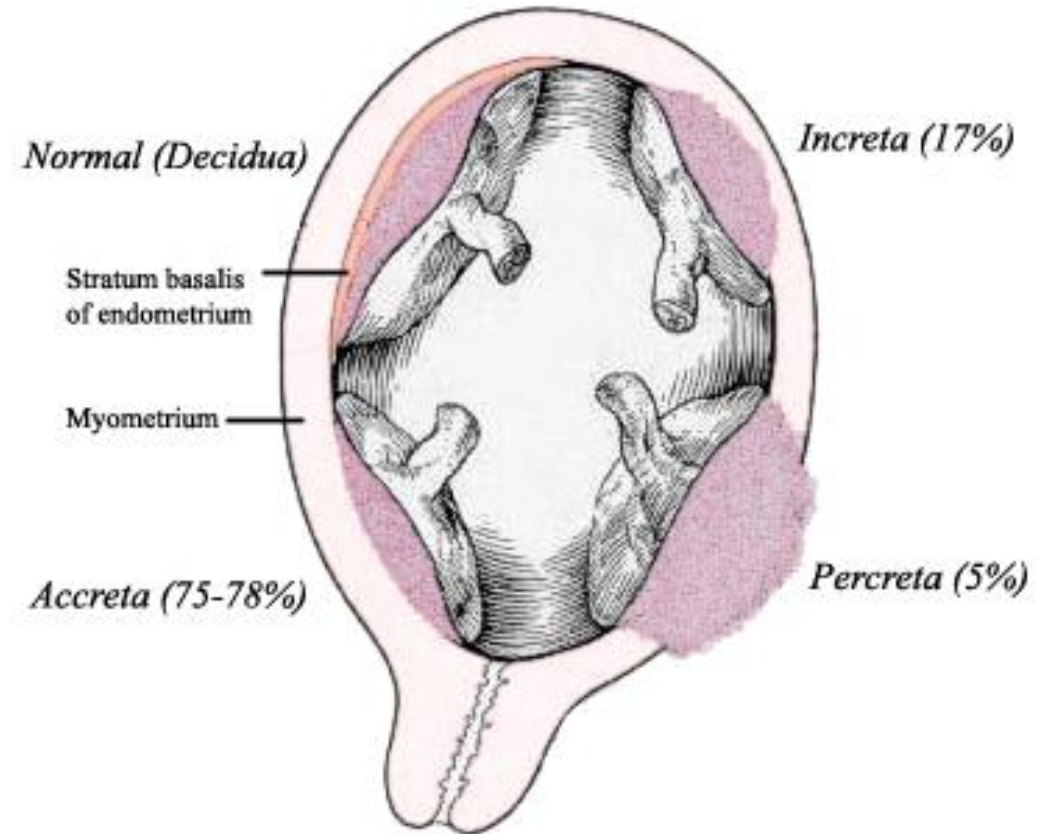
## Management

- **Prenatal diagnosis**
  - Betamethasone 28 to 32 weeks
  - Hospital admission for fetal surveillance
  - Cesarean delivery before ROM or labor (34 - 35 weeks)
- If no prenatal diagnosis
  - Emergency cesarean delivery at ROM/labor



# Abnormal Attachment

- Normal placenta attaches to decidua
- Abnormal decidua → abnormal attachment
- Placenta attaches directly to myometrium
- Leads to bleeding after delivery
- Three forms
  - Placenta accreta (most common)
  - Placenta increta
  - Placenta percreta



# Abnormal Attachment

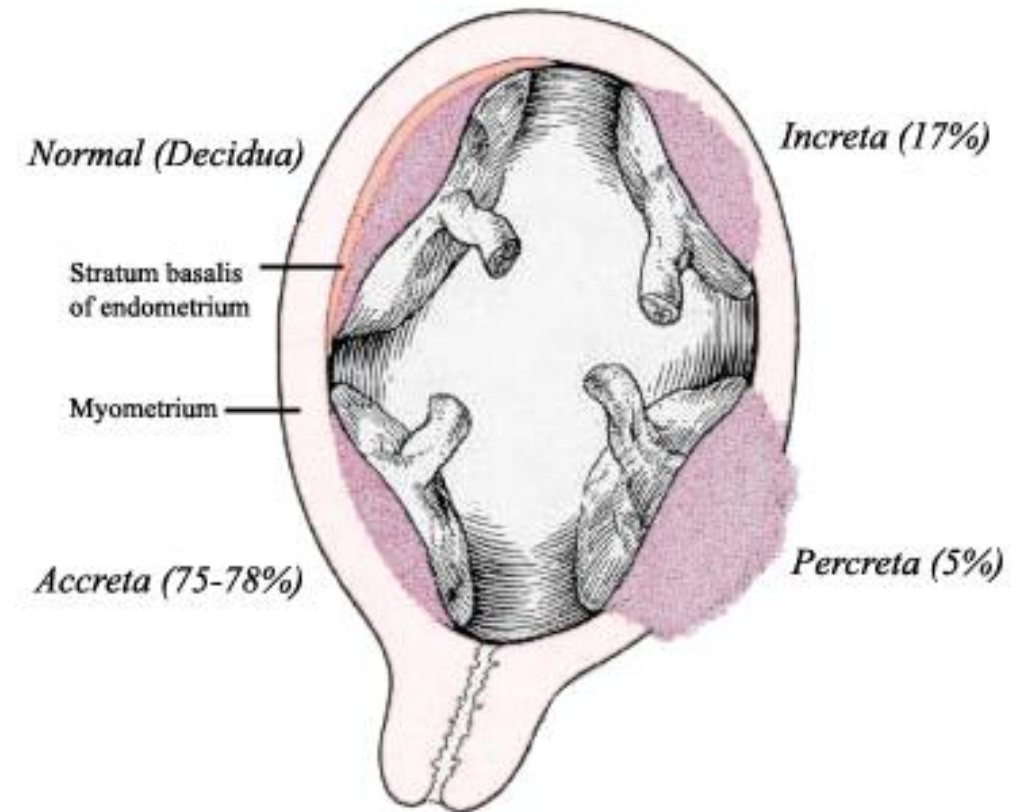
- Caused by defective uterine decidualization
- Most important risk factor: **prior C-section**
  - Especially with placenta previa
- Other risk factors:
  - Prior uterine surgery or D&C

Cesarean Delivery



# Abnormal Attachment

- Placenta accreta
  - Placenta attached to myometrium
  - No penetration into myometrium
- Placenta increta
  - Placenta penetrates myometrium
- Placenta percreta
  - Placenta penetrates through myometrium
  - Invades uterine serosa (outer layer)
  - Can attach to bladder/rectum

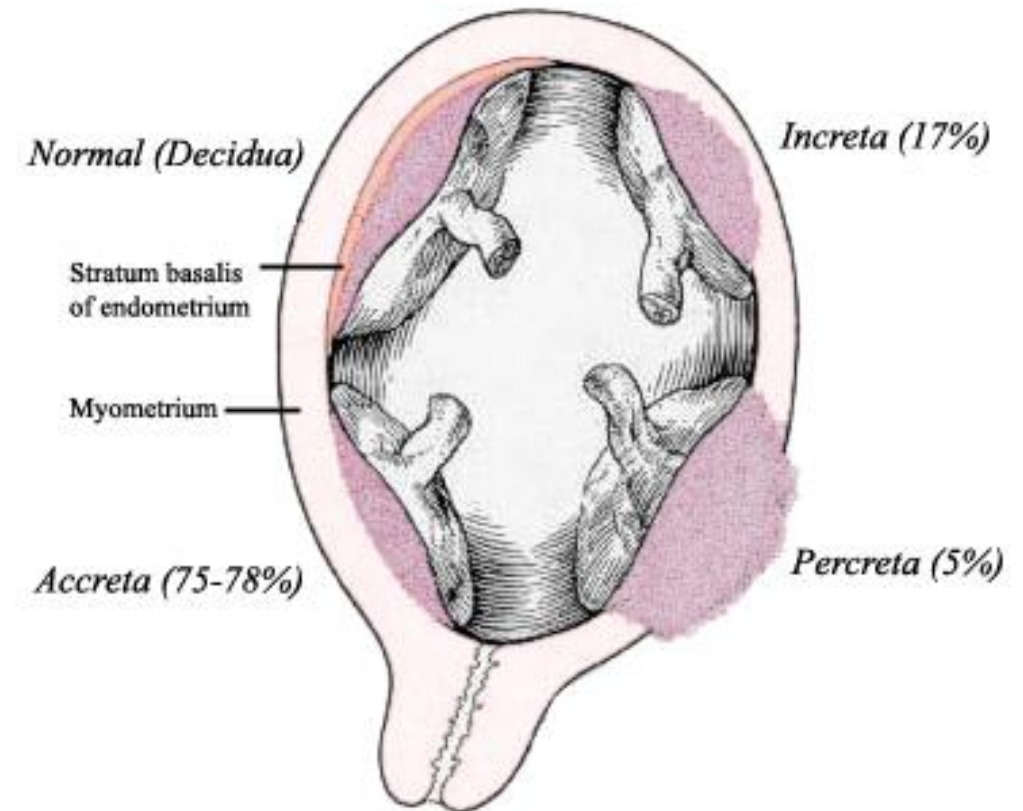




# Abnormal Attachment

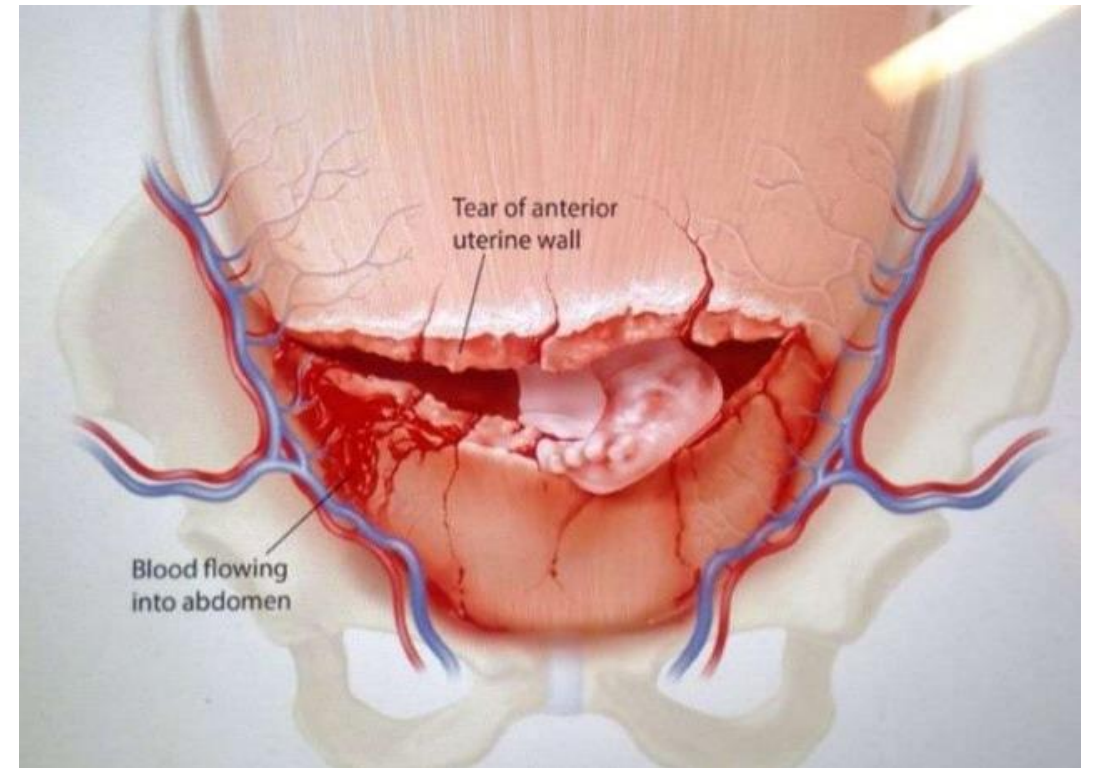
## Clinical Presentation

- Usually diagnosed by **prenatal ultrasound**
- Undetected: placenta fails to detach after birth
  - Part/all of placenta remains attached to uterus
  - Breaks into pieces
  - Massive bleeding
- Maternal hemorrhage
- Shock, DIC, ARDS
- Delivery usually by C-section
- Often requires hysterectomy



# Uterine Rupture

- Rupture of uterine wall
- Associated with **prior uterine surgery**
  - Often cesarean section
  - Leaves weakened uterine wall



# Uterine Rupture

- Onset often during labor
- Sudden worsening of abdominal pain
- Irregular contractions with decreased intensity
- Vaginal bleeding
- Abdominal bleeding → shock
- Sudden **loss of fetal station**
- Fetal parts may cause **protuberance of abdomen**
- Fetal distress: bradycardia, late or variable decelerations
- Treatment: emergency laparotomy and cesarean delivery



# Multiple Gestation

Jason Ryan, MD, MPH

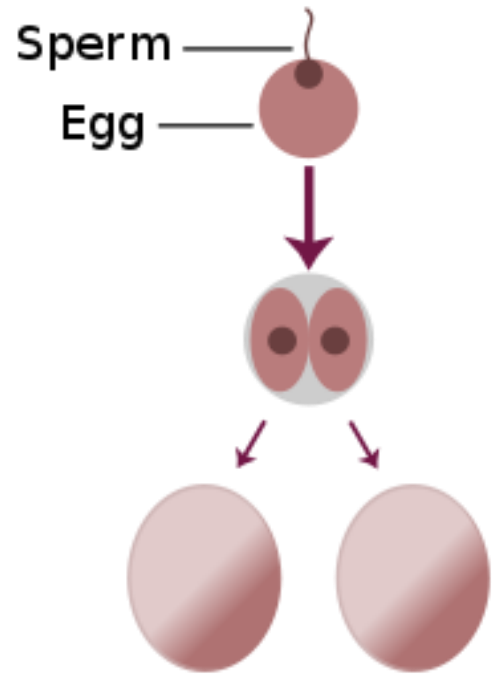


# Twins

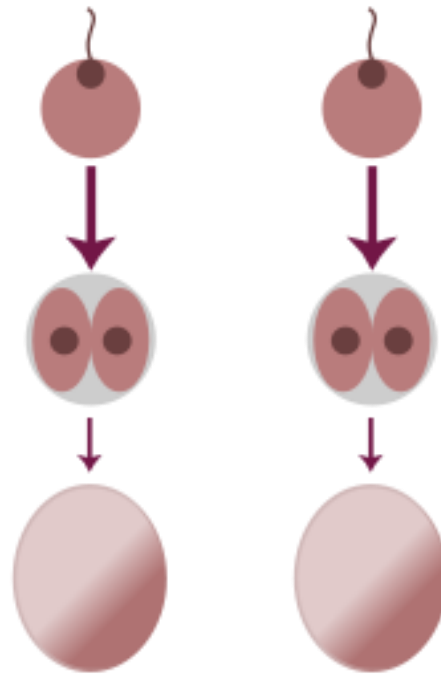
- One pregnancy: two babies
- **Dizygotic twins**
  - Two zygotes
  - Two separate ova fertilized by two separate sperm
  - Two siblings born from single pregnancy
  - “Fraternal twins”
- **Monozygotic twins**
  - One zygote divides in two
  - One ova fertilized by one sperm
  - “Identical twins”



## Identical (Monozygotic)



## Fraternal (Dizygotic)



# Twins

- One twin may die in utero
  - Resorption of fetus/embryo (“vanishing twin”)
  - Delivery of single baby
- More fetuses = shorter pregnancy
  - Single fetus ~ 40 weeks
  - Twins ~ 37 weeks
  - Triplets ~ 33 weeks
  - Half of twins born before 37 weeks
- Higher hCG levels

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
28	29	30	31 New Year's Eve	1 New Year's Day	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19 Martin Luther King Day	20	21	22	23	24
25	26	27	28	29	30	31

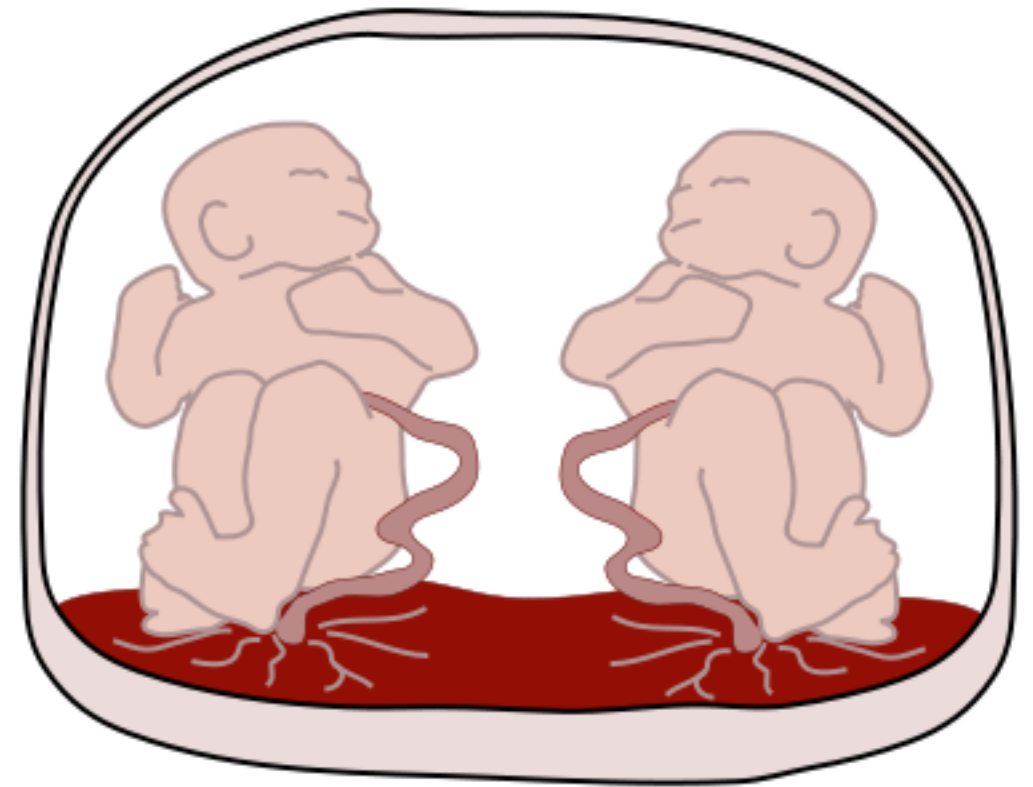
# Dizygotic Twins

- Each baby has own amnion and chorion
- “Dichorionic diamniotic”
- Two separate placentas
- Most common type
- Common in mothers using IVF



# Monozygotic Twins

- May have a single shared placenta
- Variable number of amnions and chorions
- Depends on when zygote divides

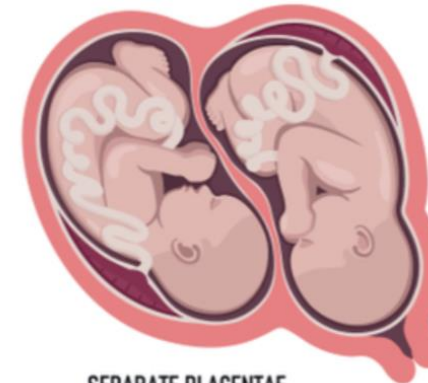




# Monozygotic Twins

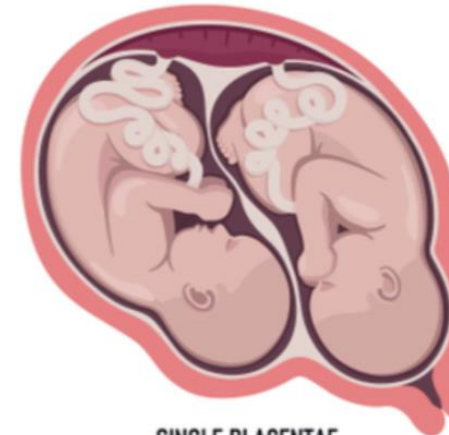
- Dichorionic, diamniotic
  - Days 1-3
  - May have two placentas
- Monochorionic diamniotic
  - Days 4-8
  - Chorion already under development
- Monochorionic monoamniotic
  - Days 9-12
  - Chorion and amnion already under development
- Conjoined twins
  - Day 13+
  - Also monochorionic monoamniotic

DICHORIONIC DIAMNIOTIC



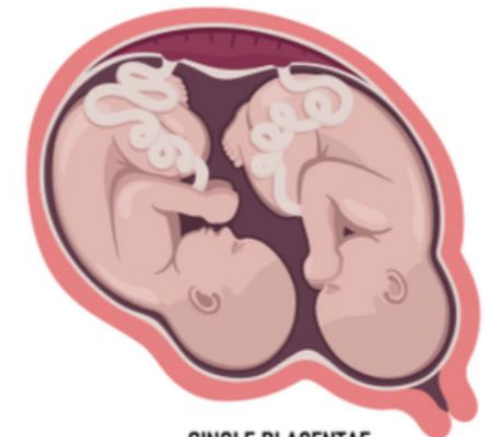
SEPARATE PLACENTAE  
2 CHORIONS  
2 AMNIONS

MONOCHORIONIC DIAMNIOTIC



SINGLE PLACENTAE  
1 CHORION  
2 AMNIONS

MONOCHORIONIC MONOAMNIOTIC



SINGLE PLACENTAE  
1 CHORION  
1 AMNION

# Twin Pregnancies

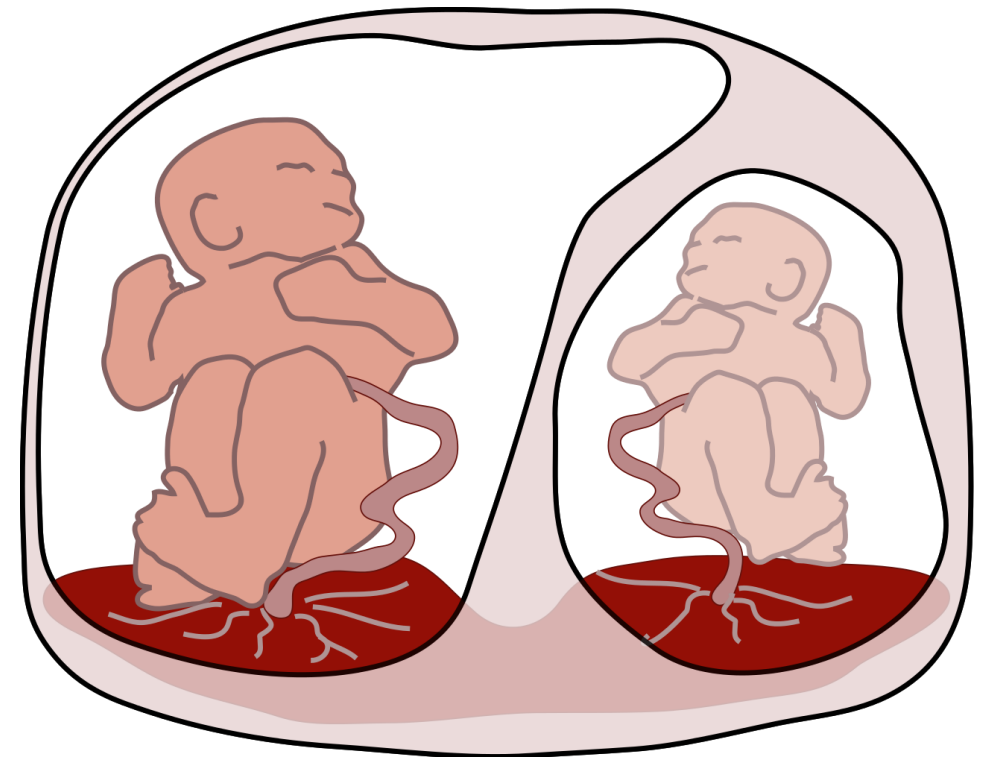
- Increased risk of **all complications except macrosomia**
- Maternal
  - Gestational hypertension and preeclampsia
  - Placenta previa
  - Caesarean delivery
- Fetus
  - Preterm delivery
  - Growth restriction
  - Congenital anomalies





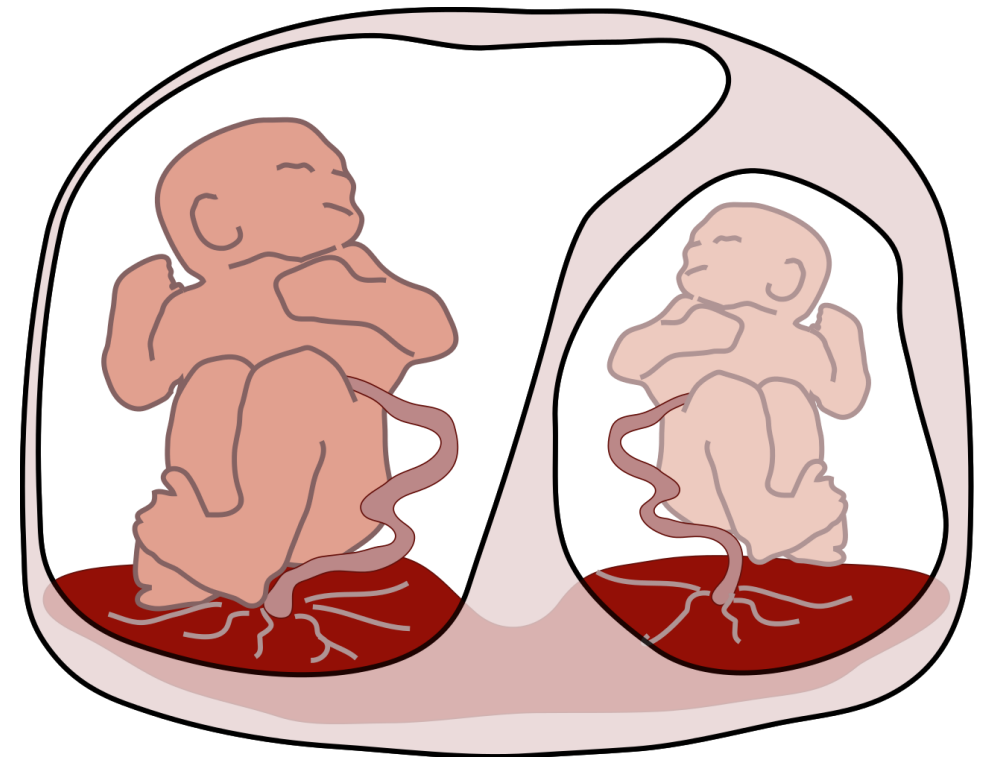
# Twin-Twin Transfusion Syndrome

- Occurs in monochorionic twins with single placenta
  - Up to 15% monochorionic diamniotic twins
  - Less common in monochorionic monoamniotic twins
- **Imbalanced blood flow**
  - Arteriovenous anastomoses in placenta
  - Vascular connection between twins



# Twin-Twin Transfusion Syndrome

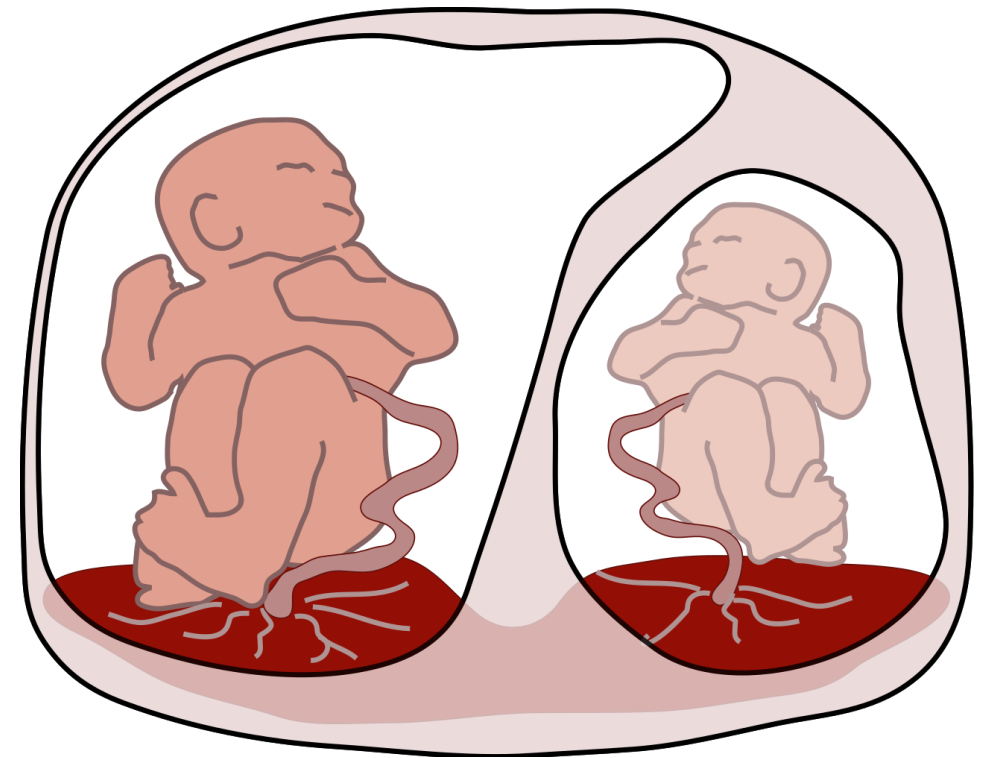
- **Recipient:** one twin receives too much blood
  - Polyhydramnios and organ enlargement
  - Hypervolemia → heart failure
- **Donor:** one twin loses volume
  - Oligohydramnios and growth restriction



# Twin-Twin Transfusion Syndrome

## Diagnosis and Management

- Diagnosis: **prenatal ultrasound**
  - Single placenta, fluid pockets  $< 2$  cm and  $> 8$  cm
- Mild cases: expectant management
- **Fetal laser coagulation**
  - Elimination of anastomoses
  - Separates placenta into two
  - Significant risk
  - Reserved for severe discordance

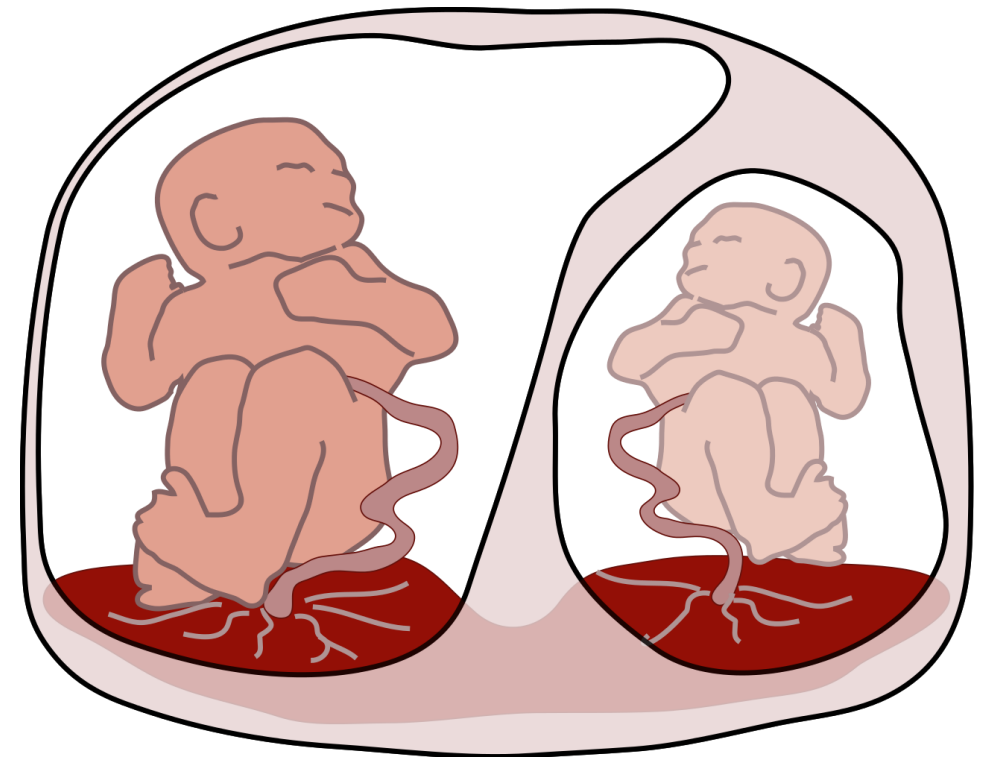


# Twin-Twin Transfusion Syndrome

## Diagnosis and Management

- **Amnioreduction**

- Removal of fluid to resolve polyhydramnios
- Improves maternal breathing
- Decreases pressure on cervix
- Lower risk preterm delivery



# Twin Pregnancy

## Delivery

- Often planned delivery (induction or cesarean)
- Mode of delivery varies with **positioning of twins**
  - Presenting twin: closest to cervix (twin A)
  - Non-presenting twin: furthest from cervix (twin B)
- Vertex/vertex: vaginal delivery
- Vertex/non-vertex: trial of vaginal delivery or cesarean delivery
- Twin A not vertex: cesarean delivery

# Labor and Delivery I

Jason Ryan, MD, MPH



# Labor

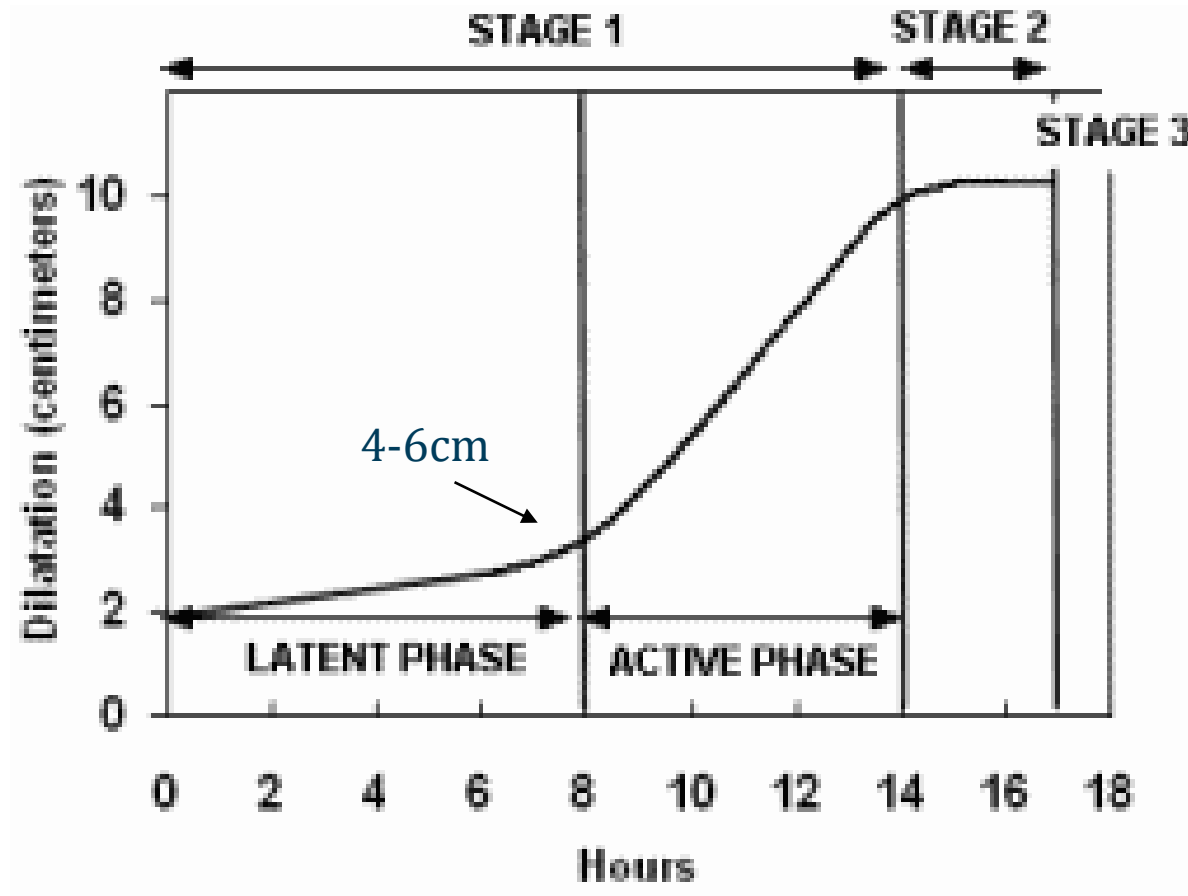
- **Uterine contractions PLUS cervical changes**
  - Cervical effacement and dilation to maximal dilation ~ 10 cm
- **Braxton-Hicks contractions:** no cervical changes
  - Often not felt until 3<sup>rd</sup> trimester
  - Occasionally felt or palpated as early as 18 weeks
  - Can be seen on sonogram during early pregnancy
  - Irregular
  - Usually do not become stronger or more frequent over time
  - Initial evaluation: ultrasound and cervix check
  - Further evaluate with non-stress test
  - If reactive: usually require no special treatment (discharge home)

# Stages of Labor

Stage	Definition	Nulliparous	Multiparous
First (Latent)	Onset of labor until 4-6 cm dilation	< 20 hours (average 10-12)	< 14 hours (average 6-8)
First (Active)	4-6 cm until complete 10 cm cervical dilation	4-6 hr (> 1-1.2 cm/hr)	2-3 hr (> 1.2-1.5 cm/hr)
Second	Complete cervical dilation to delivery of infant	< 2 hours (3 hr if epidural)	< 1 hour (2 hr if epidural)
Third	From delivery of infant to delivery of placenta	< 30 minutes	< 30 minutes



# Stages of Labor



# Fetal Lie and Presentation

- **Fetal lie:** long axis of fetus compared to long axis of mother
  - Longitudinal, transverse or oblique
- **Fetal presentation:** part of fetus overlying pelvic inlet
- Most common presentation: longitudinal, cephalic
- Breech presentation: longitudinal, buttocks presenting



CEPHALIC



BREECH



OBLIQUE



TRANSVERSE

# Vertex

- Area of fetal head
- **Vertex presentation:** fetal vertex is presenting part
  - Subtype of cephalic presentation
- Malpresentation: presenting part is not vertex
  - Breech
  - Transverse/oblique lie
  - Face or brow presentation



CEPHALIC

# Breech Presentation

- Most common malpresentation
- Frank breech (50 -75%): rear first, flexed hips, extended knees
- Footling breech (20%): one or both legs first
- Complete breech (5-10%): rear first, flexed hips and knees



Frank



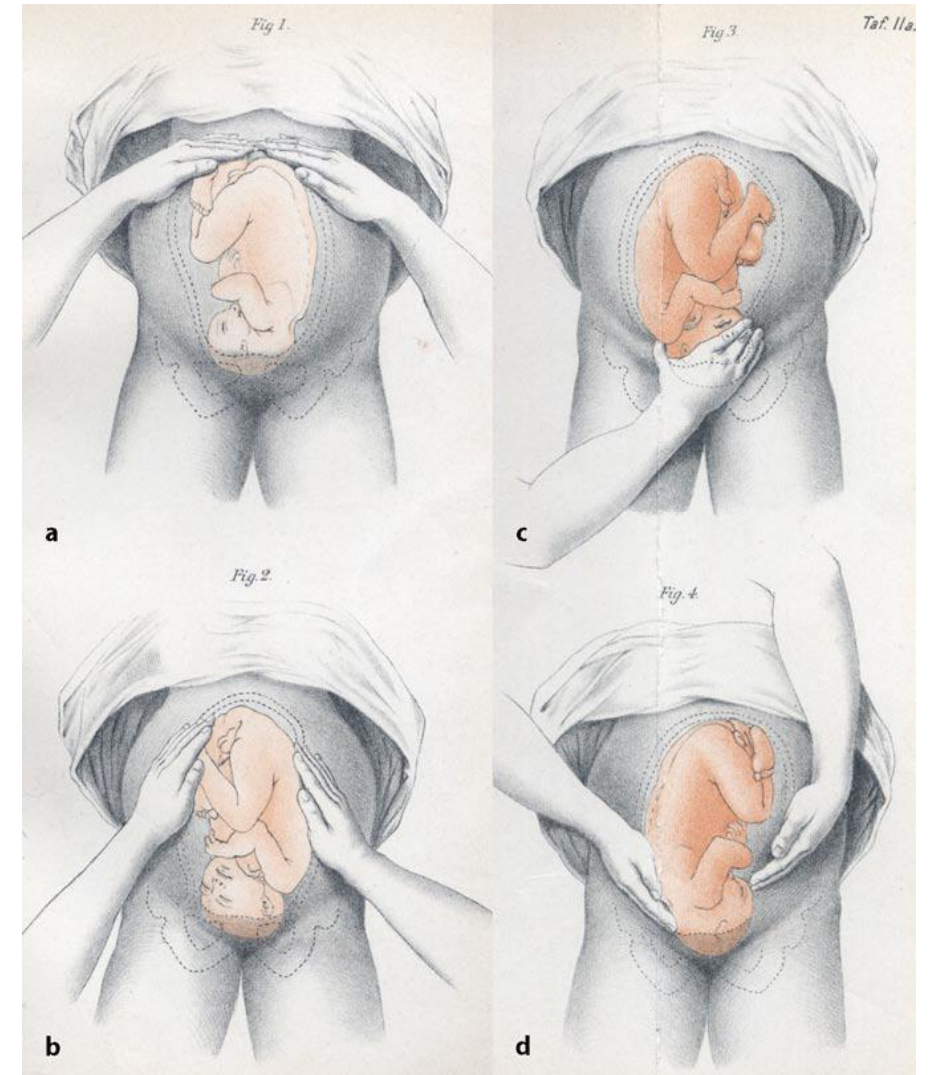
Complete



Footling

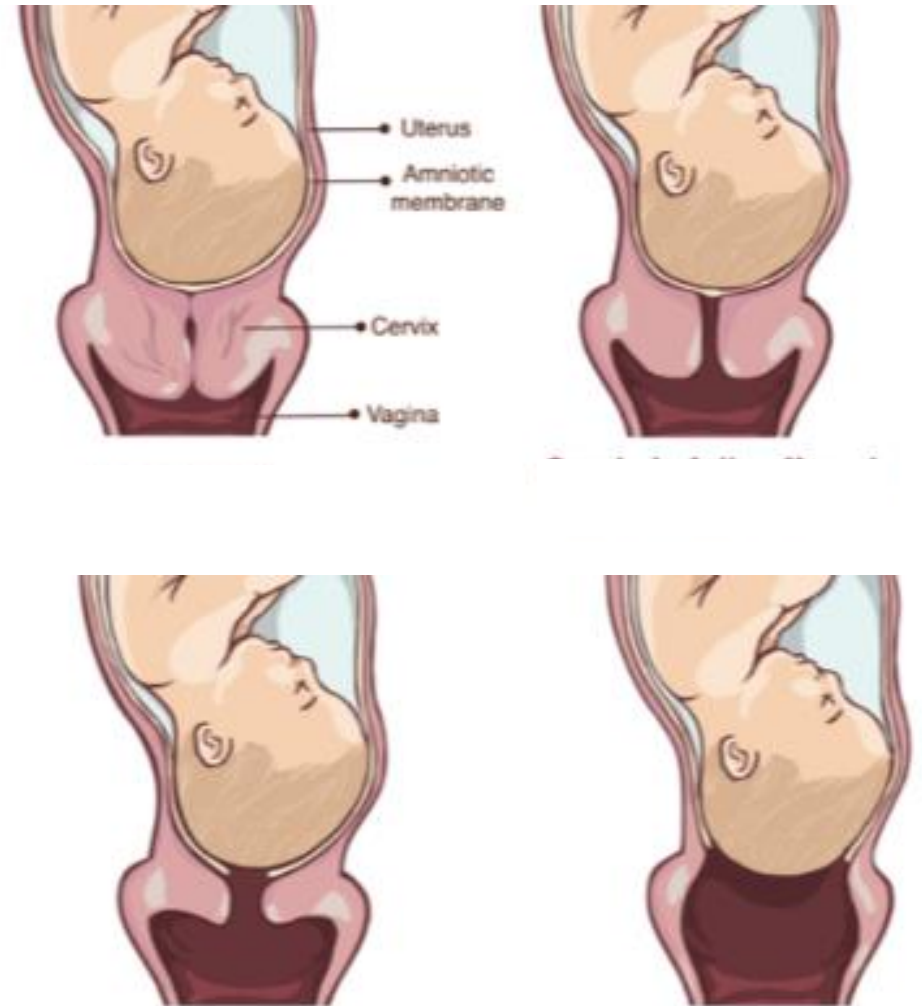
# Leopold maneuvers

- Four palpations of abdomen
- Used to assess lie and positioning
- Also to estimate fetal weight
  - Shown to be accurate as US at term for predicting weight



# Cervical Changes

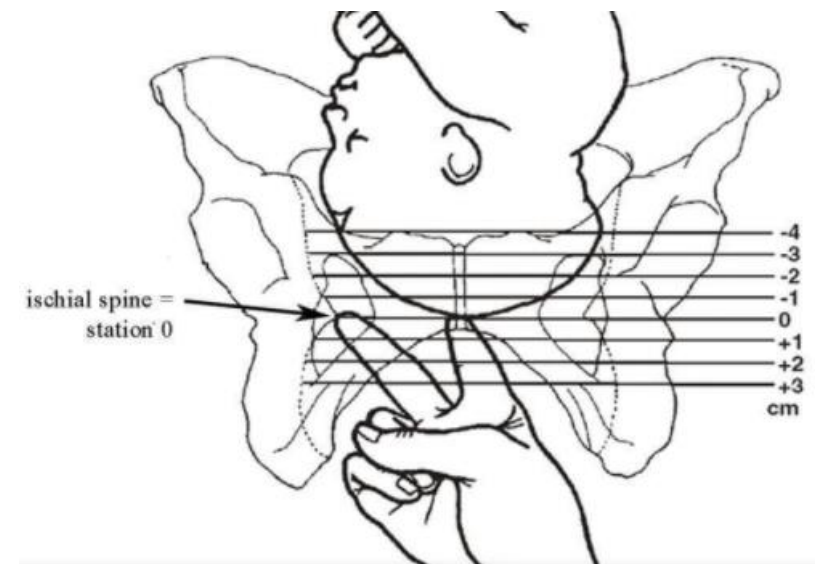
- **Dilation:** progresses to 10 cm
- **Effacement:** thinning of cervix during labor
  - Cervix normally ~ 4 cm long
  - During labor, cervix effaces (thins, softens, shortens)
  - 0% effaced = no effacement
  - 100% effaced = fully thinned
- “Bloody show”
  - Blood-tinged mucous released vaginally
  - Associated with onset of effacement



# Labor Evaluation

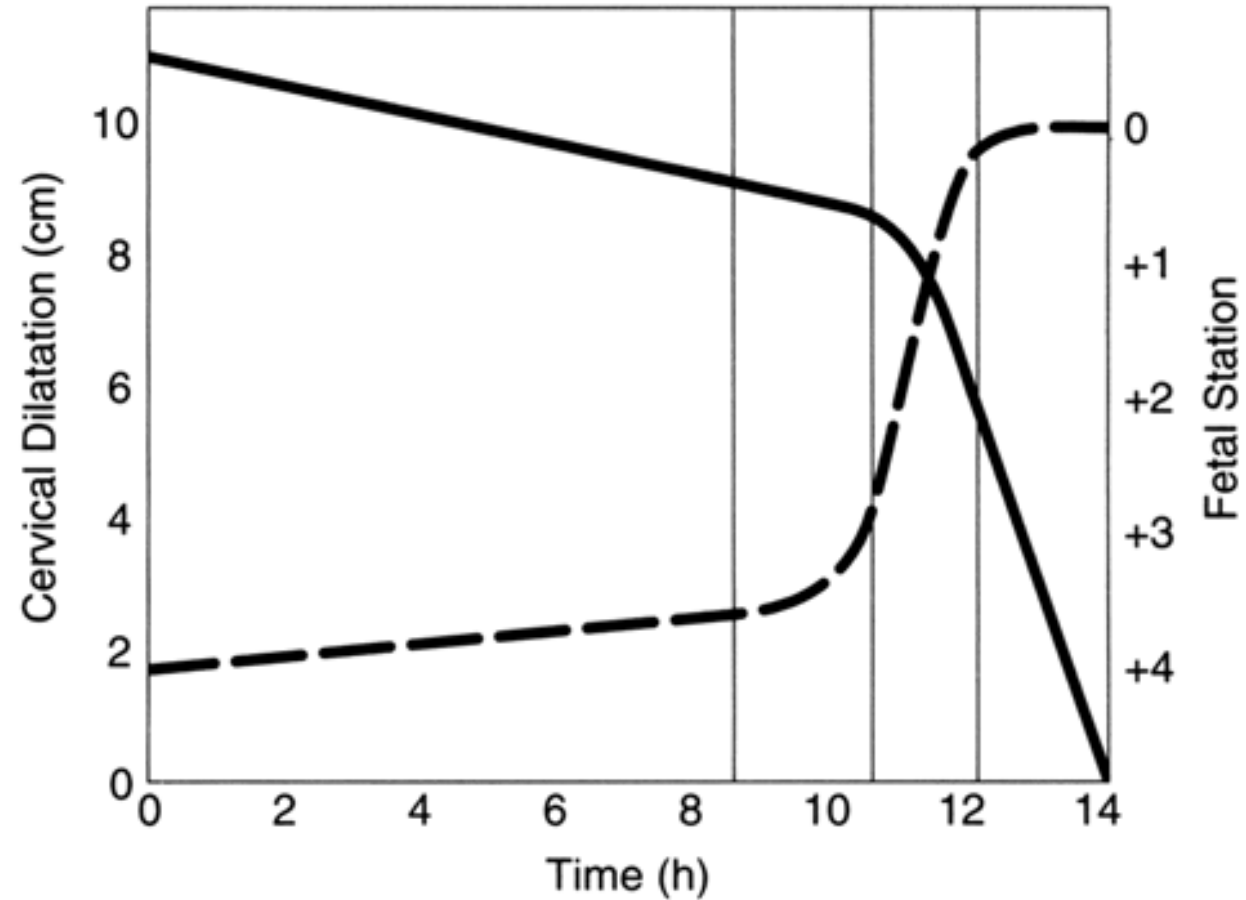
- **Fetal station:** assessment of leading edge
  - Centimeters of leading edge of presenting part
  - Above or below the level of the ischial spines
  - Negative is inside uterus; positive is outside uterus
  - Ranges from -5 to +5
- **Cervical consistency:** firm, medium or soft
  - Firm like nose
  - Medium like lips
  - Soft like butter
- **Cervical positioning:** posterior, midposition, anterior

## Fetal Station





# Dilation and Fetal Station





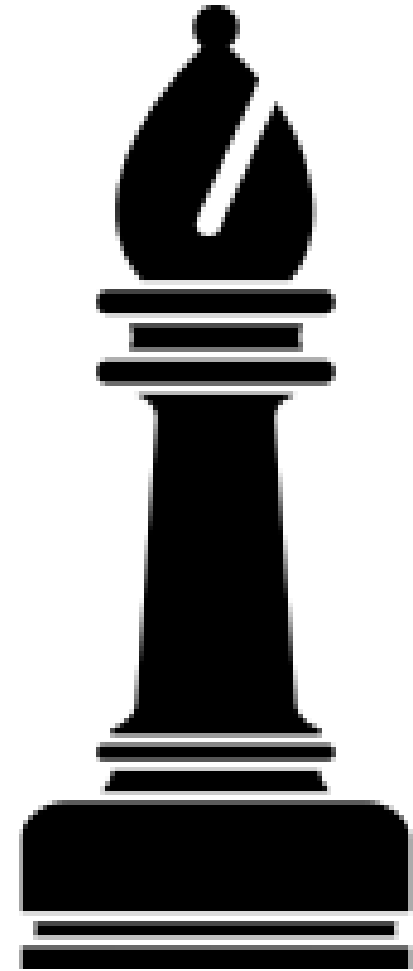
# Bishop Score

- Clinical tool for assessment of cervix in pregnant women
- Maximum score = 13

Cervical Status	0	1	2	3
Dilatation	Closed	1-2 cm	3-4 cm	> 5 cm
Effacement	< 30%	30-50%	50-80%	> 80%
Station	-3	-2	-1 or 0	≥ +1
Consistency	Firm	Intermediate	Soft	
Position	Posterior	Intermediate	Anterior	

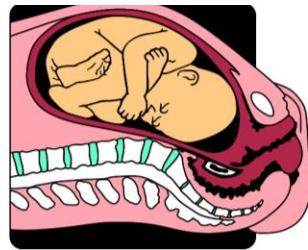
# Bishop Score

- Developed to determine likelihood of natural labor
- Used to predict success of labor induction
- Higher score = cervix if “favorable” for vaginal delivery
  - Higher chance of vaginal delivery after induction
- Lower score = cervix is “unfavorable”
  - Higher chance of cesarean delivery
  - Cervix can be “ripened” to prepare for labor induction



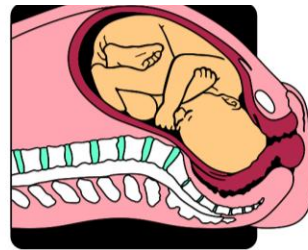
# Cardinal Movements

- Changes in fetal position during vaginal delivery for vertex presentation
- Head must move to accommodate bony pelvis



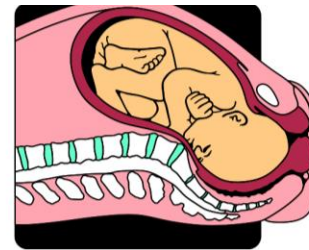
Head Floating Before Engagement

1



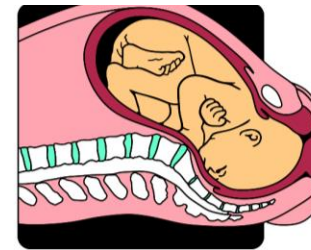
Engagement, Flexion, Descent

2



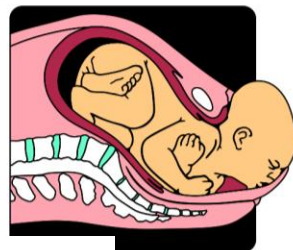
Further Descent, Internal Rotation

3



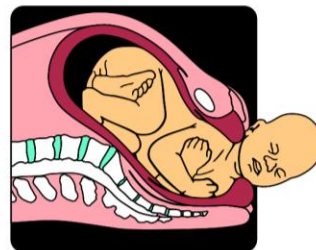
Complete Rotation, Beginning Extension

4



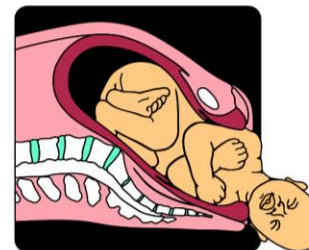
Full Extension

5



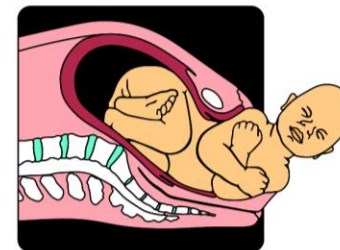
Restitution (External Rotation)

6



Delivery of Anterior Shoulder

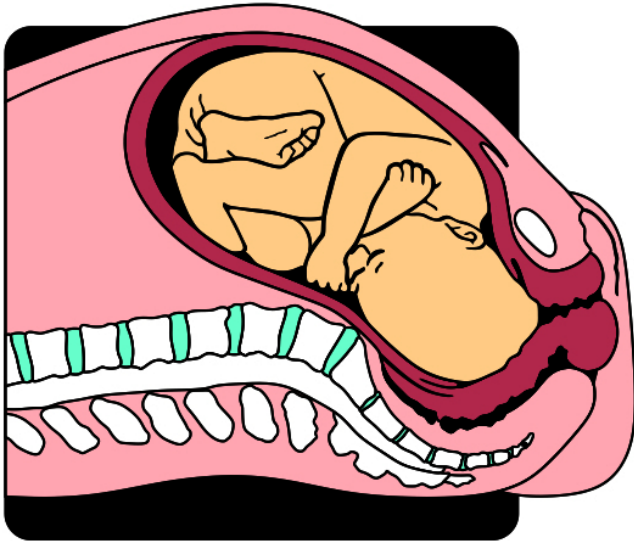
7



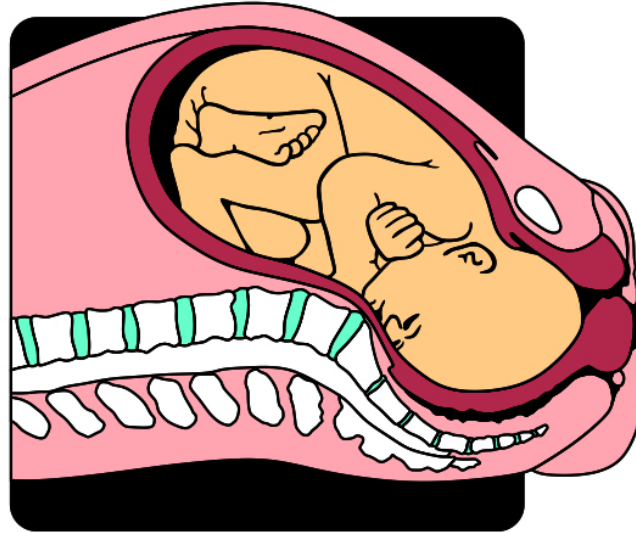
Delivery of Posterior Shoulder

8

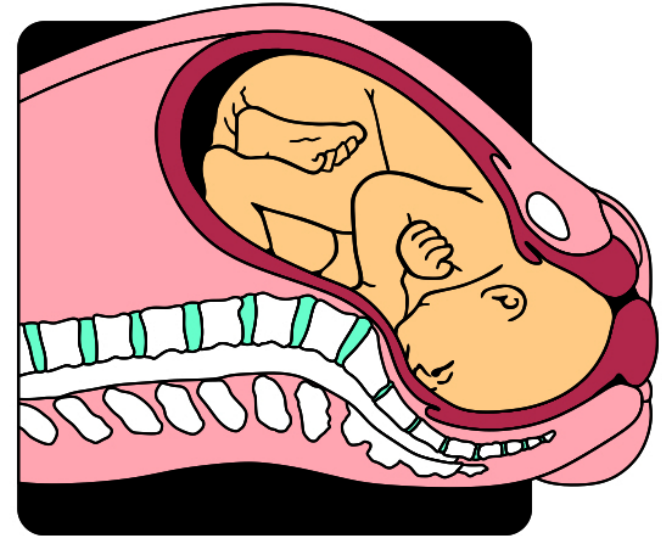
# Cardinal Movements



**Engagement, Flexion, Descent**

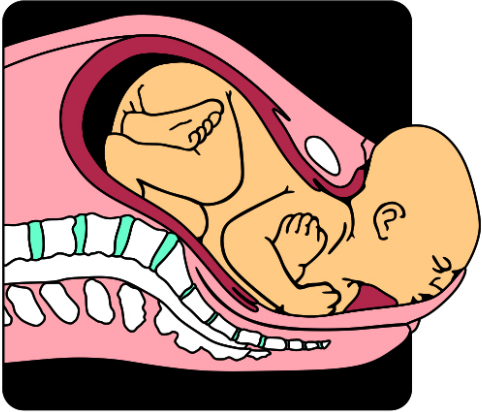


**Further Descent, Internal Rotation**

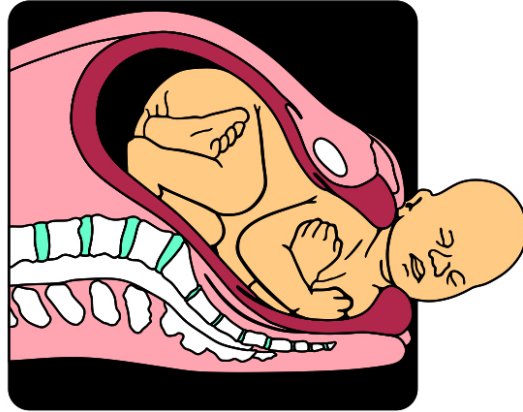


**Complete Rotation, Beginning Extension**

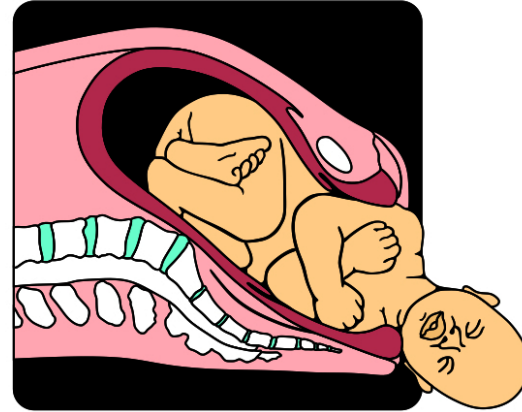
# Cardinal Movements



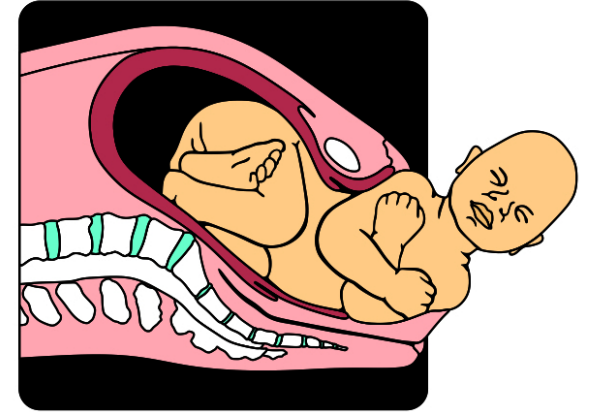
Complete Extension



Restitution (External Rotation)



Delivery of Anterior Shoulder



Delivery of Posterior Shoulder

# Cardinal Movements

- Engagement
- Flexion
- Descent
- Internal rotation
- Extension
- External rotation/restitution
- Expulsion

# Labor and Delivery II

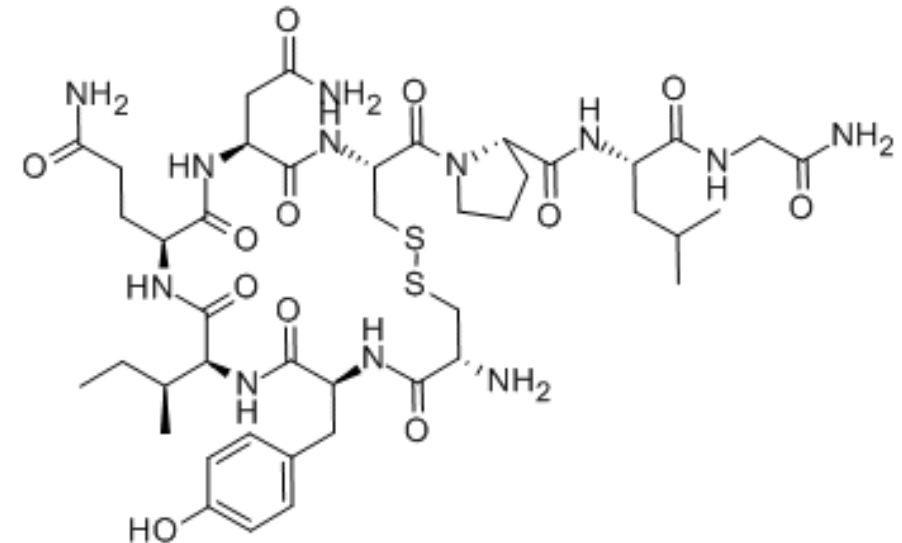
Jason Ryan, MD, MPH



# Induction of Labor

- **Stimulation of uterine contractions**
- Prior to spontaneous onset of labor
- Intravenous synthetic **oxytocin**
- May be done after spontaneous rupture of membranes
- Or after amniotomy
- Common indications:
  - Post-term pregnancy
  - Premature rupture of membranes
  - IUGR
  - Oligohydramnios
- Not done for fetal distress (C-section)

Oxytocin





# Induction of Labor

## Cervix

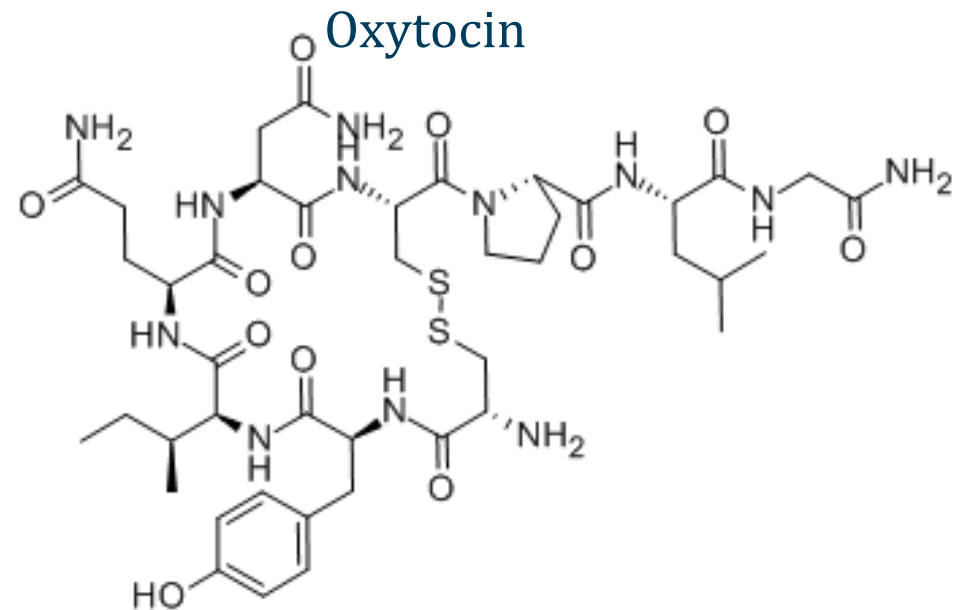
- Must be **“favorable”** or **“ripened”**
- Usually defined as **Bishop score  $\geq 6$**
- Cervical ripening techniques:
  - Misoprostol (prostaglandin E1 analog – oral or vaginal)
  - Prostaglandin E2 gels (Prepidil and Cervidil)
  - Mechanical dilators

## Bishop Score

Cervical Status	0	1	2	3
Dilatation	Closed	1-2 cm	3-4 cm	> 5 cm
Effacement	< 30%	30-50%	50-80%	> 80%
Station	-3	-2	-1 or 0	$\geq +1$
Consistency	Firm	Intermediate	Soft	
Position	Posterior	Intermediate	Anterior	

# Augmentation of Labor

- Oxytocin administration during active phase of labor
- Used with inadequate contractions or prolonged labor

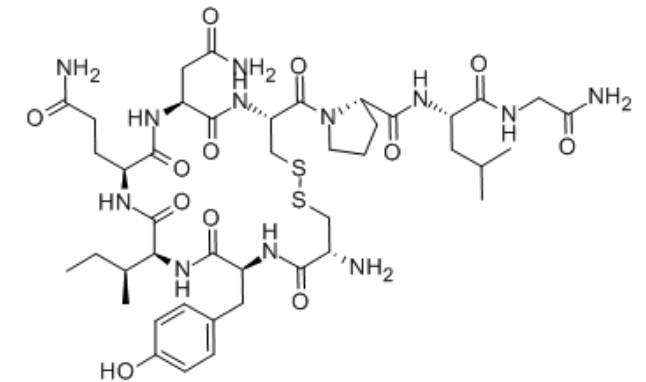


# Oxytocin

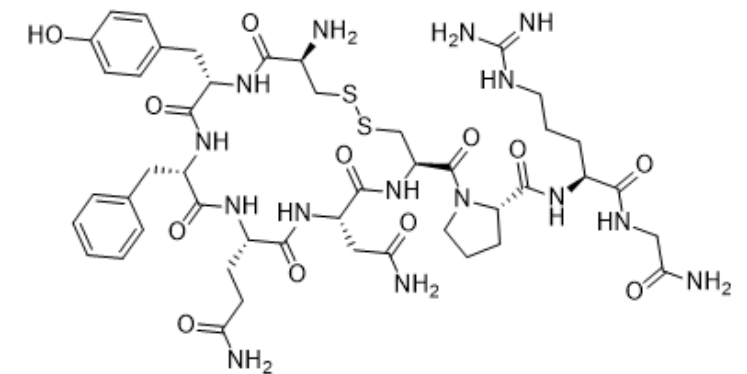
## Adverse Effects

- **Tachysystole**
  - More than 5 contractions in 10 minutes averaged over 30 minutes
  - May cause fetal hypoxemia and acidemia
  - Rarely causes uterine rupture
  - Treatment: reduce dose, stop oxytocin or add terbutaline
- **Hyponatremia**
  - Similar structure to ADH
- Hypotension
  - Oxytocin relaxes vascular smooth muscle
- Maternal fatigue/sleepiness

Oxytocin



Antidiuretic Hormone



# Analgesia and Pain Management

- **Neuraxial anesthesia:** spinal or epidural anesthesia
- Local anesthetic (bupivacaine)
- Opioid (Fentanyl)



Privatarchiv Foto von MrArifnajafov

# Cesarean Delivery

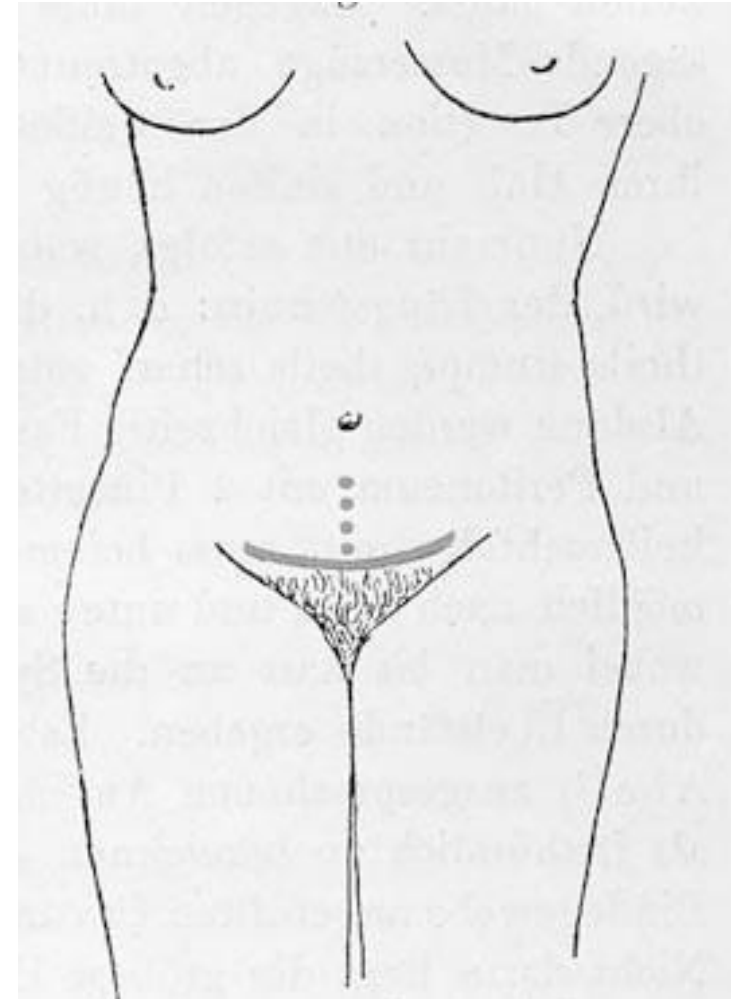
- Surgical delivery of baby
- Many **maternal and fetal indications**
  - Failure to progress
  - Fetal distress
  - Multiple gestation
  - Macrosomia
- Most often done with transverse skin incision
- Lower uterine transverse incision
- Vertical (classical) incision



# Cesarean Delivery

## Long-term complications

- **Uterine scarring**
- Increased risk for:
  - Uterine rupture
  - Placenta previa/accreta
  - Placental abruption
- Subsequent deliveries often by C-section
- TOLAC: trial of labor after cesarean
- VBAC: vaginal birth after cesarean
- No VBAC if prior vertical (classical) incision



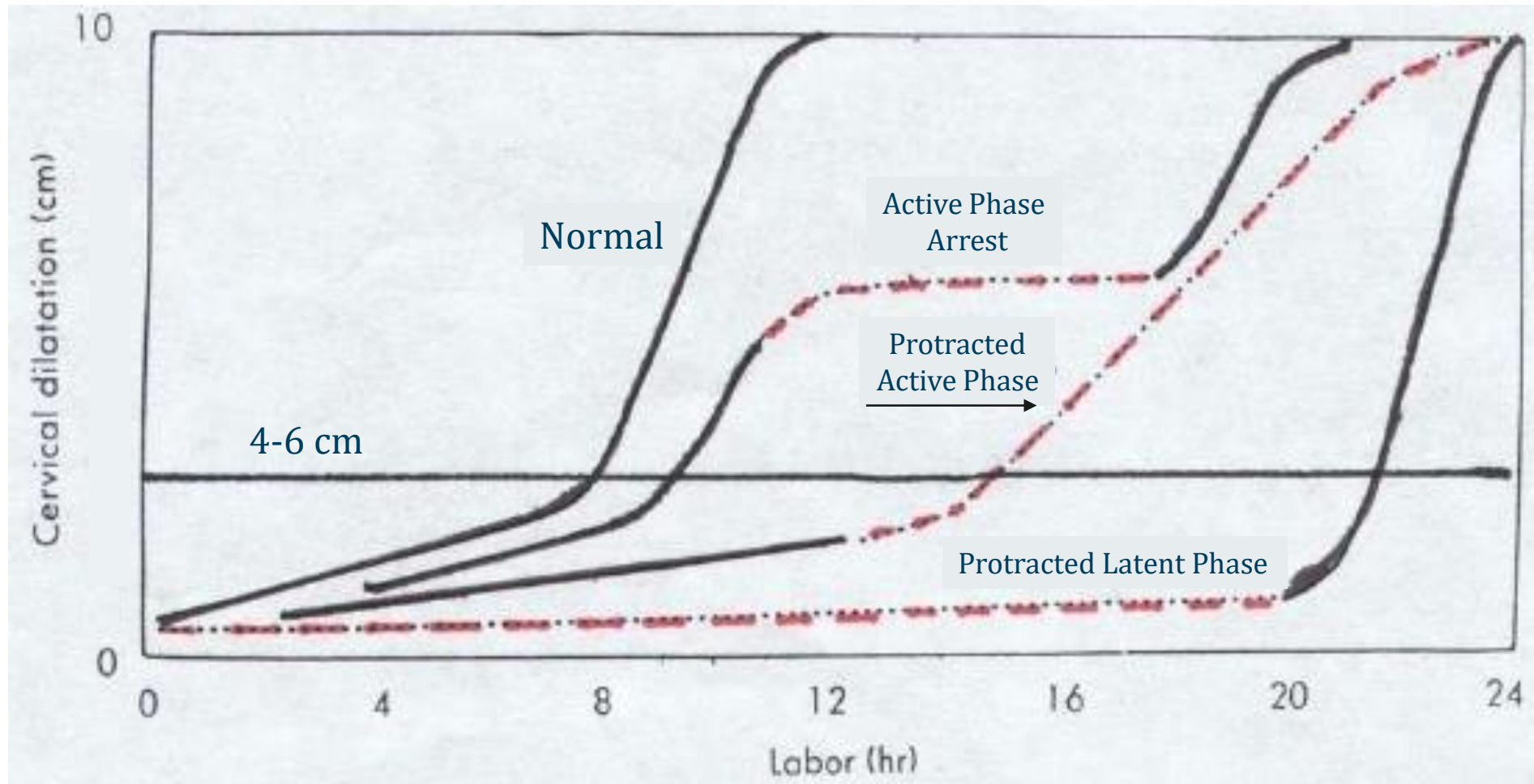
# Abnormal Labor Patterns

- Protracted labor = prolonged labor phase
- Labor arrest = no progress through labor stage
- “Failure to progress” or “dystocia”
- May require augmentation or cesarean delivery

Stage	Definition	Nulliparous	Multiparous
First (Latent)	Onset of labor until 4-6 cm dilation	< 20 hours (average 10-12)	< 14 hours (average 6-8)
First (Active)	4-6 cm until complete 10 cm cervical dilation	4-6 hr (> 1-1.2 cm/hr)	2-3 hr (> 1.2-1.5 cm/hr)
Second	Complete cervical dilation to delivery of infant	< 2 hours (3 hr if epidural)	< 1 hour (2 hr if epidural)
Third	From delivery of infant to delivery of placenta	< 30 minutes	< 30 minutes



# Abnormal Labor Patterns





# Abnormal Labor Patterns

## First Stage

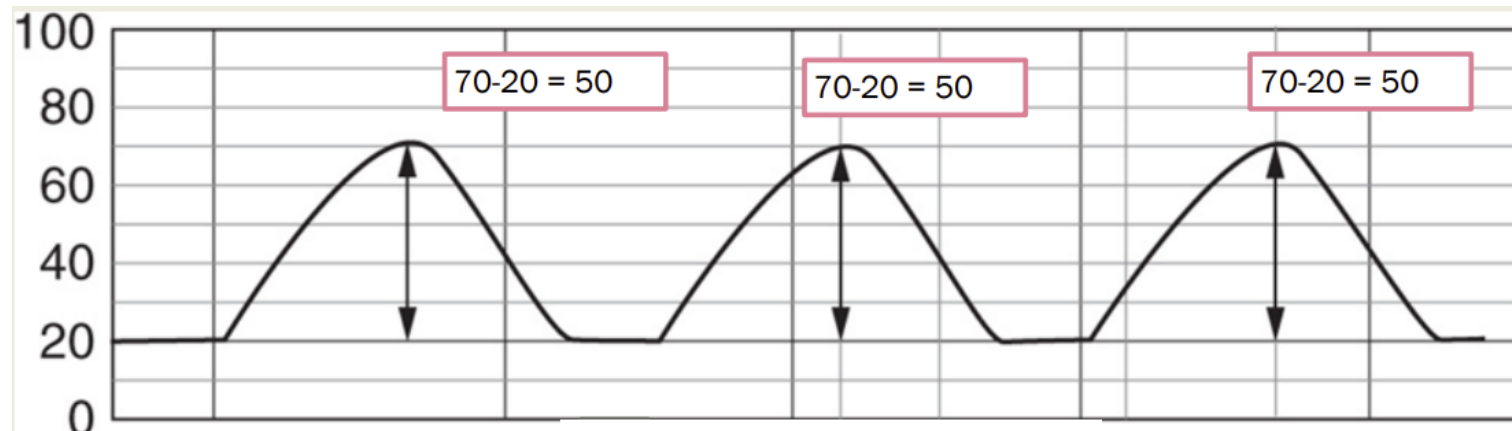
- Protracted latent phase (dilation < 6 cm)
  - > 20 hours (nulligravida)
  - > 14 hours (multigravida)
- Protracted active phase (dilation  $\geq$  6 cm)
  - Dilation progress less than 1 cm/hour
- Arrested active phase
  - No cervical change for  $\geq$  4 hours with adequate contractions
  - No cervical change for  $\geq$  6 hours with inadequate contractions

Stage	Definition	Nulliparous	Multiparous
First (Latent)	Onset of labor until 4-6 cm dilation	< 20 hours (average 10-12)	< 14 hours (average 6-8)
First (Active)	4-6 cm until complete 10 cm cervical dilation	4-6 hr (> 1-1.2 cm/hr)	2-3 hr (> 1.2-1.5 cm/hr)
Second	Complete cervical dilation to delivery of infant	< 2 hours (3 hr if epidural)	< 1 hour (2 hr if epidural)
Third	From delivery of infant to delivery of placenta	< 30 minutes	< 30 minutes

# Abnormal Labor Patterns

## First Stage Causes

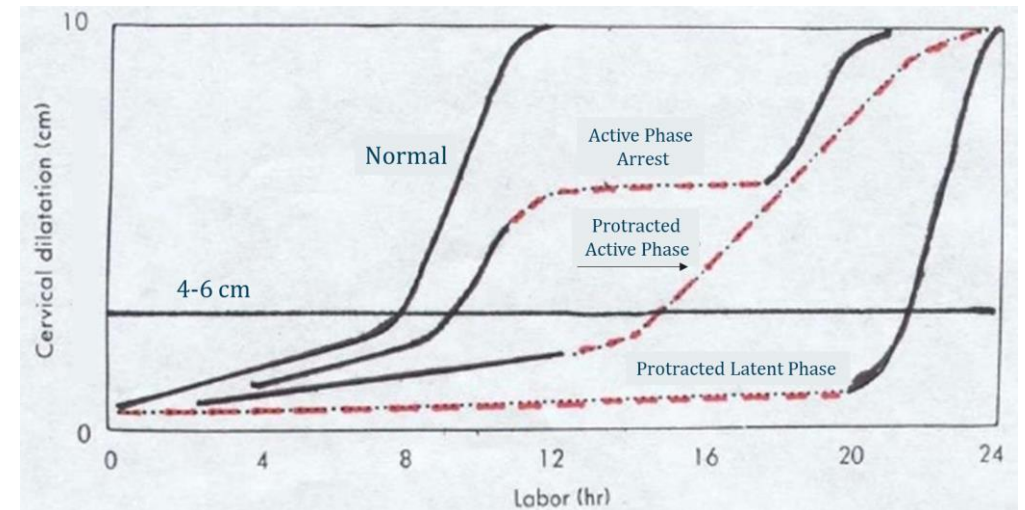
- **Hypocontractile uterine activity**
  - Monitored quantitatively using internal pressure catheter
  - Montevideo units (MVUs) = peak uterine pressure - baseline
  - Normal > 200 MVUs
- Obesity: ↑ BMI associated with ↑ length of first stage



# Abnormal Labor Patterns

## First Stage Interventions

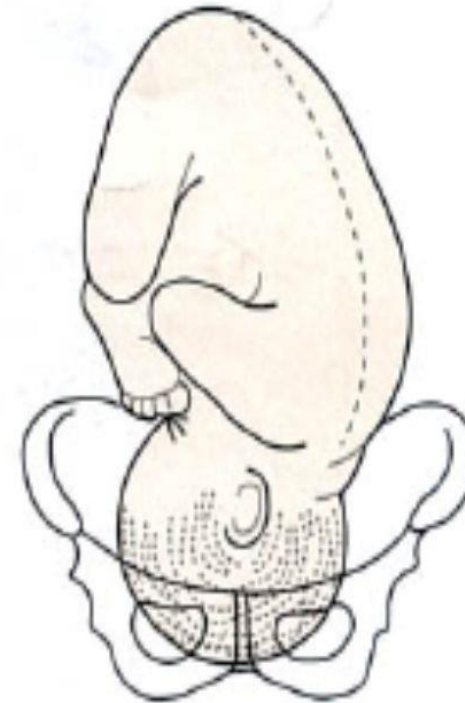
- Protracted active phase: **oxytocin** plus amniotomy
  - Amniotomy only if membranes not already ruptured
  - Oxytocin may be used even if contractions are adequate
- Active labor arrest: **cesarean delivery**
- Prolonged latent phase: discharge home versus inpatient



# Abnormal Labor Patterns

## Second Stage Causes

- **Cephalopelvic disproportion**
  - Mismatch in size of fetus relative to maternal pelvis
- **Fetal malposition**
  - Most common is **occipitoposterior**
  - Back of head toward mother's spine
- Inadequate contractions
- Poor maternal efforts



Normal



Malposition (OP)

# Abnormal Labor Patterns

## Second Stage Interventions

- Oxytocin
- **Operative delivery**
  - Forceps
  - Vacuum
- Cesarean delivery



# Rupture of Membranes

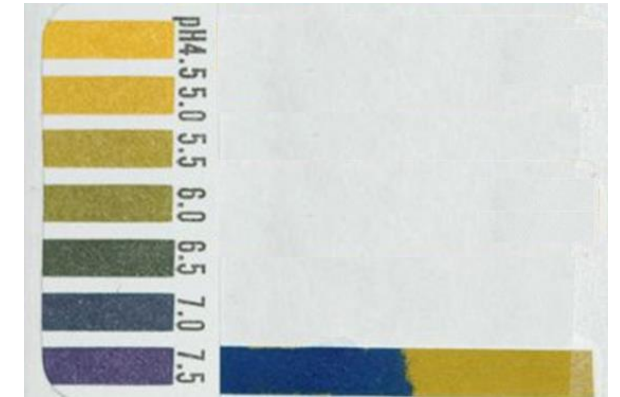
- Rupture of amniotic sac
- Presents as **vaginal fluid leakage**
- Classically a “gush”
- Clear or pale-yellow fluid (green if meconium)
- May occur spontaneously after onset of labor: SROM
- Before onset of labor (pre-labor): PROM
- Before 37 weeks (premature): PPRM
- Artificial (amniotomy) rupture: AROM

# Rupture of Membranes

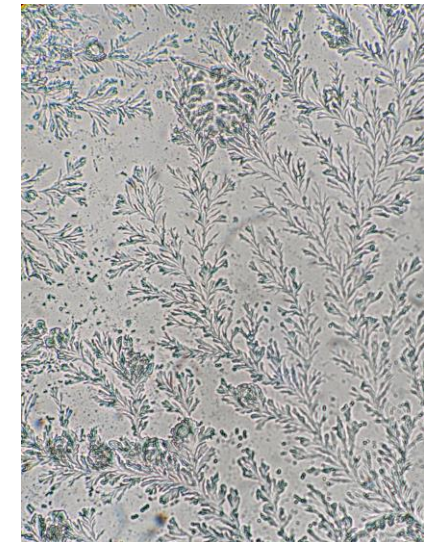
## Diagnosis

- **Nitrazine test**
  - Vaginal fluid onto Nitrazine paper strips
  - Amniotic fluid has high pH range (7.0 to 7.3)
  - Paper turns blue if fluid pH is high
- **Fern test**
  - Vaginal fluid mixed with estrogen
  - ROM: “Fern-like” pattern under the microscope
- Dye tests
  - Dye injected into amniotic sac through the abdomen
  - Colored fluid will appear in vagina

Nitrazine Paper



Fern Test





# Prelabor Rupture of Membranes

- Rupture of membranes prior to regular uterine contractions
- Occurs in 10 to 15% of pregnancy after 37 weeks
- Increased risk of infection (chorioamnionitis)
- Diagnosis: **sterile speculum exam** +/- **testing of fluid**
  - Avoid digital exam before labor – may lead to infection
  - Cultures often obtained for Neisseria and GBS
- Expectant management: await onset of labor
- Active management: induction with oxytocin

Normal pregnancy



Premature rupture of membranes





# Post-term Pregnancy

- Late term:  $\geq 41$  weeks
- Post-term:  $\geq 42$  weeks gestation
- Risk of macrosomia, dysmaturity syndrome, perinatal mortality
- Induction usually done at 41 weeks
- Late term: non-stress test and AFI done
- Oligohydramnios: **urgent induction**



# Group B Strep Infection

- Colonizes genital tract
- Frequent cause of **pregnancy-related infections**
- Asymptomatic bacteriuria (screening in early pregnancy)
- Urinary tract infection
- Chorioamnionitis
- Postpartum endometritis
- Neonatal sepsis

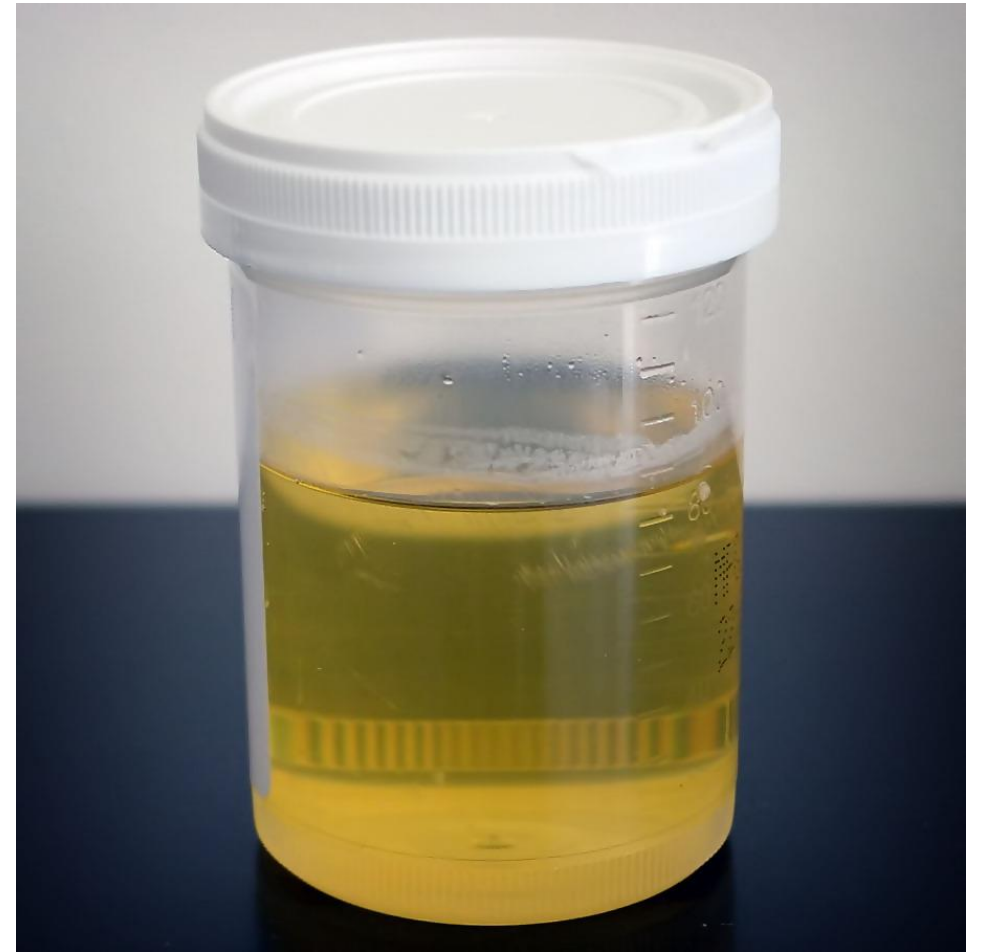
Group B Streptococcus



# Group B Strep Infection

## Diagnosis

- Urine culture
- **Nucleic acid amplification test (NAAT)**
  - Amplifies DNA or RNA sequences
  - Rapid results (less than two hours)
  - Less sensitive than culture
  - Used for women in labor with unknown GBS status



# Group B Strep Infection

## Intrapartum Antibiotic Prophylaxis

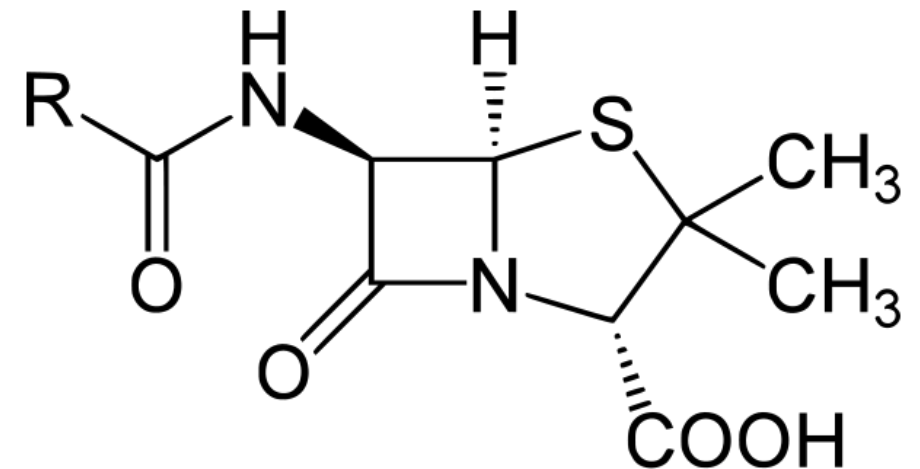
- Positive screening culture during pregnancy
- History of infant with neonatal GBS disease
- GBS infection during pregnancy
- Unknown GBS status at delivery plus one of following:
  - Fever  $\geq 100.4^{\circ}\text{F}$
  - Preterm labor
  - Preterm pre-labor rupture of membranes
  - Prolonged rupture of membranes ( $\geq 18$  hours)
  - Positive intrapartum (NAAT) test

# Group B Strep Infection

## Intrapartum Antibiotic Prophylaxis

- Administer at least 4 hours prior to delivery
- First-line: **penicillin** or **ampicillin**
  - Rapidly accumulate in amniotic fluid
- Penicillin allergy with low anaphylaxis risk (rash): **cefazolin**
- High anaphylaxis risk allergy: **GBS isolate testing**
  - Determine clindamycin sensitivity
  - Clindamycin for sensitive isolates
  - GBS resistant to clindamycin: vancomycin
- Avoid fetal scalp electrode if possible

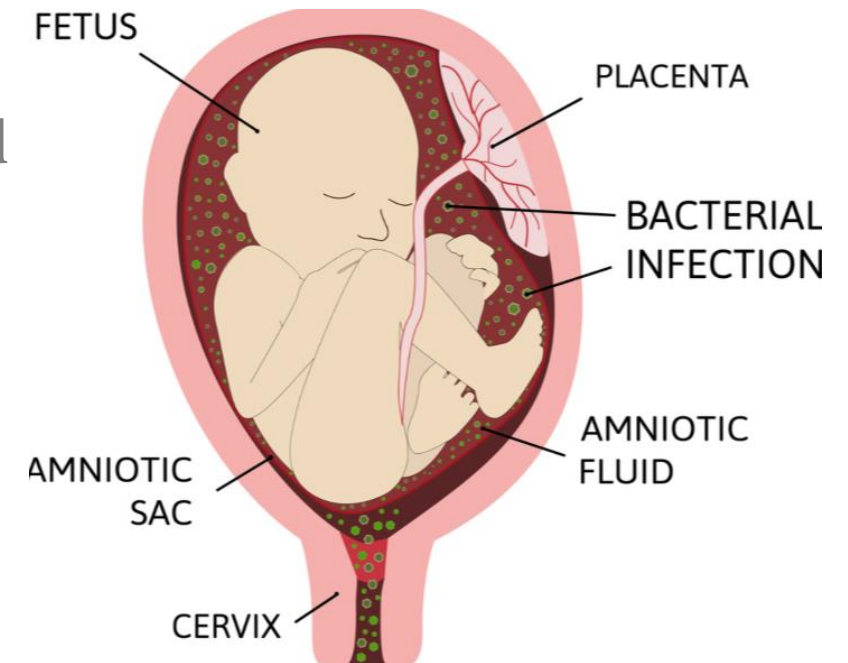
Penicillin



# Chorioamnionitis

## Intra-amniotic Infection (IAI)

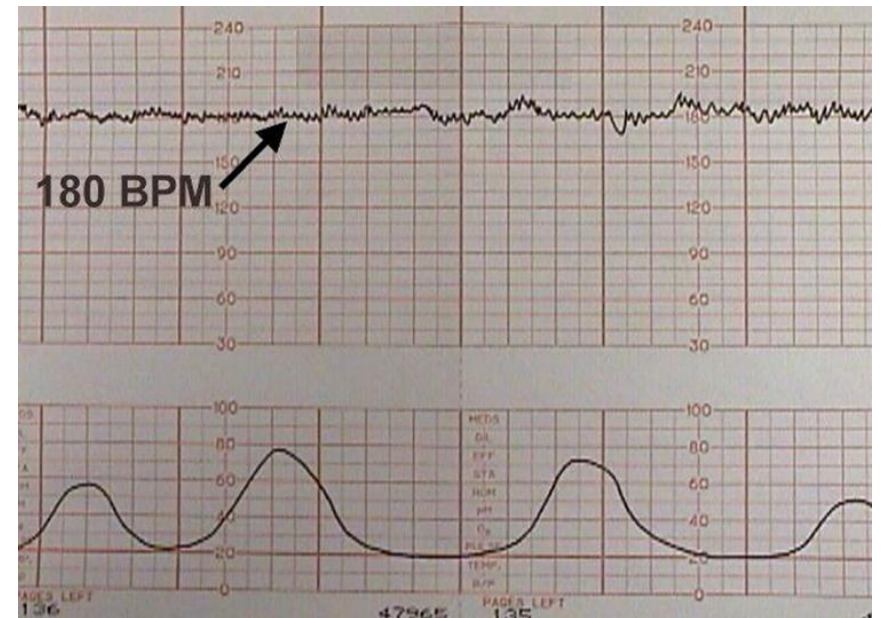
- Infection of chorion, amnion and amniotic fluid
- Usually occurs after **rupture of membranes**
- Most important risk factor: **duration of rupture of membranes**
- Polymicrobial: gram-negatives, gram-positives, GBS
- Often diagnosed clinically
- Gold standard: Gram stain and culture of amniotic fluid



# Chorioamnionitis

## Clinical Features

- Fever
- Maternal leukocytosis
- Maternal tachycardia
- Fetal tachycardia ( $> 160/\text{min}$ )
- Uterine tenderness
- Purulent or malodorous amniotic fluid
- Rarely bacteremia (usually with GBS or E. coli)

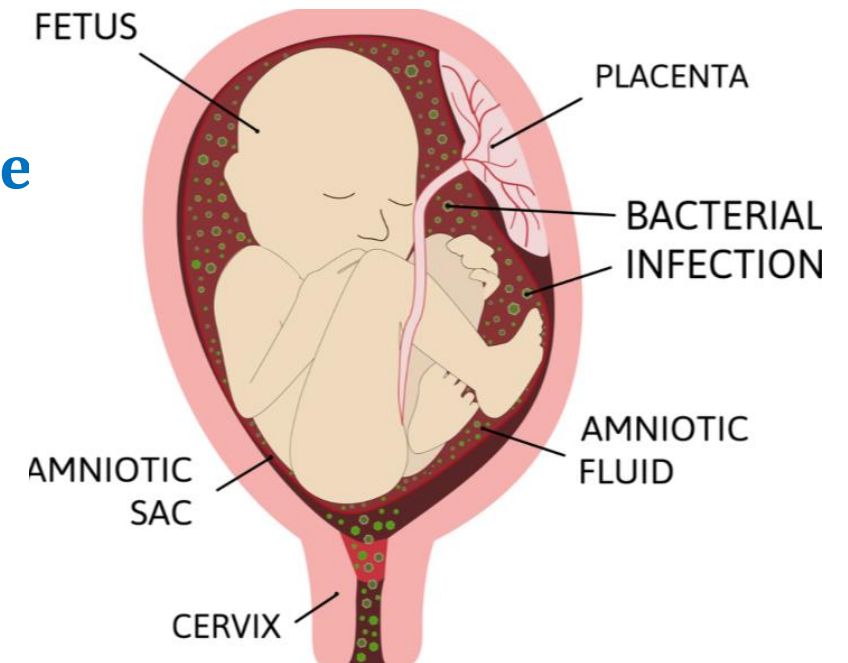




# Chorioamnionitis

## Management

- Broad-spectrum antibiotics plus immediate delivery
  - Prompt induction of labor or cesarean delivery
  - Standard indication for cesarean delivery apply
  - Vaginal delivery safe if mother and fetus stable
  - Uterus with infection may not contract well
- Intrapartum: **ampicillin and gentamycin**
- Cesarean delivery: add **clindamycin or metronidazole**
  - Coverage for anaerobes which may cause endometritis

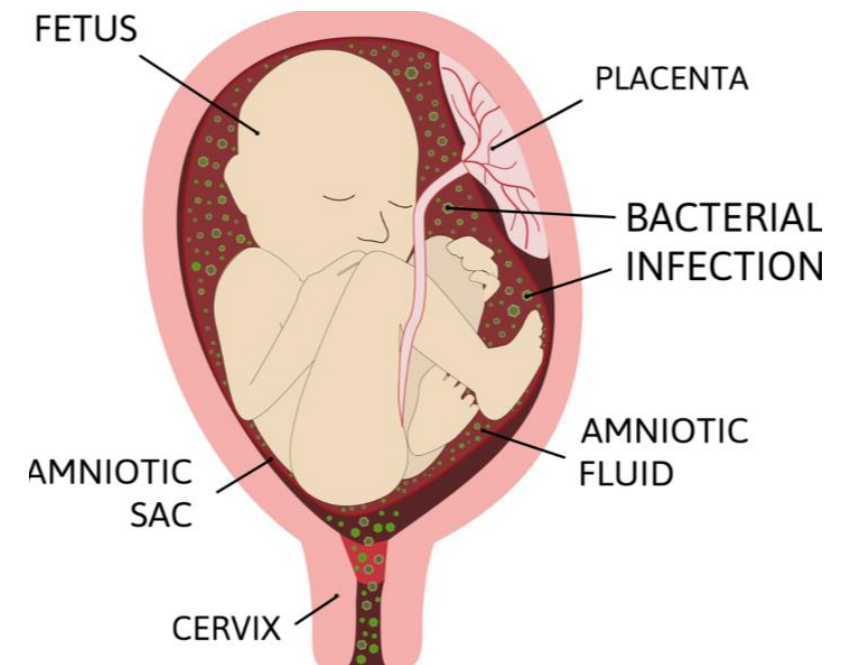




# Chorioamnionitis

## Prevention

- Prophylactic antibiotics in women with **PPROM**
- Reduces risk of clinical chorioamnionitis
- Also prolongs latency and improves neonatal outcomes
- Indicated for PPRM < 34 weeks
- Not indicated for PPRM > 34 weeks or PROM at term



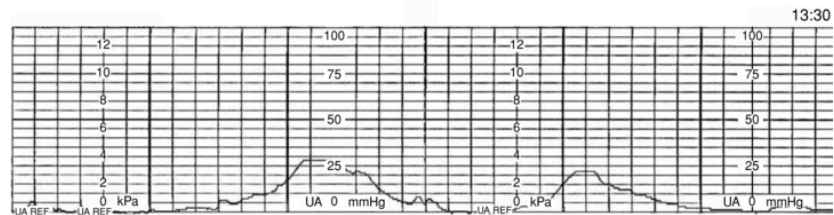
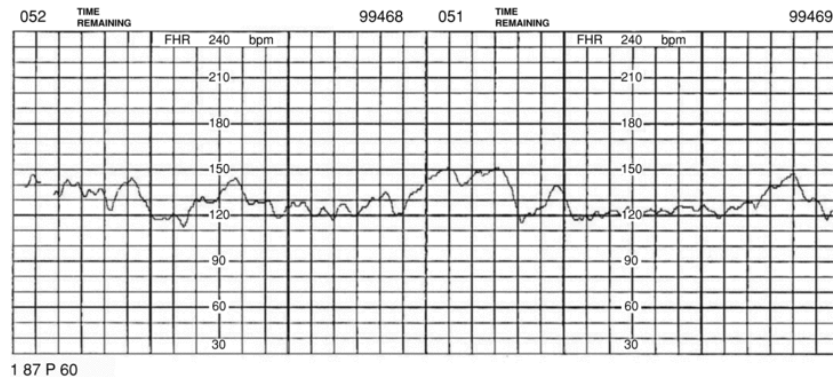
# Intrapartum Fetal Monitoring

Jason Ryan, MD, MPH



# Intrapartum Fetal Monitoring

- Fetal heart rate monitoring
  - **Doppler ultrasound** on mother's abdomen
  - **Fetal scalp electrode** (electrode directly on fetal scalp through cervix)
- Tocometry: measurement of uterine contractions

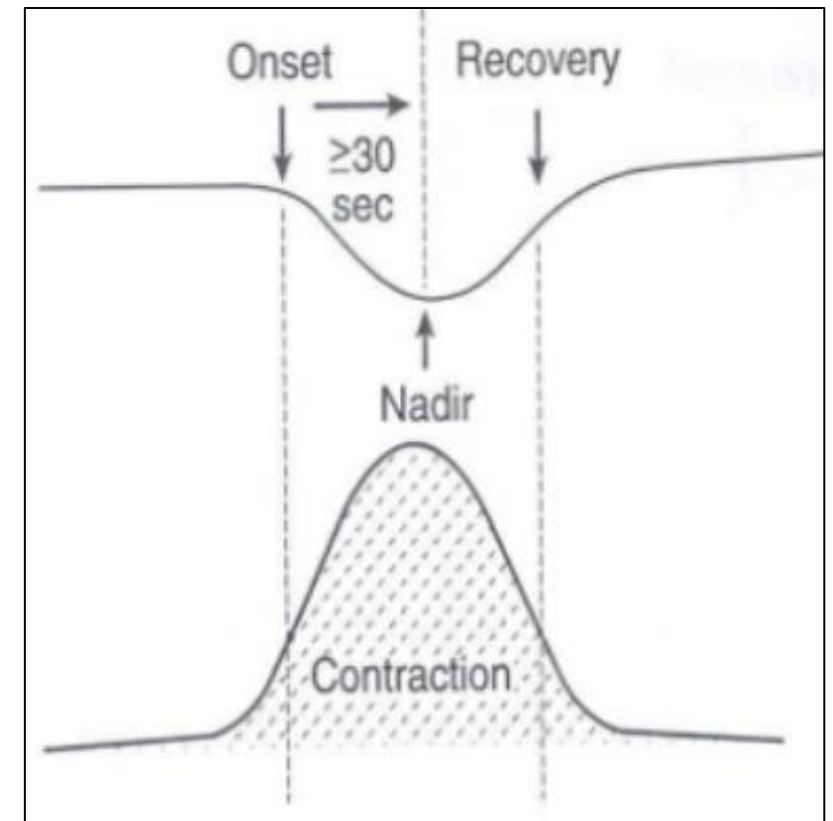


# Fetal Heart Rate Monitoring

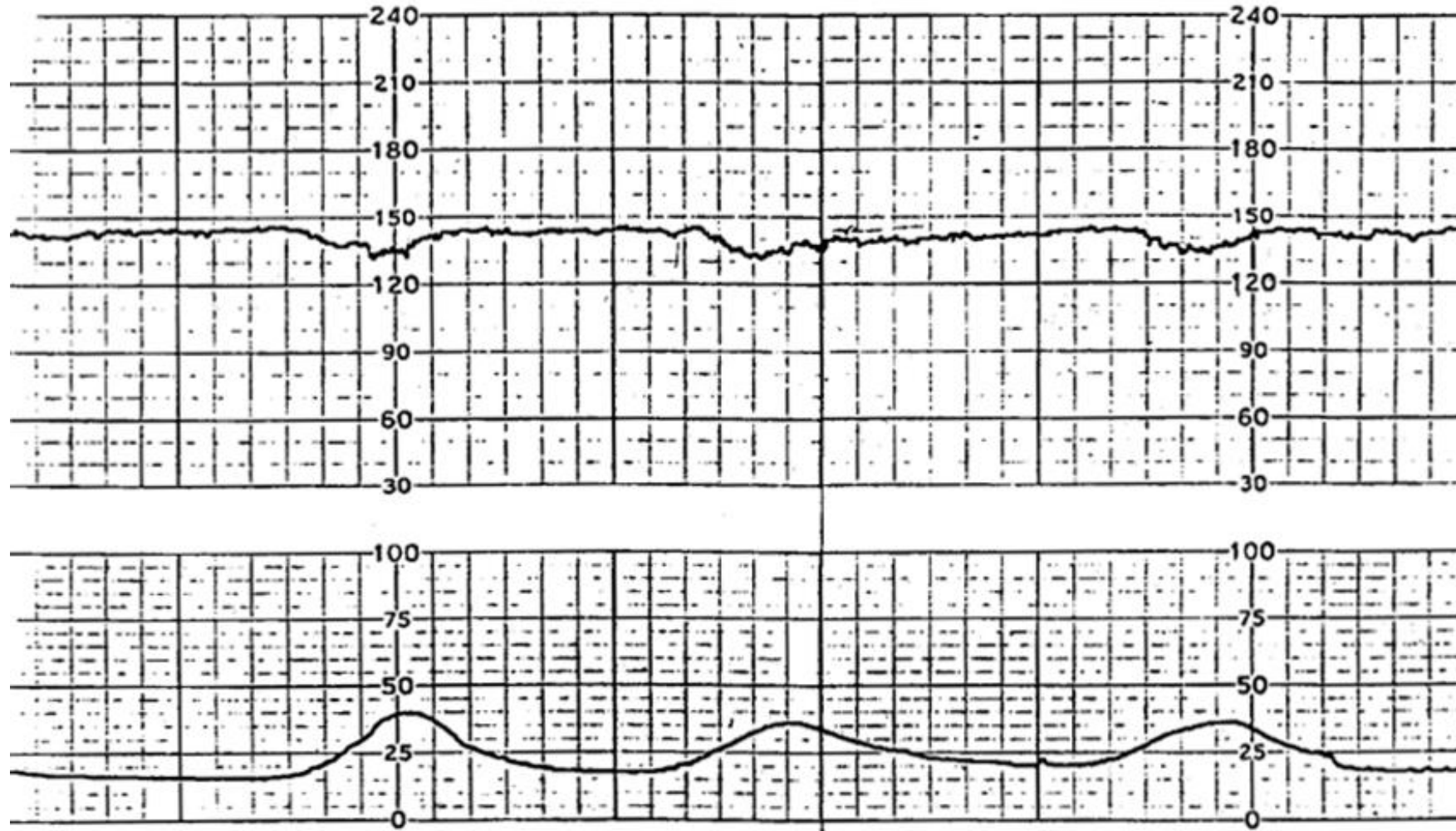
- Normal rate: 110 to 160/min
- Bradycardia: less than 110/min
- Tachycardia: more than 160/min
- Accelerations common with fetal movement
- Decelerations occur with labor: early, late or variable

# Early Decelerations

- Occur **synchronously with contraction**
- Slow onset: 30 seconds onset to nadir
- Nadir occurs near peak of contraction
- Caused by **fetal head compression**
  - Uterine contractions → head compression
  - Transient change in cerebral blood flow
  - Stimulates vagal response → ↓ HR
- Generally **benign and physiologic**
- Do not usually require intervention

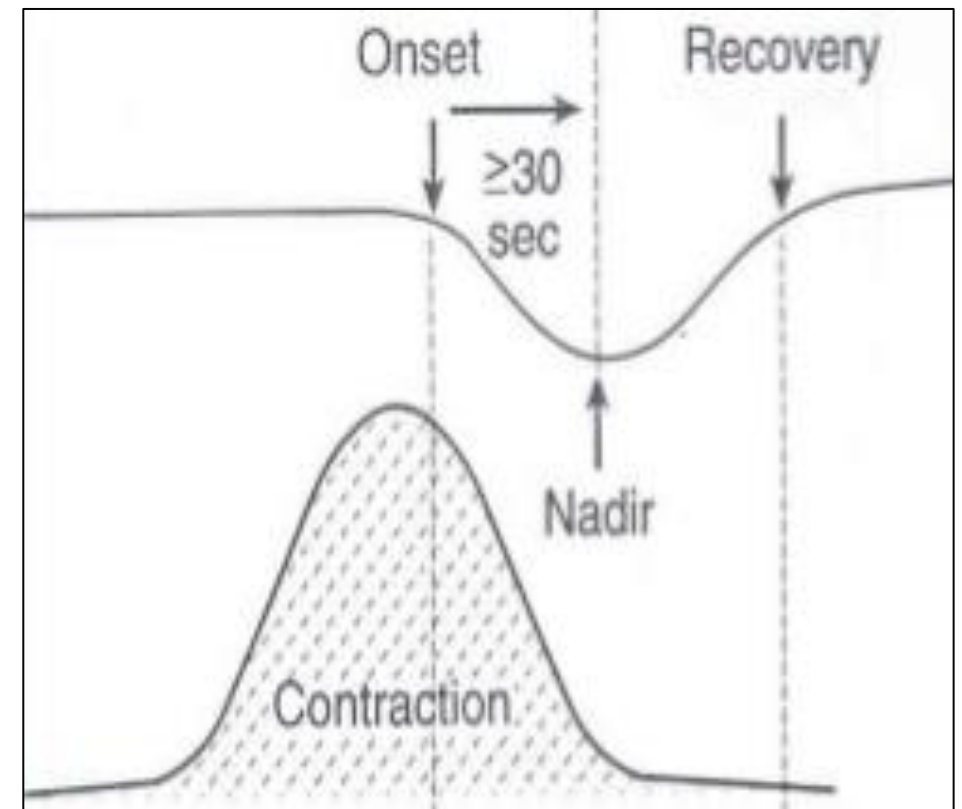


# Early Decelerations



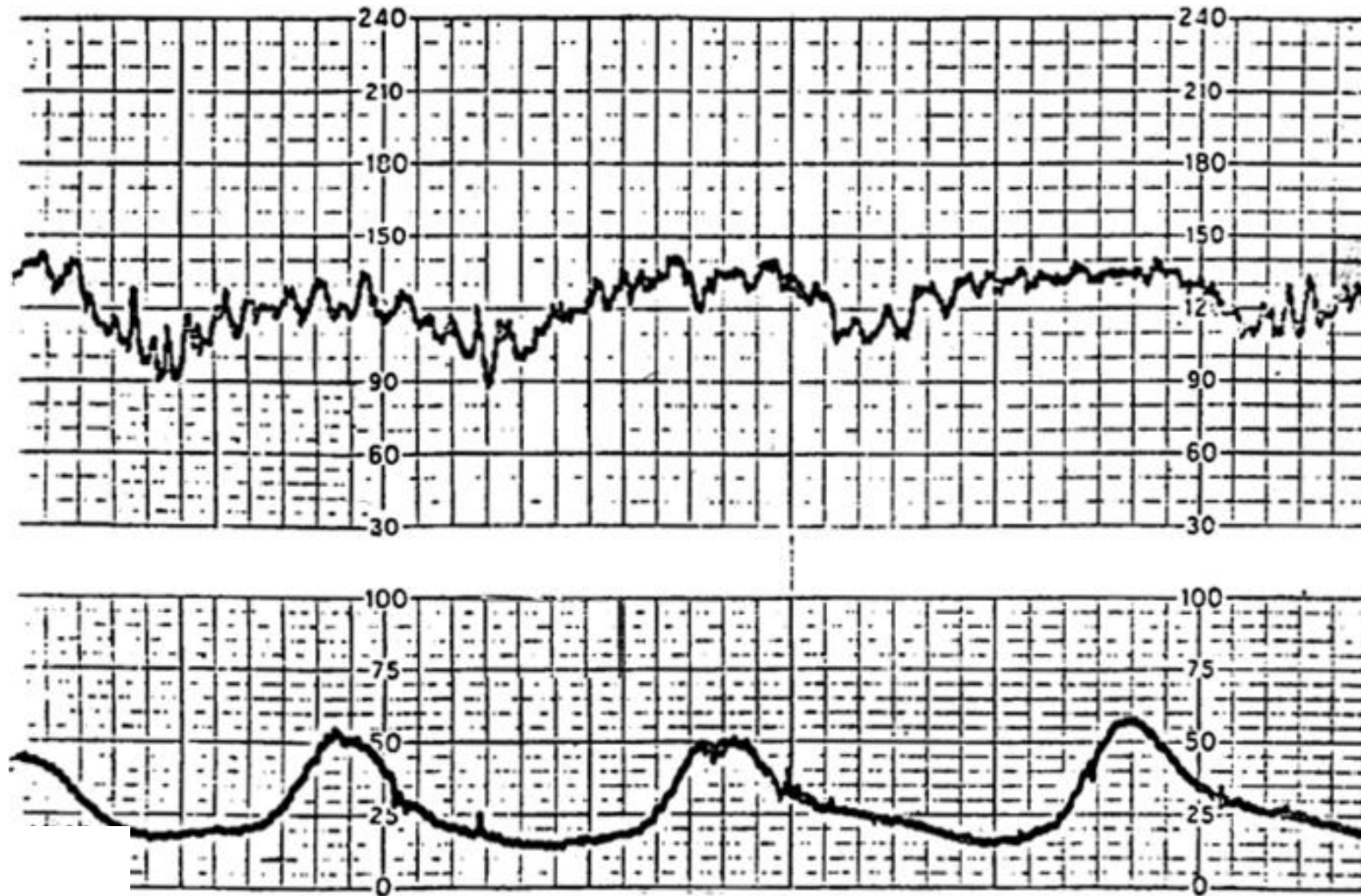
# Late Decelerations

- Decrease in HR begins after contraction onset
- Return to baseline after contraction ends
- Indicates transient **fetal hypoxemia**
- Contractions compressing blood vessels
- Uteroplacental insufficiency
- Require maternal-fetal evaluation





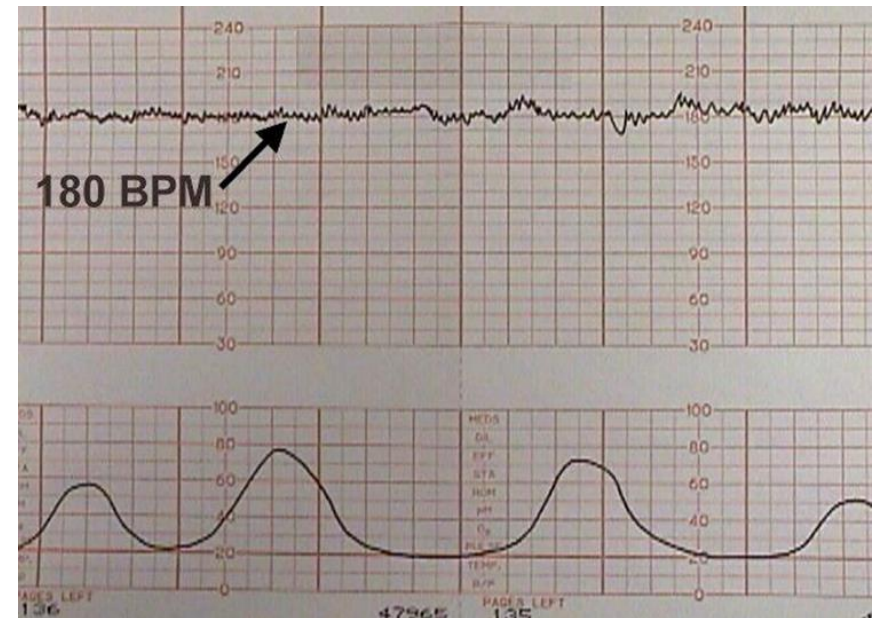
# Late Decelerations





# Fetal Tachycardia

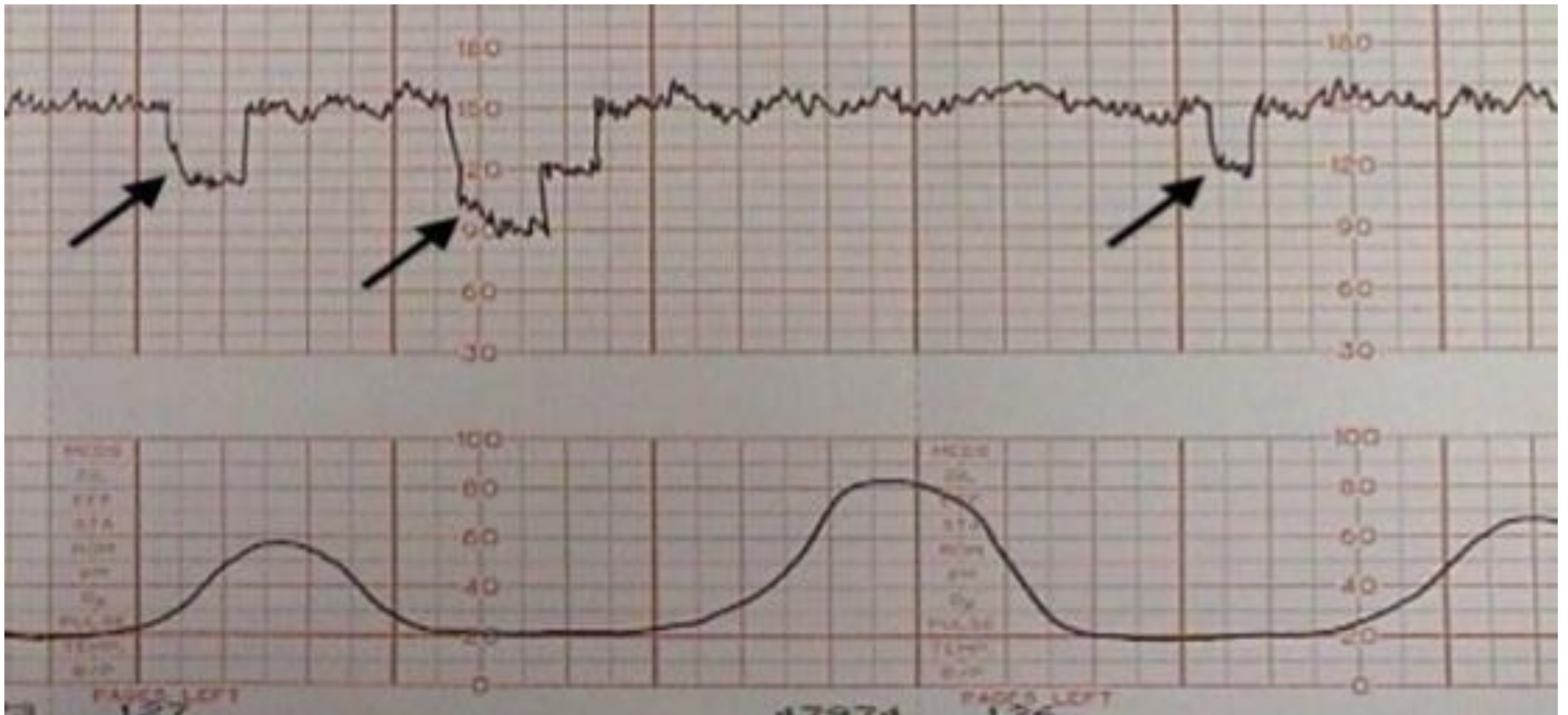
- Fetal movement: short bursts of sinus tachycardia up to 200 bpm
  - Do not require further investigation
- Persistent tachycardia: **maternal and fetal evaluation**
- Many possible causes
- Anemia
- Maternal infection/fever



# Variable Decelerations

- No relationship to contractions
- Abrupt onset
- Less than 30 seconds onset → nadir
- Fetal reflex response to transient **umbilical cord compression**
- Also associated with **oligohydramnios** → cord compression

# Variable Decelerations



# Persistent Variable Decelerations

## Management

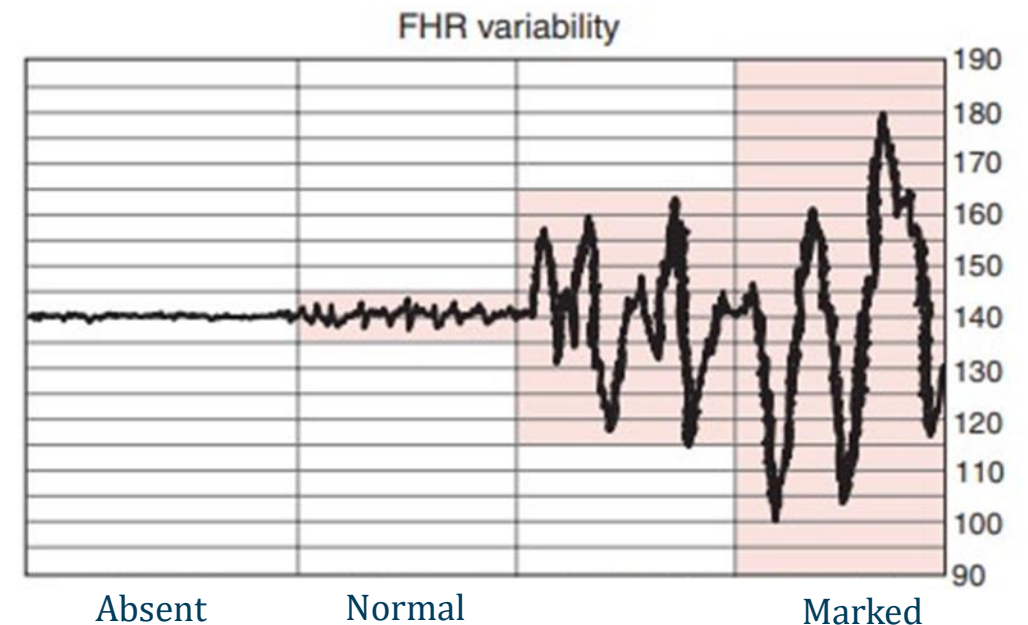
- First-line intervention: **change maternal position**
  - Shift to left or right side
  - May also try knee-chest or all fours
- Second-line: **transcervical amnioinfusion**
  - Infusion of fluid into amniotic cavity
  - May cause temporary improvement in decelerations
- Consider operative delivery

# VEAL-CHOP

- **V**ariable → **C**ord compression
- **E**arly → **H**ead compression
- **A**cceleration → **O**kay
- **L**ate → **P**lacental insufficiency

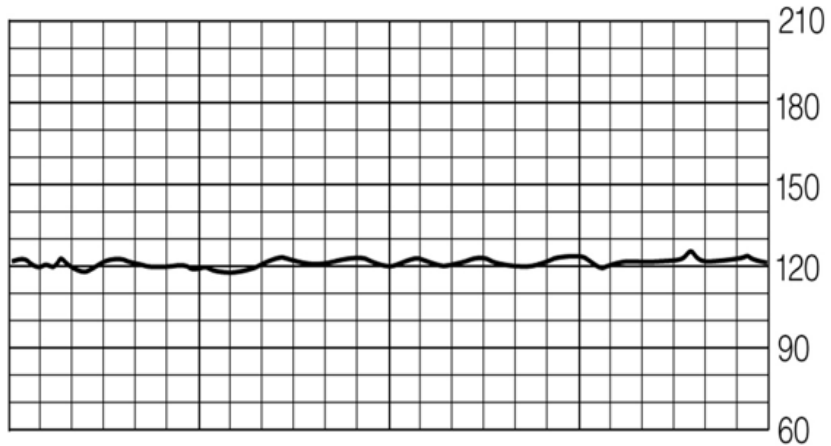
# Fetal Heart Rate Variability

- Caused by activity of sympathetic and parasympathetic systems
- Normal: 6 to 25 bpm
- Marked more than 25 bpm
- Absent variability: **fetal distress**

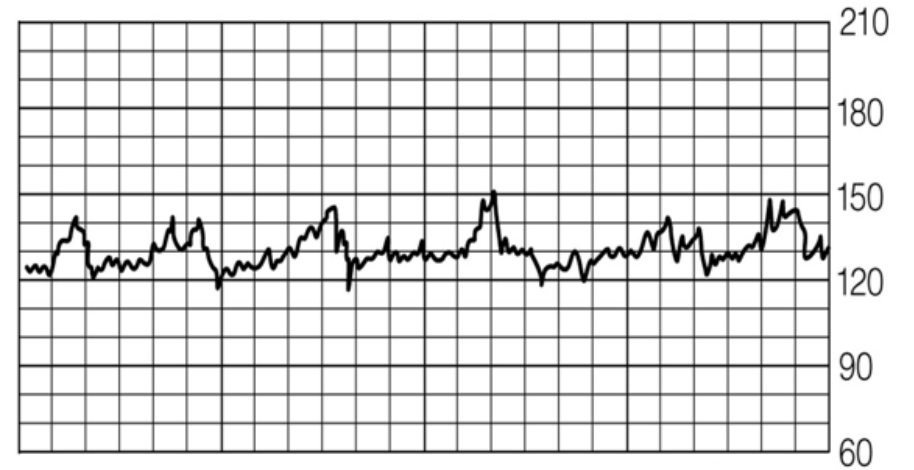


# Fetal Heart Rate Monitoring

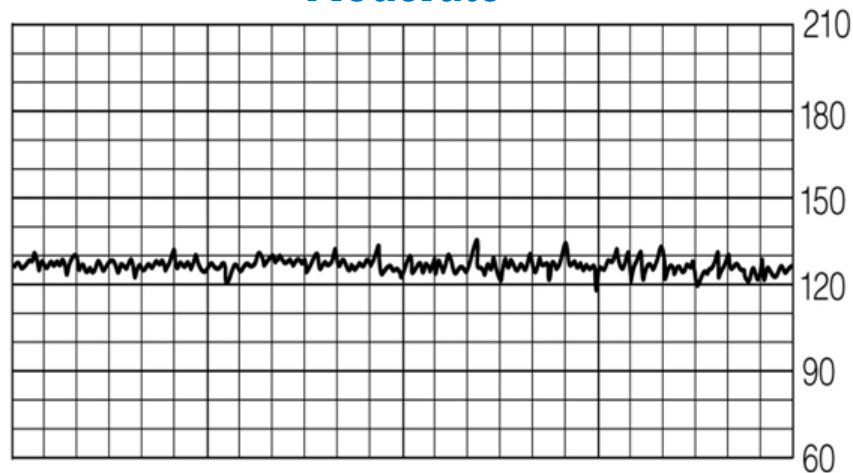
Minimal or Absent



Marked

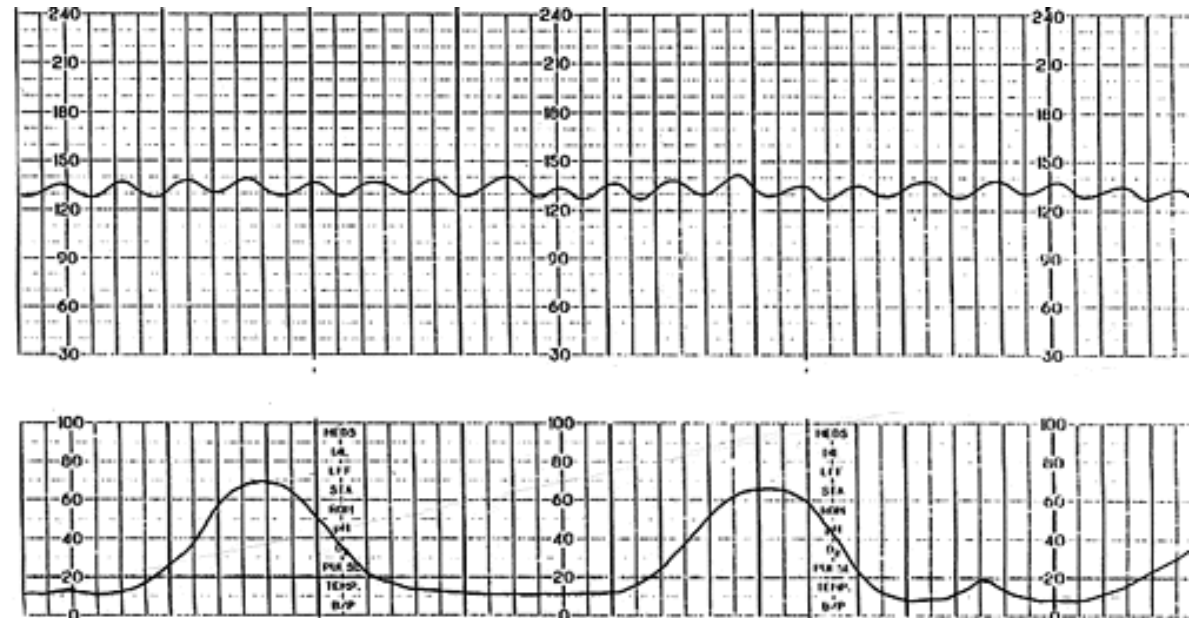


Moderate



# Sinusoidal Pattern

- Rare finding
- Sine-wave pattern
- Regular amplitude and frequency
- Associated with **severe fetal anemia**





# Fetal Heart Rate Patterns

Category I	Category II	Category III
Baseline 110 to 160/min Moderate variability No late or variable decelerations	Does not meet I/III criteria	Recurrent late decelerations Recurrent variable decelerations Fetal bradycardia Sinusoidal pattern

# Category III

## Management options

- Maternal oxygen and IV fluids
- **Change maternal position** to relieve umbilical cord pressure
- Discontinue oxytocin
- Consider tocolytic (terbutaline)
- Prepare for operative delivery

# Preterm Labor

Jason Ryan, MD, MPH



# Premature Birth

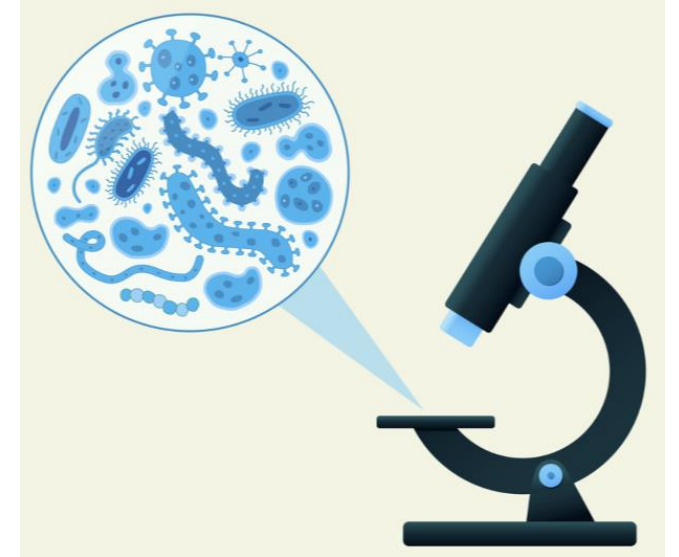
- Delivery before 37 weeks
- Strongest risk factor: **prior preterm birth**
- Other risk factors:
  - **Multiple gestation**
  - Short cervix (cervical insufficiency)
  - Prior cervical surgery (conization or excision for CIN)
  - Short interpregnancy interval (< 6 months)
  - Smoking
  - **Infection** (UTI, asymptomatic bacteriuria )
  - Polyhydramnios



# PPROM

## Preterm Pre-labor Rupture of Membranes

- Rupture of membranes prior to regular uterine contractions
- Occurs **before 37 weeks**
- Occurs in one-third of preterm births
- Increased risk with prior PPRM or short interval pregnancy
- Associated with **genitourinary infections**
  - Increase membrane fragility
  - Screening at initial visit; treat all infections even asymptomatic



# PPROM

## Preterm Pre-labor Rupture of Membranes

- Requires **inpatient monitoring**
- Preterm labor and birth
- **Intra-amniotic infection**
- Placental abruption (loss of fluid → decompression)
- Umbilical cord prolapse (especially if breech)
- **No digital exams**

# PPROM

## Preterm Pre-labor Rupture of Membranes

- Infection or fetal/maternal compromise: **delivery**
  - Maternal fever
  - Fetal tachycardia
- Stable patients 34 to 37 weeks: **delivery**
  - ACOG recommendation\*: induction of labor
- Stable patients < 34 weeks: **hospitalize**
  - Expectant management
  - Maternal corticosteroids
  - **Prophylactic “latency” antibiotics**

# Latency Antibiotics

- **Prophylactic antibiotics**
- Reduce risk of infection → labor and delivery
- Prolong **“latency”** – period between ROM and delivery
- Usual regimen: azithromycin and ampicillin
- Cover GBS, some gram negatives and anaerobes
- ACOG recommendation: antibiotics for **PPROM < 34 weeks**
- Not indicated for PPRM ≥ 34 weeks



# Premature Labor

## Clinical Features

- Regular contractions plus cervical change
- Diagnosis may be unclear
- Especially if dilation  $< 3$  cm and intact membranes
- Further testing: **TVUS** and **fetal fibronectin**

Transvaginal Ultrasound

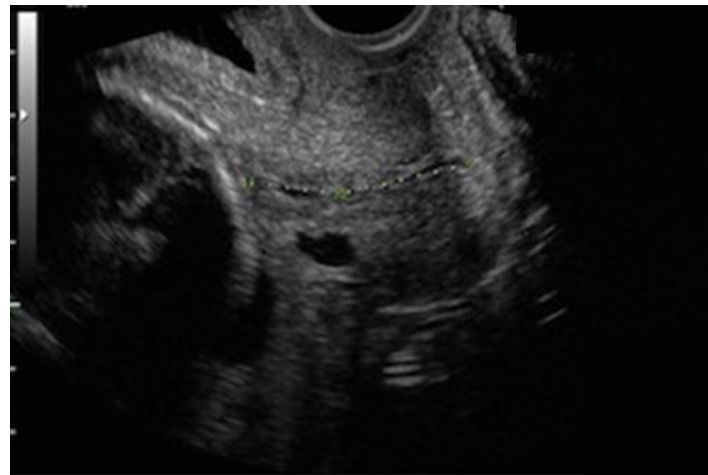


# TVUS

## Transvaginal Ultrasound

- Used for measurement of **cervical length at 16 to 23 weeks**
- Cervical length shortens in pregnancy
- Short cervix before 34 weeks =  $\uparrow$  risk preterm birth
- Long cervix ( $\geq 30$  mm): high **negative predictive value** for preterm birth

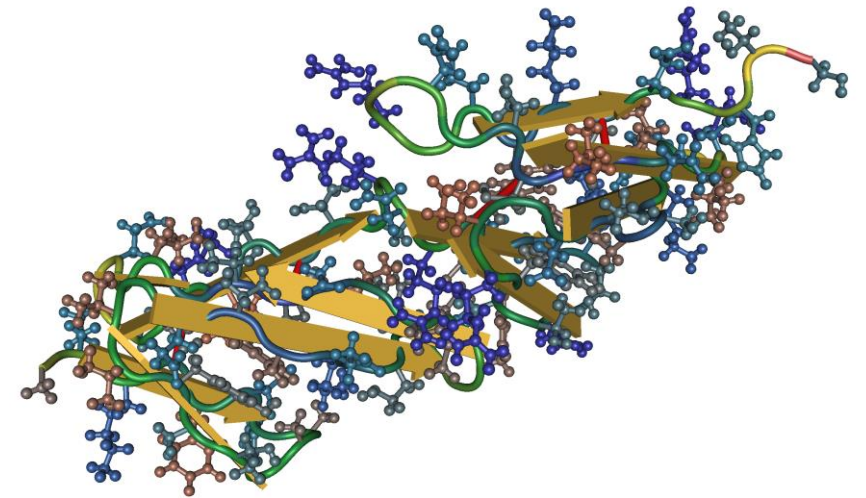
TVUS of Cervix



# Fetal Fibronectin

- Used between **22 and 34 weeks**
- Always high before 20 weeks (not useful for diagnosis)
- Protein found at decidual-chorionic interface
- Can be detected in cervicovaginal secretions
- Positive test: ↑ risk of preterm delivery within 7 days
- High **negative predictive value**

Fetal Fibronectin

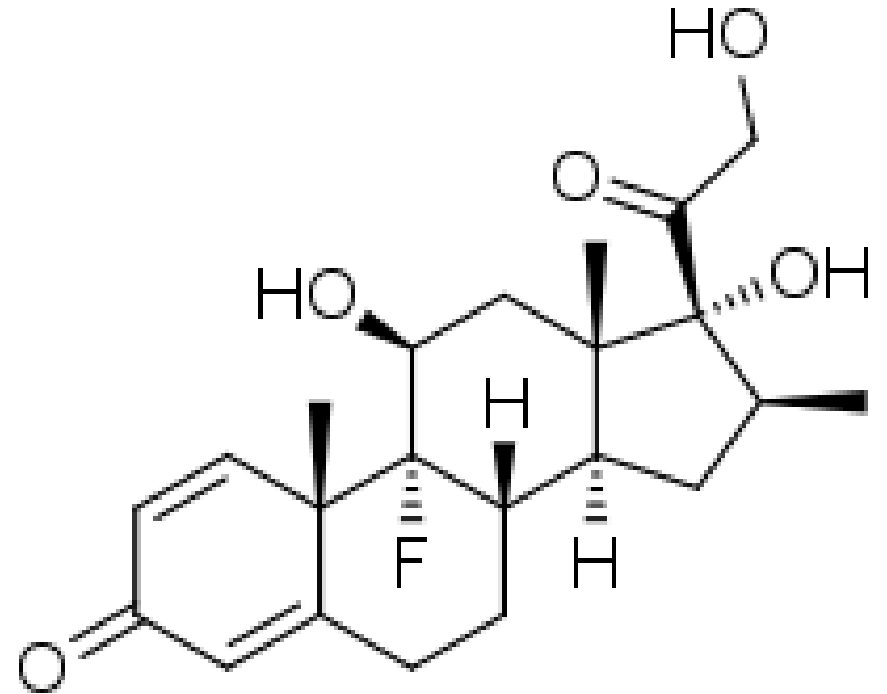


# Premature Labor

## Management

- Beyond 34 weeks: **admit and deliver**
- Before 34 weeks:
  - Maternal **betamethasone**
  - GBS prophylaxis (penicillin, ampicillin or clindamycin)
  - Tocolytic drugs to delay labor after maternal steroids
- Magnesium sulfate: neuroprotective
  - May reduced risk of cerebral palsy
  - ACOG recommendation in early preterm births

Betamethasone



# Tocolytic Drugs

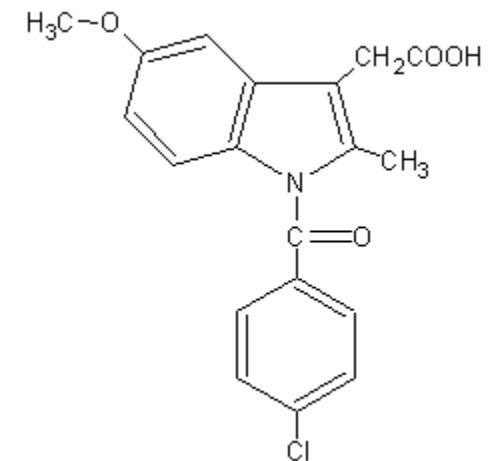
- **Indomethacin**

- Prostaglandin inhibitor
- First-line therapy 24 to 32 weeks
- Avoided beyond 72 hours (constriction of ductus arteriosus and oligohydramnios)

- **Nifedipine**

- Calcium channel blocker
  - Often used when indomethacin fails
  - First-line if contraindication to indomethacin
  - Causes hypotension, flushing and fatigue
- Ritodrine or terbutaline (beta-2 agonists)

Indomethacin

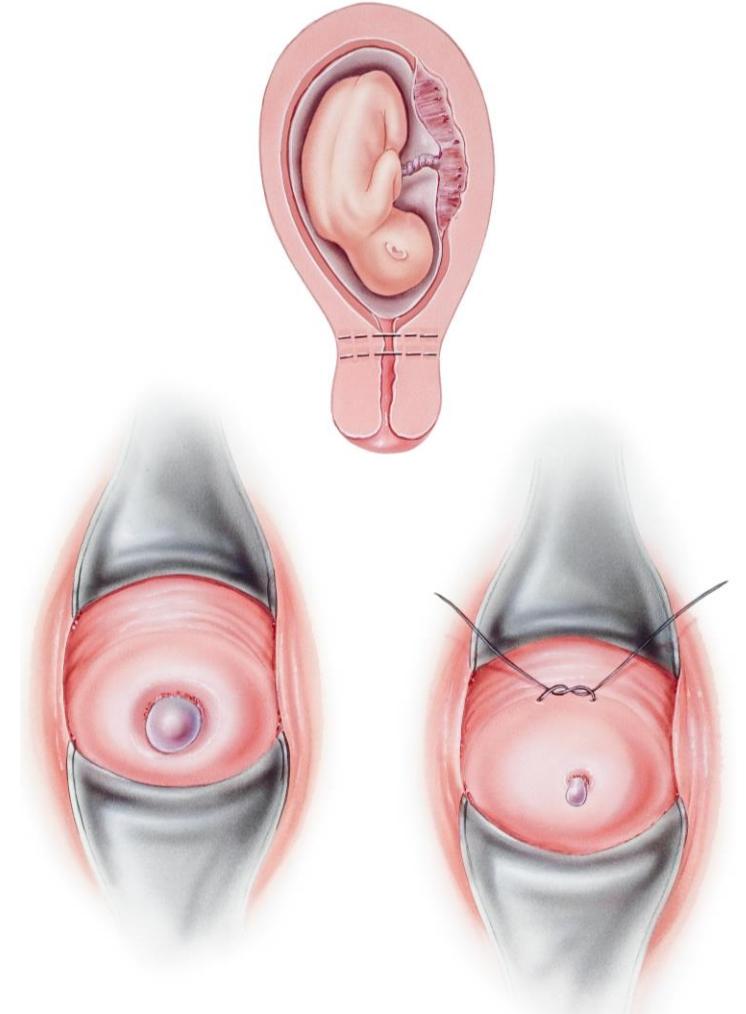


# Premature Labor

Prevention in high-risk groups

- **Progesterone**
  - Maintains uterine quiescence
  - Decreases risk of ROM
- **Cerclage**: surgical reinforcement of cervix

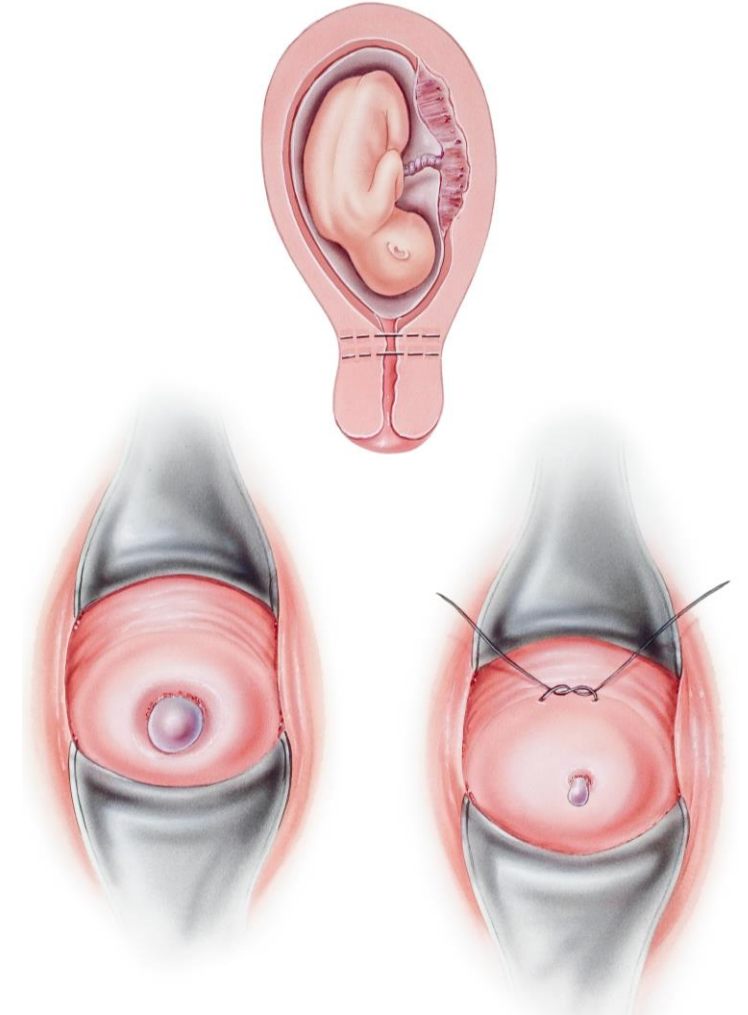
Cervical Cerclage



# Premature Labor

## Prevention in high-risk groups

- **Prior preterm labor**
  - High risk group
  - Consider progesterone
  - Serial TVUS until 24 weeks
  - Short cervix (< 30 mm): progesterone + cerclage
- Short cervix: progesterone
  - Cervical length  $\leq 25$  mm before 24 weeks



# Labor and Delivery Complications

Jason Ryan, MD, MPH





# Shoulder Dystocia

- Inability to deliver shoulders after fetal head
- Fetal head may retract against perineum (turtle sign)
- Obstetric emergency – asphyxia may occur
- Difficult to predict or prevent
- Most cases idiopathic with no risk factors
- More likely with:
  - Macrosomia or post-term pregnancy
  - Maternal diabetes or obesity



# Shoulder Dystocia

## Management

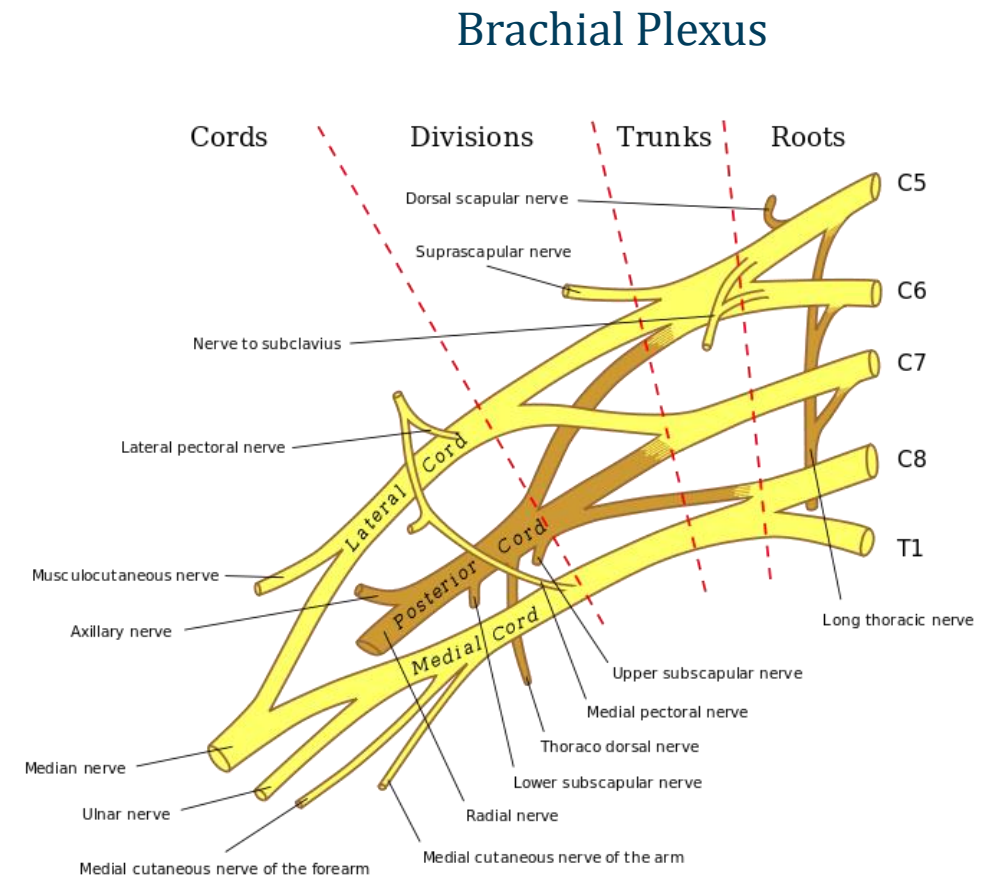
- **B**reathe, do not push
- **E**levate the legs (McRoberts maneuver)
- **C**all for help
- **A**pply suprapubic pressure
  - No fundal pressure
- **E**n**L**arge vaginal opening
- **M**aneuvers



# Shoulder Dystocia

## Adverse outcomes

- **Brachial plexus palsy**
  - Usually transient, rarely permanent
  - Most commonly upper plexus injury (Erb's palsy)
- Clavicle fracture (often intentional)
- Humerus fracture
- Hypoxic encephalopathy
- Death



# C5-C6 Trunk

## Erb's Palsy/Upper Plexus Injury

- Caused by excessive angle at neck/shoulder
- Stretches/tears nerve roots → nerve damage
- Axillary, musculocutaneous and suprascapular nerves
- **Arm straight at side**
- **Internally rotated (hand facing out)**
- “Waiter’s tip”
- Usually self-limited and improves over months



# Breech Presentation

- Occurs when buttocks and/or feet are presenting part
- Diagnosis by Leopold maneuvers or ultrasound
- 75% spontaneously convert by week 38
- May require cesarean delivery



Frank



Complete



Footling

# Breech Presentation

## Risk Factors

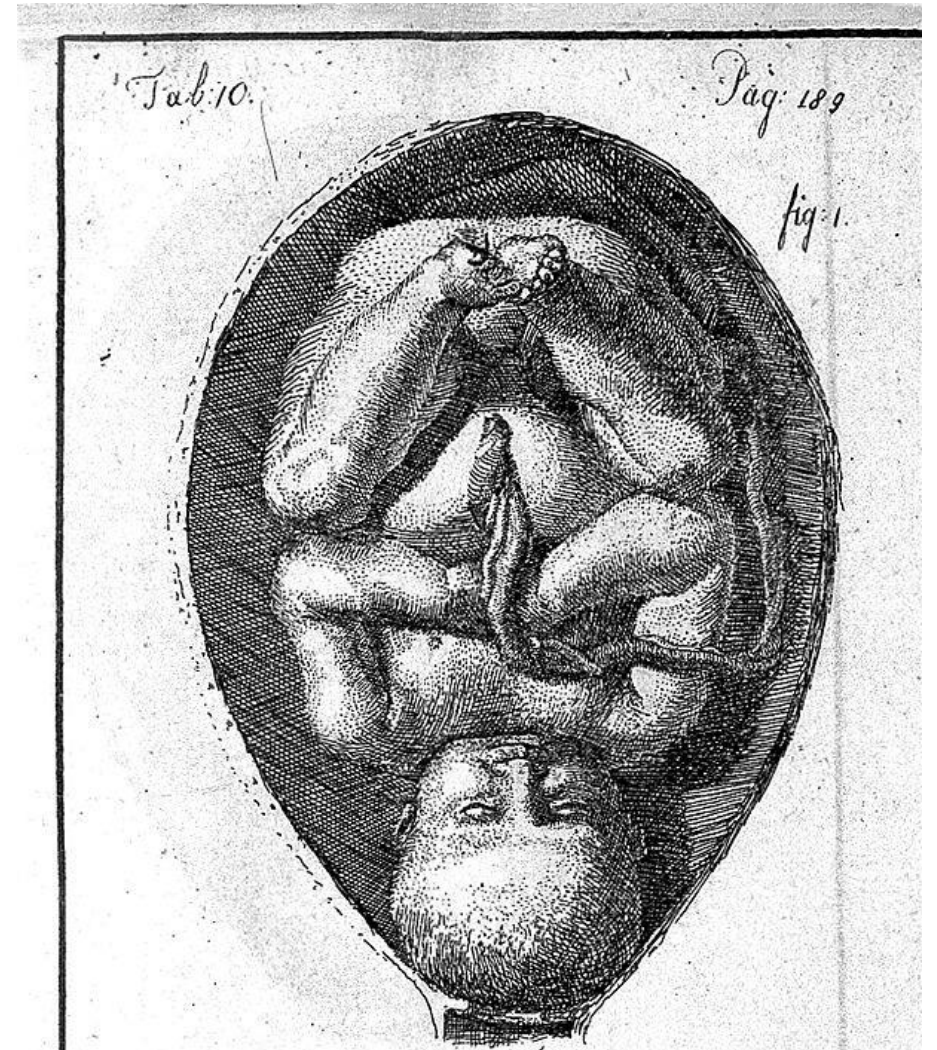
- **Limited fetal movement**
  - Uterine leiomyomas
  - Oligohydramnios
- **Excess fetal movement**
  - Polyhydramnios
  - Fetal growth restriction
- **Multiparity**
  - Prior pregnancy alters uterine/abdominal shape



# Breech Presentation

## Management with Cephalic Version

- **External cephalic version**
  - Performed after week 37
  - Abdominal pressure to turn fetal position
  - Successful about 50% of cases
  - More often successful in parous women
- Selection criteria:
  - Normal fetal heart tracing
  - Adequate amniotic fluid – absence of ROM
  - Presenting part not descended to birth canal
  - No placental abruption or previa



# Breech Presentation

## Management with Cephalic Version

- Active labor: relative contraindication
  - Contractions may be paused with terbutaline
- **Absolute contraindications**
  - Prior classical cesarean section (vertical incision)
  - Prior uterine myomectomy
  - Placenta previa





# Breech Presentation

## Management

- **External cephalic version risks**
  - Rupture of membranes
  - Placental abruption
  - Cord compression
  - Uterine rupture
- Prepare for emergency C-section
- RhoGAM if indicated



# Breech Presentation

## Management

- Vaginal breech delivery carries increased risks
  - Head and shoulders may wedge against pubic bone
  - Umbilical cord may prolapse into vagina → hypoxia
- **Cesarean section preferred**
  - If cephalic version cannot be performed or unsuccessful
  - Malpractice insurers often require CS for breech babies
  - Studies outside US show vaginal delivery safe in many cases
- C-section often performed before labor onset



# Fetal Growth Restriction

## Intrauterine Growth Restriction

- Estimated fetal weight < **10<sup>th</sup> percentile** for gestational age
- Often leads to small-for-gestational-age (SGA) infant
- Assessed by ultrasound
- Increased risk for neonatal morbidity and mortality
- **Symmetric**: all organs and body parts affected
- **Asymmetric**: head growth preserved

# Symmetric FGR

- Body, head, and length **proportionally affected**
- Occurs in 20 to 30% of FGR cases
- Usually present before 20 weeks
- No underlying etiology in 40% cases
- Caused by **intrinsic factors**
- Congenital infections
- Chromosomal abnormalities



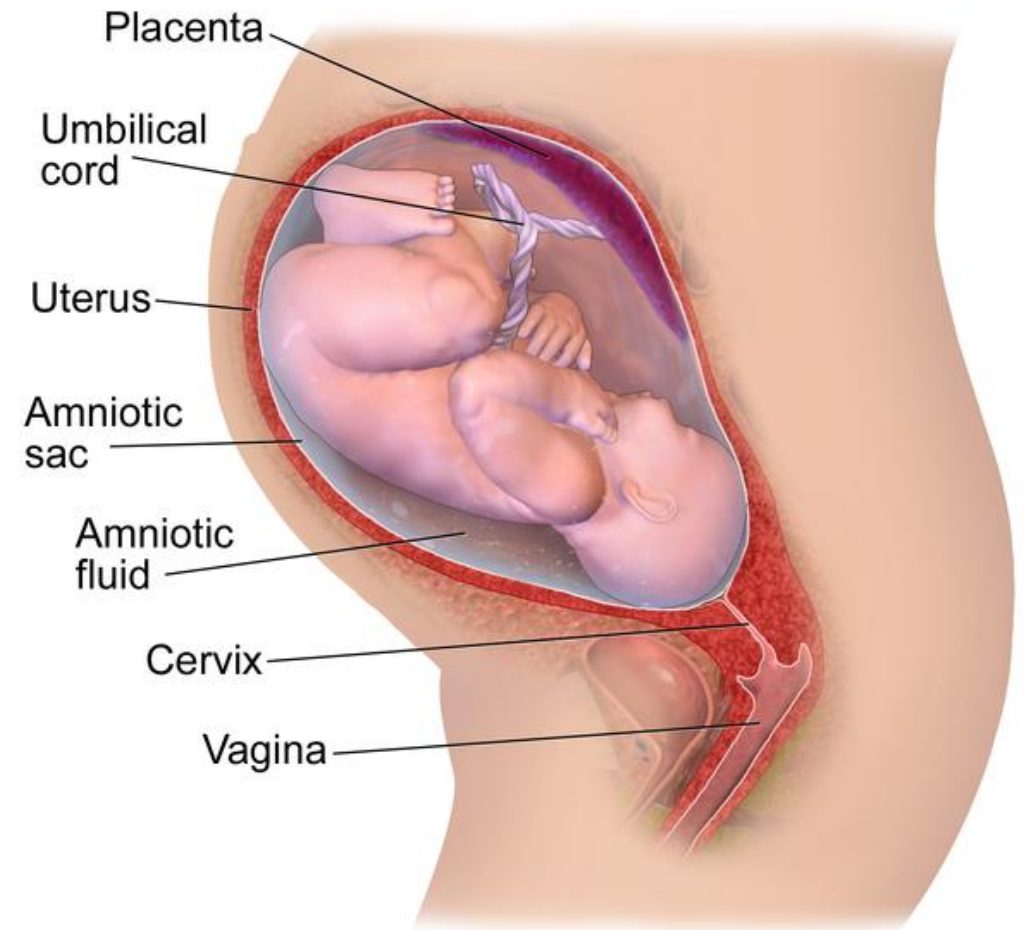
# Asymmetric FGR

- Disproportionate growth restriction
- Head circumference preserved (“head sparing”)
- Length somewhat affected
- Weight is most compromised
- Occurs in 70 to 80% FGR cases
- Begins late second or third trimesters
- Caused by reduced fetal nutrients
- Placental insufficiency (**hypertension**, diabetes)
- Malnutrition
- Smoking



# Amniotic Fluid Disorders

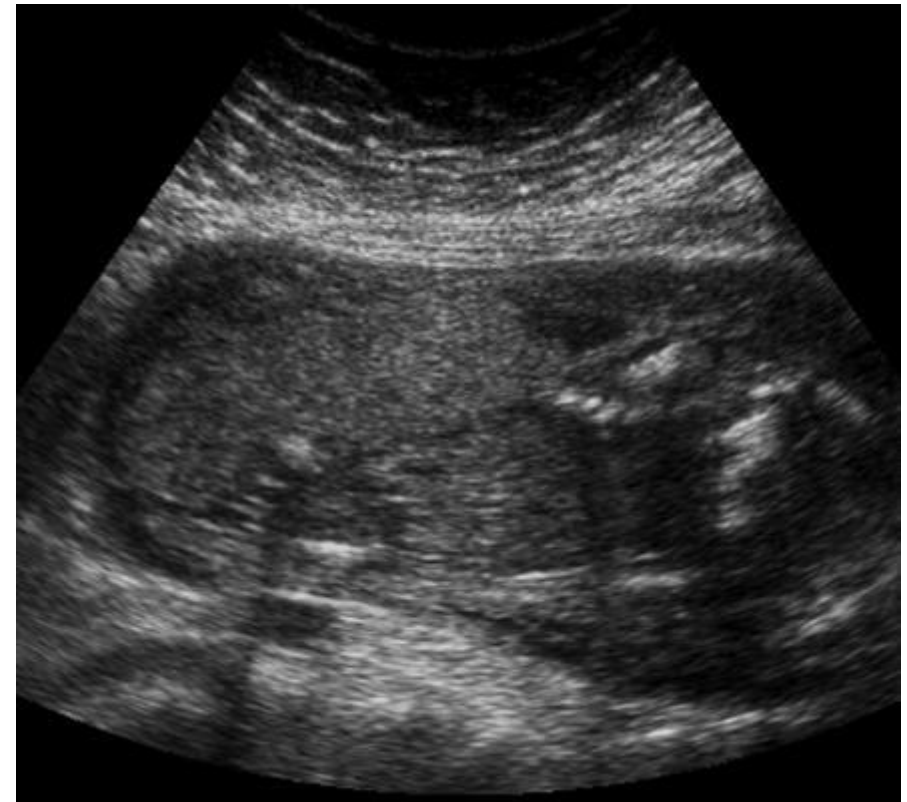
- Oligohydramnios: amniotic fluid index < 5 cm
- Polyhydramnios: amniotic fluid index > 25 cm



# Oligohydramnios

## Causes

- Rare in first trimester
- Second trimester: **fetal urine** increases volume
  - Decreased fetal urine production
  - Renal agenesis
  - Cystic kidneys
  - Posterior urethral valves
- Third trimester: **PROM** or placental insufficiency
  - Most commonly idiopathic in 3<sup>rd</sup> trimester
- Indication for delivery at 36 to 37 weeks





# Oligohydramnios

- Associated with poor outcomes
  - Umbilical cord compression
  - Placental insufficiency
  - Meconium aspiration
  - Potter sequence
- Transabdominal amnioinfusion: saline infusion
  - Rarely used in actual practice
  - *Temporary* increase in amniotic fluid volume
  - Used to improve US images in 2<sup>nd</sup> trimester
  - Used to facilitate cephalic version in 3<sup>rd</sup> trimester





# Polyhydramnios

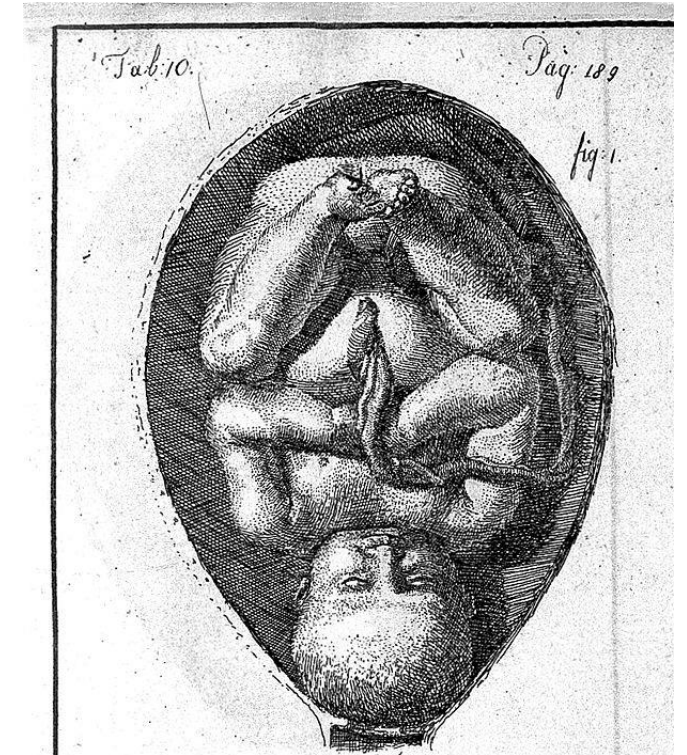
## Causes

- **Decreased fetal swallowing**
  - GI obstruction (intestinal atresia)
- **Fetal anemia**
  - High fetal cardiac output → ↑ fetal urine production
  - Alloimmunization, B19 infection
- Maternal diabetes
- Multiple gestation
- Twin-twin transfusion syndrome



# Polyhydramnios

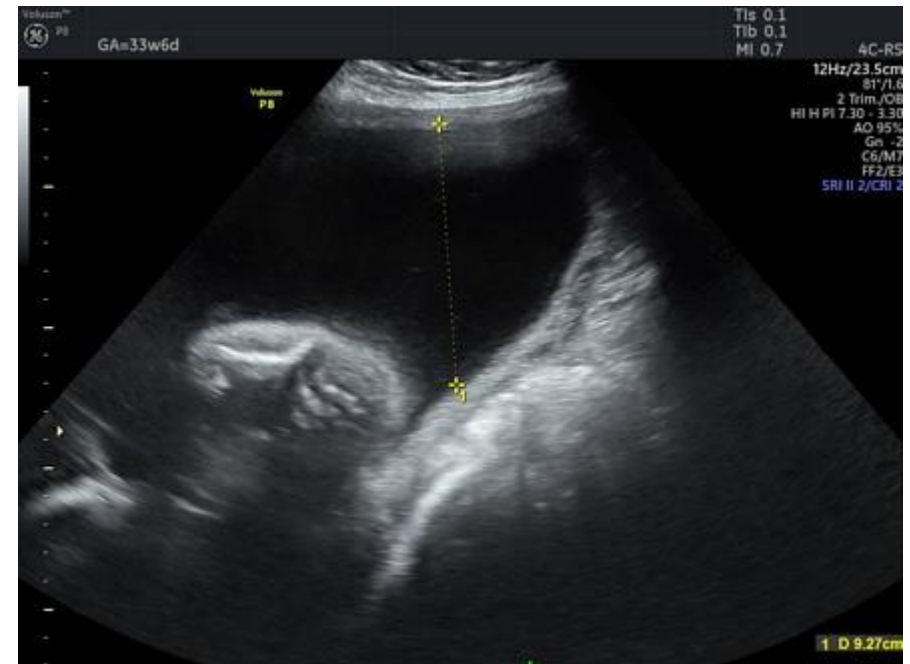
- May cause **premature rupture of membranes**
- Associated with preterm delivery or fetal malpresentation
- Evaluate and treat underlying causes
- Most idiopathic
- Mild cases resolve without intervention



# Polyhydramnios

- Intervention only for **severe cases (AFI > 35)** with **symptoms**
  - Maternal dyspnea, abdominal pain or uterine contractions
- Amnioreduction
  - Removal of amniotic fluid
- Indomethacin
  - Tocolytic
  - Also reduces amniotic fluid volume
  - Cannot be used past 32 weeks (DA closure)

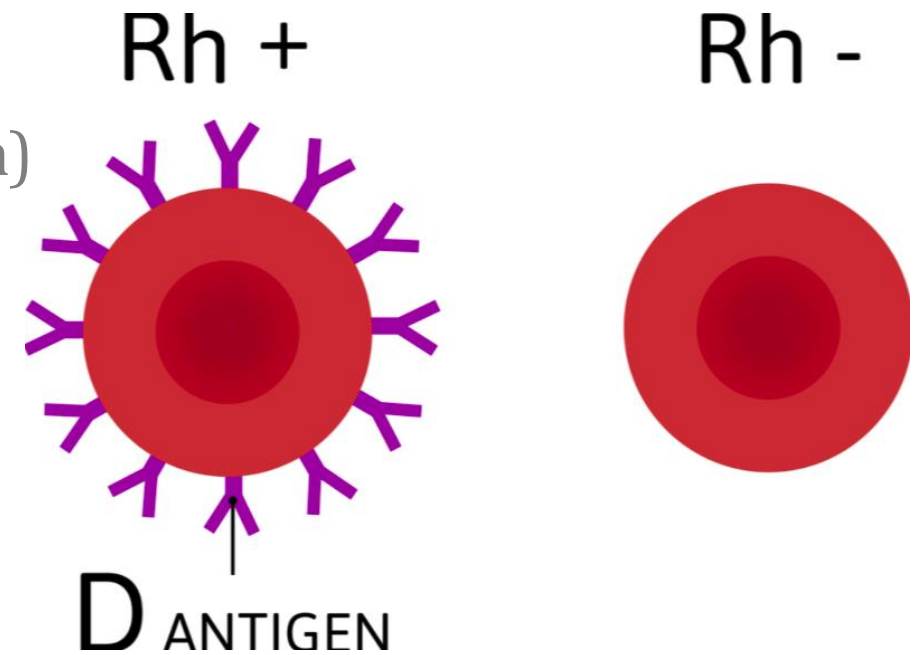
AFI Measurement



# HFDN

## Hemolytic Disease of the Fetus and Newborn

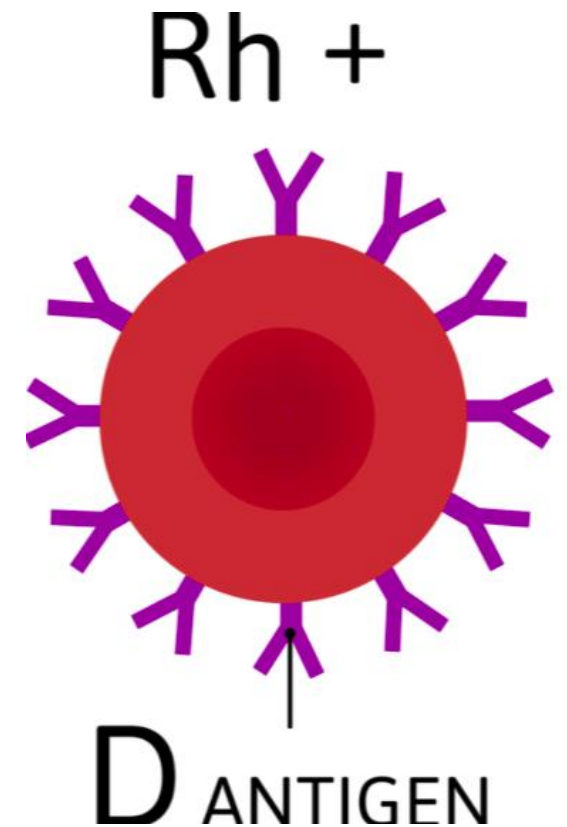
- Fetal hemolysis caused by maternal red cell antibodies
- Usually occurs in **Rh negative mothers**
- Rh system: more than 50 antigens
- **D antigen** highly immunogenic
- “Rh positive:” has the D antigen (of the Rh system)
- “Rh negative:” lacks the D antigen (of the Rh system)



# HFDN

## Hemolytic Disease of the Fetus and Newborn

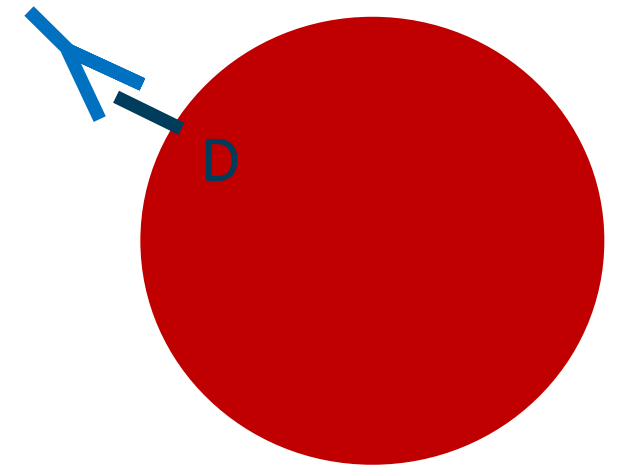
- Alloimmunization: D- mother forms anti-D antibodies
  - Occurs in D- mother with D+ baby
  - Mother capable of developing anti-D antibodies
  - If father is D+ baby may also be D+
- First pregnancy: mother exposed D+ RBCs at delivery
- Second pregnancy: anti-D IgG mother → fetus
- If second baby D+ hemolysis may occur in utero



# HFDN

## Prevention

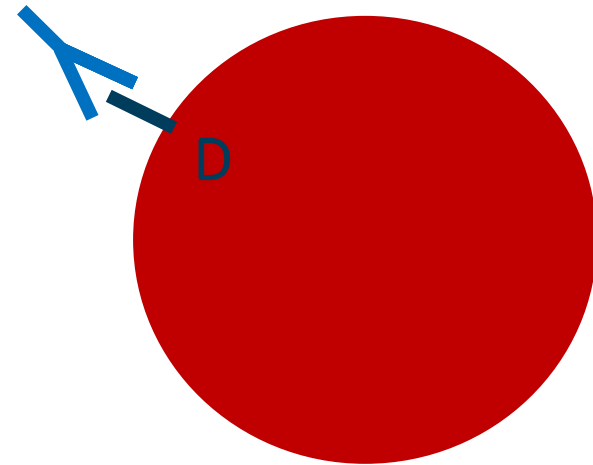
- **Maternal screening** for D antigen and anti-D antibodies at first prenatal visit
- D+ mother: no risk of HFDN
- D- mother without antibodies: **anti-D immune globulin (“RhoGAM”)**
  - IgG antibodies to D antigen
  - Rapid macrophage clearance of D+ RBCs
  - Blocks/prevents alloimmunization
  - Given to D- mothers with negative antibody screen
- Standard dose: 300 micrograms IM



# RhoGAM Indications

## D- Mothers

- **28 weeks or within 72 hours of birth**
- Abortion
- Ectopic or molar pregnancy
- Vaginal bleeding 2<sup>nd</sup>/3<sup>rd</sup> trimesters
- External cephalic version
- CVS or amniocentesis
- Abdominal trauma



# RhoGAM Indications

## Additional doses

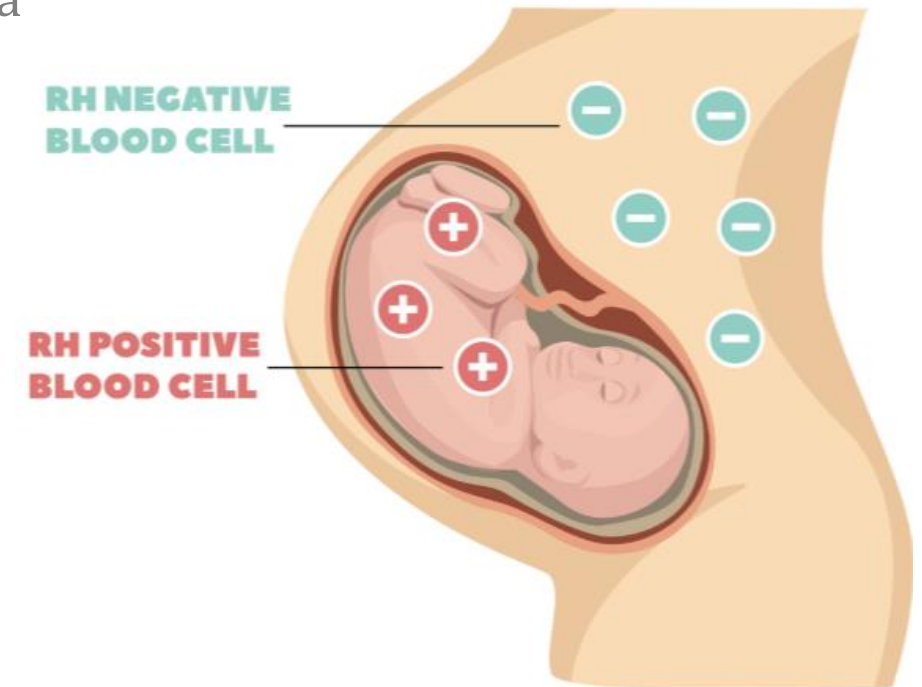
- Excessive **fetomaternal bleeding** may need larger dose of RhoGAM
- **Rosette test**
  - Quantitative test
  - Negative when amount of fetomaternal bleeding < 2 ml
  - Positive test followed by Kleihauer-Betke test
- **Kleihauer-Betke test**
  - Determines percentage of fetal red cells in maternal circulation
  - Additional RhoGAM administered if percentage is high



# HFDN

## Diagnosis and Management

- Anti-D antibodies: determine fetal blood type (test father or baby)
- **Mother with anti-D antibodies and D+ fetus**
  - Serial maternal antibody titers
  - Fetal transcranial MCA Doppler: high flow occurs in anemia
  - Fetal H/H via umbilical cord sampling
- Severe anemia interventions
  - Fetal transfusions
  - Delivery at > 35 weeks



# HFDN

## Hemolytic Disease of the Fetus and Newborn

- **Hydrops fetalis**
  - Massive edema: pleural/pericardial effusion, ascites
- **Hemolytic anemia** in the newborn
  - May cause neonatal jaundice **in first 24 hours of life**



# Other RBC Antigens

- Non-Rh alloantibodies can rarely cause HDFN (anemia, jaundice)
- Testing generally only done in mothers with prior HDFN pregnancy
- No interventions for prevention like RhoGAM
- **ABO antibodies**
  - Naturally occurring ABO antibodies: IgM
  - IgG ABO antibodies may occur O mothers who have a non-O fetus
  - Rarely causes fetal anemia
  - Can cause newborn anemia in first 24 hours of life
- Other antigens associated with HDFN: Kell and Duffy
- Kell kills, Duffy Dies, Lewis Lives

# Maternal Pregnancy Complications

Jason Ryan, MD, MPH



# Hyperemesis Gravidum

- Nausea and/or vomiting common in early pregnancy
- Mild cases: “morning sickness”
- Severe cases: hyperemesis gravidum
  - Vomiting causing **hypovolemia**
  - May lead to weight loss
- **Check electrolytes and urinalysis**
  - May see alkalosis or hypokalemia
  - Urinary ketones may be present



# Hyperemesis Gravidum

## Treatment

- Intravenous fluids
- **Thiamine**
  - Rare cases of maternal **Wernicke's encephalopathy** reported
- Correct magnesium, calcium and phosphorus if low



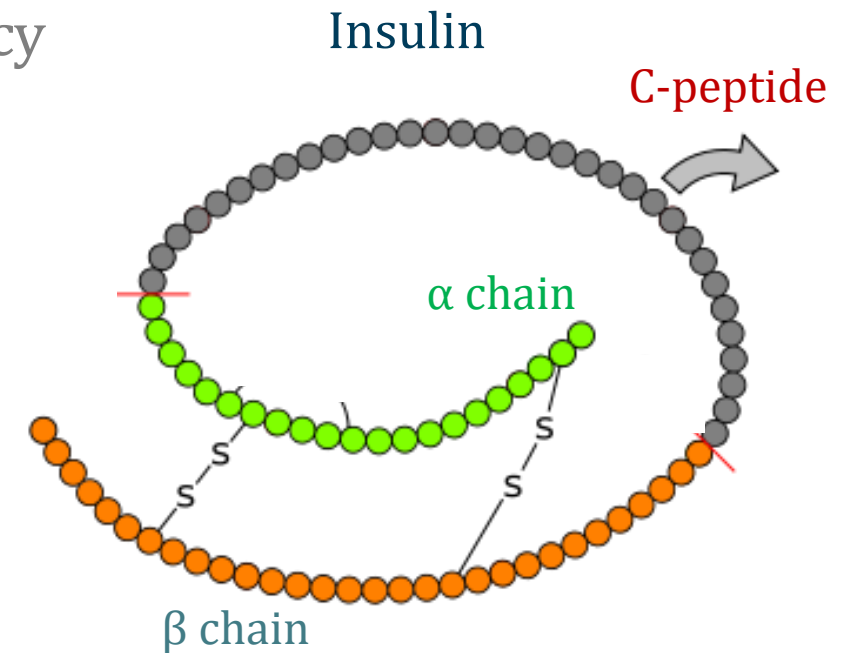
# Hyperemesis Gravidum

## Treatment

- Lifestyle changes
  - Eat when hungry – avoid empty stomach
  - Avoid triggers: odors, lying down after eating
- Usual first-line medical treatment: **doxylamine-pyridoxine**
  - Doxylamine: anti-histamine
  - Pyridoxine: vitamin B6 (improves nausea through unknown mechanism)
- Severe cases: other antihistamines, dopamine agonists, ondansetron

# Diabetes in Pregnancy

- Pregnancy is an **insulin-resistant state**
- Decreased maternal response to insulin
- Diabetes mellitus: worsened by pregnancy
- Gestational diabetes: onset of diabetes during pregnancy
- May adversely affect fetus
- Screening with **serum glucose testing**
- Glycosuria occurs in normal pregnancy
- Hemoglobin A1c limited use in pregnancy





# Diabetes in Pregnancy

## Adverse effects

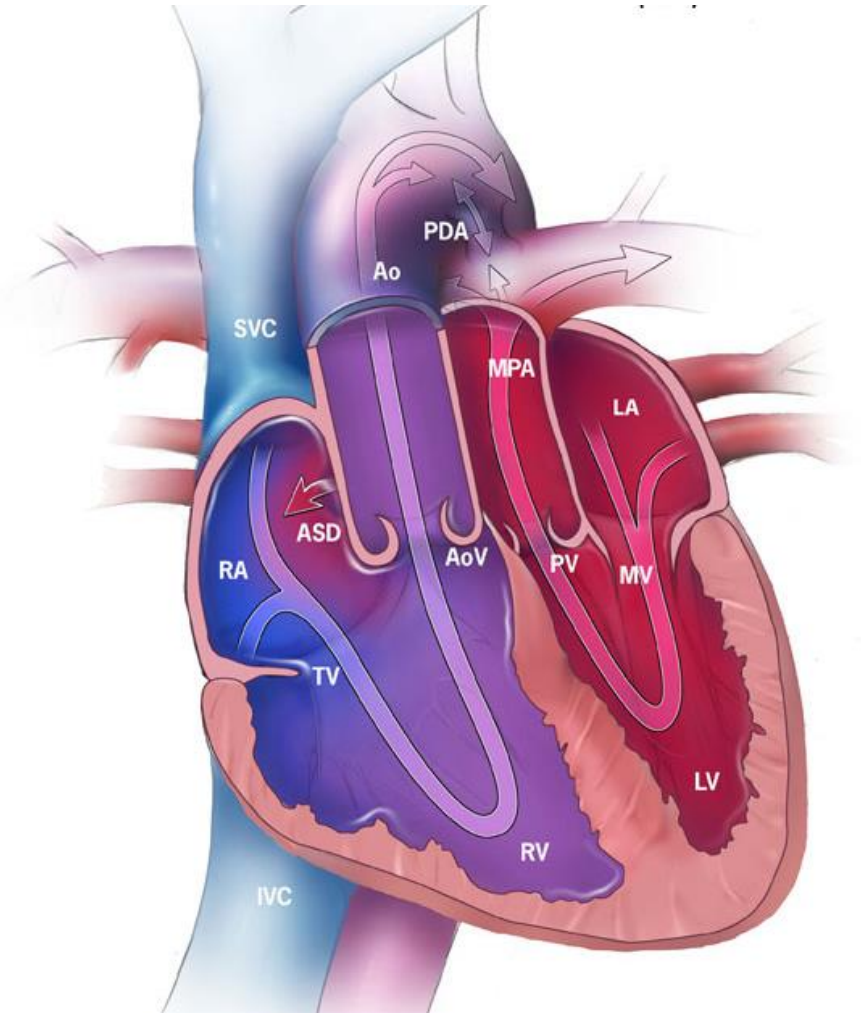
- Many potential adverse effects for mother and baby
- **Large for gestational age**
- Macrosomia
- Birth trauma (shoulder dystocia)
- Cesarean delivery
- Polyhydramnios
- Spontaneous abortion or stillbirth
- Preeclampsia
- **Neonatal hypoglycemia**



# Diabetes in Pregnancy

## Risks

- Congenital heart defects: 3-9% of babies
- **Transposition of the great arteries (TGA)**
- Ventricular septal defects (VSDs)
- Truncus arteriosus
- Tricuspid atresia
- Patent ductus arteriosus (PDA)



# Caudal Regression Syndrome

## Sacral Agenesis

- Classically associated with maternal diabetes
  - Usually children of insulin-dependent mothers
- Incomplete development of **sacrum**
- May include **sirenomelia**
  - “Mermaid syndrome”
  - Fusion of legs
- Often includes a neural tube defect



Stanislav Kozlovskiy/Wikipedia



H. Aslan et al. Prenatal diagnosis of Caudal Regression Syndrome: a case report. BMC Pregnancy and Childbirth. 1, 8. 2001.

# Gestational Diabetes

## Treatment

- Mainstay of treatment: **diet plus exercise**
- Controlled carbohydrate intake to meet caloric needs
- Medical therapy if > 30% of glucose values above threshold
- Mainstay of medical treatment: **insulin**
- Can use metformin in selected patients (2<sup>nd</sup>/3<sup>rd</sup> trimester)

### Glucose Targets

Time	Glucose (mg/dL)
Fasting	< 95
1 hr Postprandial	< 140
2 hr Postprandial	< 120

# Gestational Diabetes

## Further Management

- Consider induction to avoid macrosomia
- Consider cesarean delivery if large baby
- Diabetes usually resolves postpartum
- Increased risk of type II DM after delivery
- **Screening 2hr GTT at 6 to 12 weeks postpartum**

White's Classification of Diabetes in Pregnancy

Type	Details
A1	Diet controlled
A2	Insulin controlled
B through D	Pregestational diabetes

# Acute Fatty Liver of Pregnancy

- Rare cause of **acute liver failure** in 3<sup>rd</sup> trimester of pregnancy
- Fatty infiltration of hepatocytes
- Classic presentation: **persistent nausea and vomiting**
- Other features: jaundice or encephalopathy
- Abnormal labs: LFTs, bilirubin
- Treatment: **immediate delivery** plus supportive care
  - Progression of pregnancy may lead to fulminant liver failure
- Most cases recover after delivery



# Intrahepatic Cholestasis of Pregnancy

- Diffuse **pruritus** with elevated serum bile acids
- Occurs in 2<sup>nd</sup> half of pregnancy due to unknown cause
- Diagnosis: **↑ serum total bile acids**
- Mild abnormalities LFTs or bilirubin
- Treatment: **ursodeoxycholic acid**
- Risk to fetus: fetal demise, preterm delivery
- Deliver at term





# Appendicitis in Pregnancy

- Abdominal pain, nausea, vomiting
- Pain may occur in RUQ due to pregnancy
- Diagnosis: **ultrasound**
- Inconclusive US: MRI
- Treatment: surgery

Appendicitis



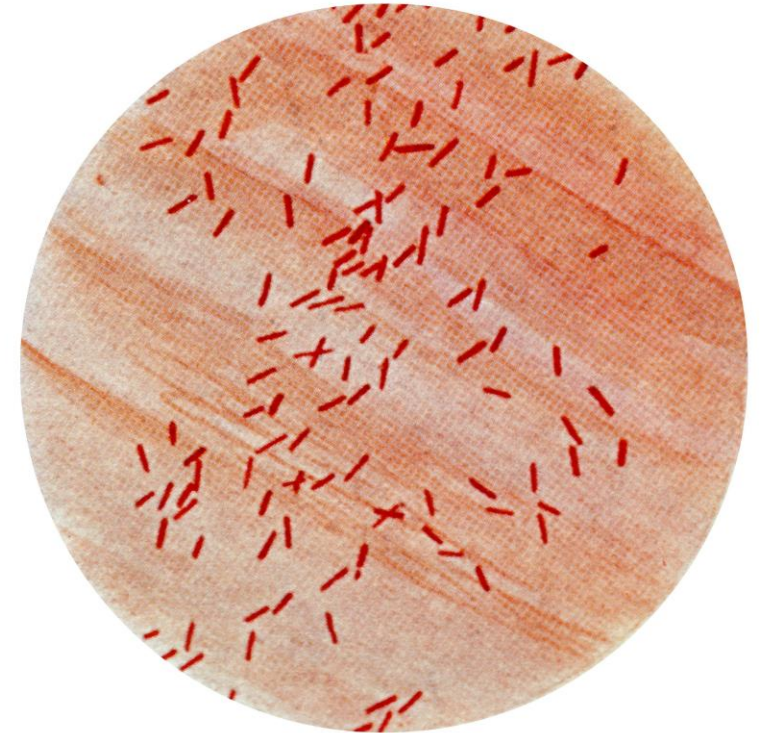
Case courtesy of Dr Matthew Lukies, Radiopaedia.org, rID: 51979



# Urinary Infections

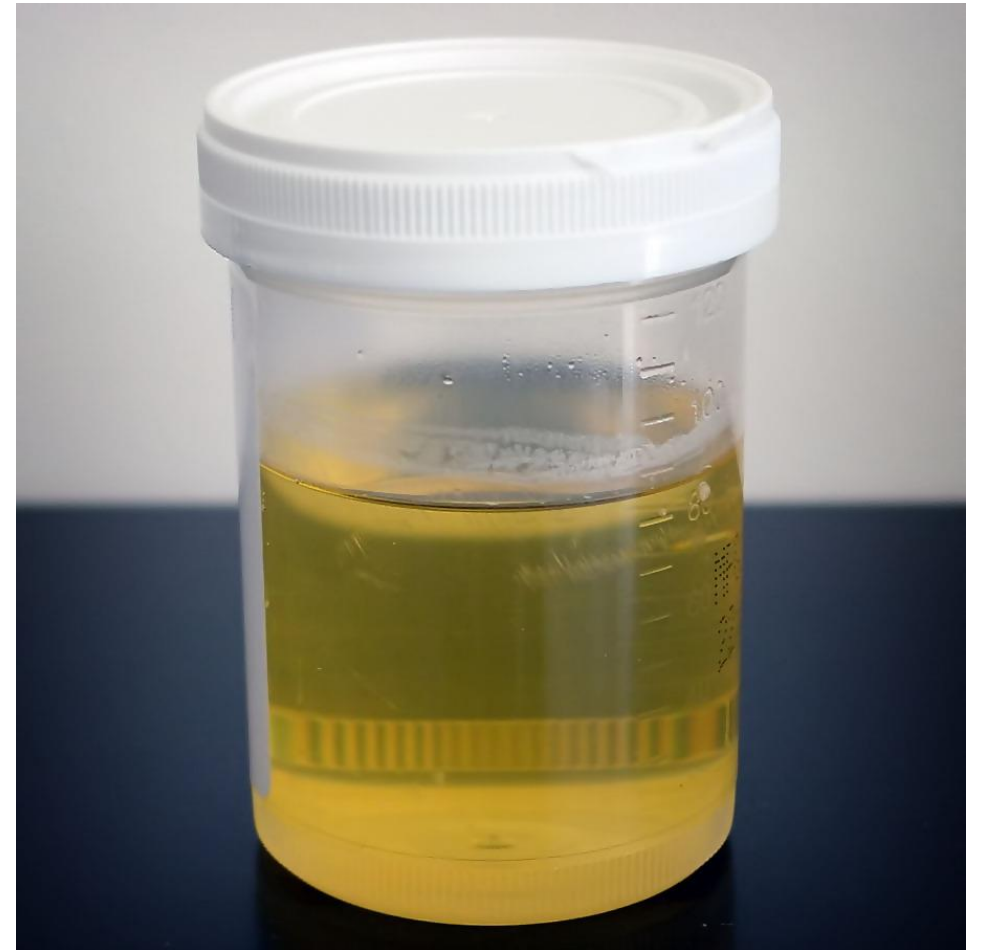
- **Progesterone** → urinary stasis
- Relaxation of smooth muscle in urinary tract
- Asymptomatic bacteriuria, cystitis, or pyelonephritis
- Most common bacteria: **E. coli**
- Others: *S. saprophyticus*, GBS, enterococcus

E. Coli



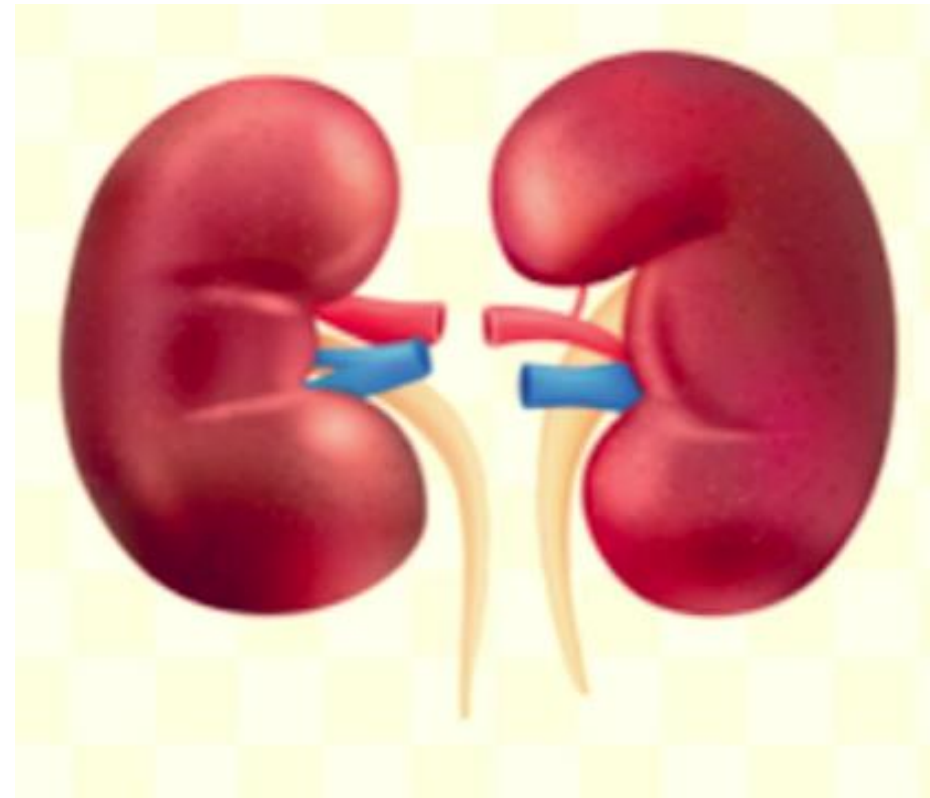
# Urinary Infections

- **Asymptomatic bacteriuria**
  - Screening at first prenatal visit with urine culture
  - High risk of pyelonephritis and preterm birth
  - Treat positive culture with antibiotics for 7 days
  - Drug choice based on bacteria sensitivity
  - Up to 30% do not clear bacteriuria after antibiotics
  - Repeat culture is usually done for test of cure
- Acute cystitis: empiric antibiotics
  - Nitrofurantoin
  - Fosfomicin
  - Modify when culture results available



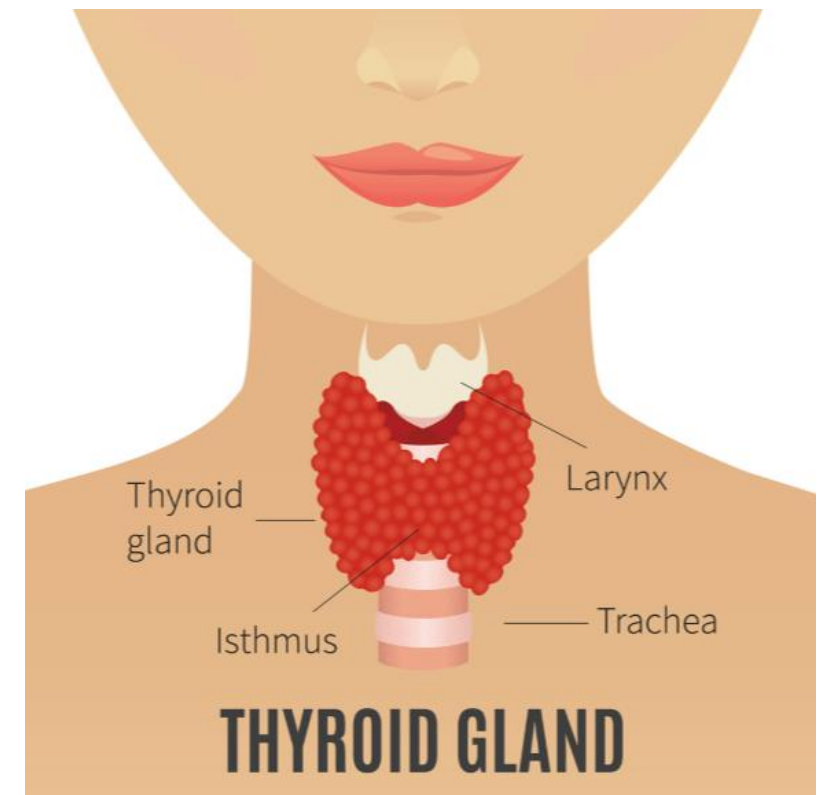
# Urinary Infections

- **Pyelonephritis**
  - Occurs in 2% of pregnancies
  - Common indication for hospitalization
- Treatment:
  - IV fluids
  - Parenteral, broad spectrum antibiotics
  - Ceftriaxone, Cefepime, ampicillin-gentamycin
- Recurrence common
- Suppressive antibiotics often used until delivery



# Thyroid Disease

- Hyperthyroidism or hypothyroidism may complicate pregnancy
- Routine screening not recommended
- **Hyperemesis gravidum**
  - Associated with high hCG → stimulates thyroid
  - Low TSH and possibly high T4
  - Thyroid studies avoided in HG patients



# Hypertension in Pregnancy

Jason Ryan, MD, MPH



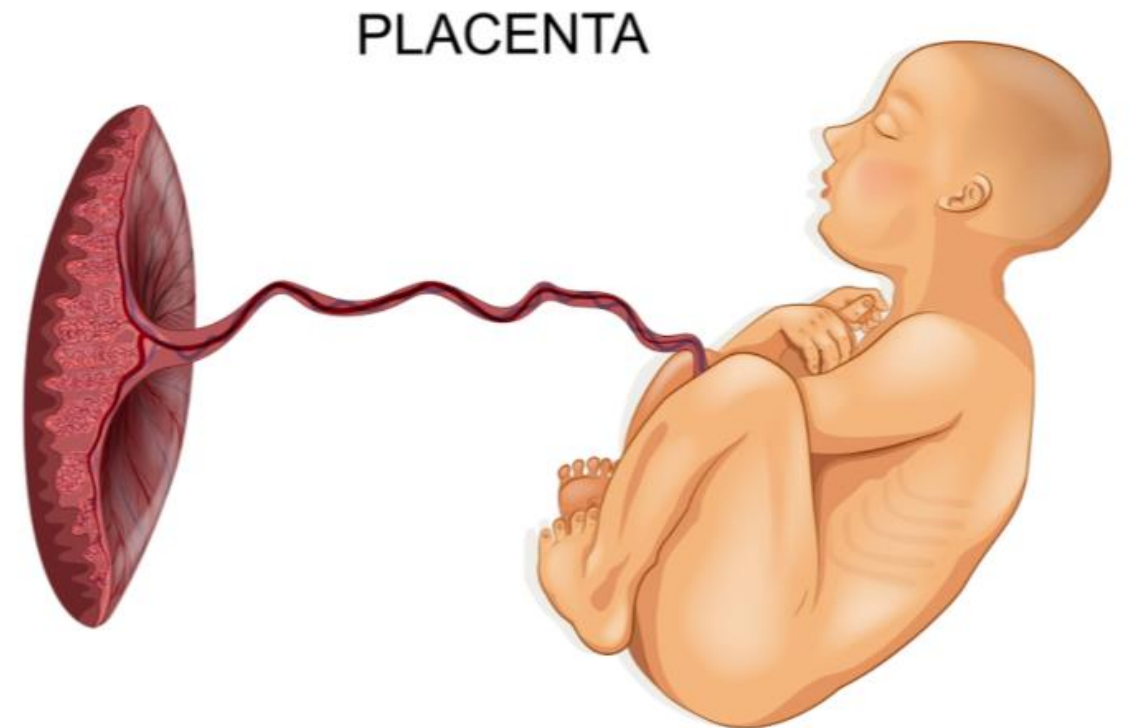
# Hypertension in Pregnancy

- Pre-existing/chronic hypertension: **prior to pregnancy or 20 weeks**
- Gestational hypertension: develops **after 20 weeks**
- Preeclampsia-eclampsia
  - Hypertension in pregnancy
  - Proteinuria
  - End-organ damage



# Hypertension in Pregnancy

- May cause **decreased placental perfusion**
- Increased risk of adverse fetal outcomes
- **Fetal growth restriction**
- Oligohydramnios
- Placental abruption





# Hypertension in Pregnancy

## Workup

- Screening for preeclampsia/eclampsia
- Urine protein
- CBC
- Renal function
- Liver function tests
- Coagulation
- Uric acid (hyperuricemia in preeclampsia)





# Hypertension in Pregnancy

## Management

- Usually not treated unless BP > 160/110 mmHg
- Labetalol ( $\beta_1\beta_2\alpha_1$  blocker)
- Nifedipine (calcium channel blocker)
- Alpha-methyldopa
- Avoid ACEi or ARBs



# Hypertension in Pregnancy

## Maternal Hypertensive Crisis

- Intravenous drugs often used
- **Labetalol** (can cause bradycardia)
- **Hydralazine** (used if bradycardia present)
- Oral nifedipine

# Hypertension in Pregnancy

## Delivery

- Poorly controlled blood pressures  $\geq 160/110$  mmHg
  - If remote from term, hospitalized until delivery
  - Fetal surveillance drives delivery
  - Delivery at  $\geq 34$  weeks per ACOG guidelines
- Controlled BP  $< 160/110$  mmHg may deliver at term



# Preeclampsia

- Multi-system disorder of pregnancy
- Hypertension
- Proteinuria
- End-organ dysfunction

# Preeclampsia

## Pathogenesis

- Disorder of the **placenta**
- Abnormal invasion/transformation of spiral arteries
- Placental under-perfusion
- Leads to release of circulating substances
- Diffuse maternal endothelial dysfunction
- Vasospasm and coagulation
- **Resolves with delivery** (placental removal)

# Preeclampsia

## Clinical Features

- Usually occurs 3<sup>rd</sup> trimester
- **New onset hypertension**
  - In mother with no known HTN
  - Systolic  $\geq 140$  mmHg and/or diastolic  $\geq 90$  mmHg
- **Proteinuria**
  - 24-hour urine collection  $\geq 300$  mg protein
  - Urine protein : creatinine ratio  $> 0.3$
  - Dipstick reading of 2+ (confirm 1+ readings)
- **End-organ damage**
  - Renal failure (vasospasm of renal vessels)
  - CNS (headache, visual changes, confusion)
  - Liver failure

# Preeclampsia

## Clinical Features

- Often presents with **severe edema**
- Proteinuria → low oncotic pressure
- Increased salt/water retention

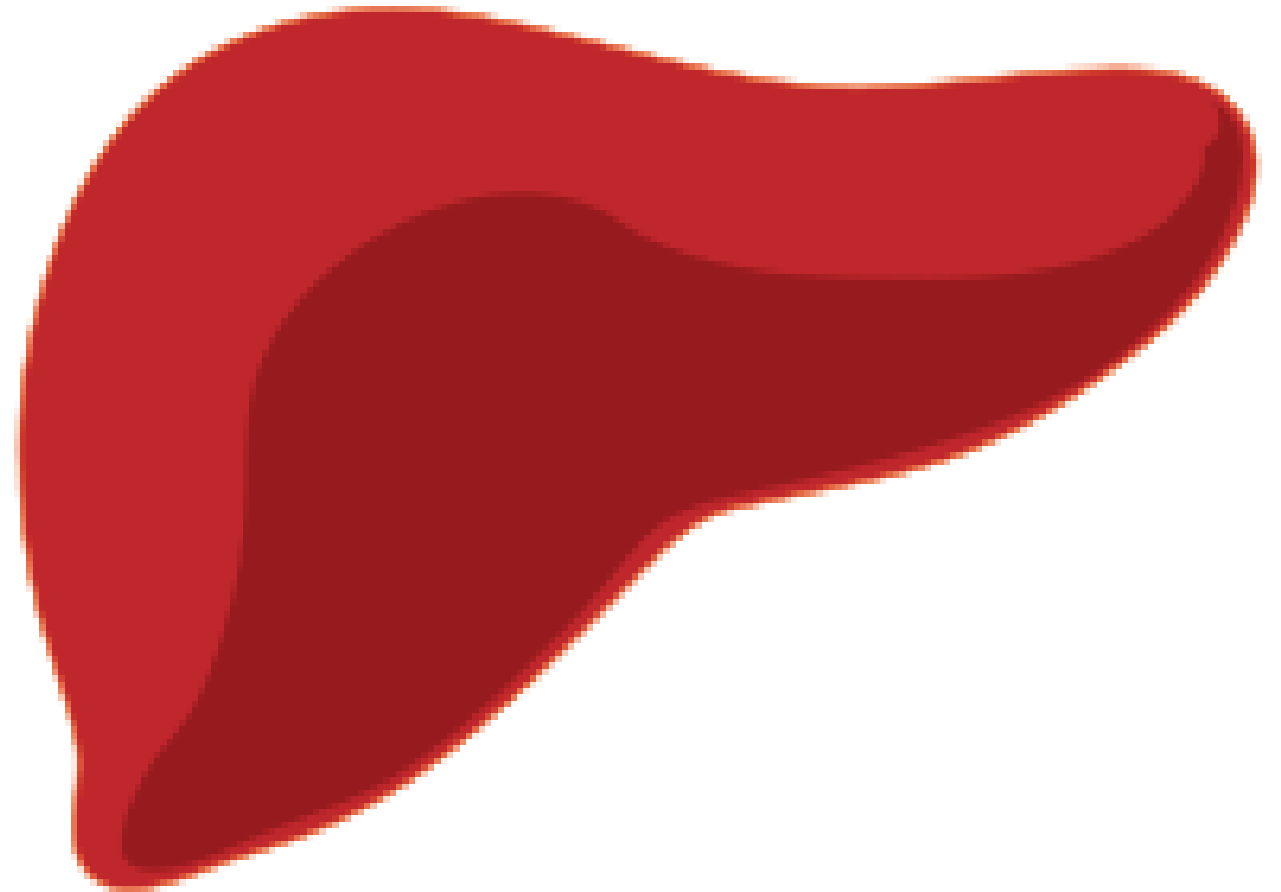
**HTN**  
**Proteinuria**  
**Edema**



# Preeclampsia

## Clinical Features

- Often involves the **liver**
- Edema of the liver
- Ischemia/necrosis
- Elevated liver enzymes common





# Preeclampsia

## Selected Risk Factors

- Prior preeclampsia
- First pregnancy
- Family history
- Multiple gestations
- Maternal conditions prior to pregnancy
  - Diabetes
  - Hypertension
  - Obesity
  - Chronic kidney disease
  - **Lupus/Antiphospholipid syndrome**

# Low-dose Aspirin

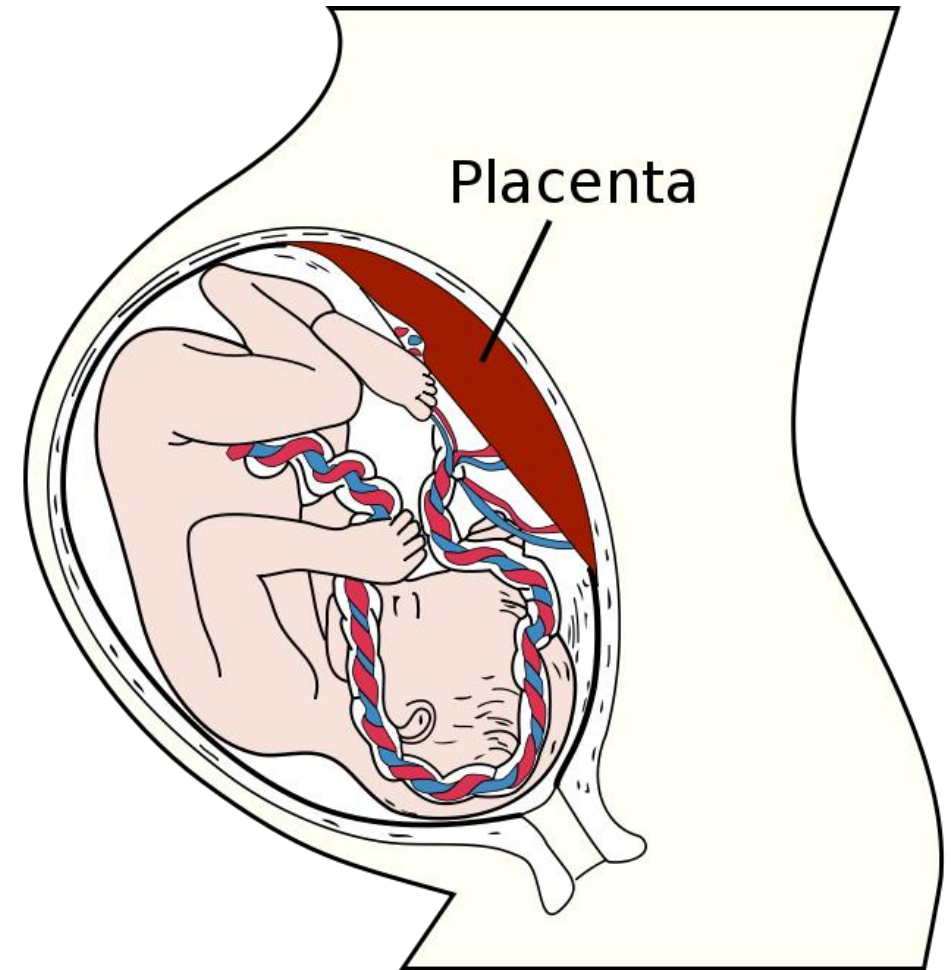
- Reduces risk of preeclampsia in high-risk patients
- No consensus definition of high risk
- Initiated after 12 weeks and before 28 weeks
- Ideally before 16 weeks
- Continued daily until delivery



# Preeclampsia

## Pregnancy Complications

- Placental insufficiency
  - Growth restriction
  - Oligohydramnios
- Placental abruption



# Preeclampsia

## Maternal Complications

- Pulmonary edema
- Heart failure
- Liver failure
- Disseminated intravascular coagulation
- Stroke
- Dialysis (advanced renal failure)

Pulmonary Edema



# Preeclampsia with Severe Features

- **Systolic  $\geq 160$  mmHg or diastolic  $\geq 110$  mmHg**
  - On two occasions at least 4 hours apart while on bedrest
- New cerebral or visual disturbance
  - Scotomata, visual loss
  - **Severe headache**
- Abnormal AST/ALT
- Platelets  $< 100,000$
- Renal insufficiency
- Pulmonary edema

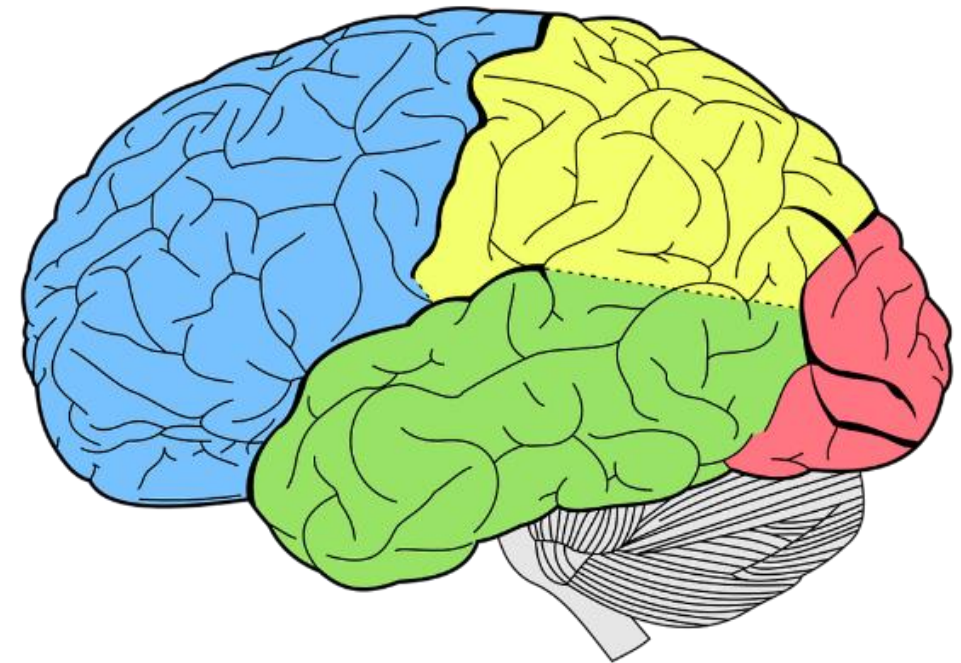
# Preeclampsia

## Management

- No severe features: may deliver at term (> 37 weeks)
- IV magnesium sulfate for seizure prophylaxis at delivery
- Severe features: delivery considered at 34 weeks

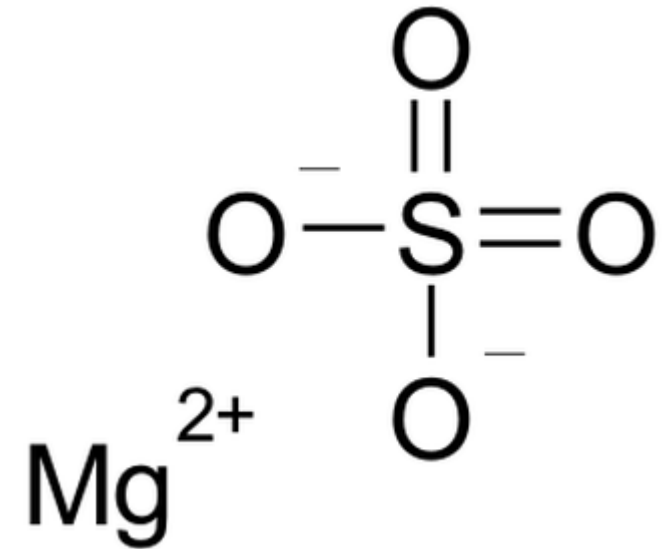
# Eclampsia

- **Seizures** in a mother with preeclampsia
- Generalized, tonic-clonic seizures
- May lead to coma/death
- Often complicated by DIC, respiratory failure
- Exact etiology of seizures unclear
- Related to blood flow/endothelial dysfunction



# Eclampsia

- Anticonvulsive of choice: **magnesium sulfate**
  - Most effective drug
  - Often given for prevention in preeclampsia
  - Inhibits acetylcholine release → may cause hyporeflexia or drowsiness
  - Contraindicated in **myasthenia gravis** → can trigger a crisis
- Definitive treatment: **delivery of baby**





# Magnesium Toxicity

- Rare if renal function is normal
- Clinical assessment for magnesium toxicity every **one to two hours**
- Check **deep tendon reflexes**
- Check for signs of respiratory paralysis or abnormal cardiac conduction
- Serum magnesium level obtained in women with renal insufficiency
- Therapeutic range: **4.8 to 8.4 mg/dL**
  - Normal magnesium level: 1.7 to 2.2 mg/dL
- Antidote is **calcium gluconate**
- Used in severe cardiac toxicity (e.g., arrest)

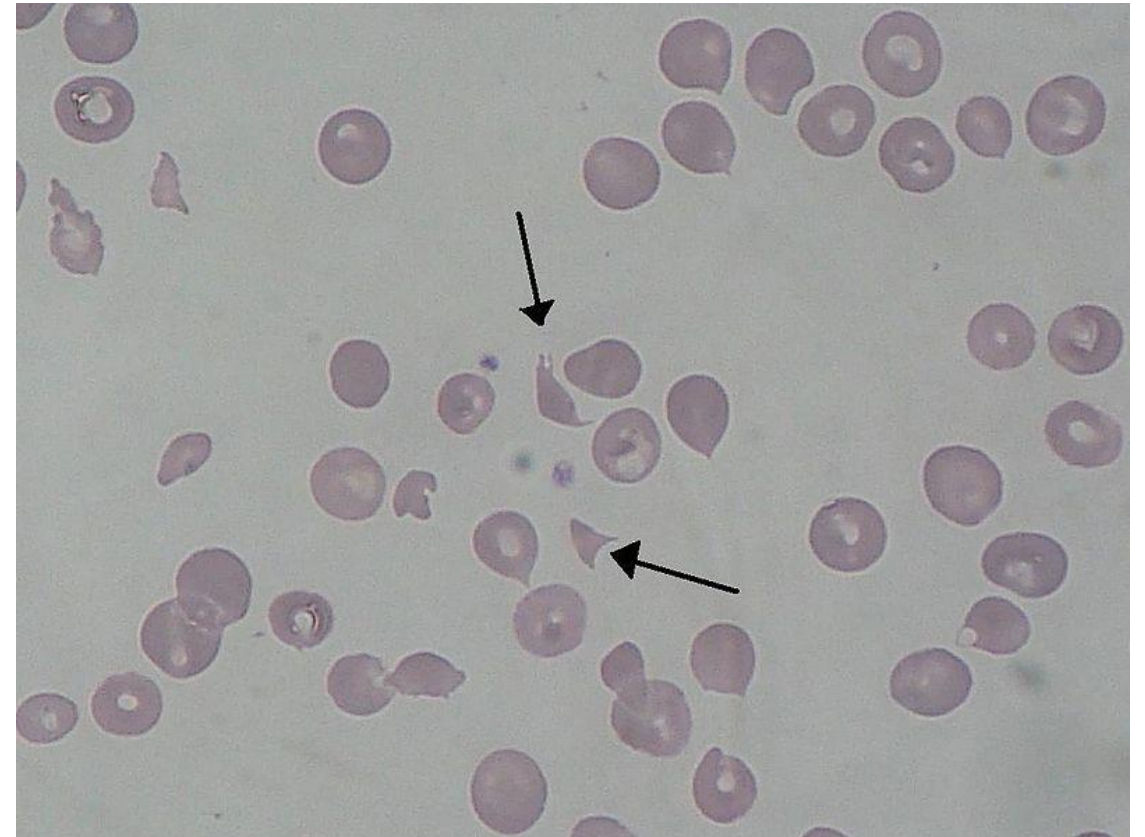
# HELLP Syndrome

- Variant of preeclampsia
- **H**emolysis
- **E**levated **L**iver enzymes
- **L**ow **P**latelet count
- Complication of preeclampsia (severe form)
- Coagulation activation and liver infarction
- Liver necrosis, hematoma and thrombi
- Liver may swell → RUQ pain



# HELLP Syndrome

- **Microangiopathic hemolytic anemia**
  - Schistocytes
  - Elevated bilirubin
  - Low haptoglobin
- Thrombocytopenia (consumption)
- Treatment: **delivery of baby**



# Gestational Thrombocytopenia

- Benign condition
- Occurs in 3<sup>rd</sup> trimester
- Platelet sequestration in spleen and placenta
- **Asymptomatic**
- Platelet count 100,000 to 150,000
- No treatment required
- May preclude epidural

# Hypertension in Pregnancy

<b>Chronic Hypertension</b>	<b>Gestational Hypertension</b>	<b>Preeclampsia Eclampsia HELLP</b>	<b>Preeclampsia superimposed upon chronic hypertension</b>
Before 20 Weeks	After 20 weeks	New-onset HTN Proteinuria End organ damage	

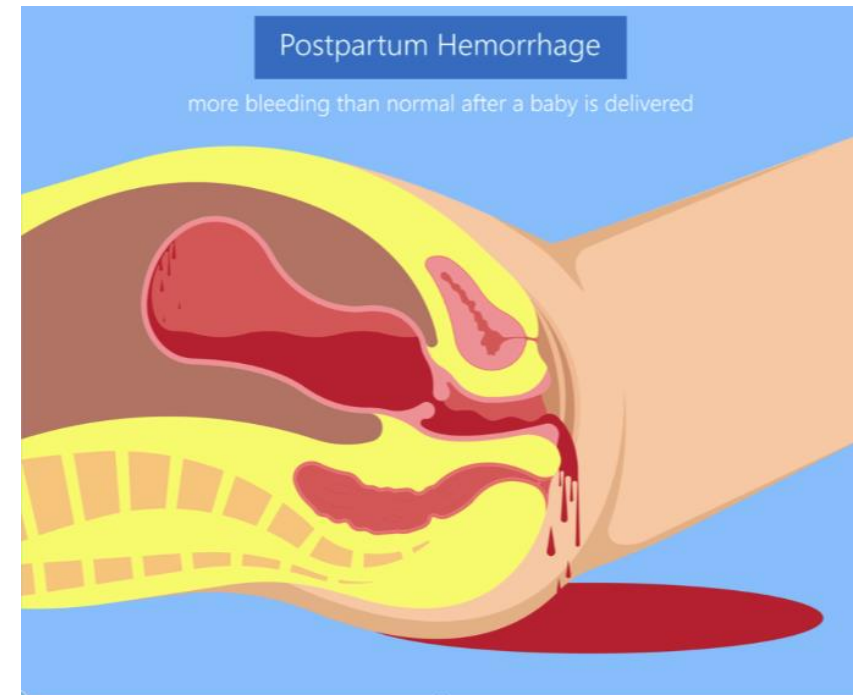
# Postpartum

Jason Ryan, MD, MPH



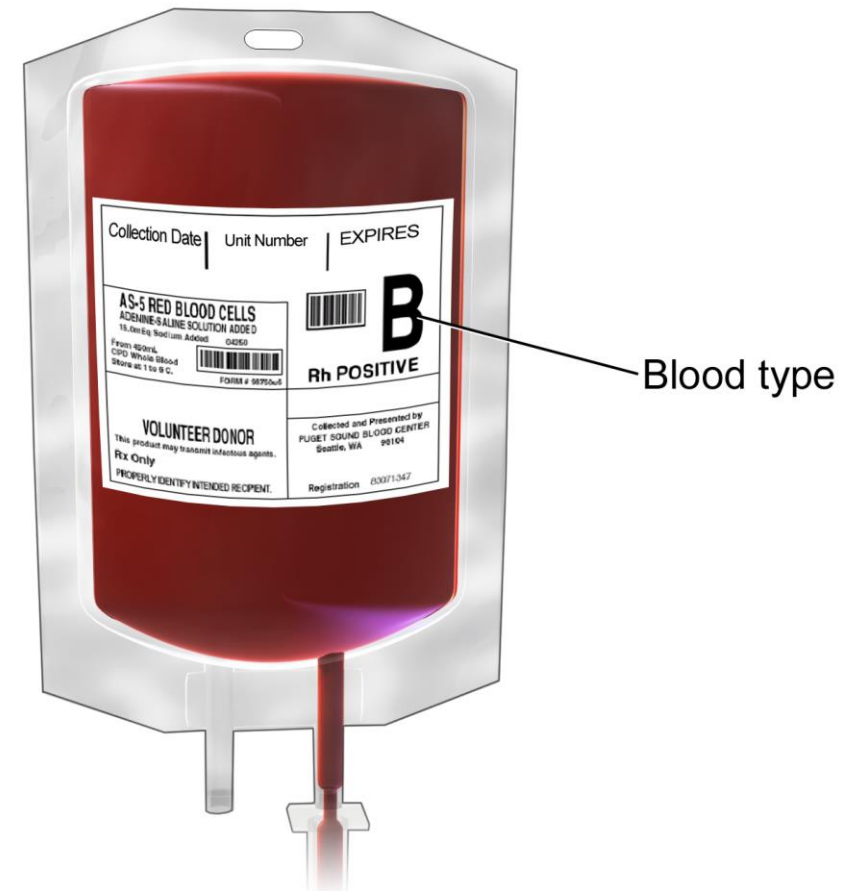
# Postpartum Hemorrhage

- Loss of > 500 cc of blood (vaginal) or > 1000 cc (cesarean)
- Or bleeding with evidence of hypovolemia **within 24 hours of birth**
- Rare cases may cause shock or Sheehan syndrome
- Treatment varies based on **underlying cause**



# Postpartum Hemorrhage

- General treatment: **IV fluids or transfusions**
- Severe hemorrhage (any cause):
  - Intrauterine balloon tamponade
  - Arterial embolization
  - Hysterectomy
  - Tranexamic acid (anti-fibrinolytic drug)





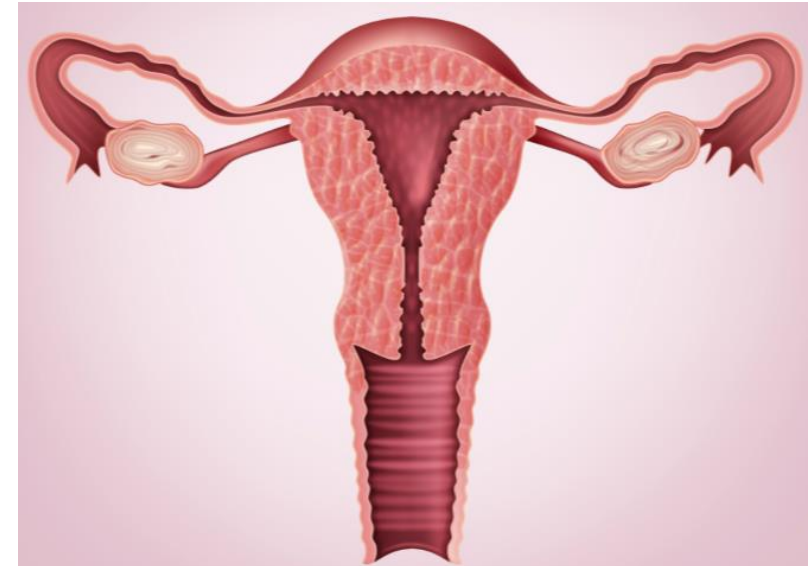
# Postpartum Hemorrhage

## Causes

- Uterine atony (most common)
- GU trauma (cervical lacerations)
- Coagulopathy
- Retained placenta or membranes

# Uterine Atony

- Uterus contracts after delivery → constricts spiral arteries
- Lack of contraction = atony → bleeding
- Increased risk:
  - Excessive uterine enlargement (macrosomia, multiple gestation)
  - Abnormal labor (prolonged labor; excessive oxytocin use)
  - Blockade of uterine contractions (fibroids; magnesium sulfate)

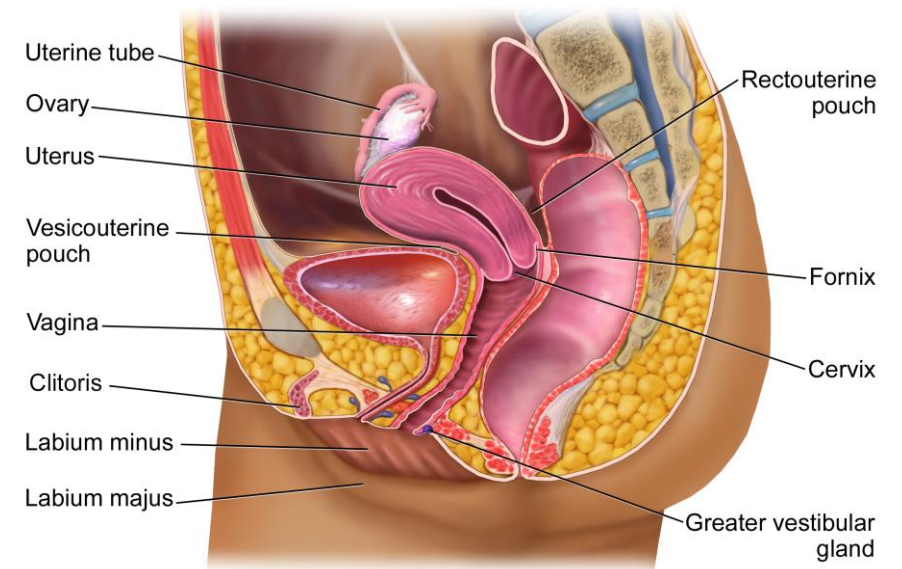


# Uterine Atony

- First-line treatments: **oxytocin** and **uterine massage**
- Additional “uterotonic” therapies may be required
- Methylergonovine
  - May raise blood pressure
  - Contraindicated with **history of hypertension**
- Carboprost
  - Prostaglandin analog
  - Contraindicated in **asthma**
- Misoprostol
- Severe cases: balloon tamponade, embolization or hysterectomy

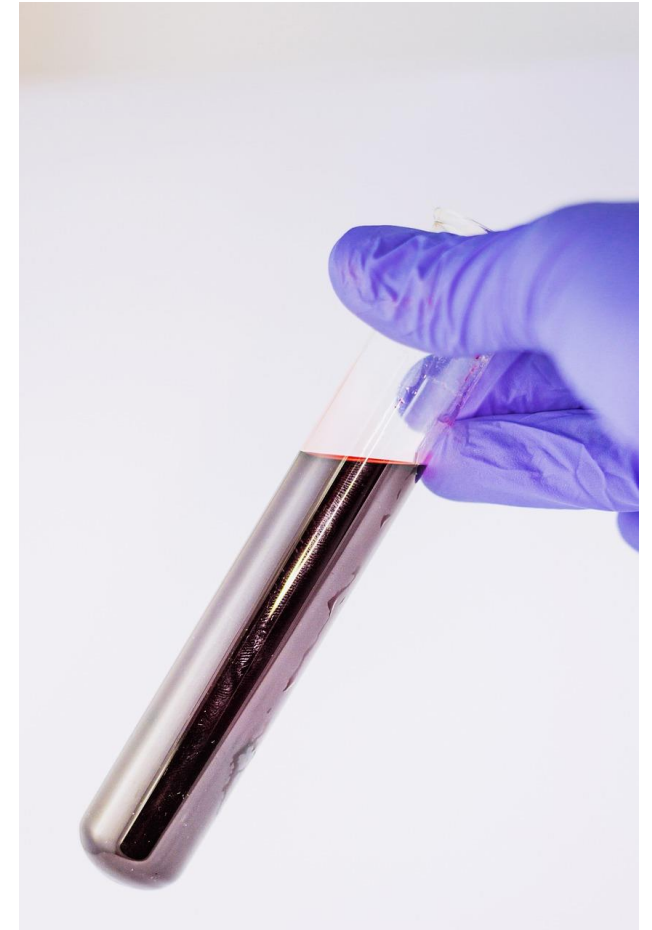
# GU Trauma

- Lacerations to lower GU tract → bleeding
  - Cervical lacerations especially difficult to access and treat → bleed more
- More common with difficult deliveries
  - Macrosomia
  - Instrumented deliveries
  - Breech extraction
  - Precipitous labor (birth within 3 hours of contractions)
- Treatment: **manual pressure** and **surgical repair**



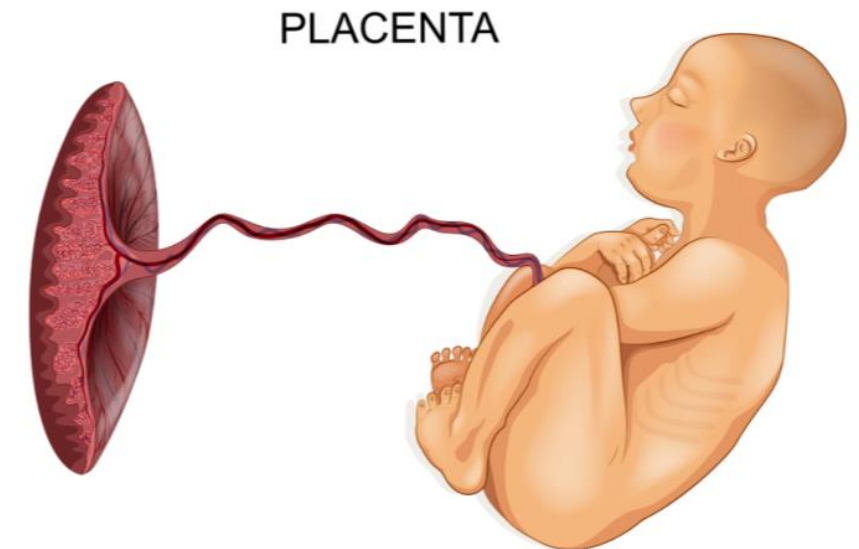
# Coagulopathy

- Pregnancy: consumption of clotting factors
  - State of “chronically compensated DIC”
- Small amount of hemorrhage may cause clinical DIC
- Blood loss may consume clotting factors
- Testing for coagulopathy with prolonged bleeding
- CBC with platelet count, PT/PTT/INR



# Retained Placenta

- Placenta expelled by uterine contractions
- Retained tissue → bleeding
- Occurs with placenta accreta, increta or percreta
- Placenta always examined after delivery
- May attempt to separate retained tissue by curettage
- Often requires hysterectomy



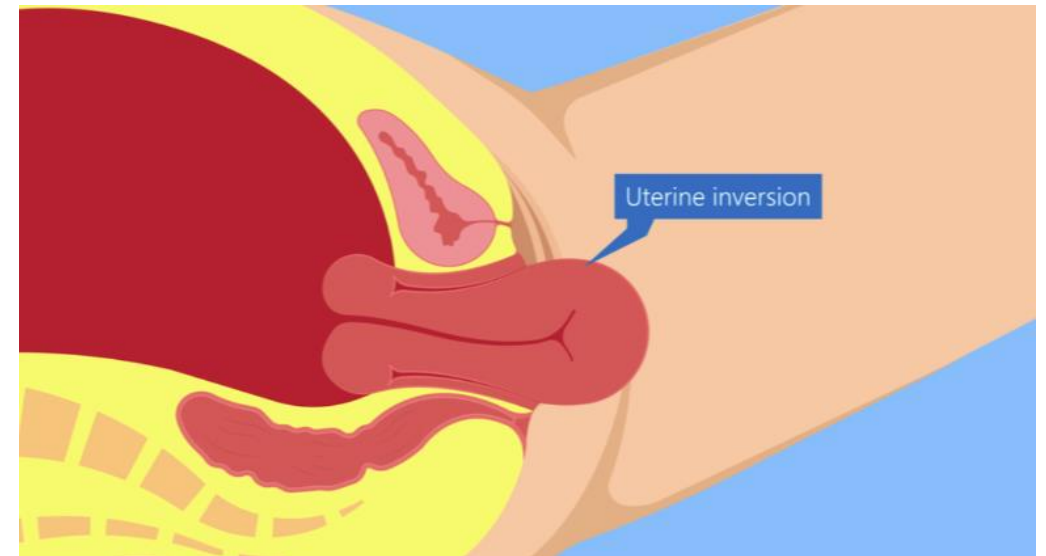
# Late Postpartum Hemorrhage

## Secondary Postpartum Hemorrhage

- Begins **more than 24 hours after delivery**
- Three major causes
- Retained products of conception
- Endometritis
- Inadequate involution

# Uterine Inversion

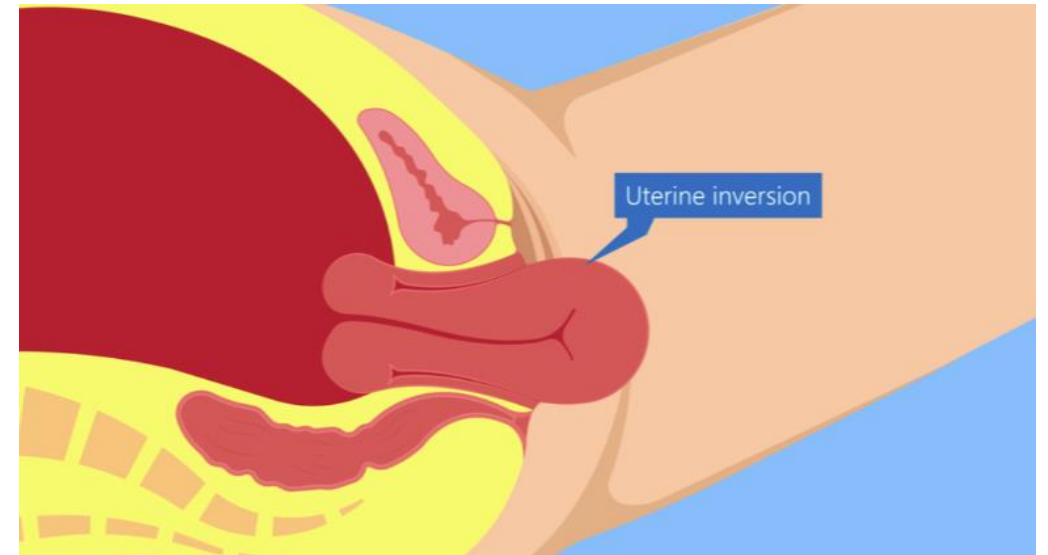
- Uterus turns inside out
- Uterine fundus protrudes through cervix
- Firm, rounded mass protruding from vagina
- Leads to severe hemorrhage
- Most often in multigravidas
- Usually iatrogenic: too much cord traction





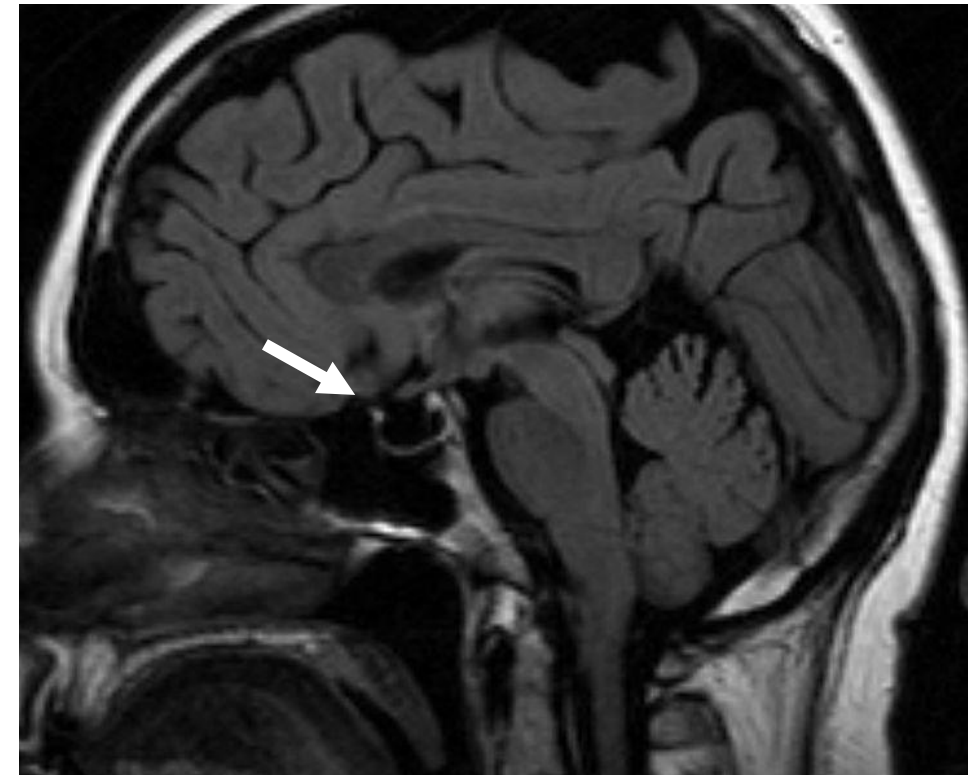
# Uterine Inversion

- Attempt **manual replacement**
- If unable to replace: **tocolytics**
  - Nitroglycerine or other drugs
  - Relaxes uterus for replacement
- Often atony and bleeding
- After replacement may need oxytocin



# Sheehan Syndrome

- Pituitary gland enlarges in pregnancy
- Vulnerable to infarction from hypovolemic shock
- Postpartum hemorrhage → hypopituitarism
- Can see **failure to lactate**
- Amenorrhea, loss of pubic hair, weight loss
- Diagnosis: hormone testing and head MRI
- Treatment: hormone replacement



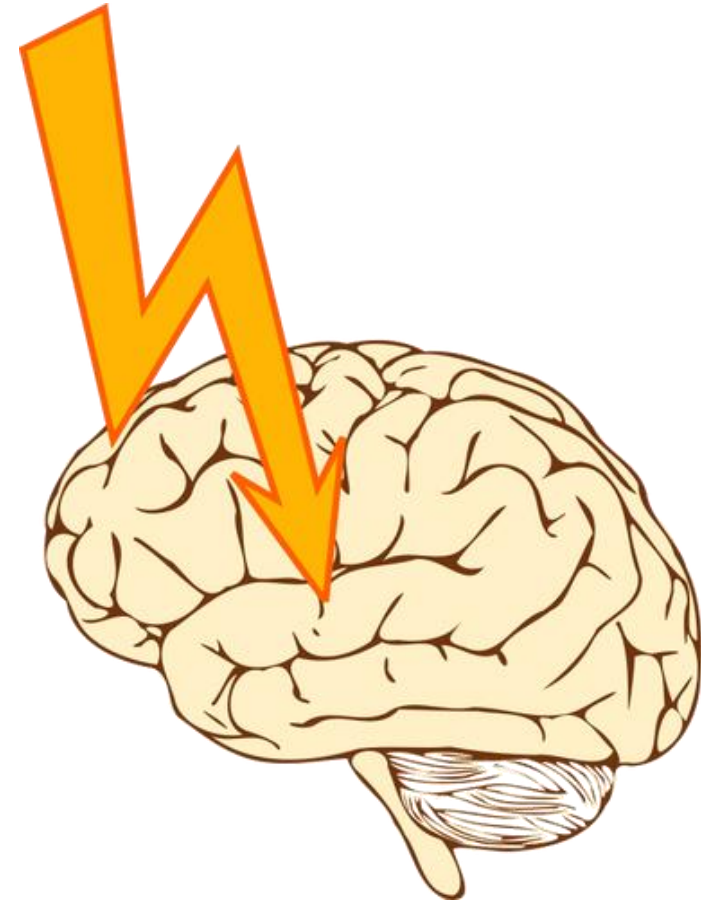
# Amniotic Fluid Embolism

- During labor or shortly after (~ 30 min)
- Amniotic fluid, fetal cells, fetal debris
- Enter maternal circulation
- Inflammatory reaction
- Often fatal
- Treatment: **supportive care**



# Amniotic Fluid Embolism

- Phase I (respiratory/shock)
  - **Respiratory distress**
  - Hypoxemia
  - **Hypotension**
- Phase II (hemorrhagic phase)
  - Massive hemorrhage
  - DIC
- **Seizures** also often occur



# Routine Postpartum Care

- Transient, low-grade fevers: normal first 24 hours
- Shivering and chills: occur in 25 to 50% of women
- **Breast engorgement**
  - Breasts become firm
  - Possible fullness, pain and tenderness
- Self-limited **hair loss** common one to five months after delivery
  - Usually mild, often unnoticed

# Uterine Involution

- Uterus returns to non-pregnant size and state
- Superficial decidua layer sheds
- **Lochia**: normal vaginal discharge after delivery
- Lochia rubra (first 3 to 4 days): red color; similar to menses
- Lochia serosa (day 4 up to 2 weeks): pinkish-brown and watery
- Lochia alba (weeks): yellow
- Subinvolution may cause late postpartum bleeding
  - Inadequate physiologic closure and sloughing

# Common Postpartum Complications

- **Urinary retention**

- Injury to pudendal nerve during birth
- Postpartum urinary retention: absence of urination by 6 hours after birth
- Improves with time and ambulation
- Treated with intermittent urinary catheterization as needed

- **Pubic symphysis diastasis**

- Rare complication: separation of joined pubic bones
- Pubic tenderness at symphysis
- Pain with ambulation
- Diagnosis: clinical or X-ray
- Treatment: analgesia, physical therapy, support truss

Pubic Symphysis Diastasis



# Postpartum Fever

- Low-grade fever common **first 24 hours after birth**
  - Especially after vaginal delivery
  - Resolves spontaneously
- Postpartum fever: temp  $\geq 100.4^{\circ}\text{F}$  any two of the first 10 days postpartum
- Surgical site infection
- Endometritis
- Mastitis or breast abscess
- Urinary tract infection
- Septic pelvic thrombophlebitis



# Wound Infections

- Infection of abdominal incision
- Infection of genital wounds incredibly rare (even deep lacs with feces)
- **Swelling and erythema** with purulent drainage at wound site
- Treatment: drainage, irrigation, and debridement plus antibiotics
- After cesarean delivery: wound infections days 4 to 7
- Prophylactic antibiotics before cesarean delivery
- Usually single dose cefazolin one hour before incision



Wu TS et al. Postcesarean section wound infection caused by *Mycobacterium massiliense*.  
J Microbiol Immunol Infect. 2016 Dec;49(6):955-961.

# Urinary Tract Infections

- Common source of persistent fever after delivery
- Cystitis or pyelonephritis
- Diagnosis and treatment as in non-postpartum patients



# Lactational Mastitis

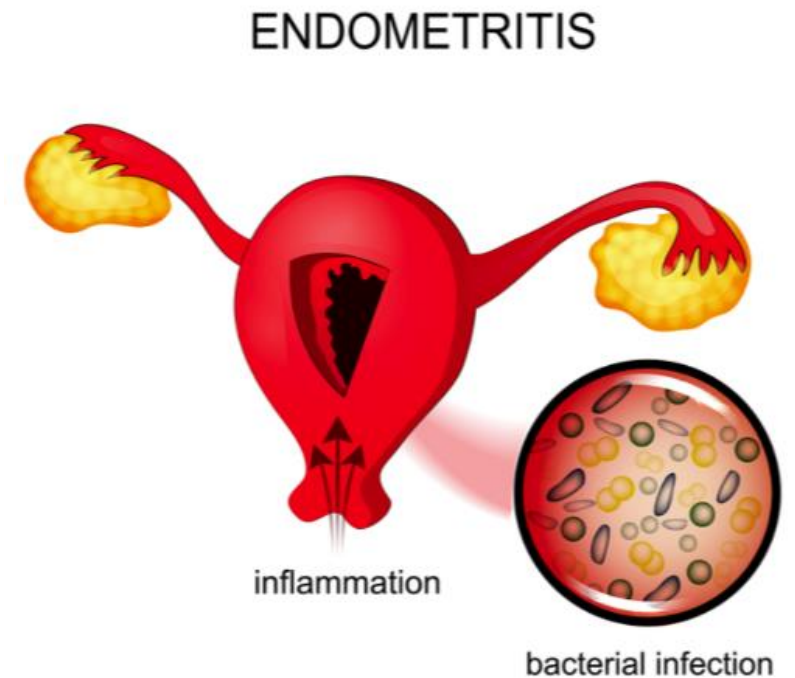
## Acute Mastitis

- Occurs in women during **breast feeding**
- Trauma to skin around nipple
- Breast erythema, tenderness
- Often fever, malaise
- Most commonly infection with **S. Aureus**
- Usual treatment: **dicloxacillin or cephalexin**
- Mother should **continue nursing**
- Can progress to abscess requiring drainage



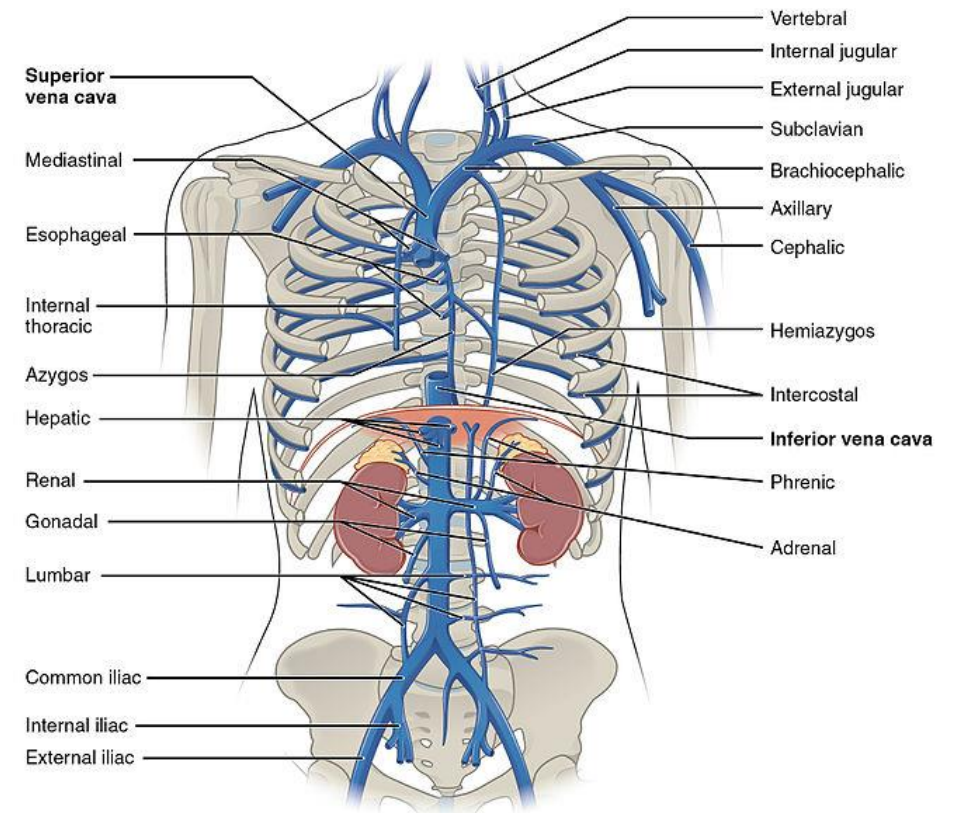
# Endometritis

- Infection of the decidua/endometrium
- Postpartum fever, uterine tenderness and leukocytosis
- Foul purulent discharge
- Polymicrobial infection
- Clinical diagnosis
- Treatment: **broad-spectrum antibiotics**
  - Common regiment: gentamycin + clindamycin
- Rarely causes **toxic shock syndrome**
  - Rash, desquamation, hypotension



# Septic Pelvic Thrombophlebitis

- Rare postpartum cause of fever
- Venous thrombosis and infection
- Occur in ovarian veins or deep pelvic veins
- Presents as **fever**
- May cause abdominal pain but not always
- Often presumed to be endometritis
- Poorly responsive to antibiotic therapy alone



# Septic Pelvic Thrombophlebitis

- **Ovarian vein SPT**
  - Occurs within 1 week of delivery
  - Acutely ill patient fever and abdominal pain localized to affected side
  - Pelvis tender to palpation
  - “Rope-like mass” on examination from uterus to lateral abdomen
- **Deep septic pelvic thrombophlebitis**
  - More subtly presentation
  - Fever but patients often not acutely ill-appearing
  - Abdominal or pelvic tenderness absent
  - Poor response to antibiotics
  - Pelvic imaging may be normal



# Septic Pelvic Thrombophlebitis

## Diagnosis

- Suspected in patients with persistent fever despite antibiotics
- Often a diagnosis of exclusion, proven by response to anticoagulant
- Diagnosis: CT or MRI
  - Best for identification of ovarian vein thrombophlebitis
  - Negative study does not exclude SPT
  - Small, deep pelvic branches not well visualized
  - Empiric treatment when imaging negative with ongoing fevers
- Treatment: **antibiotics plus anticoagulation**
  - Broad-spectrum antibiotics (gentamycin + clindamycin)
  - Intravenous heparin or LMWH

Pelvic CT Scan



# Postpartum Mood Disorders

- Postpartum blues (up to 85% some studies)
  - Depressed mood, insomnia, fatigue, poor concentration
  - Mild symptoms that starts 2-3 days after delivery
  - Resolves within **two weeks**
  - Treatment: supportive
- Postpartum depression (~ 15%)
  - Symptoms that persist after two weeks
  - Meets DSM criteria: SIGECAPS
  - Treatment: CBT and medications (SSRIs)
- Postpartum psychosis (rare)





# Postpartum Psychosis

- Rare disorder (0.1 to 0.2% of births)
- Usually women with known psychiatric disorder
  - Most commonly **bipolar disorder**
  - Also depression with psychosis, schizophrenia, schizoaffective
  - Especially if meds stopped during pregnancy
- Occurs within 2 weeks after delivery



# Postpartum Psychosis

- Delusions, hallucinations, disorganized thought
- **Delusions often involve the baby**
- Example: “Something is wrong with my baby!”



# Postpartum Psychosis

- Risk factors
  - Personal or family history of postpartum psychosis
  - Bipolar disorder, schizophrenia, or schizoaffective disorder
  - First pregnancy
  - Discontinuation of psychiatric medications in pregnancy
- **Requires hospitalization**
  - High risk of suicide
  - Risk of harm to baby
  - Mother cannot care for herself or baby
- Treatment: antipsychotics and ECT

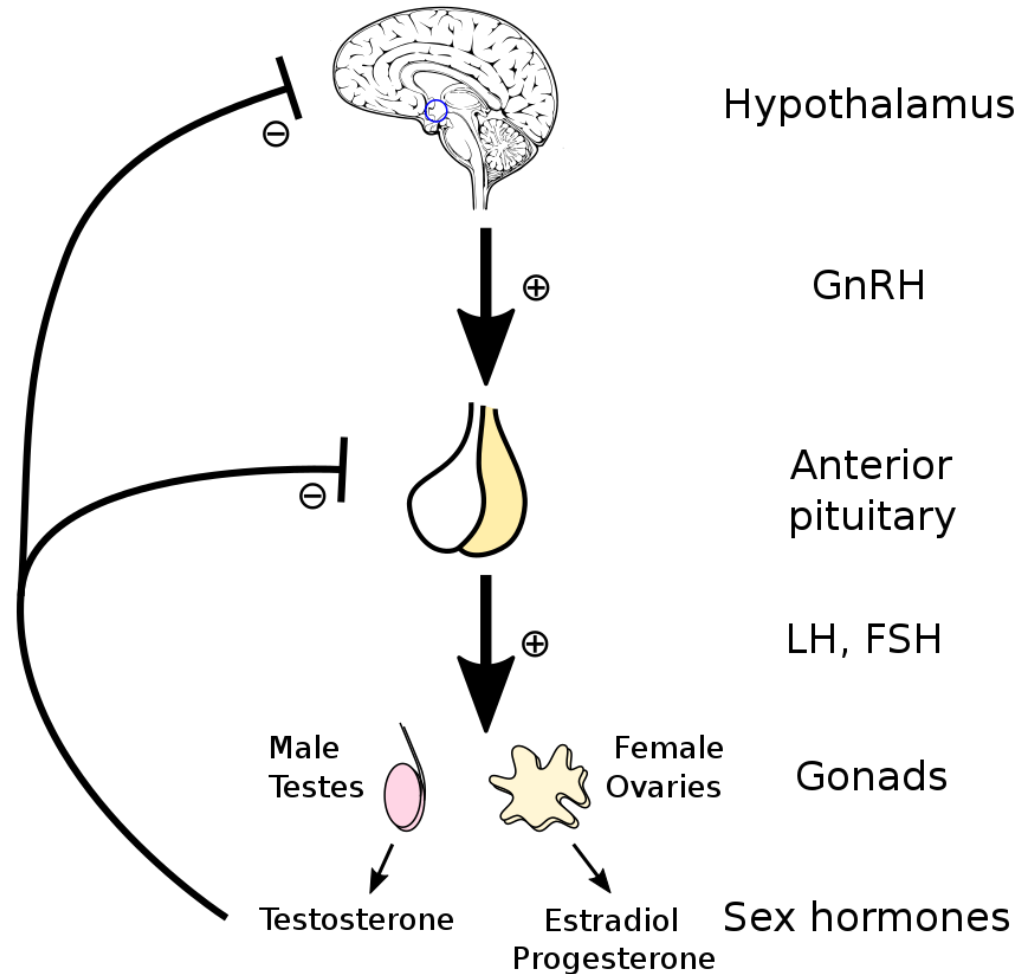


# Menstrual Cycle

Jason Ryan, MD, MPH



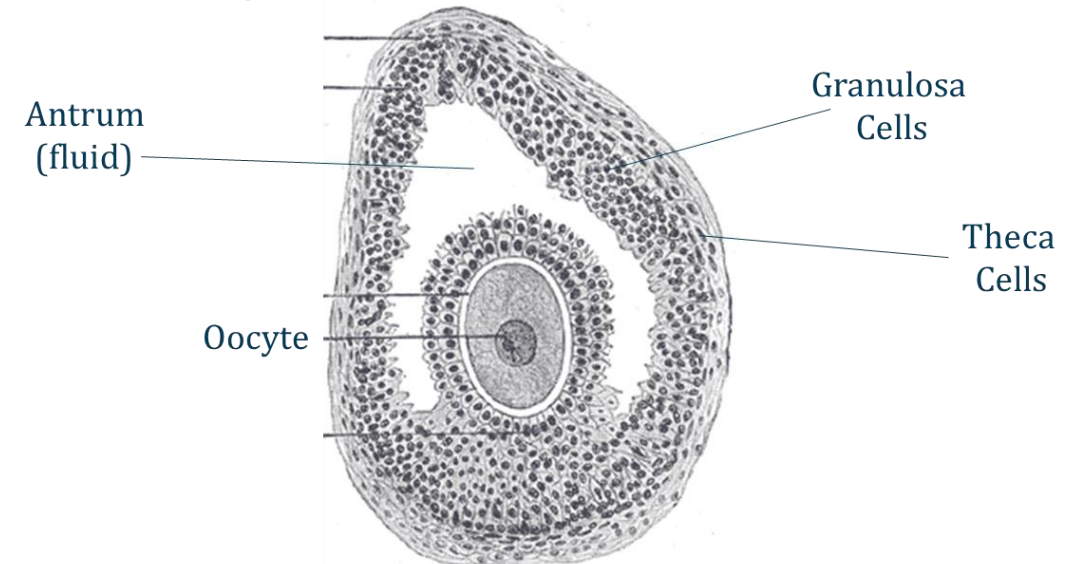
# Female Reproductive System



# Ovaries

## Basic Principles

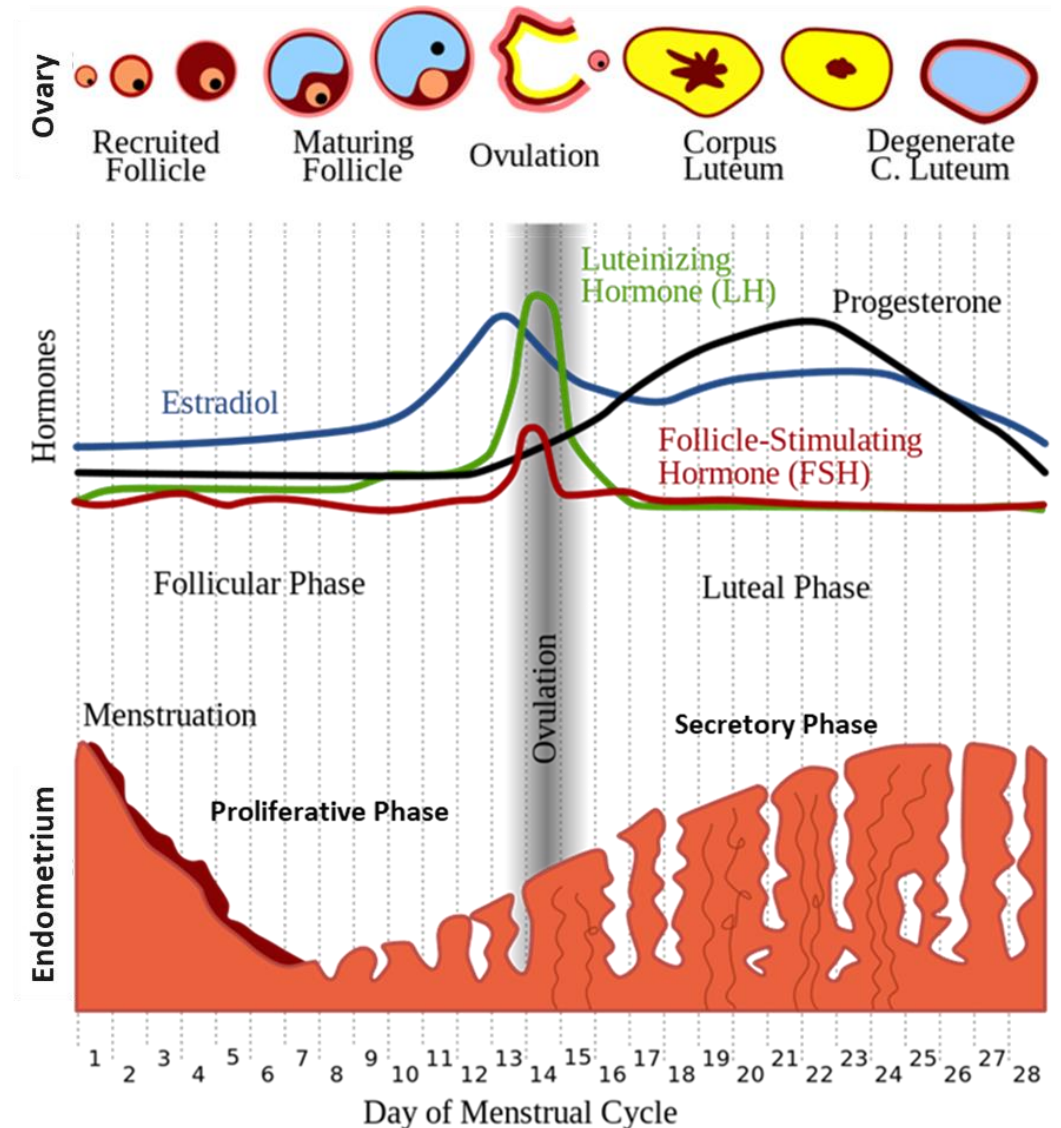
- Contain **follicles**
  - Spherical collection of cells
  - Contains a single oocyte
- Oocyte surrounded by cells **theca and granulosa** cells
- Each menstrual cycle one dominant follicle releases oocyte (ovulation)



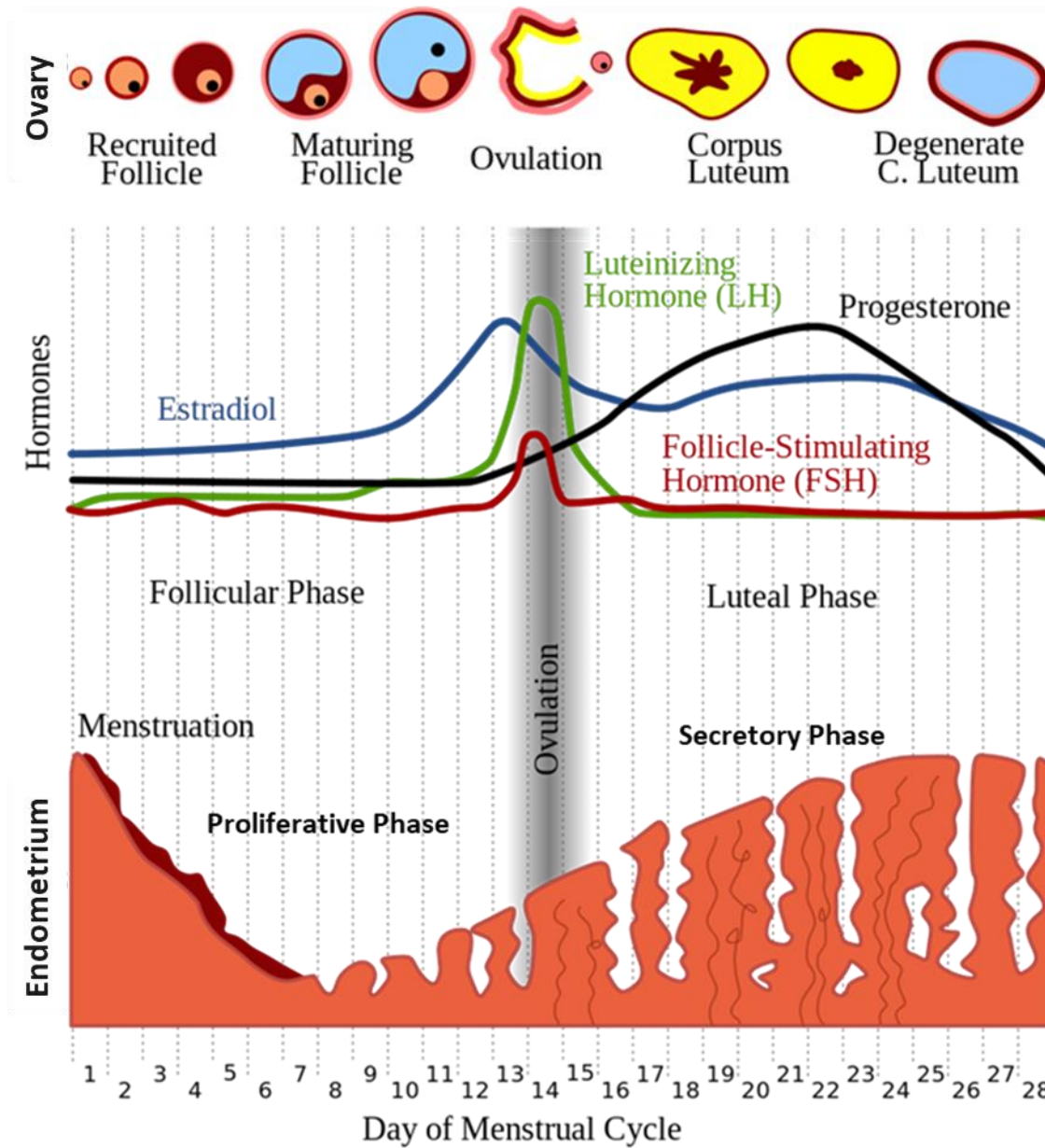
# Menstrual Cycle

## Basic Principles

- Series changes in ovaries and endometrium
- **Ovarian phases**
  - Follicular (growth of follicles)
  - Ovulation
  - Luteal (preparation for pregnancy)
- **Endometrial phases**
  - Proliferative
  - Secretory





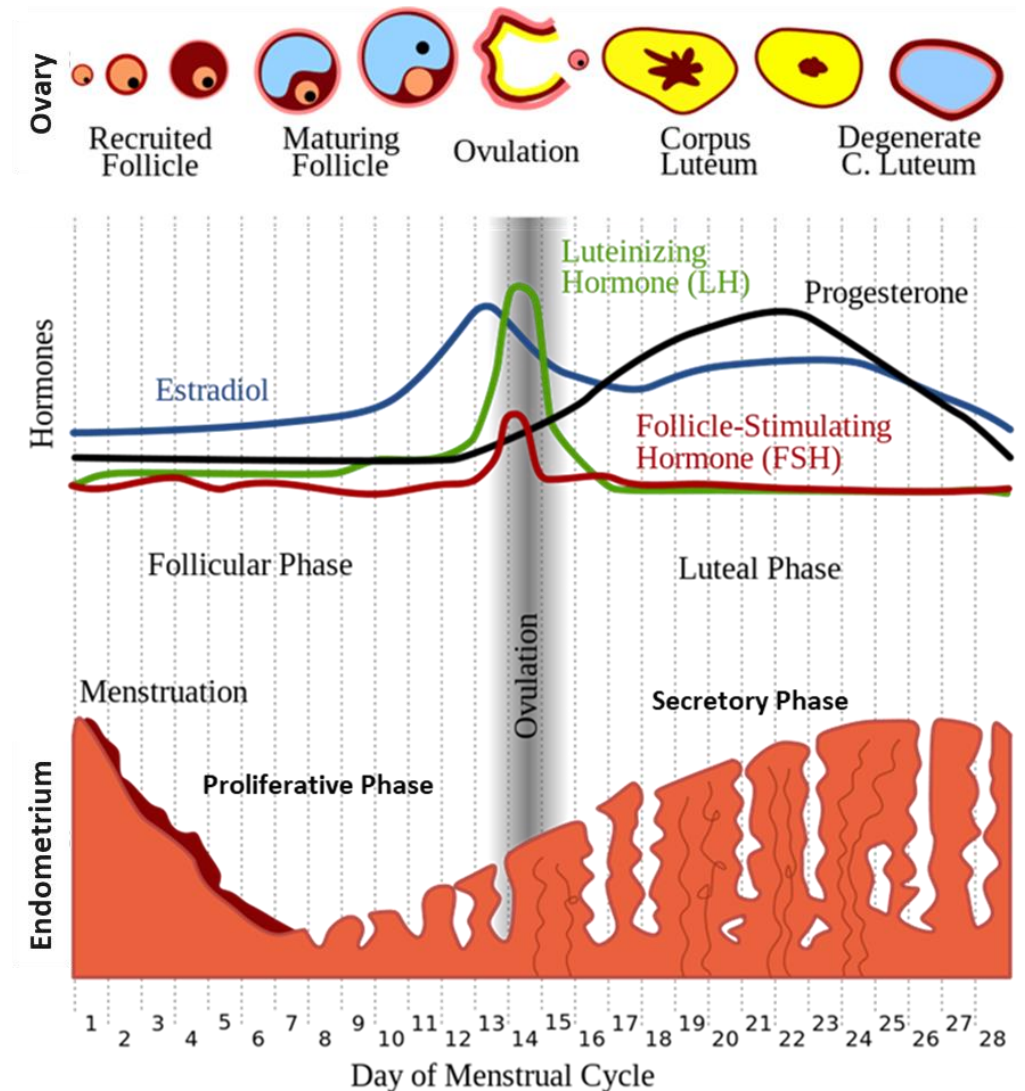




# Menstrual Cycle

## Follicular and proliferative phases

- Menstruation through LH surge and ovulation
- Slowly rising estradiol levels
- Dominant follicle oocyte released at ovulation
- Varies in length: 10-14 days
- Uterine proliferation
- Endometrial thickness increases (> 10x)
- Growth of glands, stroma, blood vessels



# Menstrual Cycle

## Ovulation

- **Mid-cycle surge**

- Estradiol triggers → **LH surge** (↑ frequency GnRH pulses )
- Oocyte released from follicle ~ 36 hours after LH surge
- Basis for ovulation testing: urine detection of LH

- **Mittelschmerz**

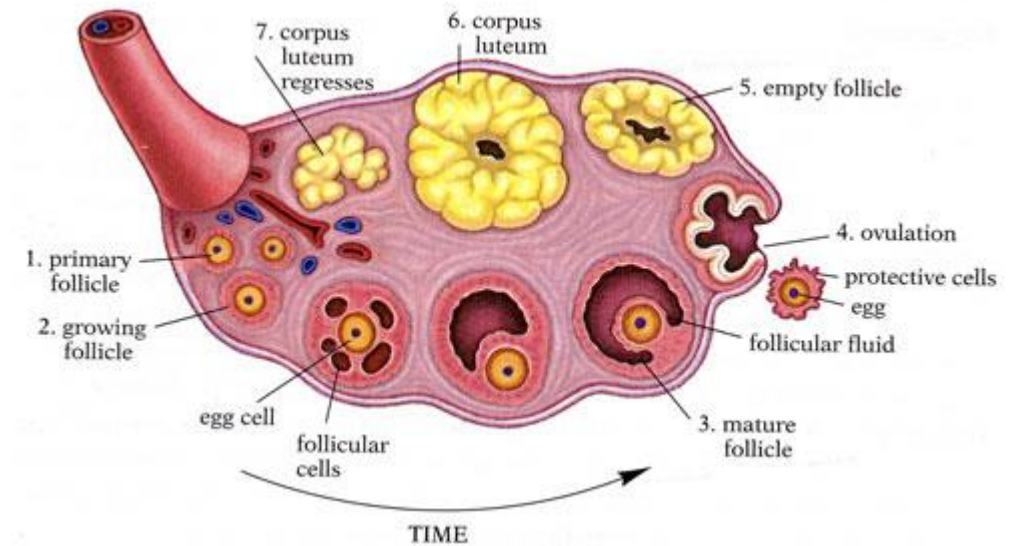
- Mid-cycle mild, unilateral pain
- Due to enlargement of follicle or follicular rupture with bleeding
- Usually resolves in hours to days
- Can mimic other disorders (appendicitis)



# Menstrual Cycle

## Luteal and secretory phases

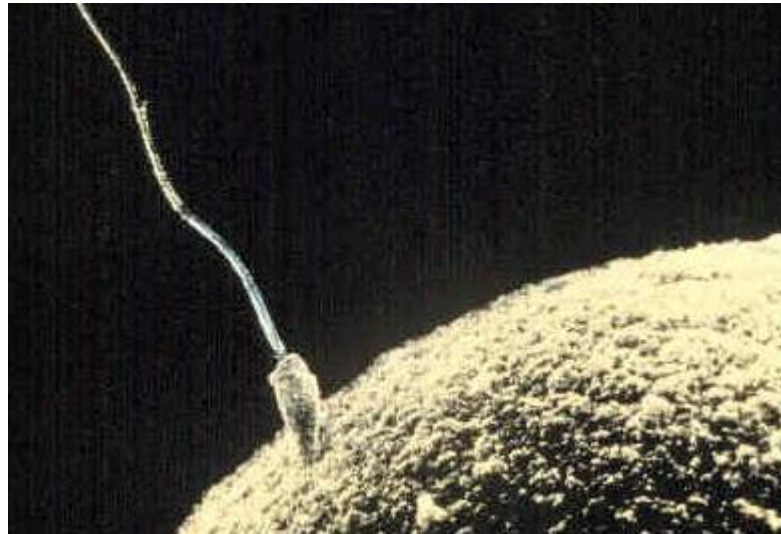
- **Corpus luteum** forms
- Temporary endocrine gland formed from follicle
- Produces large amounts of **progesterone**
- Progesterone inhibits proliferation of endometrium
- Numerous secretions released to prepare for embryo
- Eventually corpus luteum degrades
- ↓ progesterone → menstruation
- Occurs 14 days after ovulation



# Menstrual Cycle

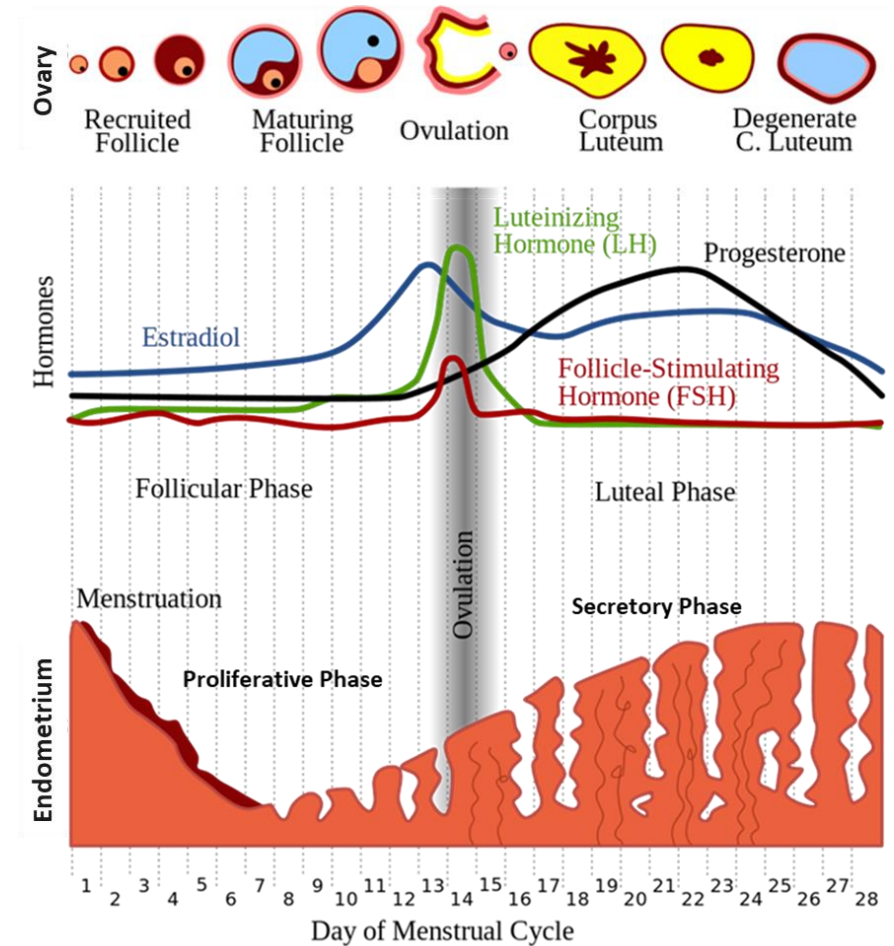
## Luteal and secretory phases

- If fertilization occurs, embryo makes **hCG**
- Maintains the corpus luteum and progesterone production
- Continued progesterone inhibits LH/FSH release



# Menstruation

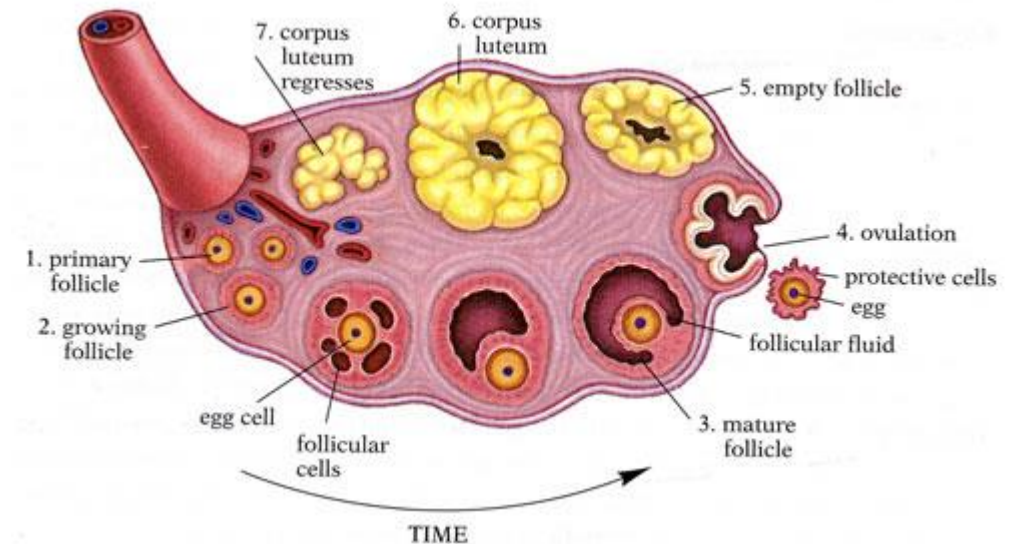
- Progesterone levels fall
- Vasoconstriction of spiral arteries
- Collapse and desquamation of endometrium





# Anovulation

- No luteal phase
- No progesterone release
- Continued estrogen release
- No progesterone withdrawal for normal menses
- Endometrial growth → **abnormal uterine bleeding**
- Classic cause: **PCOS**
- Also seen at menarche and perimenopause
- Common cause of **infertility**



# Premenstrual Syndrome

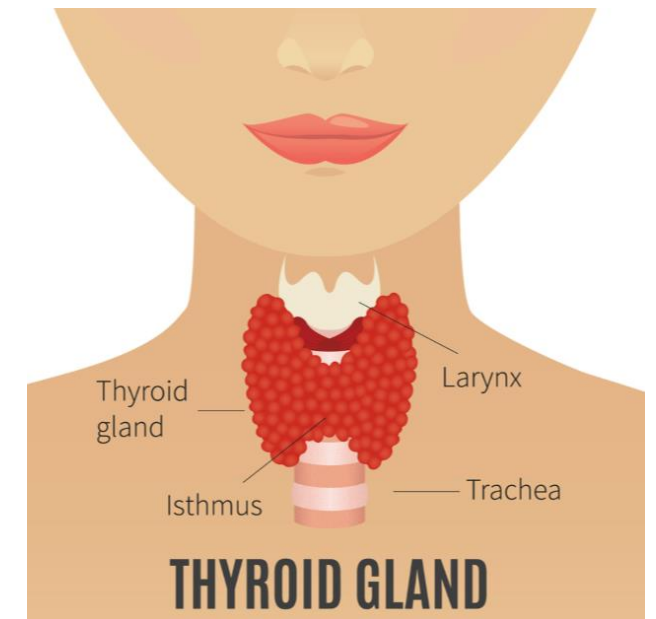
## PMS

- Physical and mood symptoms
- Occur 3 to 5 days before menses
- Up to 150 symptoms described
- Most common behavioral symptom: **mood swings**
- Most common physical symptoms: **bloating and fatigue**
- Symptoms resolve with menses
- Symptom free during the follicular phase

# Premenstrual Syndrome

## Diagnosis

- Patient should record symptoms prospectively for two months
- ACOG: at least one symptom that leads to impairment in functioning
- Patients must be symptom free in follicular phase
- Must exclude **thyroid disease** and other psychiatric disorders





# Premenstrual Dysphoric Disorder

## PMDD

- Severe form of PMS
- Prominent symptoms of anger and irritability
- DSM-V: at least 5 symptoms before menses in most menstrual cycles

### DSM-V Criteria

<b>At least one of following</b>	<b>One or more to reach total of 5</b>
Affective lability (mood swings) Irritability or anger Depressed mood Anxiety or tension	Decreased interest in activities Difficulty concentrating Lethargy or lack of energy Change in appetite Hypersomnia or insomnia Sense of being overwhelmed Physical symptoms

# Premenstrual Syndrome

## Treatment

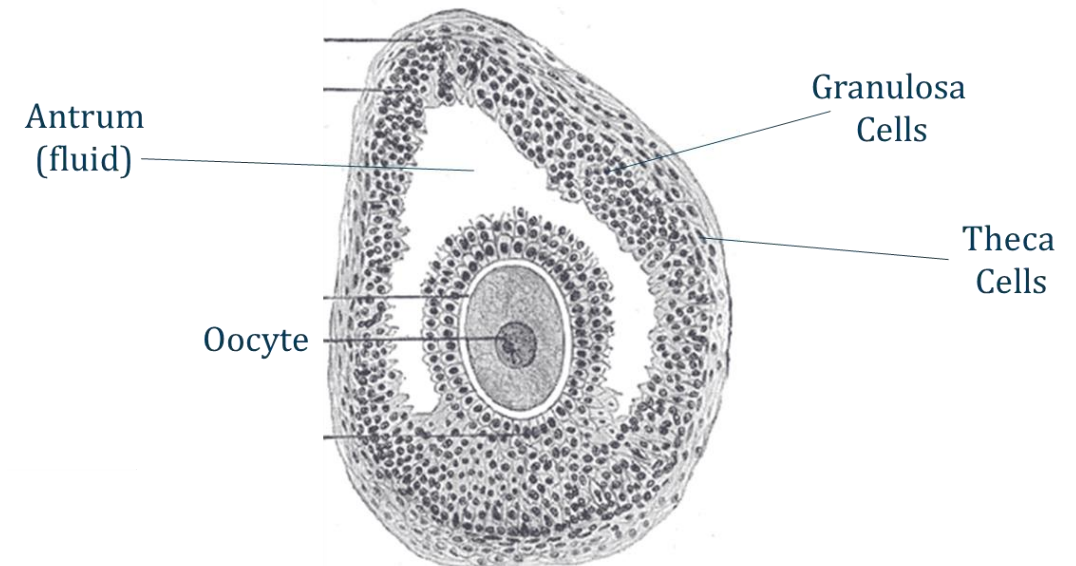
- Mild PMS: exercise and stress reduction
- Severe PMS or PMDD:
  - Combined oral contraceptives
  - SSRIs

## Oral Contraceptive Pills



# Menopause

- Permanent cessation of menstrual periods
- Cause by **depletion of ovarian follicles**
- Median age = 51 years
- Usually preceded by irregular menses
- ↓ estrogens and progesterone from ovaries
- Eventually FSH and LH levels will be elevated



# Menopause

## Symptoms

- **Hot flashes**
  - Also called vasomotor symptoms or hot flashes
  - Subjective sensation of warmth
  - Usually lasts a few minutes and passes
  - Associated with drop in estrogen levels
- Vaginal atrophy
  - Thin, dry or friable from loss of estrogen stimulation
  - Can be treated with topical estrogen
- Fatigue
- Sleep disturbance



# Menopause

## Associated risks

- Osteoporosis
  - Bone loss from lack of estrogen
- Cardiovascular disease
  - Risk increases after menopause
  - May be due in part due to estrogen deficiency
- Altered lipids: ↓ HDL, ↑ LDL



# Menopause

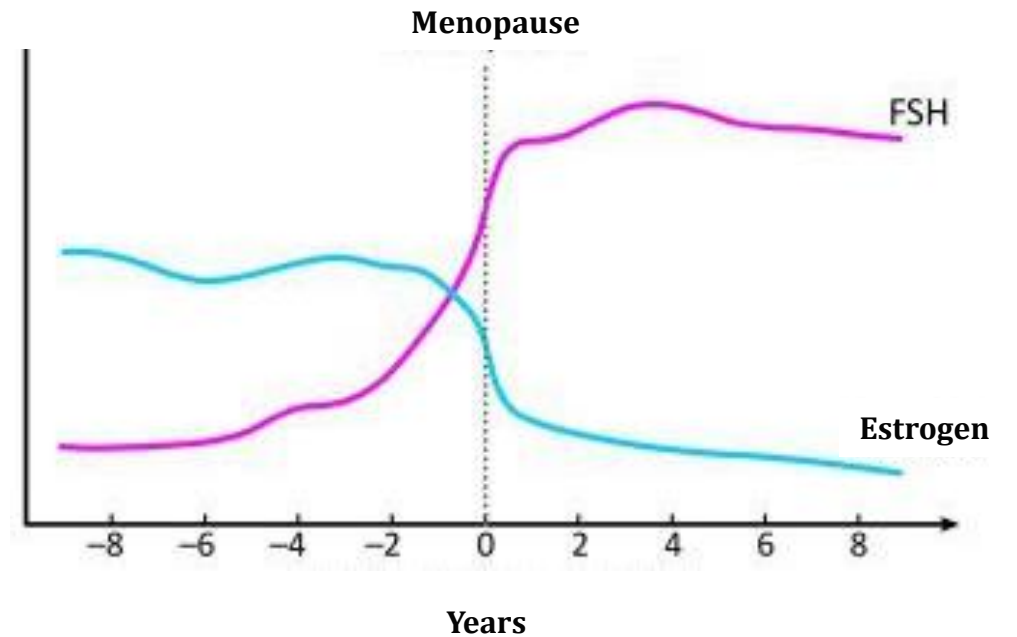
## Evaluation

- Often presents as hot flashes with irregular menses
- Diagnosis usually made clinically
- Requires 12 months of amenorrhea not due to other cause
- Women under 45: exclude other causes of amenorrhea
  - hCG
  - TSH
  - Prolactin
  - FSH

# Menopause

## Evaluation

- Serum hormone level changes not required for diagnosis
- **Increased FSH**
  - Normal: 6 to 10 mIU/mL
  - Perimenopause: 10 to 30 mIU/mL
  - Menopause: > 30 mIU/mL
- **FSH:LH ratio > 1**
  - FSH rises more than LH



# Menopause

## Symptom Management

- Lifestyle modifications for hot flashes
  - Cooler temperature, lighter clothing, fans
- Herbal supplements often used
- Hormone replacement therapy
  - Primary goal is treatment of hot flashes
  - Not used for long-term prevention
  - Risk > benefits for osteoporosis or CAD

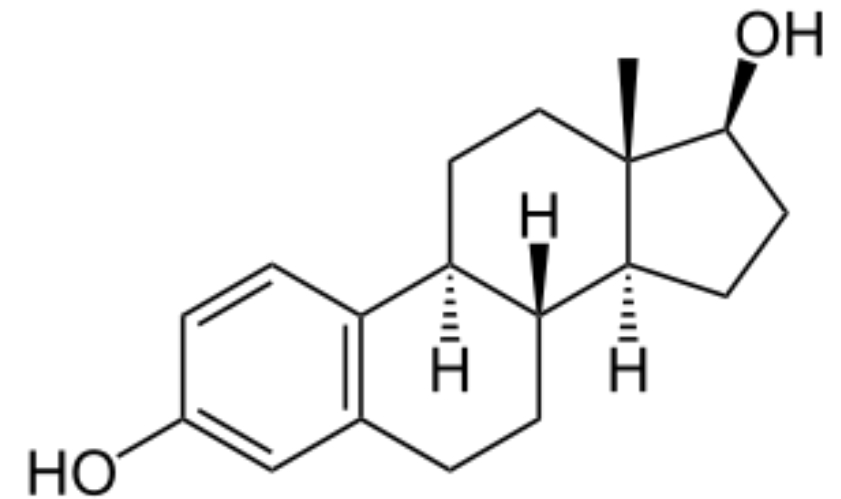




# HRT

## Hormone Replacement Therapy

- Estrogens and/or progestins
- Estrogens limit menopausal symptoms
- Progestin added in women with intact uterus
  - Prevents endometrial hyperplasia and bleeding
  - Not required in women after hysterectomy



Estradiol  
(17 $\beta$ -estradiol)

# HRT

## Hormone Replacement Therapy

- Transdermal estrogen patch (less thrombotic risk)
- Oral estrogen
- Oral progestin
- Cyclical progestins
  - Used several days per month or less
  - Results in withdrawal bleeding

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
28	29	30	31 <small>New Year's Eve</small>	1 <small>New Year's Day</small>	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19 <small>Martin Luther King Day</small>	20	21	22	23	24
25	26	27	28	29	30	31

# HRT

## Risks

- ↑ risk of DVT, stroke and myocardial infarction
- ↑ risk of breast cancer

Deep Vein Thrombosis



# HRT

## Contraindications

- History of ER+ or PR+ breast cancer
- History of estrogen-dependent endometrial cancer
- Coagulopathy
- Prior venous thromboembolic event (DVT/PE)
- Prior stroke or TIA
- Coronary artery disease
- Active liver disease
- Unexplained vaginal bleeding

# Primary Ovarian Insufficiency

- Impaired ovarian function before 40 years of age
- Presentation and treatment similar to menopause
- Causes:
  - Chemotherapy or radiation therapy
  - Familial
  - Autoimmune disease
  - Genetic disorders (Fragile X mutation carriers, Turner syndrome)

# Contraception

Jason Ryan, MD, MPH

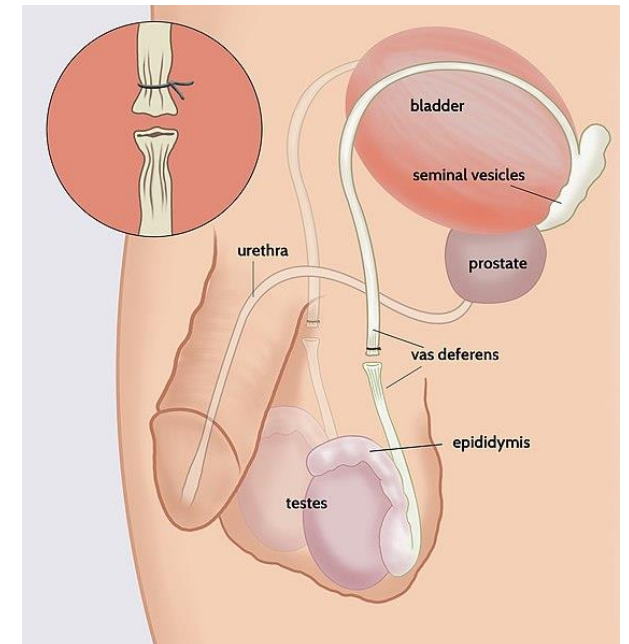


# Contraception

- Barrier (condoms, diaphragm, sponge)
- Vasectomy
- Tubal ligation
- Intrauterine device
- Hormonal

# Vasectomy

- Ligation of bilateral **vas deferens**
- Usually outpatient under local anesthesia
- Semen analysis three months postoperatively to confirm sterility
  - If sperm at 3 months → follow-up test 1 to 2 months later
  - Failure if sperm at follow-up after > 20 ejaculations and > 3 months
- Use alternate method of contraception until semen analysis
- Usually permanent
- Rare cases of recanalization (~ 0.2% of patients)
- Reversal possible in some cases





# Female Permanent Contraception

## Sterilization or Tubal Ligation

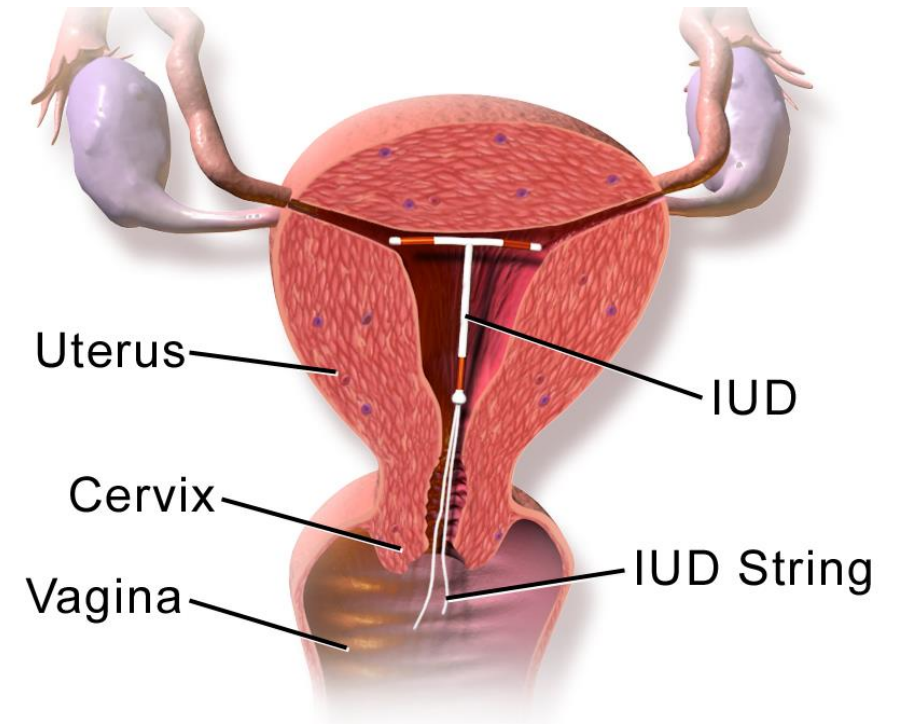
- Variety of surgical techniques
- Goal is disruption of fallopian tubes
- Often done postpartum
- Also performed outside pregnancy (“interval”)
- Very low failure rate
- Reversible in some cases based on technique
- Long-term risks: **ectopic pregnancy**

Ectopic Pregnancy



# Intrauterine Devices

- Long-acting *reversible* contraception
- Low failure rate similar to permanent sterilization
- Two major types
  - Copper IUD
  - Levonorgestrel (LNG) IUD



**Intrauterine Device (IUD)**

# Copper IUD

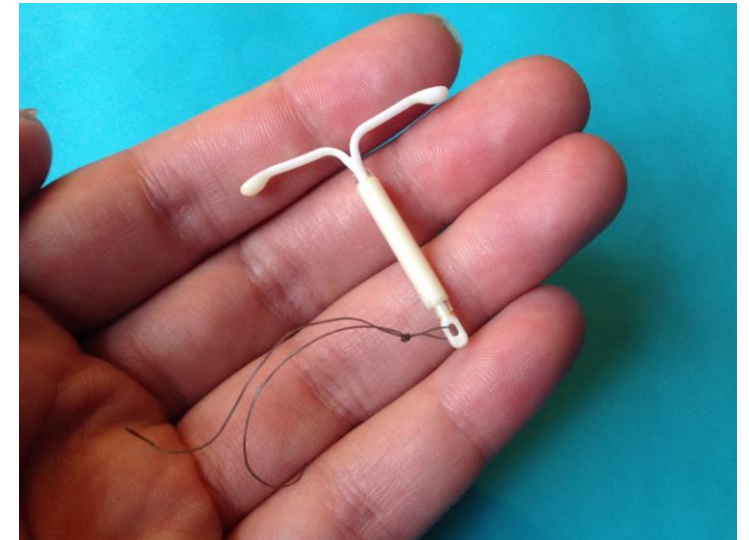
- Copper → inflammatory response in endometrium
- Impairs sperm migration/viability and implantation
- Heavier and more painful **menstrual bleeding**
- Especially first 6 months
- Commonly leads to patient request for removal
- Marketed as hormone free IUD
- Last up to 10 years

Copper IUD



# Levonorgestrel IUD

- Polyethylene frame with LNG (progestin)
- Thickens cervical mucus as barrier and impairs implantation
- Last up to 7 or 8 years
- Causes amenorrhea and **improves abnormal uterine bleeding**
- Good option in women with heavy menses
- Safest and most effective form of contraception



# Intrauterine Devices

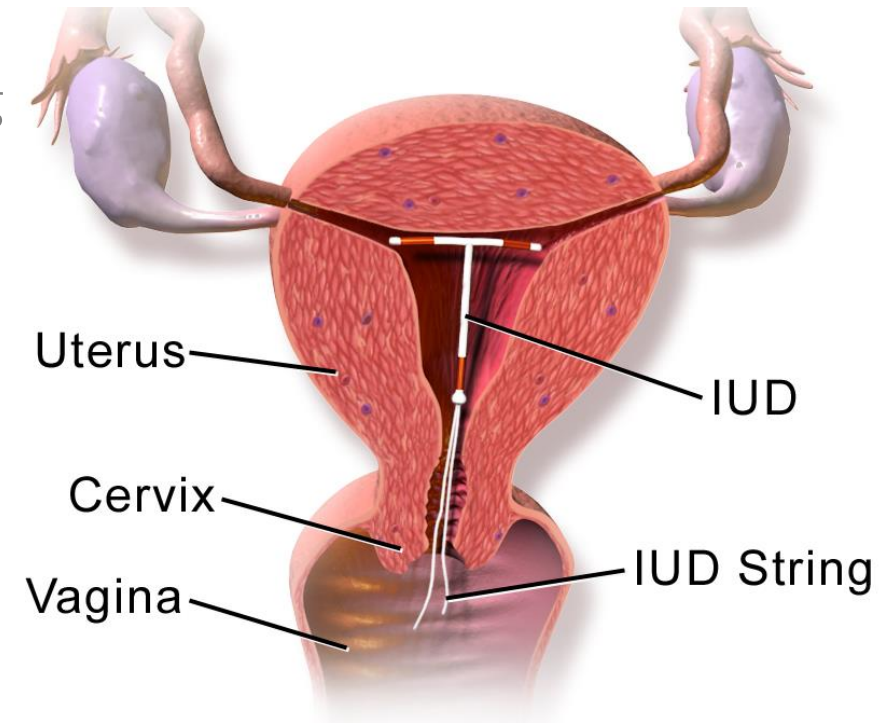
## Complications

- Irregular bleeding or cramping
  - Usually resolves over first few months
  - Does not indicate decreased efficacy
- Altered menstrual periods
  - Copper IUD: heavier periods with stronger cramping
  - LNG IUD: amenorrhea or irregular periods

# Intrauterine Devices

## Complications

- Rare complication: **uterine perforation**
  - Often asymptomatic and found when IUD string not felt
  - Rarely leads to pelvic pain with excessive cervical bleeding
- If failure occurs: ↑ risk of **ectopic pregnancy**

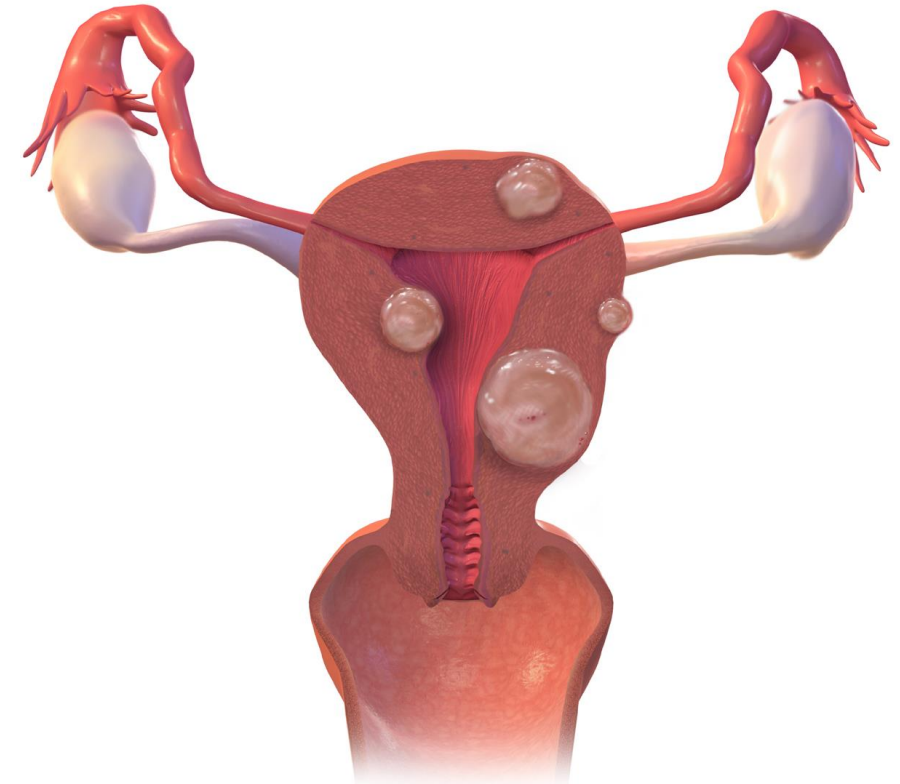


**Intrauterine Device (IUD)**

# Intrauterine Devices

## Contraindications

- Anatomic uterine abnormalities
  - Bicornuate uterus
  - Leiomyoma (fibroids)
  - Sometimes IUD can be placed with US guidance
- Unexplained uterine bleeding
- Pregnancy or pelvic infection
- Endometrial or cervical cancer
- LNG IUD:
  - History of PR+ breast cancer
  - Active liver disease

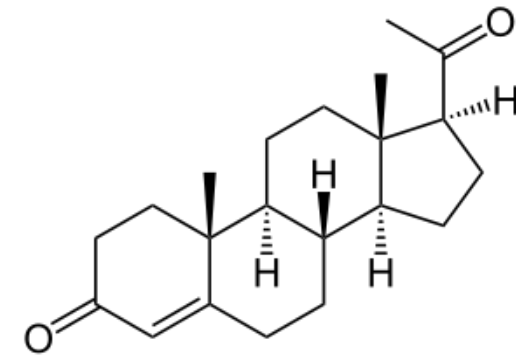


Uterine Fibroids

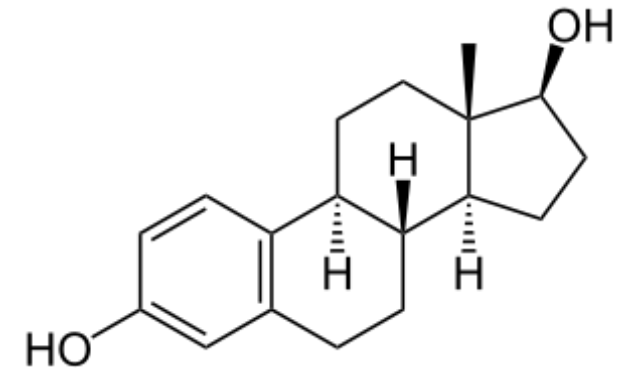


# Hormonal Contraceptives

- **Progestins**
  - Thickens cervical mucous
  - Thins endometrium to prevent implantation
  - High dose blocks LH surge → absence of ovulation
- **Estrogens**
  - Suppress FSH release
  - Limits follicular maturation
  - Increases effects of progestins
  - Main benefit: stabilizes endometrium
  - **Less breakthrough bleeding**



Progesterone



Estradiol



# Progestin Only Contraceptives

- Mini pill (norethindrone)
  - Thickens cervical mucous for 20 hours
  - Must be taken same time every day
- Implant (etonogestrel)
  - Placed in upper arm - 3-year lifespan
  - Rarely used due to irregular bleeding



# Progestin Only Contraceptives

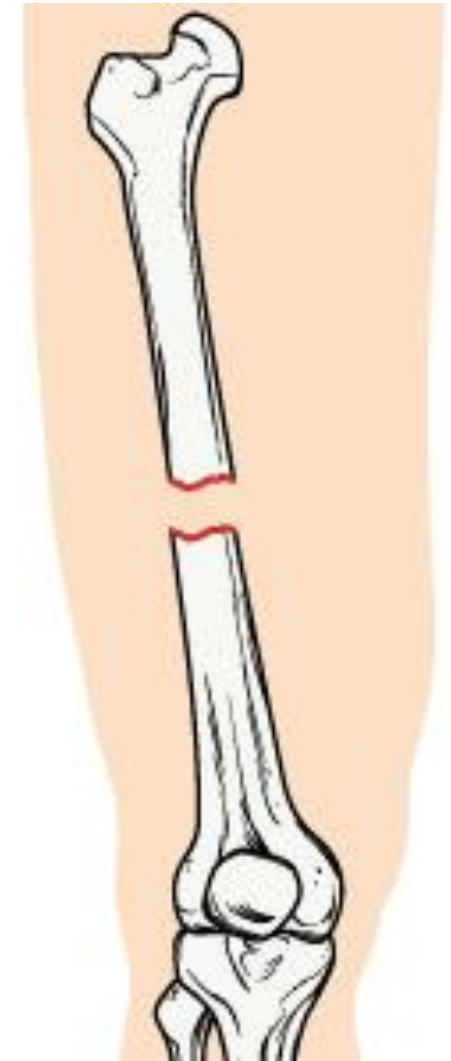
- Injection
  - Depo Provera (medroxyprogesterone)
  - Given every 3 months
  - Irregular bleeding
  - May cause weight gain<sup>1</sup>
  - 3 years: + 11 lbs
  - COCs: + 3 lb
- Many non-contraceptive uses
  - Endometriosis
  - Adenomyosis
  - AUB
  - Fibroids
  - Endometrial hyperplasia



1. Berenson et al. *Am J Obstet Gynecol.* 2009;200(3):329

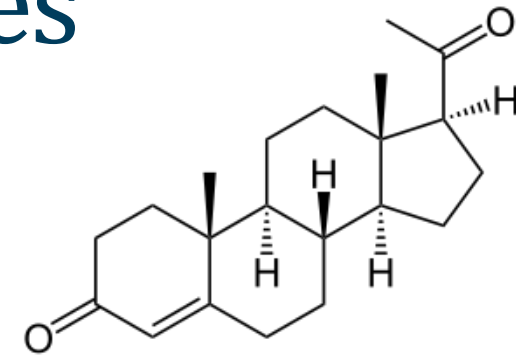
# Progestin Only Contraceptives

- All associated with **irregular bleeding**
- Often used in women with estrogen contraindications
- Cannot be used in women with breast cancer
- Depo-Provera associated with **↓ bone mineral density**
  - Suppression of estrogen production
  - Improves with cessation of contraception
  - Encourage calcium, vitamin D and exercise
  - Routine monitoring of BMD not recommended
- Mood changes (depression) may occur
- Very rare with progesterone IUD

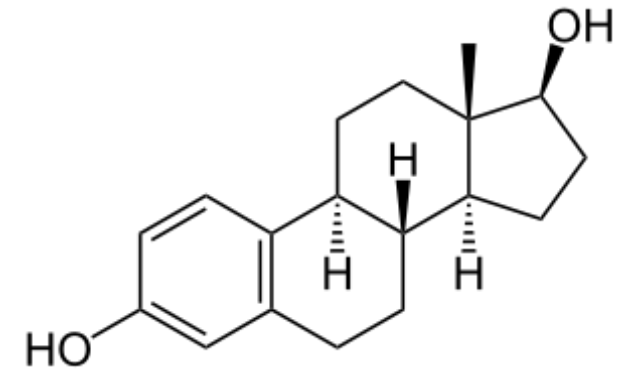


# Combination Oral Contraceptives

- Combination of **progestin and estrogen**
- Better suppression of follicular growth
  - Progesterone suppresses LH
  - Estrogen suppresses FSH
- Estrogen increases effect of progesterone
- **Less breakthrough bleeding**
  - Estrogen stabilizes endometrium
- Many have 24/4 formulation
  - 24 days of hormone pills
  - 4 days of placebo pills



Progesterone

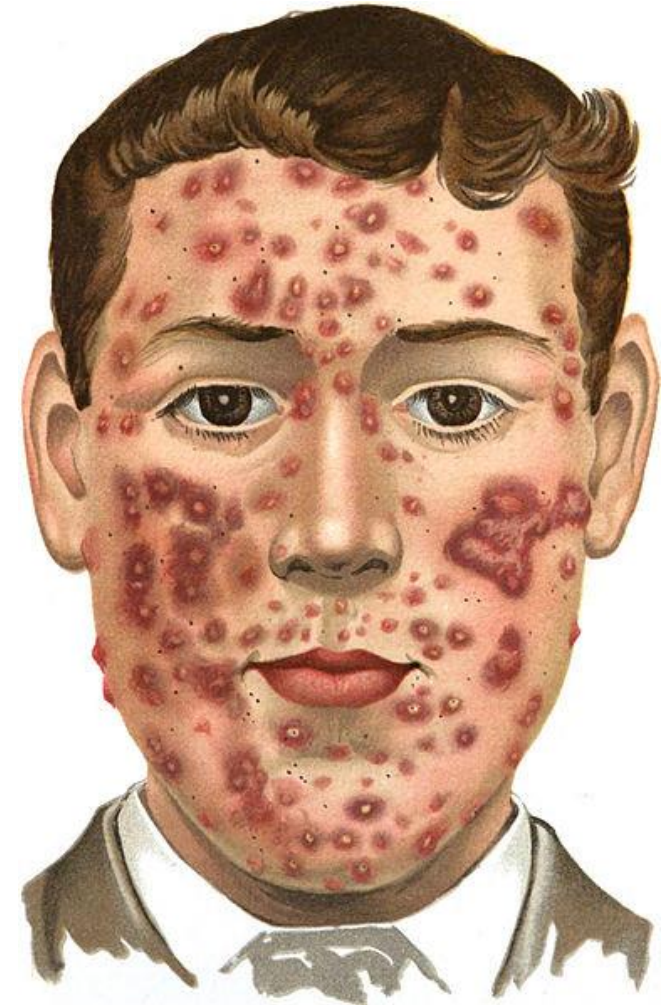


Estradiol

# Combination Oral Contraceptives

## Non-contraceptive benefits

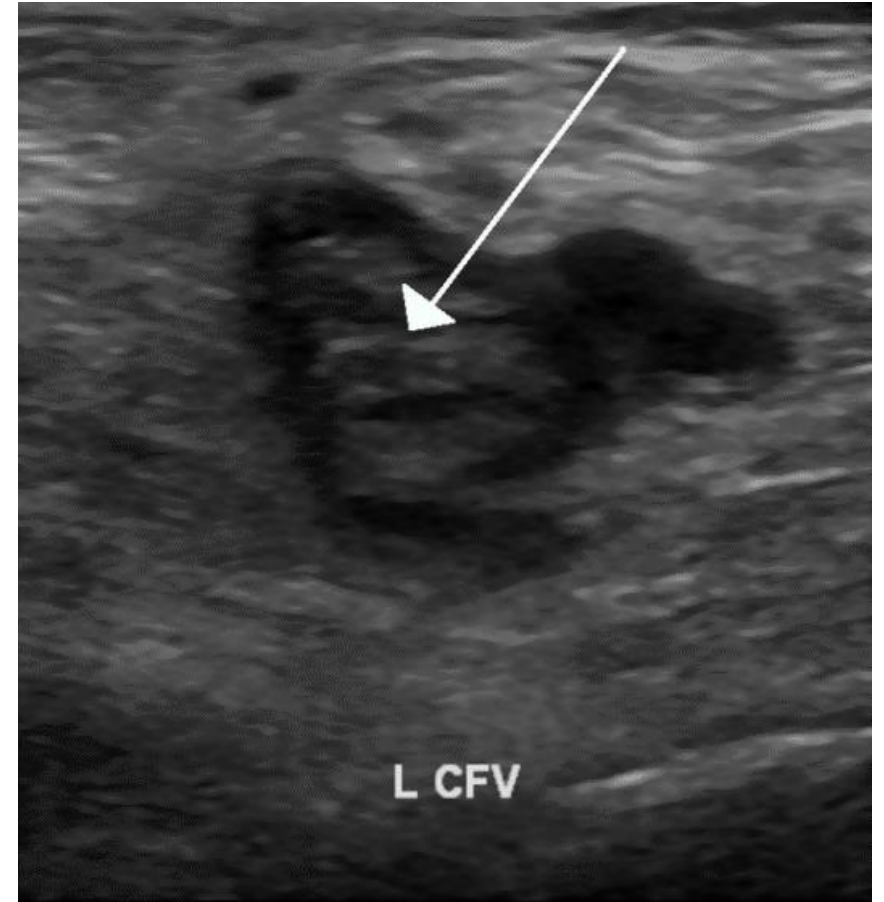
- Decreased risk of ovarian and endometrial cancer
- Menses more predictable and lighter
- Improves acne



# Combination Oral Contraceptives

## Adverse Effects

- Most common: nausea and headache
- **Breakthrough bleeding**
  - More frequent if low estrogen component
  - Does not indicated decreased efficacy
  - Usually resolves spontaneously
- Hypertension (usually mild)
- **Thrombosis**
  - Estrogen increases clotting factors
  - Usually venous thrombosis: DVT/PE
  - Rarely arterial thrombosis: stroke/MI





# Combination Oral Contraceptives

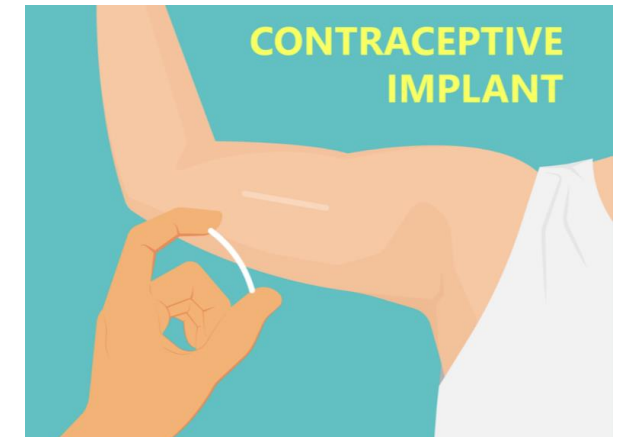
## Estrogen contraindications

- **Smokers > 35 years of age**
- History of DVT, PE, stroke or MI
- Breast cancer
- Hepatocellular adenoma
- Cirrhosis
- Migraine with aura
- Hypertension
  - CDC: systolic  $\geq 140$  mmHg or diastolic  $\geq 90$  mmHg
  - WHO: systolic  $\geq 160$  mmHg or diastolic  $\geq 100$  mmHg



# Postpartum Contraception

- Lactational amenorrhea may occur but unreliable
- Barrier methods can be used
- Estrogen avoided for at least 1 month postpartum
  - Increased risk of thromboembolism
  - Decrease breast milk production
- Common options: IUD or progestin implant
  - Copper IUD may cause bleeding: avoided if ongoing bleeding or anemia
  - LNG IUD may be used but some risk of expulsion
  - Progestin implant often used (more reliable than pills)





# Primary Amenorrhea

Jason Ryan, MD, MPH



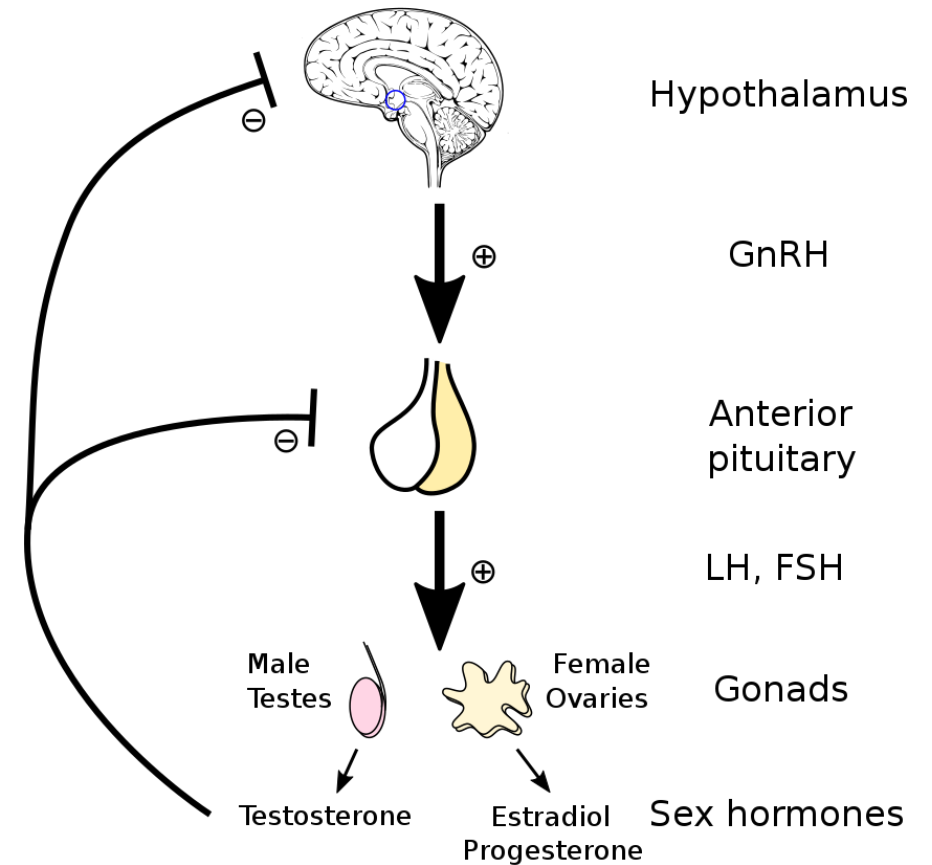
# Amenorrhea

- **Primary amenorrhea**
  - Failure to menstruate by age 15 with normal secondary sexual characteristics
  - Or no menses by age 13 years with absence of secondary sexual characteristics
- **Secondary amenorrhea**
  - Cessation of menses after menarche



# Primary Amenorrhea

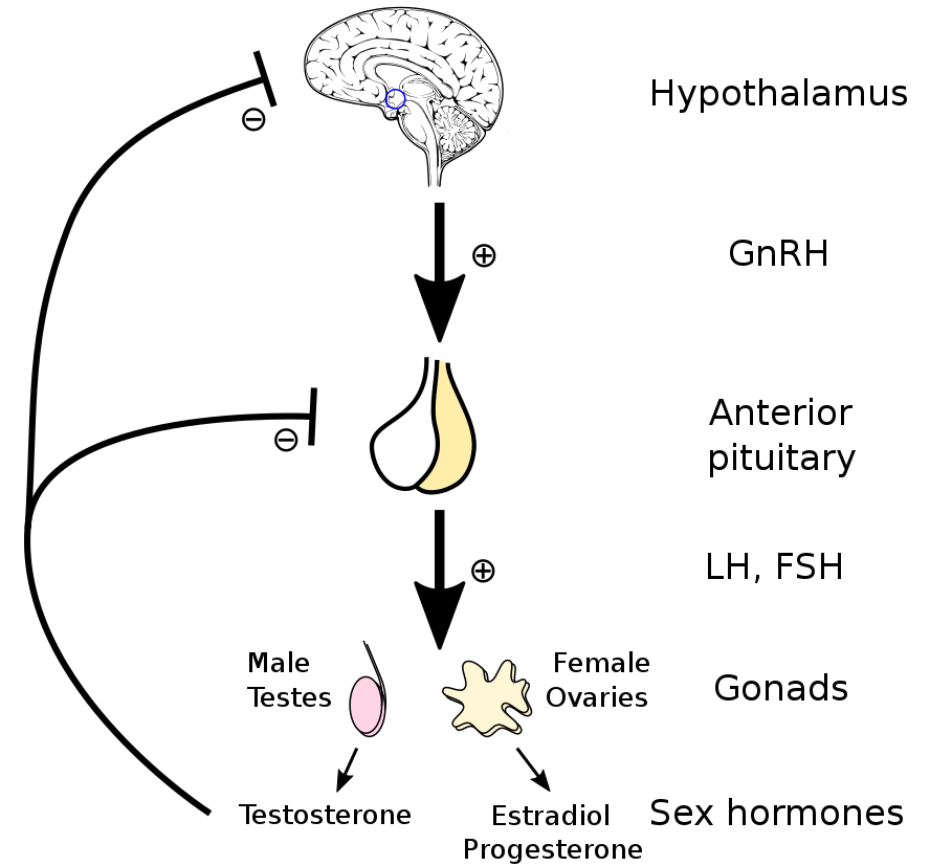
- Pituitary disorders:  $\downarrow$  FSH/LH
- Ovarian disorders:  $\downarrow$  estrogen  $\rightarrow$   $\uparrow$  FSH/LH
- Anatomic disorders: absent vagina/uterus
- Hormonal disorders:  $\downarrow$  synthesis/response
- Must always rule out pregnancy



# Primary Amenorrhea

## Pituitary Disorders

- “Central hypogonadism”
- Functional hypothalamic amenorrhea
- Constitutional delay of puberty
- GnRH deficiency
- Hyperprolactinemia
- Tumors (e.g., craniopharyngioma)



# Functional Hypothalamic Amenorrhea

- More commonly causes secondary amenorrhea
- Decreased GnRH secretion
- Low serum estradiol
- LH/FSH low or normal
- **Risk factors usually present**
  - Eating disorders
  - Excessive exercise
  - Weight loss
  - Stress



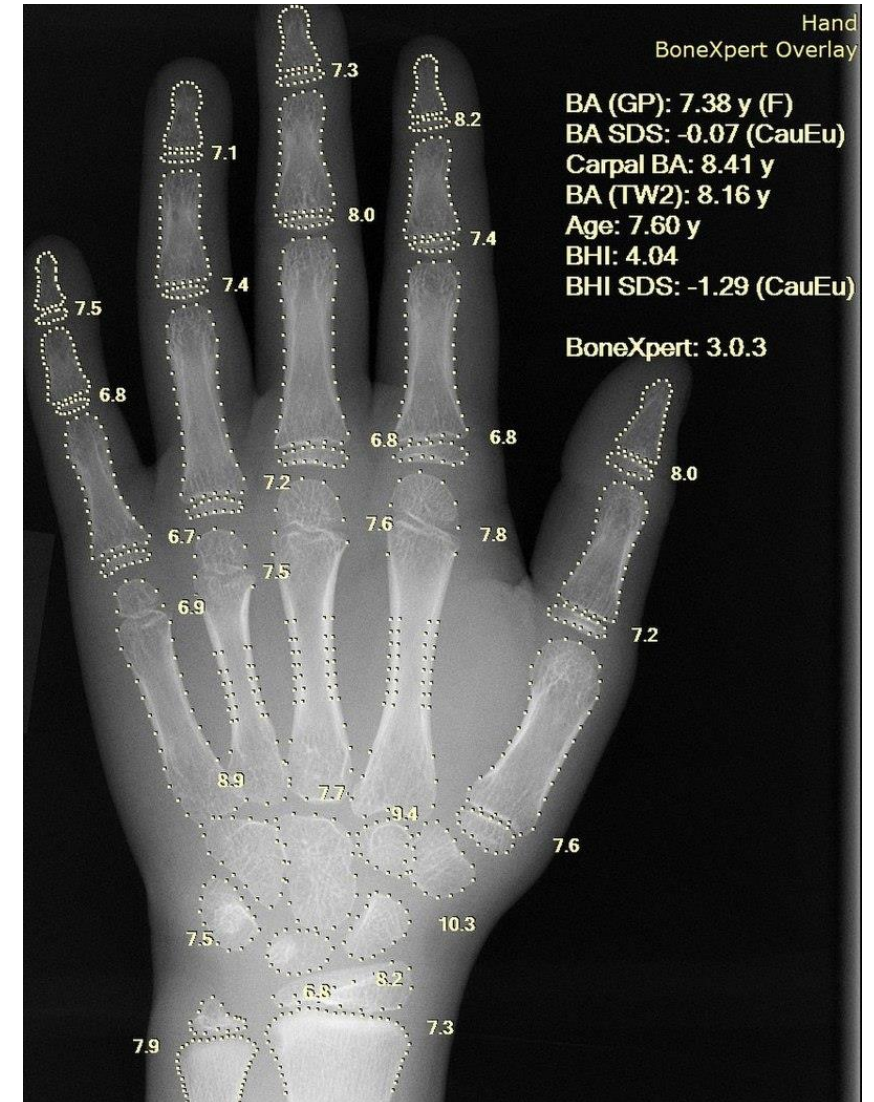
# Constitutional Delay of Puberty

- Most common cause of **delayed puberty**
- **Temporary** defect in GnRH release from hypothalamus
- Much more common in **boys**
- Runs in families with “late bloomers”
- Normal puberty eventually occurs at later age
- Often evaluated with bone age determination



# Bone Age

- X-ray of left hand and wrist
- Bone age determined from population norms
- Used in children with abnormal growth
- Bone age less than chronologic age
  - Seen in constitutional delay of growth and puberty
  - Child should eventually grow
- Bone age identical to chronologic age
  - Seen in familial short stature



# GnRH Deficiency

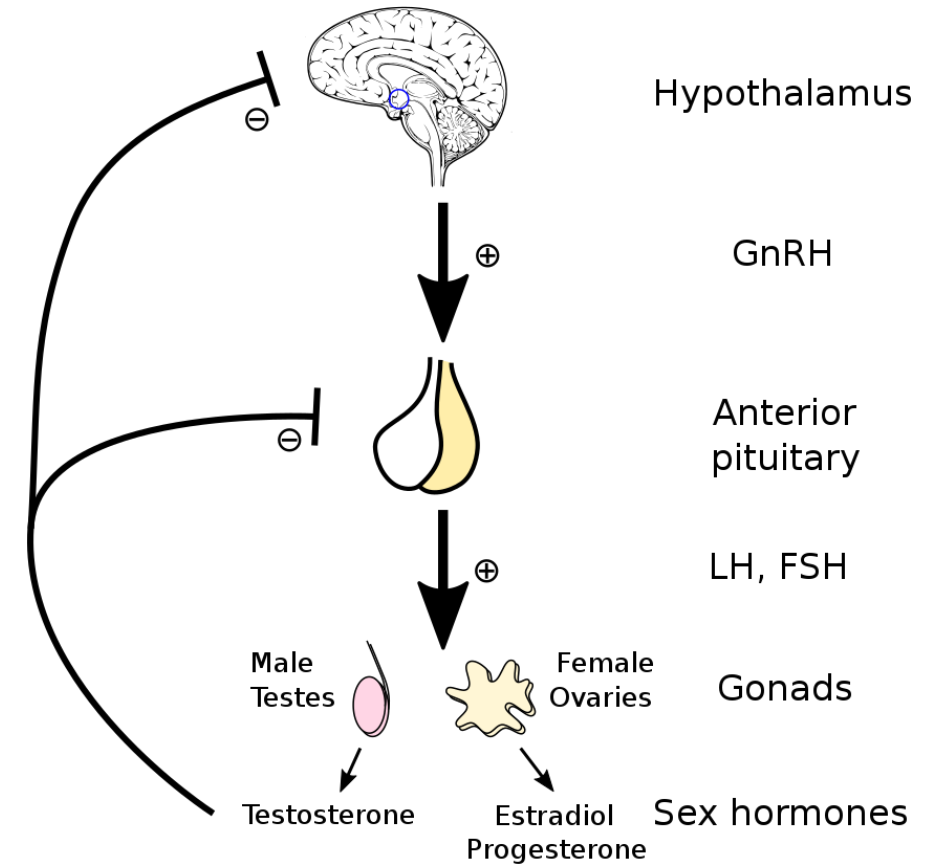
- Idiopathic hypogonadotropic hypogonadism
- **Kallmann syndrome** when associated with anosmia
- Autosomal dominant, autosomal recessive, and X-linked forms
- Much more common in males
- Difficult to distinguished from constitutional delay



# Primary Amenorrhea

## Ovarian Disorders

- Turner syndrome (45,X0)
- Chemotherapy or radiation
- Low estrogen → ↑ FSH/LH



# Mullerian agenesis

- Underdevelopment of Mullerian system
- External genitalia appear normal
- Usually no cervix or uterus
- Shortened vaginal canal
- Small pouch or dimple at vaginal opening



# Mullerian agenesis

- Primary amenorrhea
- Ovaries functional
- Normal secondary sexual characteristics
  - Breasts, pubic hair
  - Normal hormone levels
- Diagnosis: **pelvic ultrasound**
  - Ovaries with no uterus or cervix
- Associated with renal and urinary abnormalities
  - Renal ultrasound or other imaging indicated

Normal Pelvic Ultrasound

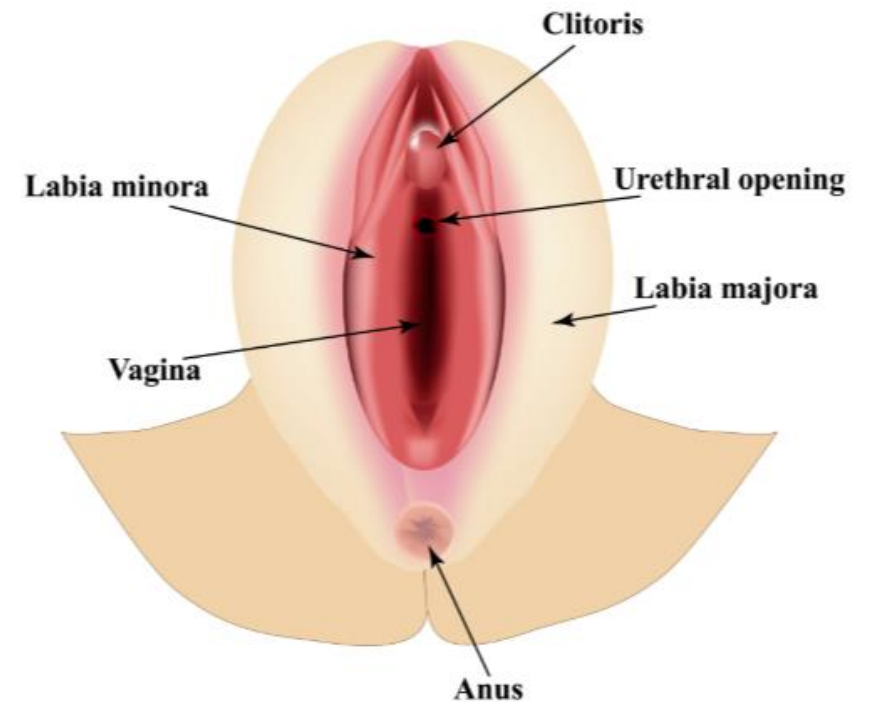


# Primary Amenorrhea

## Lower Genital Tract Lesions

- Imperforate hymen
  - Presents with amenorrhea and pelvic pain
  - Exam: bulging obstruction of the vagina
- Transverse vaginal septum
  - Wall of tissue crossing vagina
  - Presents with amenorrhea and pelvic pain
  - Diagnosis: pelvic examination

ANATOMY OF THE FEMALE EXTERNAL GENITALIA



# Primary Amenorrhea

## Hormonal Causes

- XY individual with female appearance
- No ovaries to cause menstrual cycle
- Androgen Insensitivity
- 5-alpha reductase deficiency

# CAIS

## Complete Androgen Insensitivity Syndrome

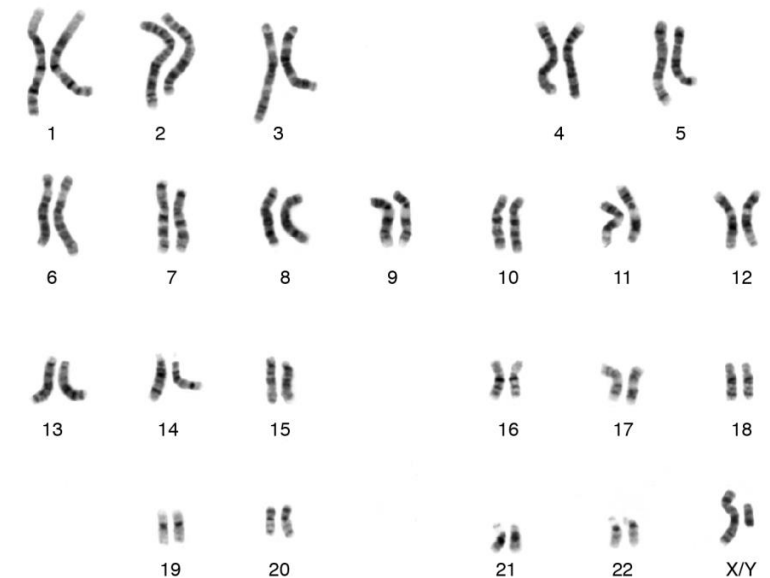
- Mutation of **androgen receptor** in XY individuals
- Testes form in utero - no ovaries
- No cellular response to androgens
- Female external appearance
- No internal or external male genital development
- Sertoli cells (testes) present → Müllerian-inhibiting hormone
- Degeneration of müllerian structures
- Absent uterus, fallopian tubes

# CAIS

## Complete Androgen Insensitivity Syndrome

- Female appearance
- XY chromosomes
- Abdominal testes
- Amenorrhea at puberty (no uterus)
- Increased testosterone at puberty
- No armpit/pubic hair (requires androgen effects)
- Breasts develop (testosterone → estrogen)
- Pelvic ultrasound: **absent uterus**
- Diagnosis: **karyotype plus testosterone level**

Karyotype



# CAIS

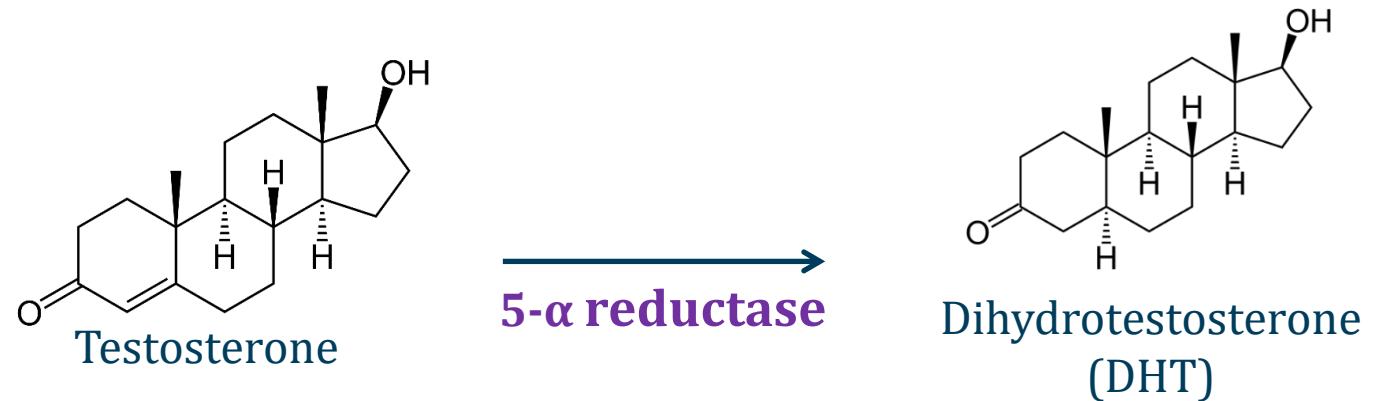
## Complete Androgen Insensitivity Syndrome

- Classic case
  - Primary amenorrhea
  - Breast development
  - Little/no pubic or axillary hair
  - Blind vagina
  - **Ultrasound: no uterus or cervix**
- Testes removed at puberty



# 5- $\alpha$ Reductase Deficiency

- Autosomal recessive disorder
- 46,XY individual able to make testosterone, not DHT
- DHT important for external male genital development
- Testes present  $\rightarrow$  variable location
- Testosterone produced at puberty



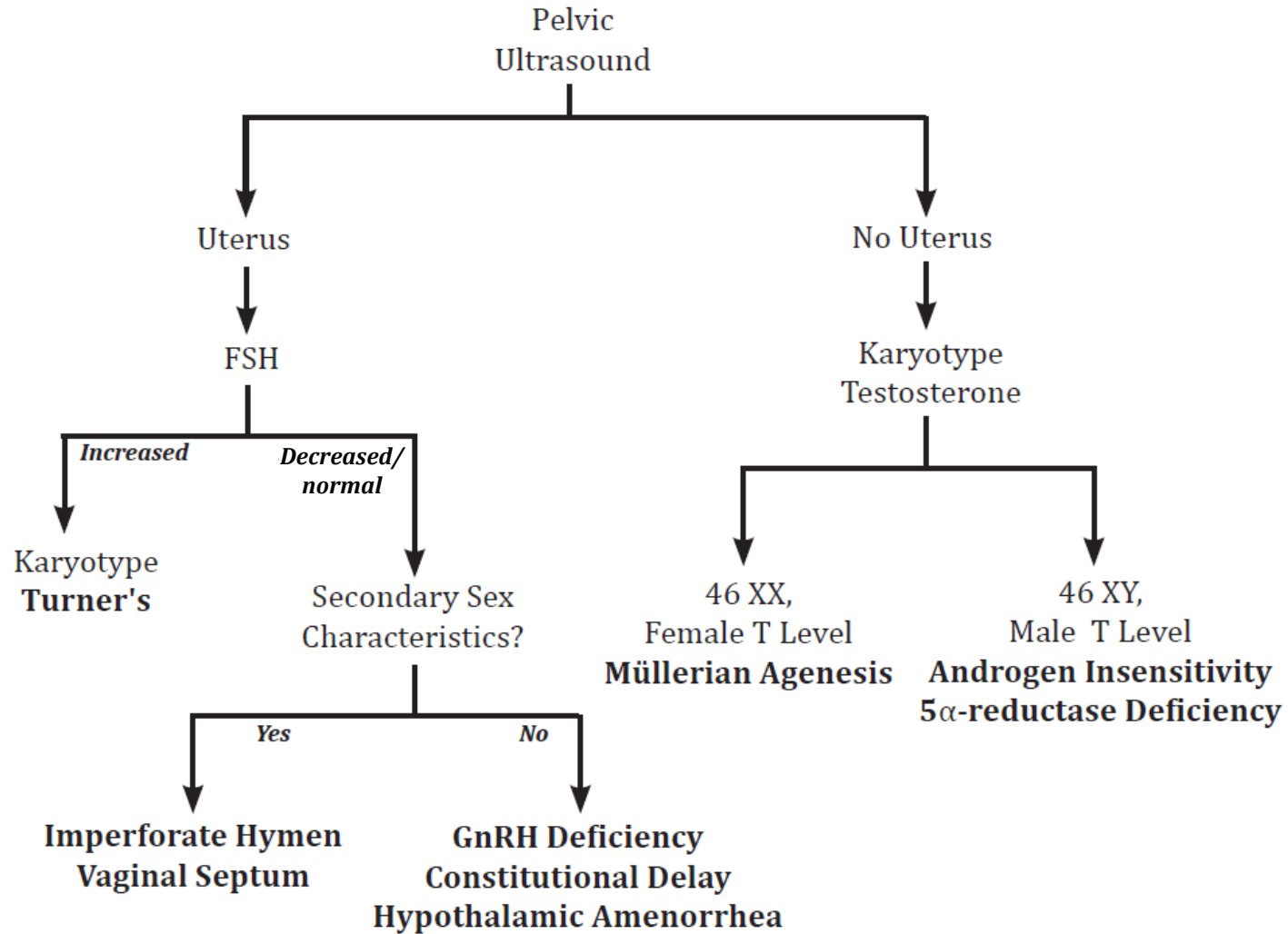
# 5- $\alpha$ Reductase Deficiency

- Normal internal male genitalia
  - Normal epididymis, vas deferens, seminal vesicles
- **Absent external male genitalia**
  - External genitalia predominately female
  - Range of female genitalia seen
  - Sometimes ambiguous genitalia
- Blind-ending vagina
- **Masculinization at puberty**
  - Increased testosterone  $\rightarrow$  muscle growth
  - Some DHT production
  - Hirsutism, deepening of voice, phallic growth

# 5- $\alpha$ Reductase Deficiency

- Diagnosis: **karyotype plus testosterone level**
  - XY chromosomes
  - Male testosterone levels
  - Increased testosterone:DHT ratio
- **Masculinization at puberty** distinguishes from CAIS
  - CAIS: breast development at puberty
  - 5- $\alpha$  deficiency: masculinization

# Primary Amenorrhea



# Secondary Amenorrhea

Jason Ryan, MD, MPH



# Amenorrhea

- **Primary amenorrhea**
  - Failure to initiate menstruation
- **Secondary amenorrhea**
  - Cessation of menses for more than three months (regular cycles)
  - More than six months (irregular cycles)



# Secondary Amenorrhea

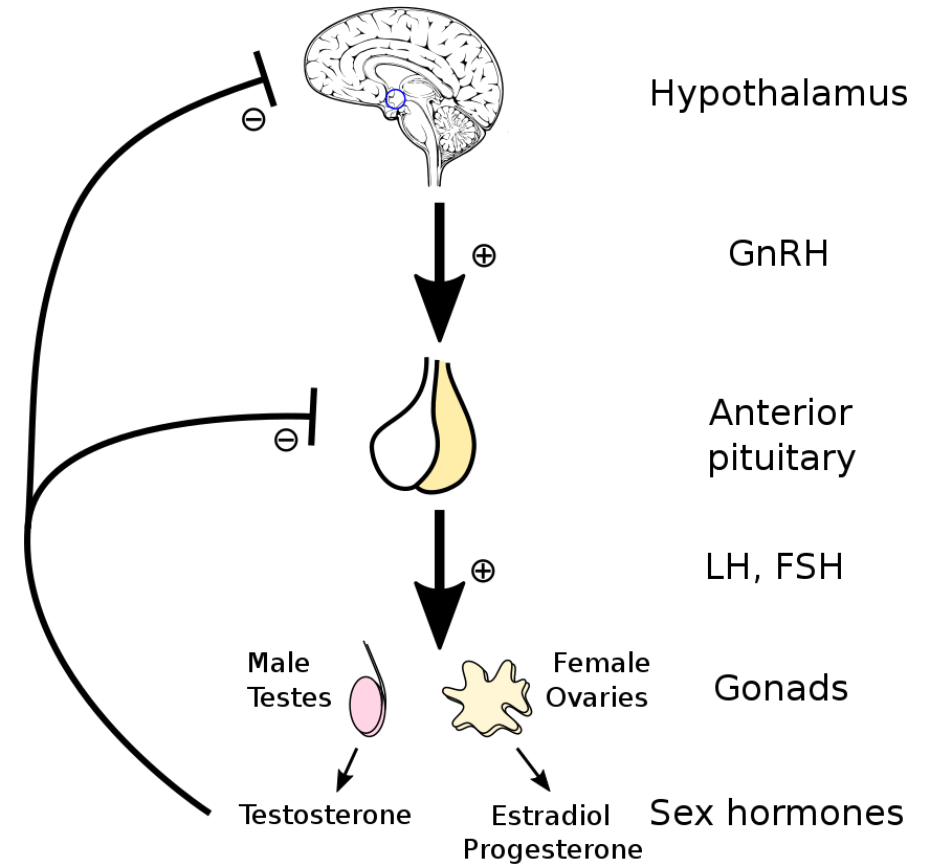
## Causes

- **Pregnancy**
- Most common cause
- Key diagnostic test: hCG



# Secondary Amenorrhea

- Hypothalamus-pituitary disorders
- Ovarian disorders
- Anatomic disorders
- Other causes: thyroid disease, medications

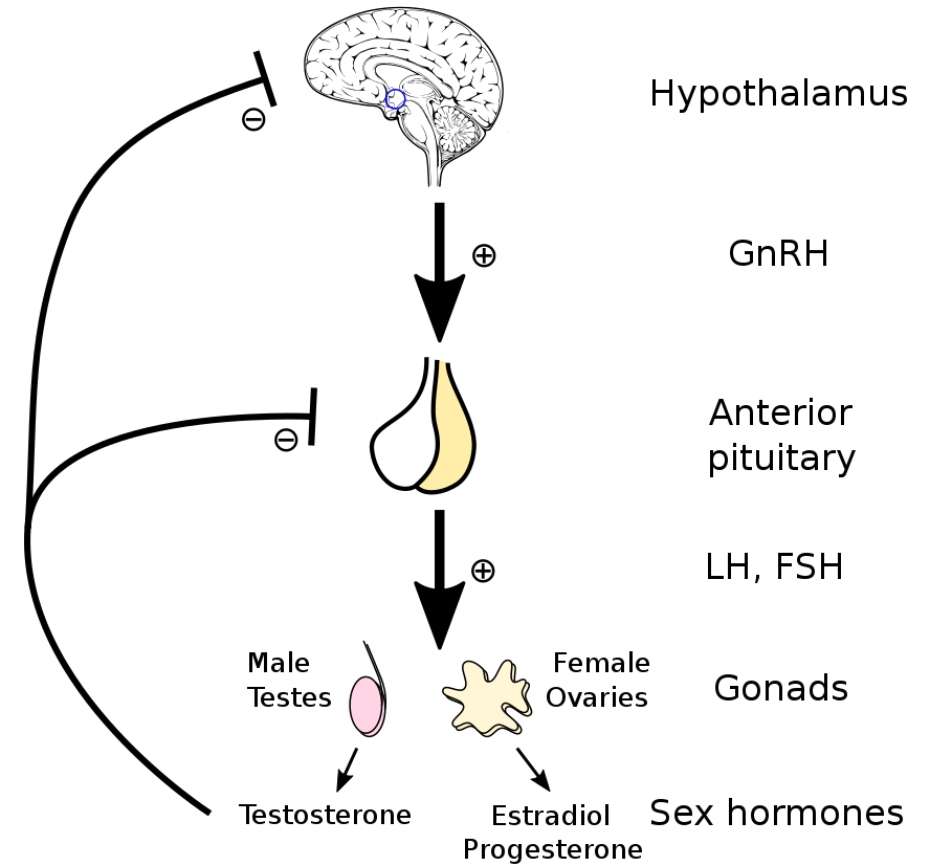




# Secondary Amenorrhea

## Hypothalamic-Pituitary Disorders

- “Hypogonadotropic hypogonadism”
- $\downarrow$  LH/FSH  $\rightarrow$   $\downarrow$  estrogen
- Functional hypothalamic amenorrhea
- Hyperprolactinemia
- Sheehan syndrome
- Tumors



# Functional Hypothalamic Amenorrhea

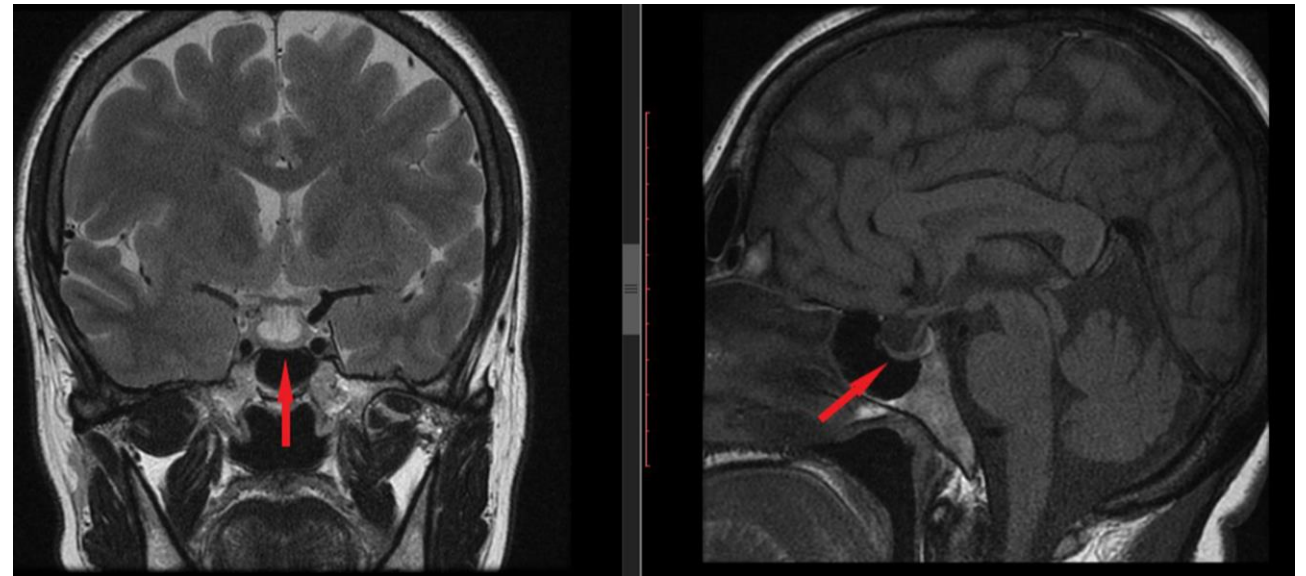
- Decreased GnRH secretion
- LH/FSH low or normal
- Low serum estradiol
- Occurs when body under **stress**
  - Eating disorders
  - Excessive exercise
  - Weight loss
  - Emotional stress



# Hyperprolactinemia

- Inhibits GnRH release → ↓ LH/FSH
- Causes amenorrhea and galactorrhea
- **Prolactinoma**
  - Often only galactorrhea and amenorrhea
  - Headaches or visual loss
  - Diagnosis: MRI
- **Antipsychotic medications**
  - Dopamine blockade → ↑ prolactin

Pituitary MRI

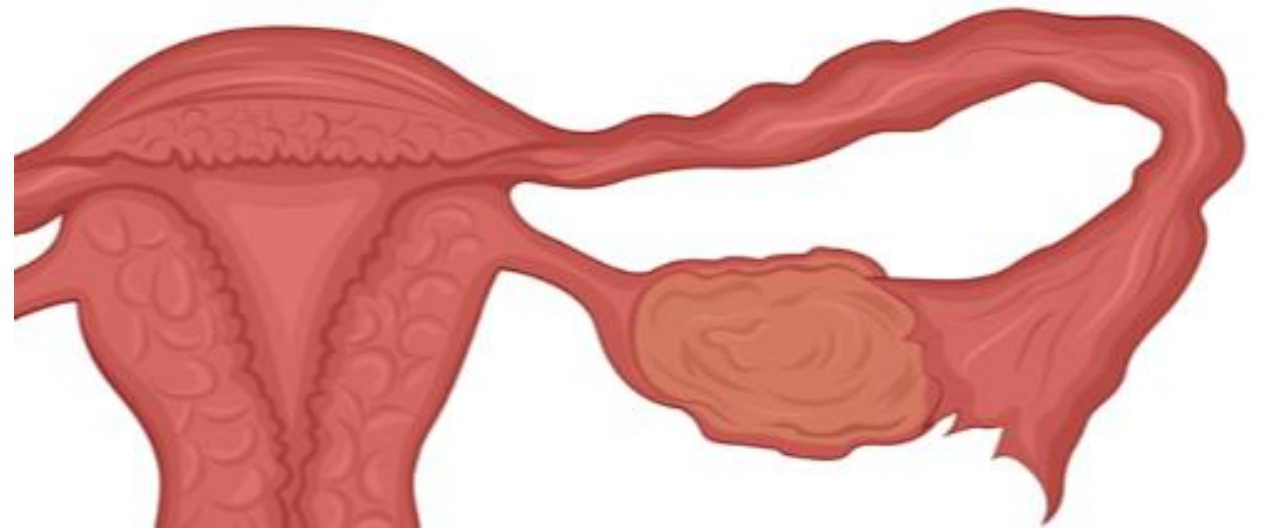


# Secondary Amenorrhea

## Ovarian Causes

- Menopause
- Primary ovarian insufficiency
- Increased FSH and LH

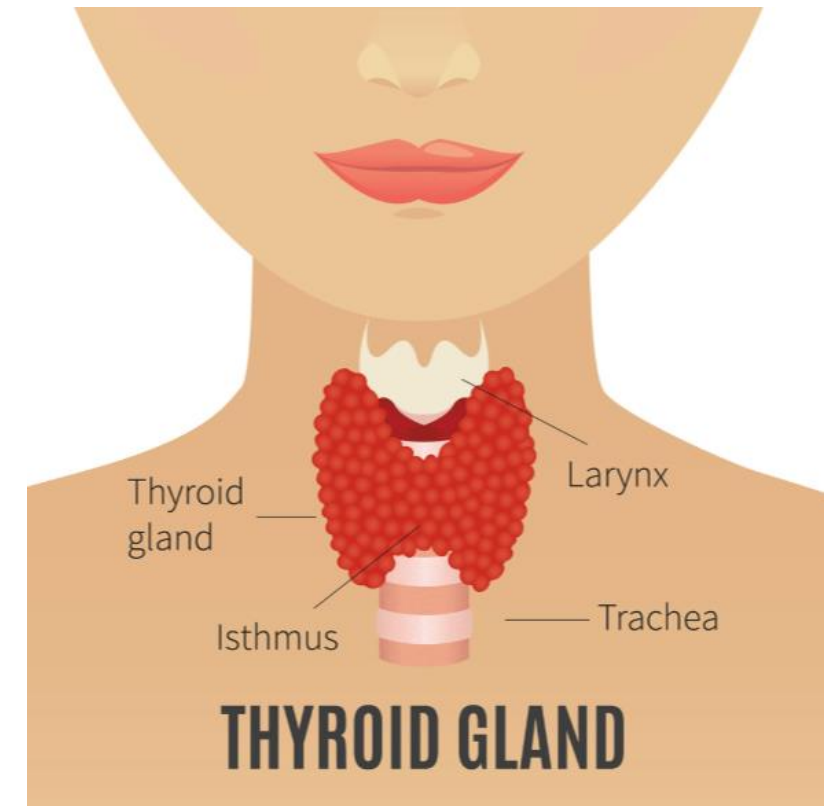
Uterus and Ovary



# Secondary Amenorrhea

## Other Causes

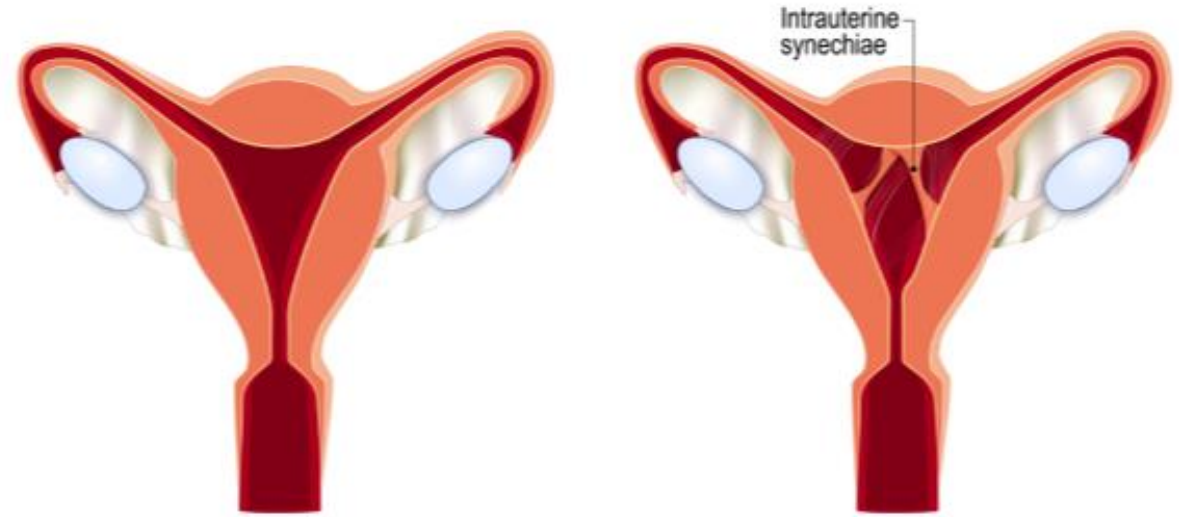
- Thyroid disease
- Hyper and hypothyroid
- Anovulation
- Multiple mechanisms



# Asherman Syndrome

- Uterine adhesions
- Infertility and amenorrhea

## INTRAUTERINE ADHESIONS



Healthy uterus

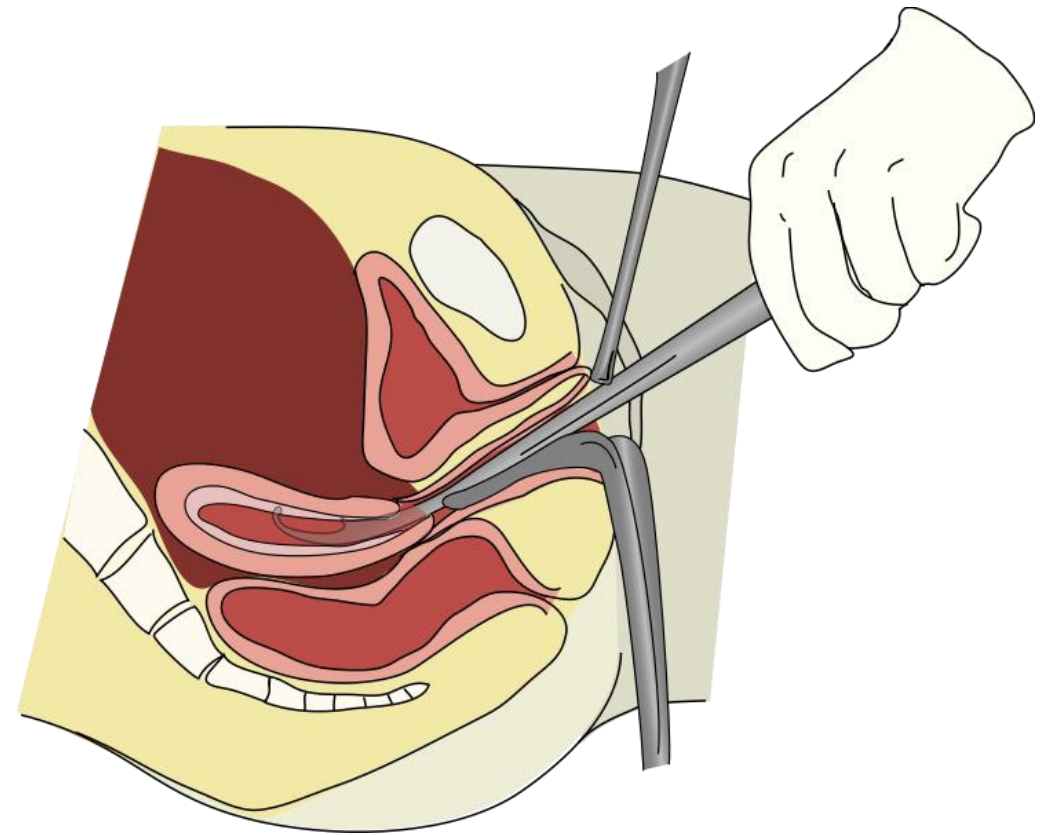
Asherman's syndrome



# Asherman Syndrome

- 90% cases from **uterine curettage**
  - Dilation and curettage (“D&C”)
  - Cervix dilated, uterus scraped with a curette
- Diagnosis: hysteroscopy
- Treatment: lysis of adhesions

Uterine Curettage



# Secondary Amenorrhea

## Other Causes

- Corticosteroids/Cushing syndrome
  - Cortisol suppresses GnRH
  - Low LH/FSH
  - Low estradiol
- Cirrhosis
  - Disruption of hormone metabolism
  - Variable levels of testosterone, estradiol, and prolactin
- Spironolactone
  - Anti-androgen (disrupts estrogen/androgen balance)
  - May stimulate progesterone receptors

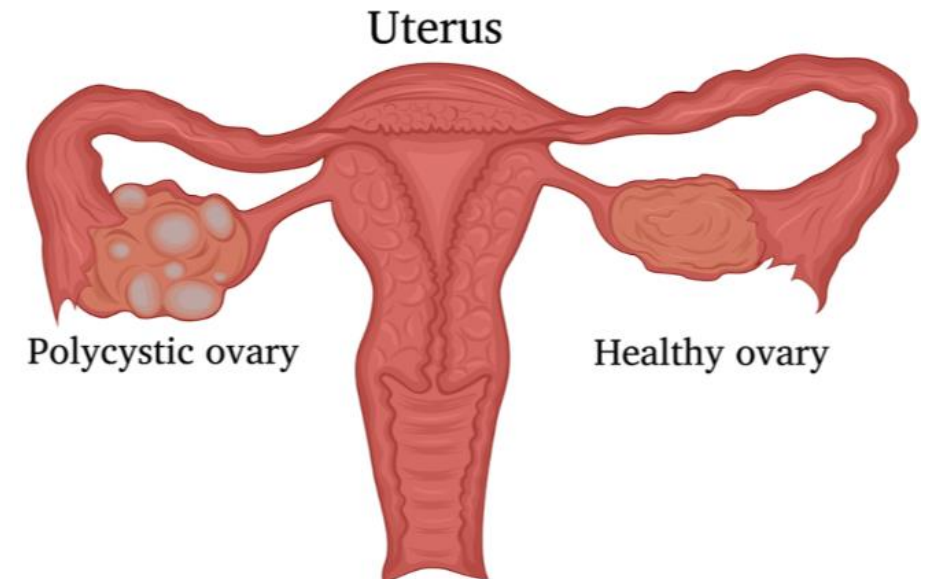


# PCOS

## Polycystic Ovarian Syndrome

- Common cause amenorrhea or oligomenorrhea
- Syndrome of **elevated androgens**
- Genetics plus diet/obesity → ↑ LH:FSH ratio
- LH drives androgen synthesis
- Some androgens → estrogens in adipose tissue
- ↑ estrogens → ↓ FSH → **anovulation**
- Associated with multiple ovarian cysts

## Polycystic ovary



# PCOS

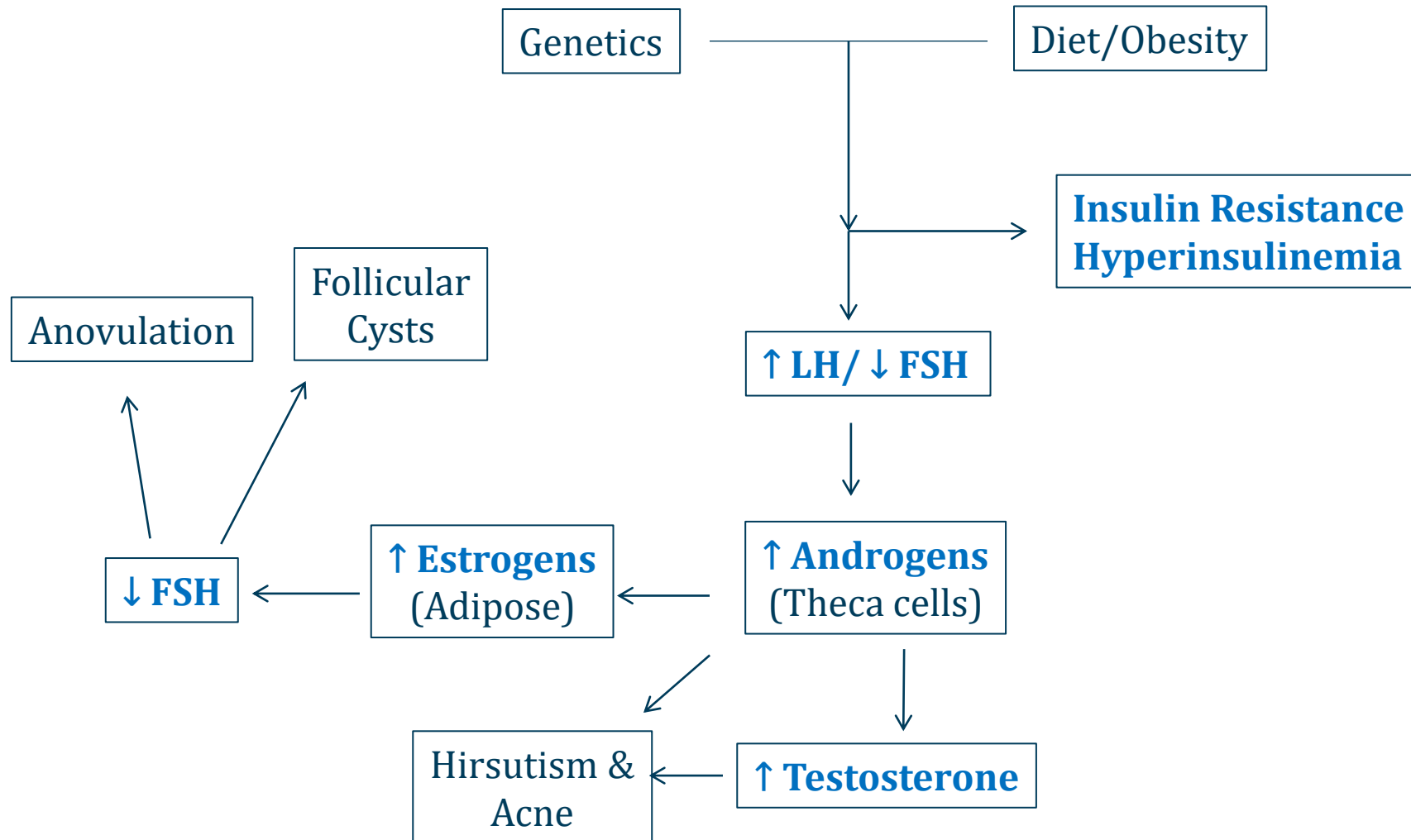
## Clinical features

- Often occurs in obese women
- **Hirsutism** (facial hair)
- Acne
- Amenorrhea or oligomenorrhea
- Infertility (no follicular maturation)
- Ultrasound: multiple follicular cysts
- Causes **insulin resistance**
  - Hyperinsulinemia
  - More than expected for degree of obesity
  - Can lead to diabetes

Hirsutism



# PCOS



# PCOS

## Diagnosis

- Usually diagnosed clinically by **Rotterdam criteria**
- Two out of three required:
  - Oligomenorrhea
  - Signs of hyperandrogenism (hirsutism, acne or  $\uparrow$  testosterone)
  - Polycystic ovaries by ultrasound
- Other potential findings:
  - LH and FSH may be within normal range
  - LH:FSH ratio usually  $> 2:1$  or  $3:1$
  - Increased testosterone
  - Increased estrogens

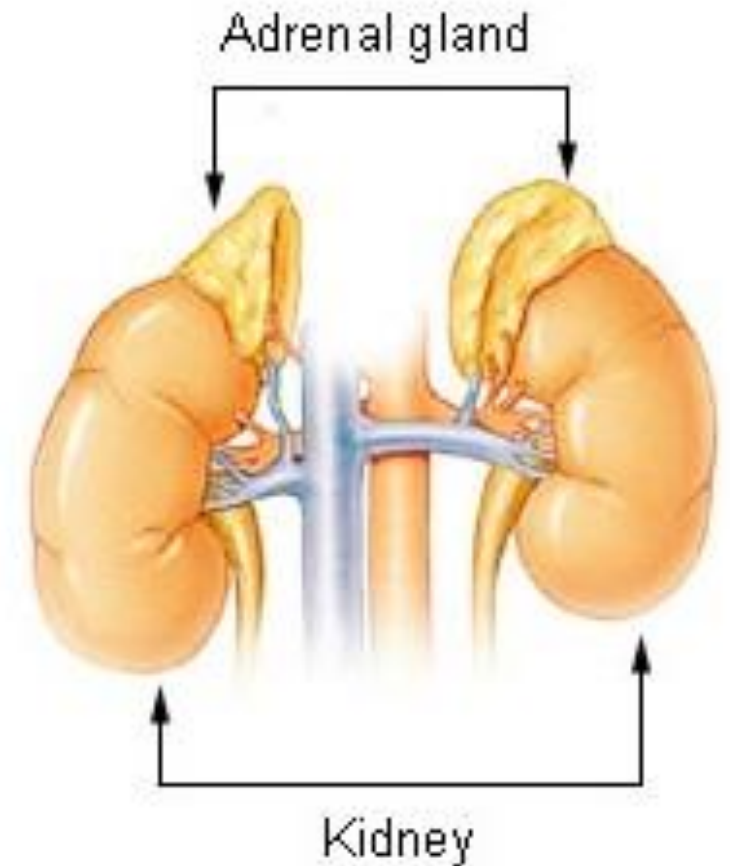
Polycystic Ovary



# PCOS

## Differential diagnosis

- Consider other causes of excess androgen production
- Ovaries will not be polycystic
- **Non-classic congenital adrenal hyperplasia**
  - Measure 17-hydroxyprogesterone
  - High level (greater than 200 ng/dL) suggest NCCAH
- **Androgen-secreting tumors**
  - Ovarian or adrenal tumors
  - Often very high serum testosterone (> 150 ng/dL)

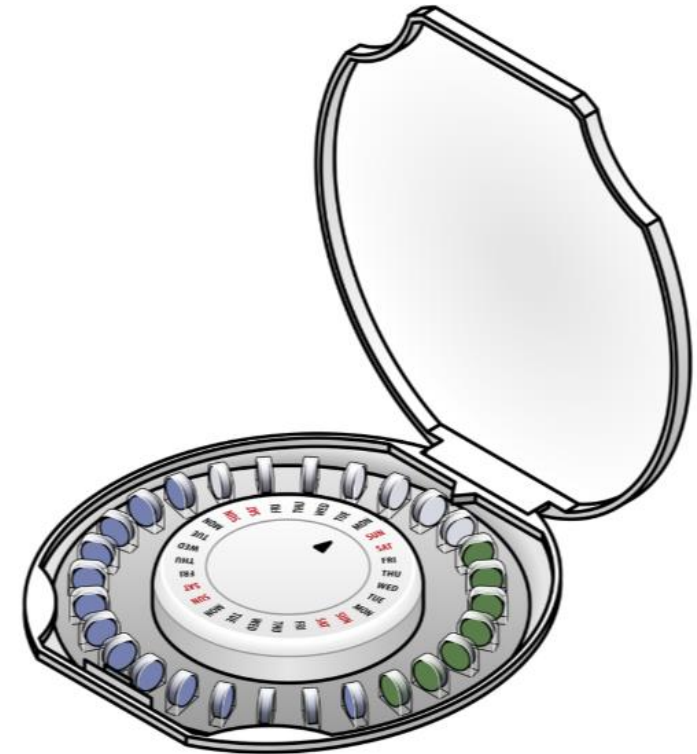


# PCOS

## Treatment

- Weight loss
- **Combination oral contraceptives**
  - Suppress LH → ↓ androgens
- Spironolactone
  - Blocks androgens
- Metformin and thiazolidinediones (glitazones)
  - Diabetes drugs that improve insulin resistance
  - Used only if patient develops diabetes

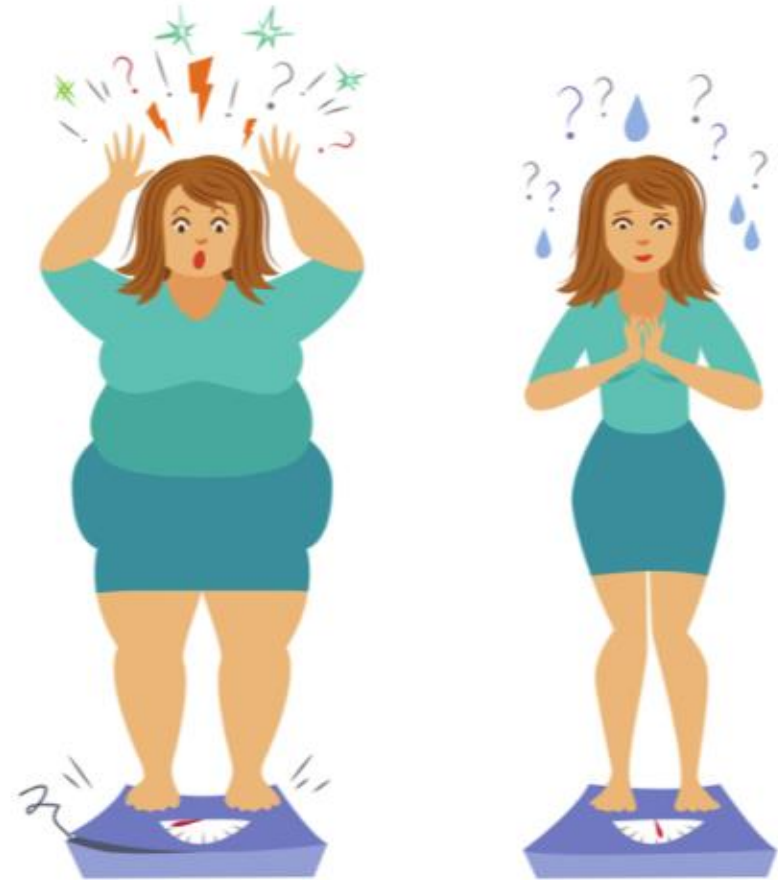
Oral Contraceptive Pills



# PCOS

## Infertility treatment

- First line: **weight loss**
  - Reduces estrogen levels
- Letrozole
- Clomiphene



# PCOS

## Other Features

- Risk of **diabetes**
  - ~10% of women with PCOS develop DM by 40 years old
- Acanthosis Nigricans
  - Plaques of darkened skin
  - Associated with insulin resistance
  - Common in diabetes, PCOS, also gastric cancer
- Endometrial cancer
  - Unopposed estrogen (lack of progesterone)
  - ↑ risk of endometrial hyperplasia and carcinoma

## Acanthosis Nigricans





# Progestin Challenge

## Progestin Withdrawal Test

- Older test for workup of amenorrhea
- Many false positives
- Administration of progestin (oral or IM)
- Observation of menstrual bleeding within 7 days
- If cause of amenorrhea is **anovulation** → bleeding
  - Anovulation → no corpus luteum formation
  - Absence of progesterone release from ovaries
  - Progesterone required for menstruation
  - Exogenous progestins → menstruation

# Progestin Challenge

## Progestin Withdrawal Test

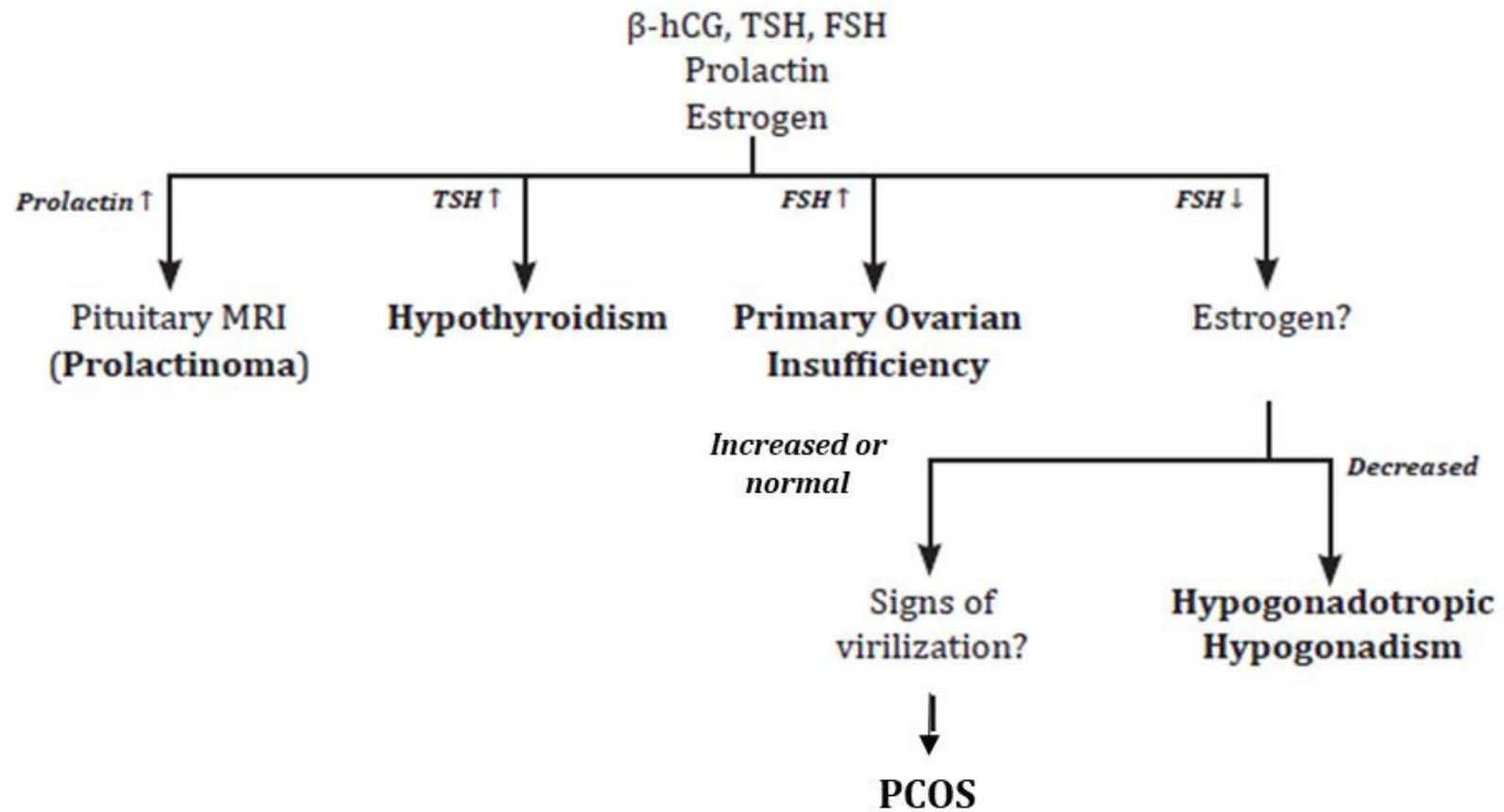
- Bleeding
  - Suggests anovulation
  - Classic cause: **PCOS**
- No bleeding
  - Ovarian failure (no estrogen) – seen in **menopause**
  - Or menstrual outflow problem (uterine adhesions/Asherman syndrome)

# Secondary Amenorrhea

## Key Diagnostic Tests

- $\beta$ -hCG
- Prolactin
- FSH (high in ovarian failure)
- Estrogens
- TSH
- Brain MRI (if elevated prolactin)

# Secondary Amenorrhea



# Dysmenorrhea

Jason Ryan, MD, MPH



# Dysmenorrhea

- **Painful menstruation**
- Primary dysmenorrhea
- Secondary dysmenorrhea



# Primary Dysmenorrhea

- Crampy lower abdominal pain during menses
- No identifiable disease to explain symptoms
- Increased uterine **prostaglandin production**
- Causes contractions and pain
- Treatment:
  - NSAIDs
  - COCs (progestins relax uterus)
  - Heat, exercise, massage



# Secondary Dysmenorrhea

## Historical Clues

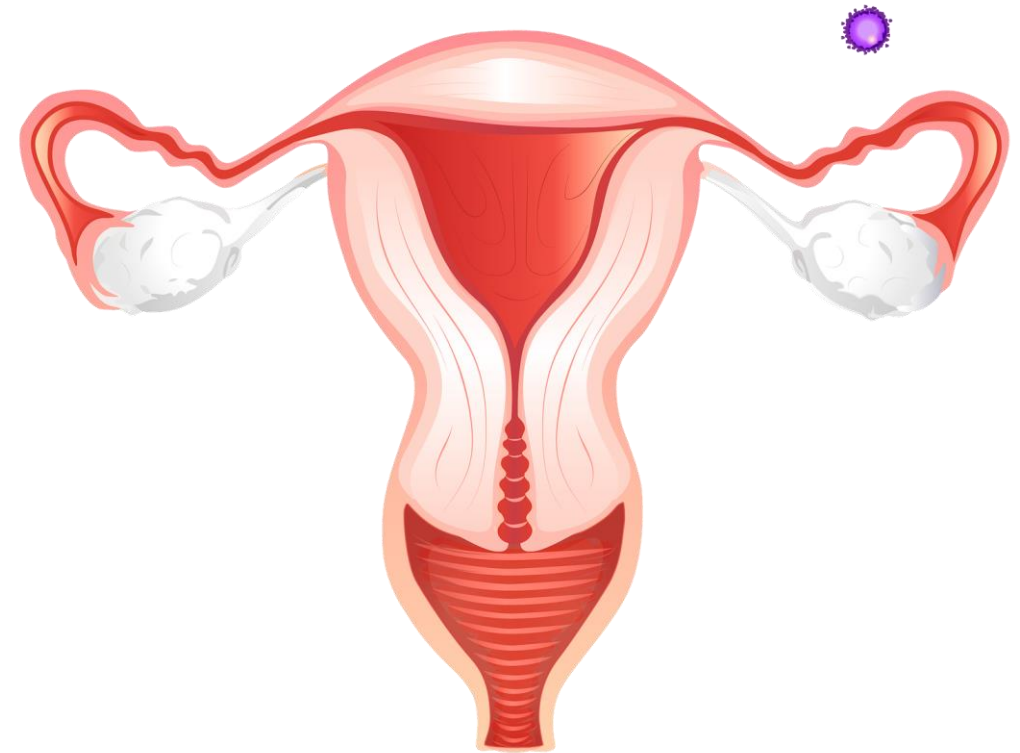
- **Onset at age > 25 years**
- **Non-midline pain**
- No other menstrual symptoms (nausea, fatigue, headache)
- Abnormal uterine bleeding
- Dyspareunia or dyschezia
- Symptom progression over time



# Secondary Dysmenorrhea

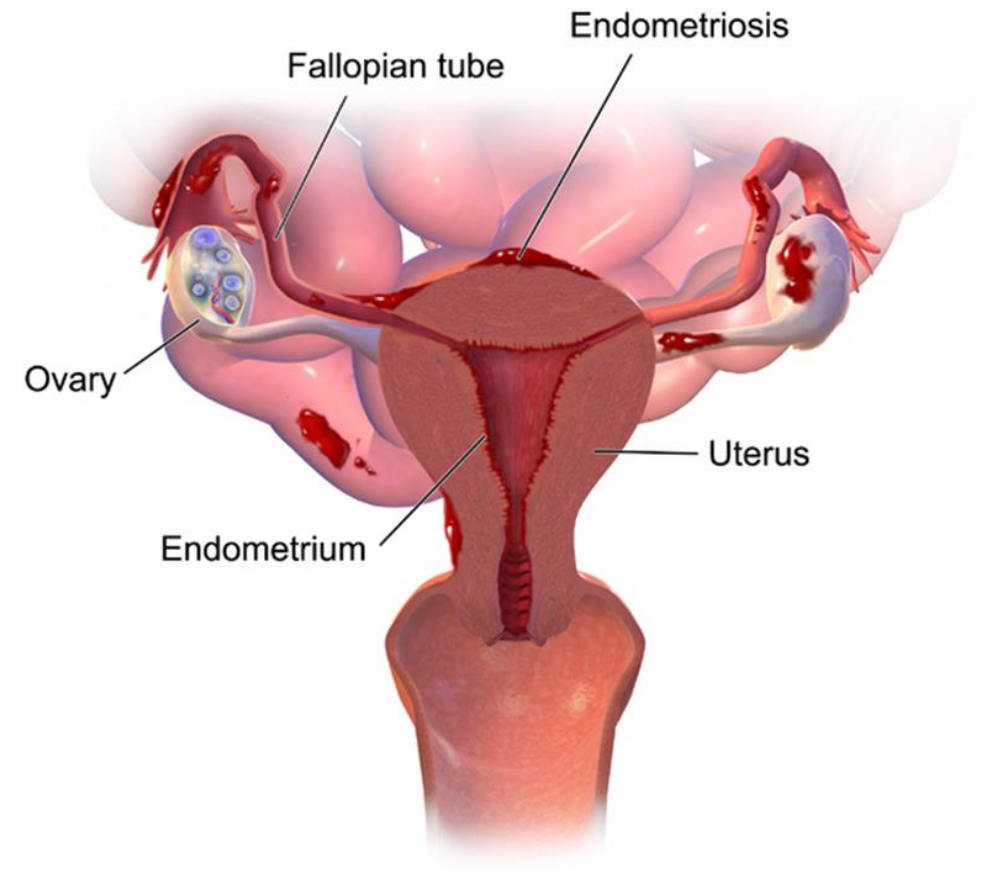
## Selected Causes

- **Endometriosis**
- Adenomyosis
- Pelvic inflammatory disease
- Obstructed menstrual flow:
  - **Fibroids**
  - Uterine adhesions
  - Obstructive polyps
  - Cervical stenosis (post cervical surgery)
- Pregnancy



# Endometriosis

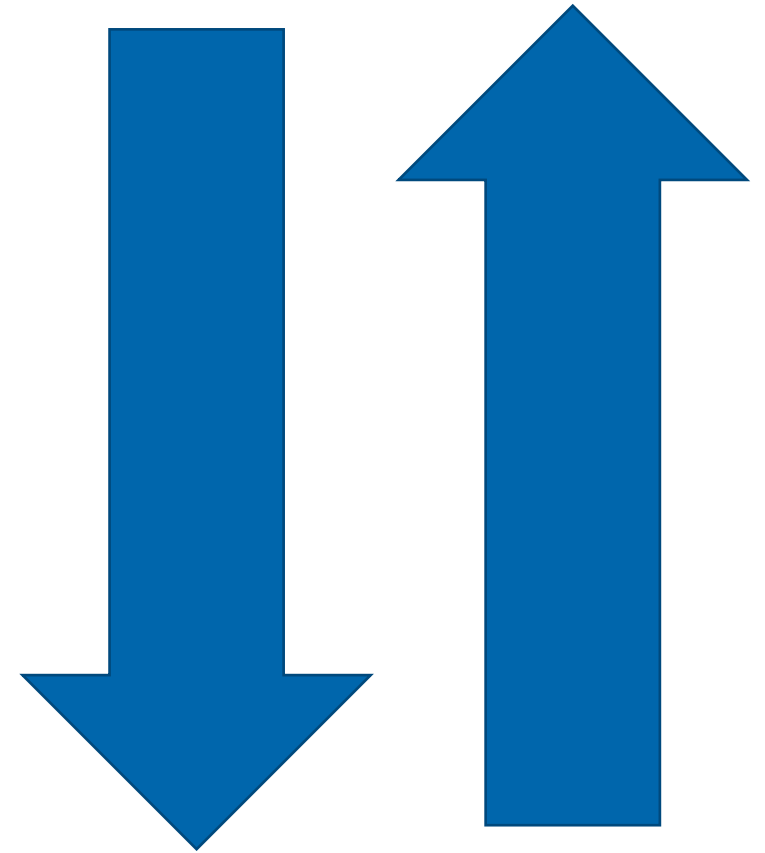
- Endometrial tissue **outside uterus**
- May occur anywhere
- Several common locations
  - Ovaries
  - Cul-de-sac (area behind vagina)
  - Broad and uterosacral ligaments
  - Uterus
  - Fallopian tubes
  - Sigmoid colon or appendix
  - Round ligaments



# Endometriosis

## Pathogenesis

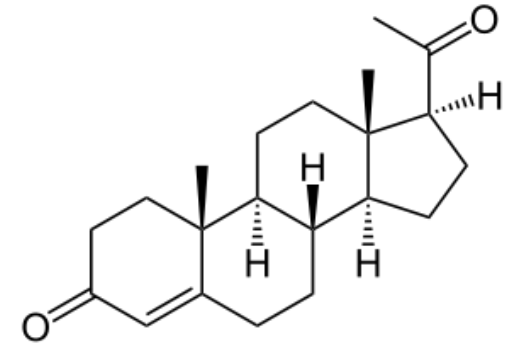
- Exact etiology unknown, several theories
- **Retrograde flow**
  - Movement of menstrual tissue through fallopian tubes
  - Travels to ovaries, peritoneum
- Metastasis
  - Spread through venous or lymphatic system
- Metaplasia
  - Endometrium from coelomic epithelium in development



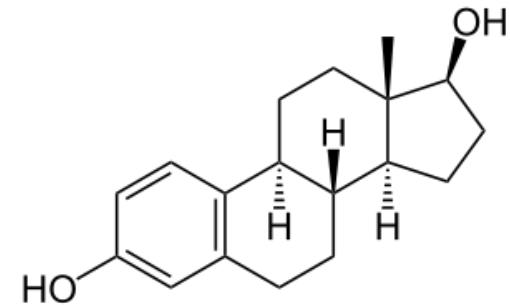
# Endometriosis

## Symptoms

- Ectopic endometrial tissue **hormone-sensitive**
  - Growth from estrogen
  - Atrophy from progesterone
  - Withdrawal bleeding
- Growth, bleeding and inflammation in ectopic sites



Progesterone



Estradiol  
(17β-estradiol)

# Endometriosis

## Classic Symptoms

- **Dysmenorrhea**
  - Cyclic menstrual pelvic pain
  - Classically 1 to 2 weeks before menses
  - Out of proportion to bleeding
- **Dyspareunia**
  - Painful intercourse
  - Ectopic tissue near vagina
- **Infertility**
  - Inflammatory changes impair fertility

# Endometriosis

## Other Clinical Features

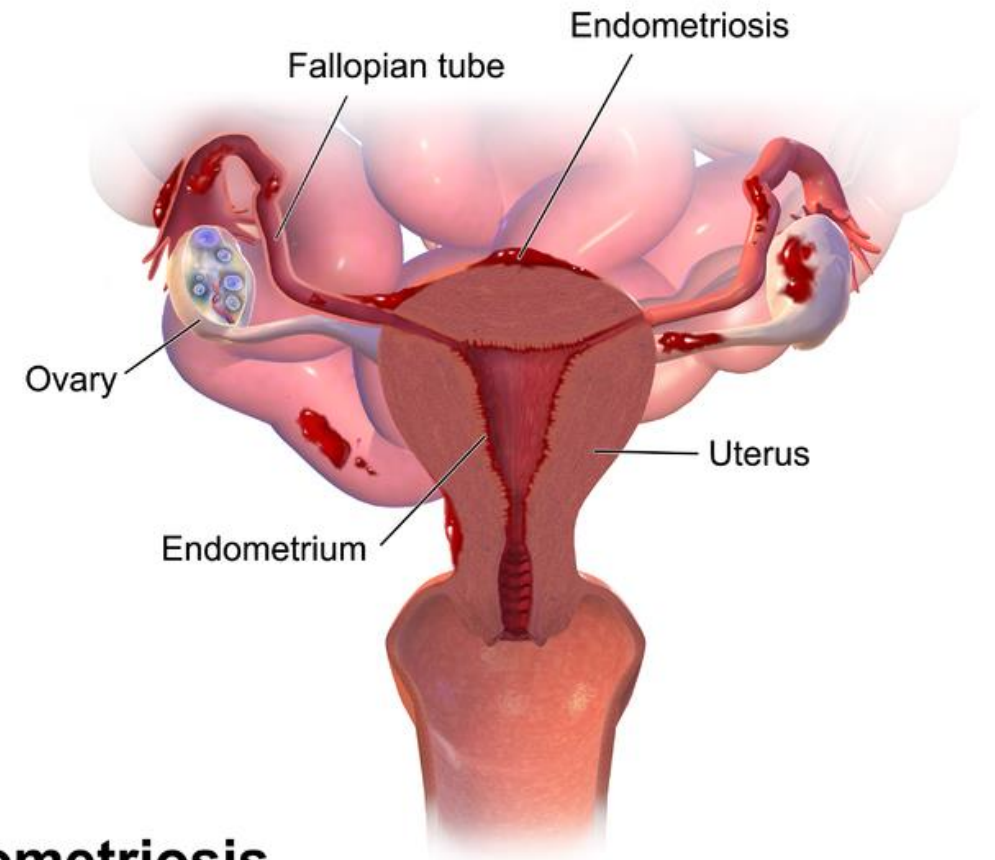
- **Dyschezia**
  - Painful defecation
  - Ectopic tissue near rectum
- **Dysuria**
  - Painful urination
  - Ectopic tissue near bladder
- Improves at menopause and in pregnancy
- Increased risk of ovarian epithelial cancer



# Endometriosis

## Physical Exam

- May be normal
- Vaginal tenderness
- Cervical motion tenderness (dull)
- Nodules along uterosacral ligaments
- Ovarian/adnexal mass

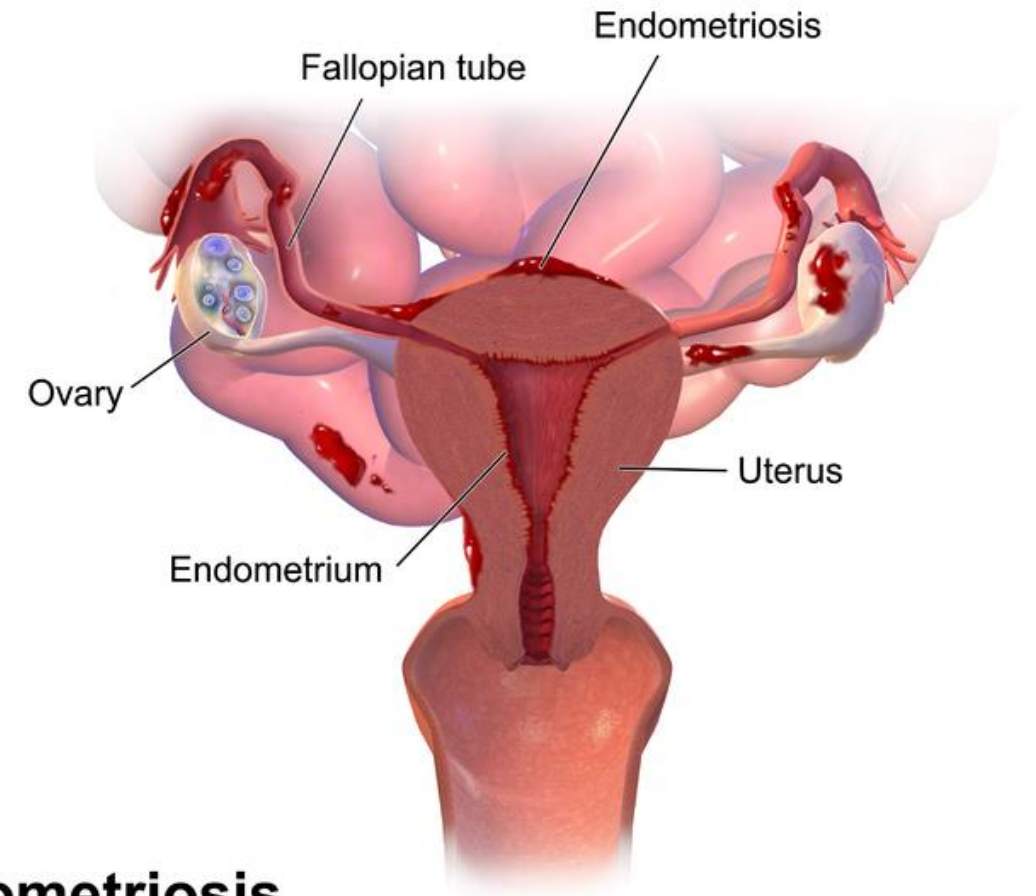


**Endometriosis**

# Endometriosis

## Physical Exam

- **Normal uterus size**
  - Enlarged uterus: adenomyosis
- Anatomic distortions of uterus
  - Lateral displacement
  - Retroverted uterus
  - May be caused by adhesions



## Endometriosis



# Endometriosis

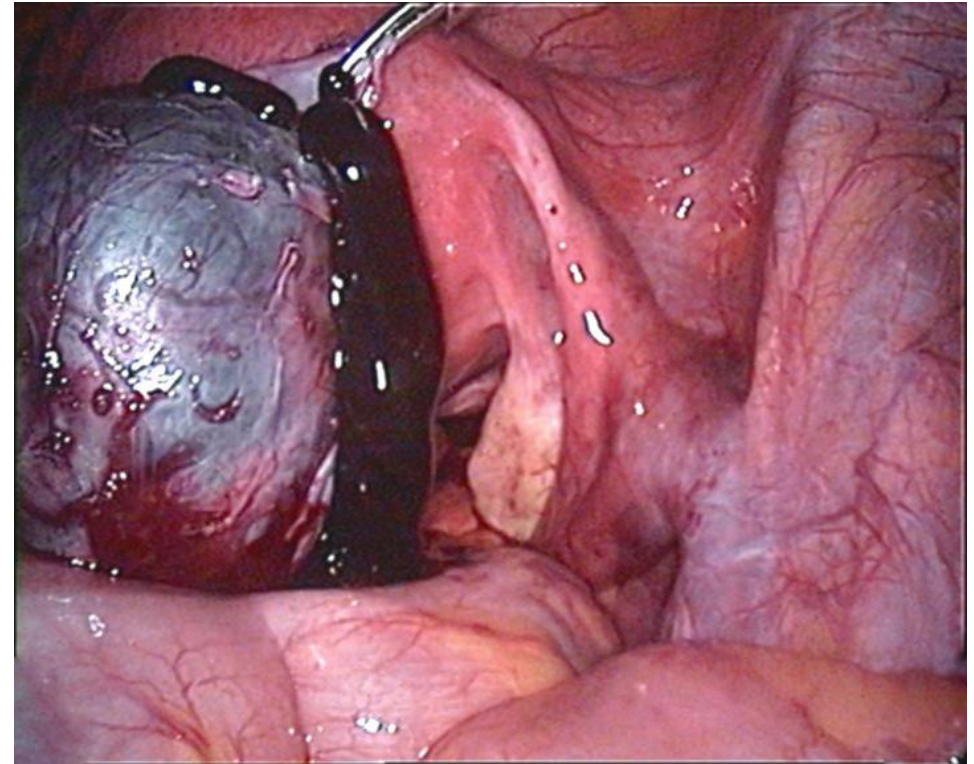
## Imaging

- **Pelvic ultrasound**
- Endometriomas
- Nodules
- Sliding sign
  - Pressure with probe
  - Rectum and sigmoid colon should slide across uterus, cervix and vaginal wall
  - Normal sliding = “positive” sliding sign
  - “Negative” sign = obliteration of the pouch of Douglas by adhesions
  - Indicates advanced endometriosis

# Endometriosis

## Diagnosis

- Often treated empirically based on symptoms
- Definitive diagnosis: **biopsy of lesion**
  - Often requires surgical exploration
  - Laparoscopy or laparotomy
  - Biopsy will show endometrial tissue (glands, stroma)
- May lead to a **chocolate cyst**
  - Endometrioma
  - Ectopic tissue in ovary bleeds
  - Forms hematoma surrounded by adhesions
  - Syrup-like chocolate material in cyst



# Endometriosis

## Treatment

- **Combination oral contraceptive pills (COCs)**
  - First line therapy
  - Suppress LH/FSH release → ↓ ovarian function
  - Cause atrophy of endometrial tissue
  - May be taken continuously (no placebo period)
- Progestin-only therapy
  - Also effective in women who cannot take estrogens
- Nonsteroidal anti-inflammatory drugs (NSAIDs)



# Endometriosis

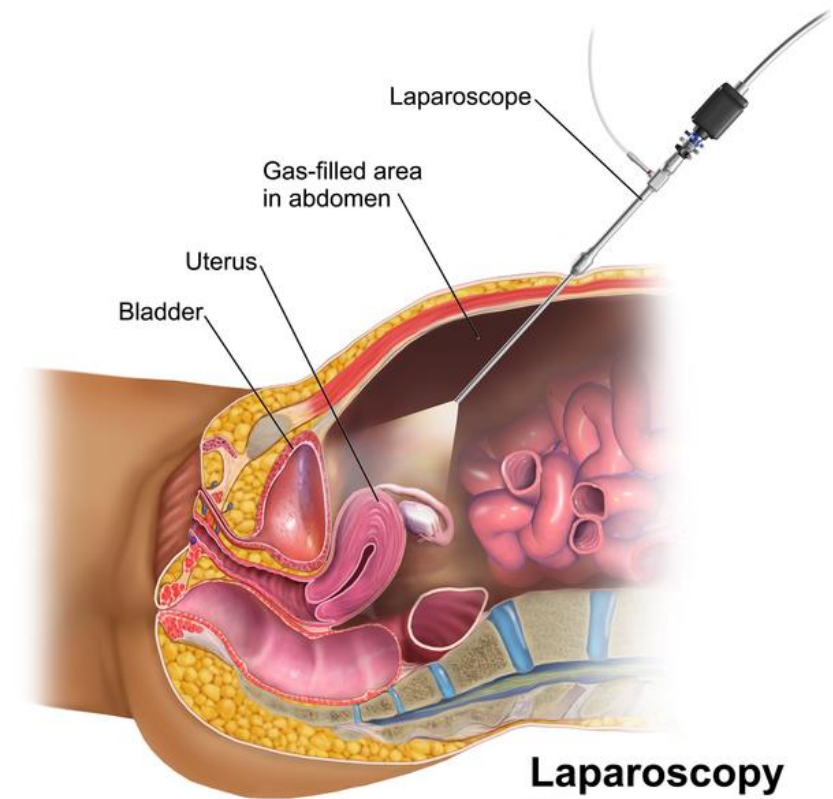
## Treatment

- **GnRH antagonists – elagolix (Orilissa)**
- Suppress pituitary LH/FSH production
- Create “hypoestrogenic” state
- Improves endometriosis-related pain
- Effective immediately (contrast with GnRH agonists)
- May cause hot flashes and night sweats

# Endometriosis

## Treatment

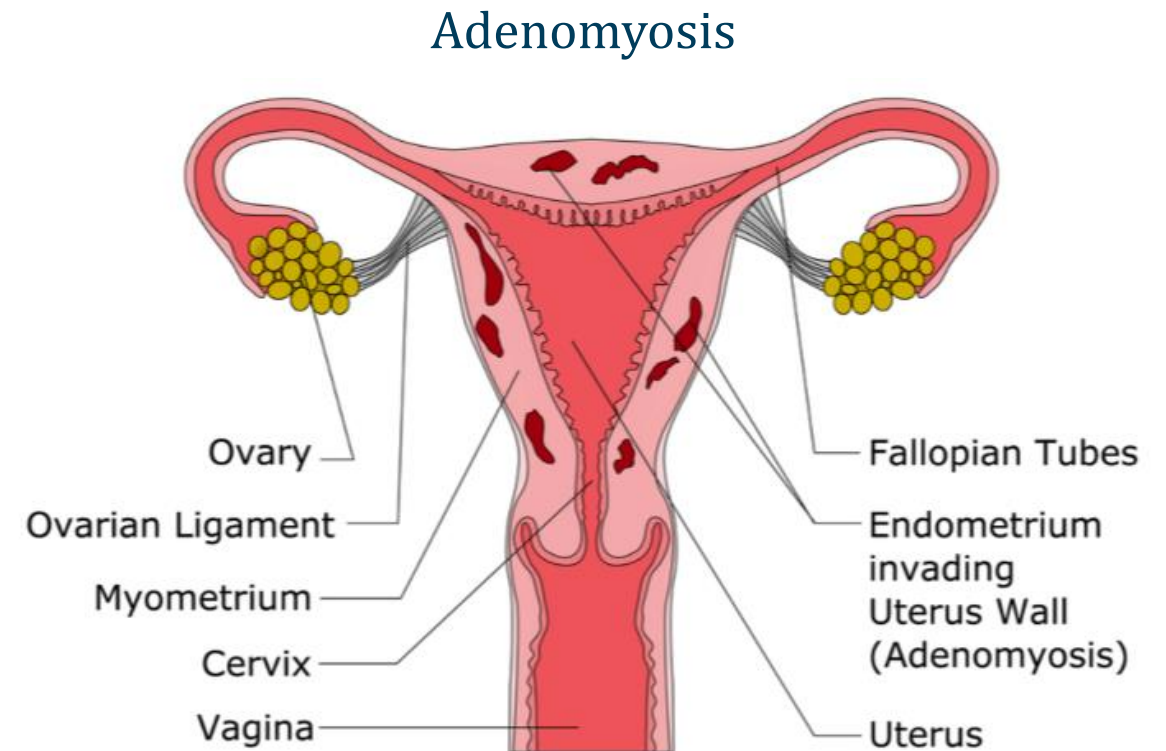
- Can be treated with **surgical removal**
- Reserved for refractory cases
- Usually done laparoscopically
- Often used after failed medical therapy
  - Establishes definitive diagnosis
  - Rules out other pathology
  - Potential to remove endometrial tissue
- Post-surgery progesterone if not desiring pregnancy
  - Often levonorgestrel IUD
  - Suppresses residual disease





# Adenomyosis

- Endometrial glands and stroma in **myometrium**
- Diffuse or segmental uterine enlargement
- “Globular” or “boggy” uterus on exam
- Menorrhagia (heavy menstrual bleeding)
- Dysmenorrhea
- Often co-exists with endometriosis





# Adenomyosis

## Workup

- Suspected based on symptoms and enlarged uterus
- Best first test: **transvaginal ultrasound**
- Alternative: MRI
- Abnormal thickening of myometrium

Adenomyosis MRI



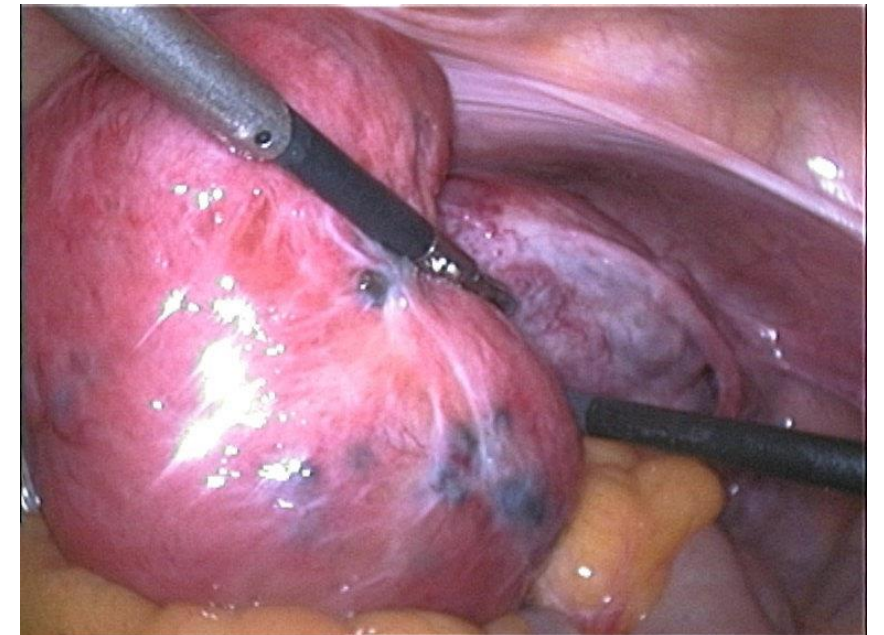


# Adenomyosis

## Treatment

- Definitive treatment: **hysterectomy**
- If continued childbearing desired: progestins
  - Usually levonorgestrel IUD
  - Generates local progestin activity
  - Improves menstrual bleeding and dysmenorrhea
  - Discontinued when patients wishes to conceive
- Other treatment: GNRH agoinsts, SERMs, NSAIDs
- Uterine artery embolization

Adenomyosis at Hysterectomy



# Dysmenorrhea

## Workup

History, Exam,  $\beta$ -hCG, STD screen  $\pm$  US

↓ Normal/Benign

Trial of COCs, progestins or NSAIDs

↓ No Improvement

Pelvic Imaging (US/MRI)  
Hysteroscopy  
Possible chronic pelvic pain syndrome

# Abnormal Uterine Bleeding

Jason Ryan, MD, MPH



# Abnormal Uterine Bleeding

- **Normal menstruation**

- Based on FIGO MDC definitions
- International Federation of Gynecology and Obstetrics Menstrual Disorders Committee
- Occurs every 24 to 38 days
- Variation less than 7 to 9 days
- Lasts up to 8 days
- Less than 80 ml of blood loss (difficult to assess)
- Abnormal uterine bleeding: variation from normal

# Abnormal Uterine Bleeding

- Frequent uterine bleeding: more often than every 24 days
- Infrequent uterine bleeding: less often than every 28 days
- Prolonged menstrual bleeding: more than 8 days
- Heavy menstrual bleeding: more than 80 ml per cycle (difficult to assess)
- Older terms:
  - Menorrhagia: heavy or prolonged bleeding
  - Metrorrhagia: bleeding between normal menses
  - Menometrorrhagia: heavy bleeding between normal menses
  - Oligomenorrhea: irregular cycles > 35 days apart

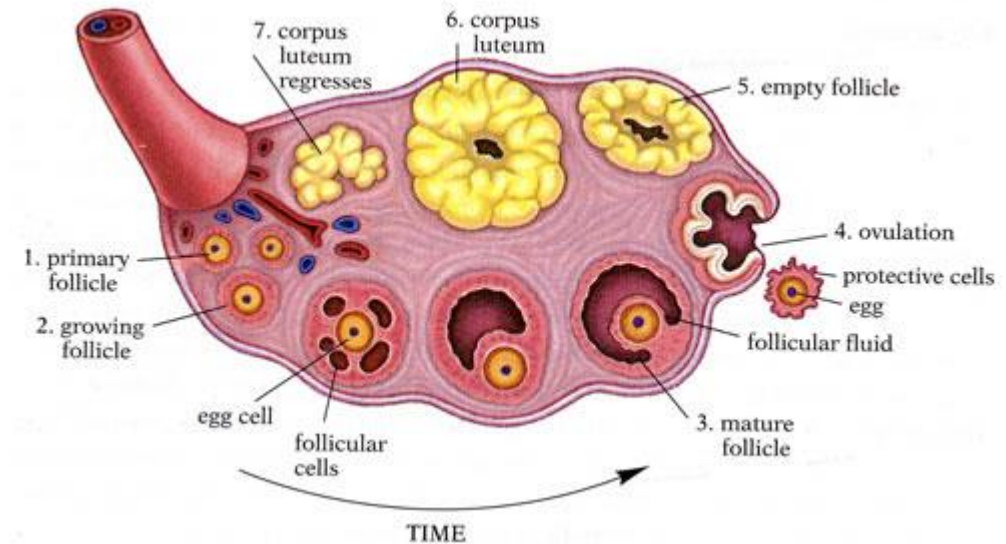
# Abnormal Uterine Bleeding

- **P**olyps
- **A**denomyosis
- **L**eiomyoma
- **M**alignancy/hyperplasia
- **C**oagulopathy
- **O**vulatory dysfunction
- **E**ndometrial causes
- **I**atrogenic (IUD, drugs)
- **NOS**

# AUB-O

## Abnormal Uterine Bleeding Due to Ovulatory Dysfunction

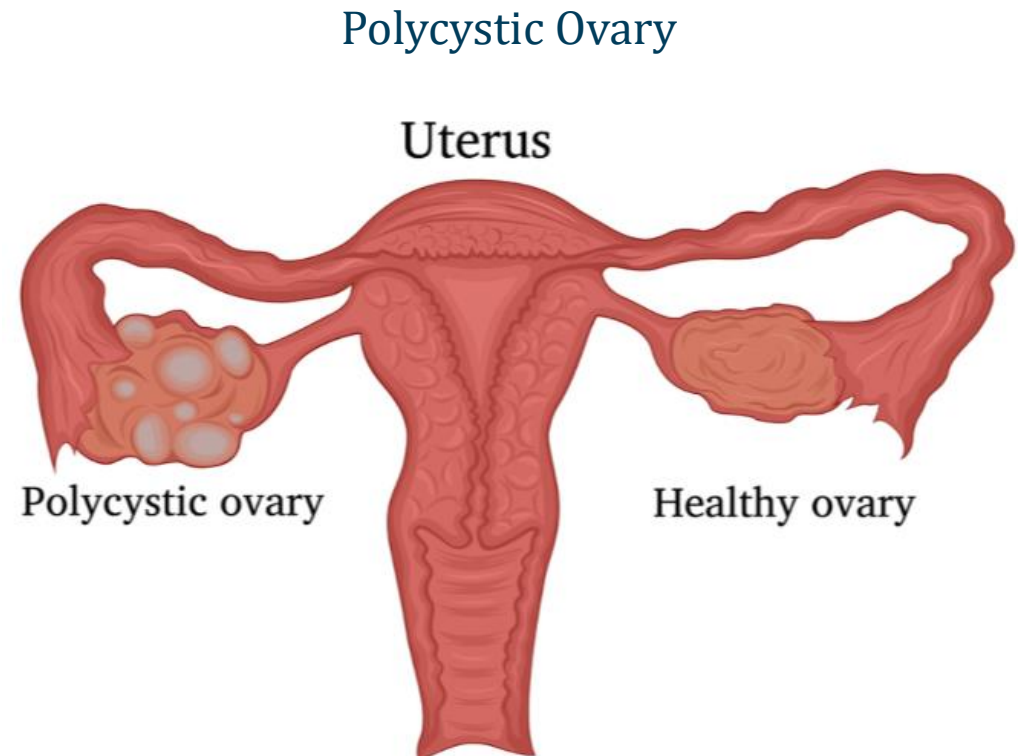
- Menstrual cycle without ovulation
- No corpus luteum formation
  - Absence of luteal phase of ovary
  - No switch to progesterone secretion
- Excessive endometrial growth from estrogen
- “Unopposed growth” from lack of progesterone
- **Irregular bleeding**
- No bleeding for one or more months
- Other phases with spotting or heavy bleeding



# AUB-O

## Abnormal Uterine Bleeding Due to Ovulatory Dysfunction

- Common at menarche
  - Underdeveloped hypothalamus-pituitary-ovary axis
- Common approaching menopause
  - Loss of ovulation
  - Continued estrogen production
- Also may result from other disorders
  - PCOS
  - Obesity
  - Thyroid disease
- Treatment aimed at underlying cause

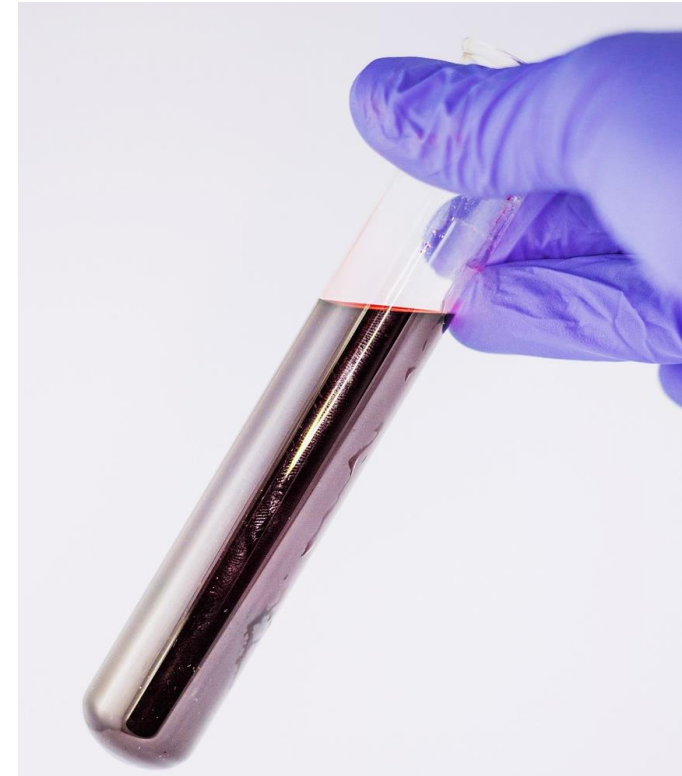




# Abnormal Uterine Bleeding

## Workup

- History and examination
- Standard testing:  $\beta$ -hCG and CBC
- Other tests used in select cases:
  - TSH
  - Prolactin
  - FSH
  - Estradiol
  - LH
  - Coagulation



# Abnormal Uterine Bleeding

## Workup

- **Pelvic ultrasound**
- First-line imaging choice for AUB in most patients
- Indicated if abnormalities on bimanual examination
- Or symptoms that persist after initial treatment
- Or pelvic exam limited by body habitus
- May identify structural causes
- Adenomyosis, leiomyomas



# Abnormal Uterine Bleeding

## Workup

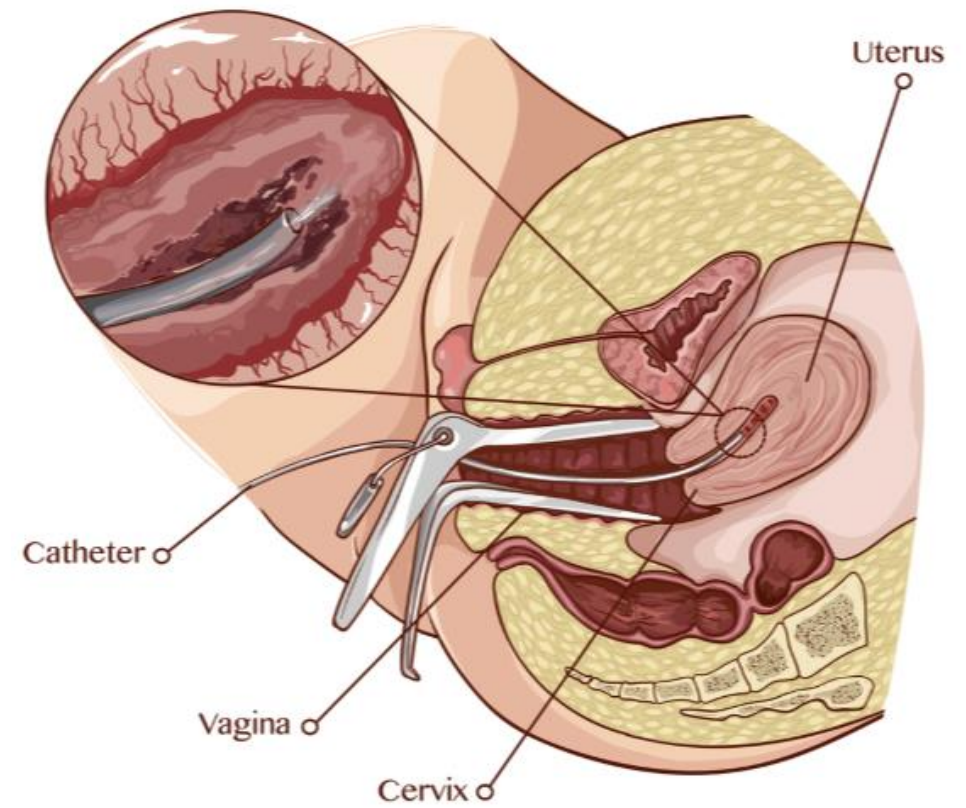
- Hysteroscopy
  - Direct visualization of endometrial cavity
  - Also detects polyps and small fibroids
  - Allows endometrial biopsy
- Saline infusion sonography (sonohysterography)
  - Saline injected into uterus during TVUS
  - Detects polyps or small fibroids better than TVUS alone

# Abnormal Uterine Bleeding

## Workup

- **Endometrial biopsy**
- Used to exclude uterine malignancy
- May be done with hysteroscopy
- Indicated in women with **AUB and risk factors**
  - Anovulatory cycles
  - Obesity
  - Nulliparity
  - Older age
  - Tamoxifen therapy
  - Abnormal US lining thickness

## Endometrial Biopsy



# Abnormal Uterine Bleeding

## Treatment

- **Combined contraceptives (COCs)**
- Make bleeding more regular and lighter
- Reduce dysmenorrhea
- Also provide contraception



# Heavy Menstrual Bleeding

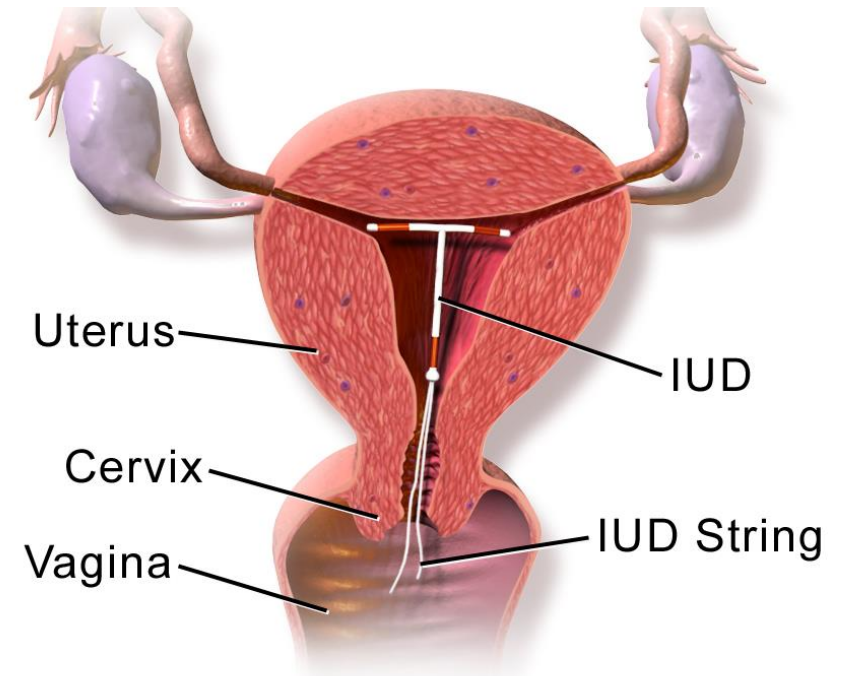
Treatment for severe blood loss

- Defined as soaking more than 1 large pad per hour for several hours
- Or passing multiple large clots (bigger than eggs)
- Assess hemodynamic stability
- May need resuscitation
- May be anemic
- May require surgical intervention
- Usually treated medically

# Heavy Menstrual Bleeding

Treatment for chronic or recurrent bleeding

- Treat underlying cause
  - Polyps, adenomyosis, fibroids, etc.
- Often high dose **progesterone**
  - Megace (megestrol acetate) often used
- **Levonorgestrel IUD**
- Combined oral contraceptives



**Intrauterine Device (IUD)**



# Heavy Menstrual Bleeding

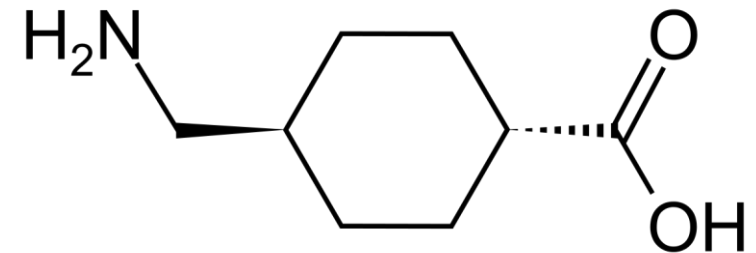
Treatment for chronic or recurrent bleeding

- **Tranexamic acid**

- Antifibrinolytic agent (reduces fibrinolysis – more clotting)
- Blocks conversion of plasminogen to plasmin
- Used in women who cannot take COCs
- Often used in women trying to conceive
- Oral drug taken daily during menses only
- Contraindicated: history of thromboembolism or ↑ risk

- NSAIDs

- Cause endometrial vasoconstriction
- Decrease volume of menstrual blood loss



Tranexamic Acid



# Heavy Menstrual Bleeding

Treatment for chronic or recurrent bleeding

- Endometrial ablation
- Uterine artery embolization
- Hysterectomy

# Vaginitis

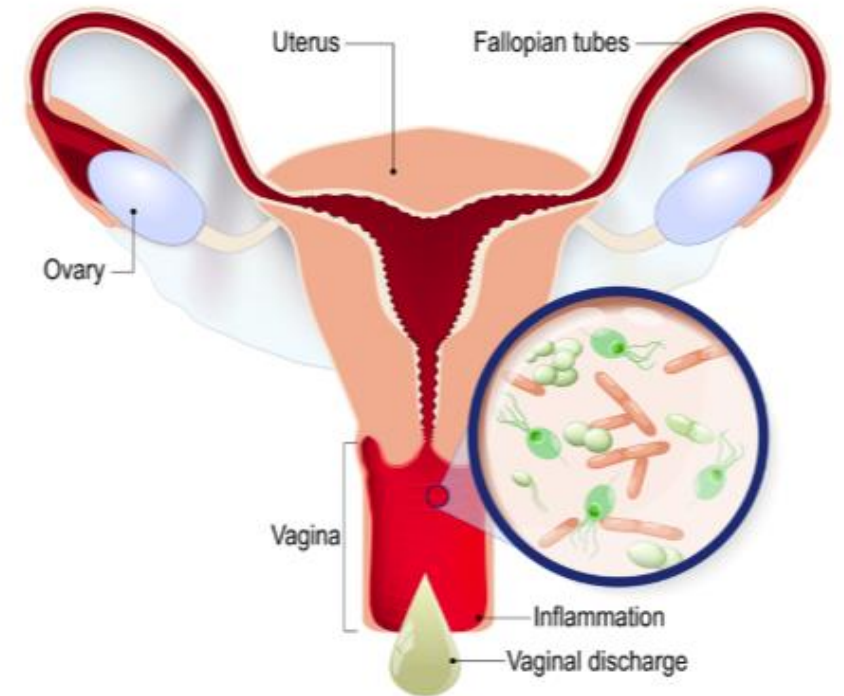
Jason Ryan, MD, MPH



# Vaginitis

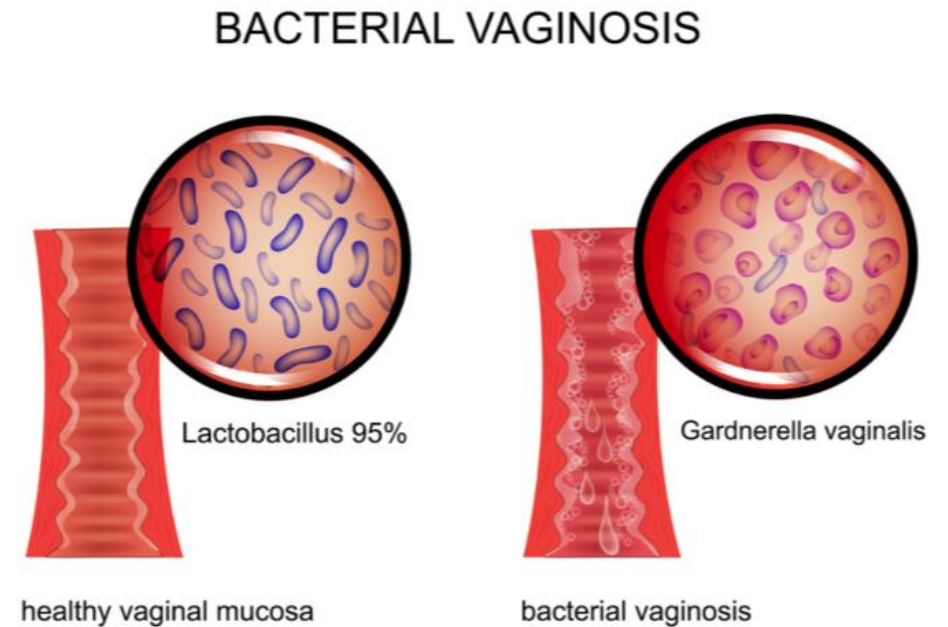
- Infection, inflammation or change in vaginal flora
- Discharge, odor, pruritus, pelvic discomfort
- Three major causes
  - Bacterial vaginosis
  - Trichomoniasis
  - Vulvovaginal candidiasis

## VAGINAL INFECTION



# Bacterial Vaginosis

- Alteration of vaginal flora
- Decrease in lactobacilli
  - Produce hydrogen peroxide
  - Maintain low pH
- Increase in many species
  - Especially Gram-negative rods
  - Major bacteria: **Gardnerella vaginalis**



# Bacterial Vaginosis

## Risk Factors

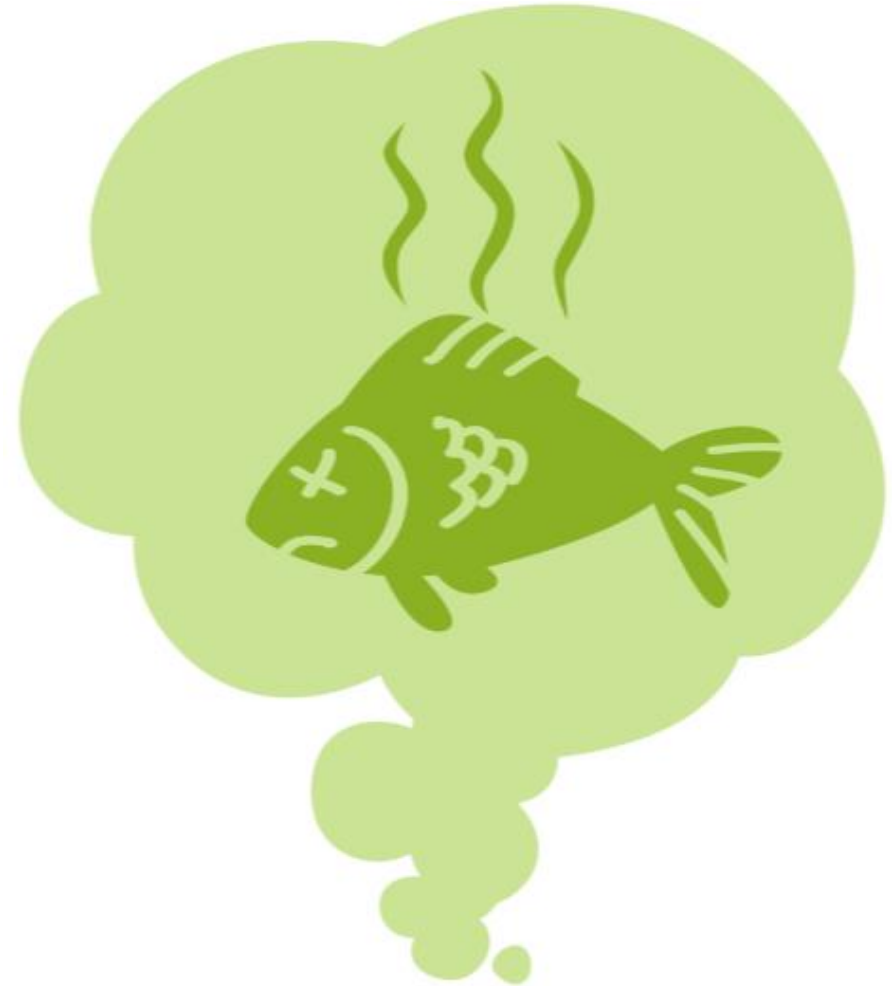
- Sexual activity
  - Strong association
  - Not classified as STI
  - Lack of specific agent
- Douching
- Smoking



# Bacterial Vaginosis

## Clinical features

- Vaginal discharge
- Thin, off-white
- Unpleasant odor: “fishy smell”

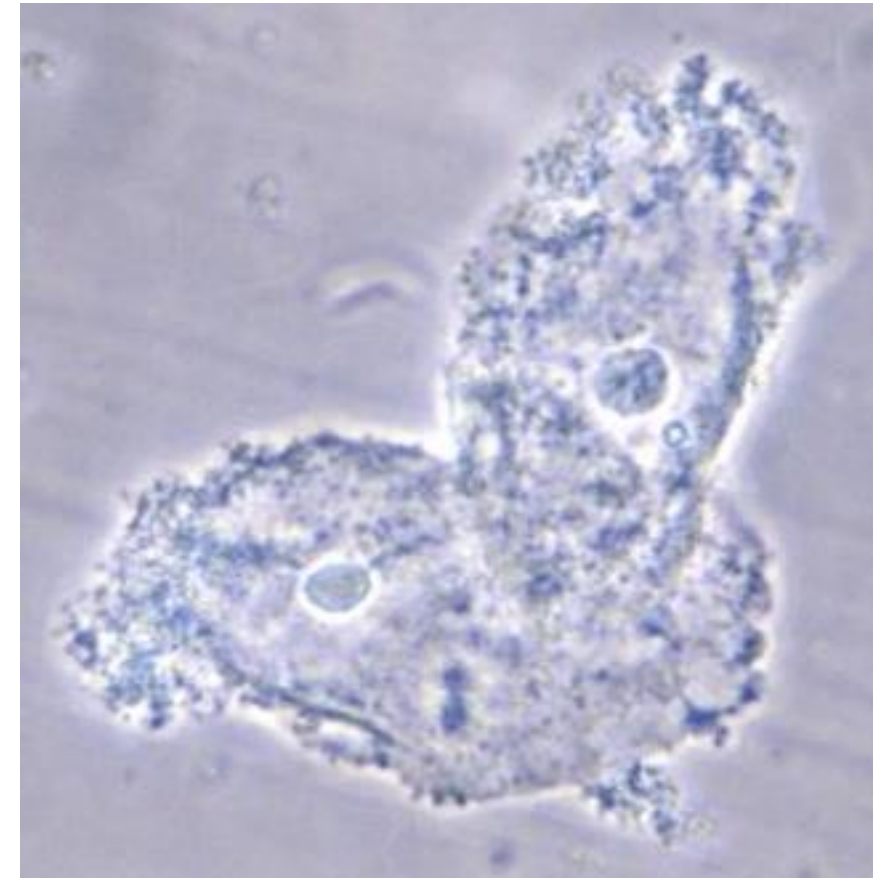


# Bacterial Vaginosis

## Diagnosis

- High vaginal pH
  - Normal 4.0 to 4.5
  - Bacterial vaginosis: > 4.5
- Saline wet mount: **clue cells**
  - Microscopic examination of discharge
  - Epithelial cells studded with bacteria

Clue Cell



# Bacterial Vaginosis

## Diagnosis

- Potassium hydroxide wet mount: negative
  - KOH destroys cells
  - Allows identification of yeast
- **Whiff test (Amine test)**
  - Smell slide after applying KOH
  - Brings out fishy (amine) odor of BV





# Bacterial Vaginosis

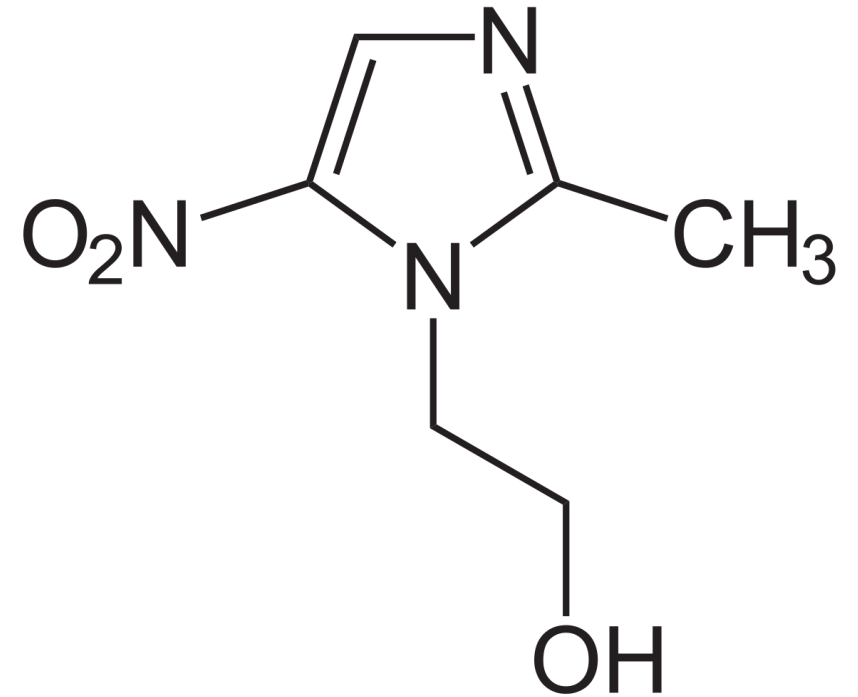
## Clinical features

- **Amsel's Diagnostic Criteria**
  - Thin, homogenous discharge
  - Positive "whiff" test
  - Clue cells on microscopy
  - Vaginal pH > 4.5
- Must have 3 of 4 criteria present

# Bacterial Vaginosis

## Treatment

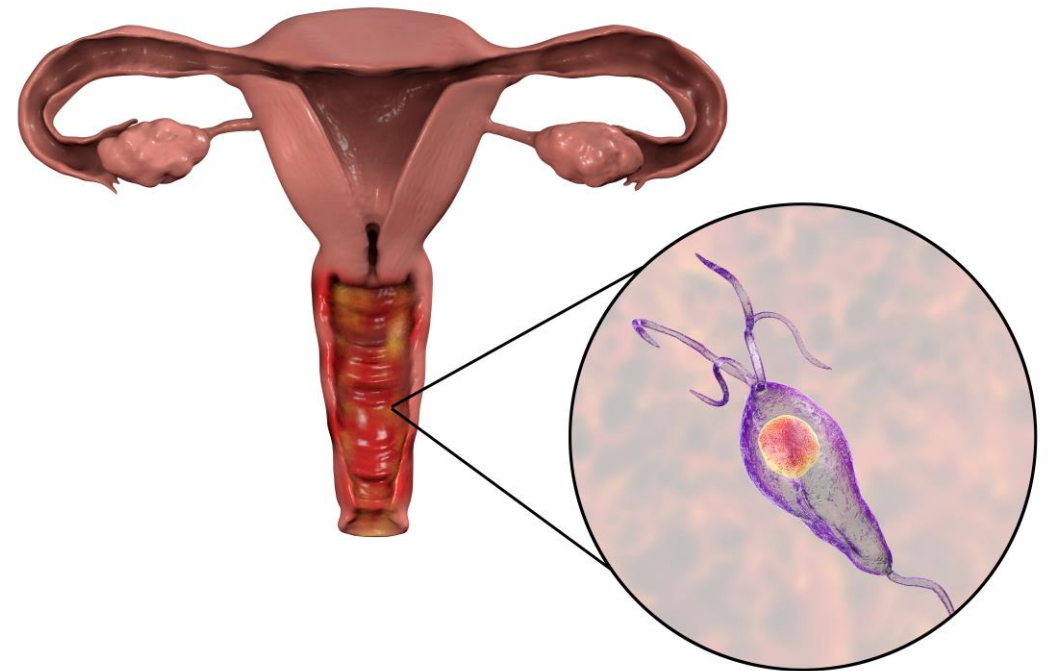
- **Metronidazole**
- Clindamycin
- Oral or topical
- Topical metronidazole gel → least side effects



Metronidazole

# Trichomonas Vaginalis

- **Protozoal infection** of urogenital tract
- Infects men and women
- Men are usually asymptomatic
- May cause vaginitis symptoms in women
- Can cause urethritis (dysuria, frequency)
- **Sexually transmitted**



# Trichomonas Vaginalis

## Clinical features

- About 50% of women asymptomatic
- Classically yellow-green, foul-smelling discharge
- Erythema of vulva and vaginal mucosa
- Itching
- Cervicitis
- Dyspareunia
- Bleeding
- Punctate hemorrhages: **“Strawberry cervix”**

Strawberry Cervix



# Trichomonas Vaginalis

## Diagnosis

- Saline wet mount: **motile trichomonads**
  - Identified in 60 to 70% of cases
- Elevated vaginal pH (> 4.5)
- Potassium hydroxide wet mount: negative
- Nucleic acid amplification test
  - Detects T. vaginalis RNA
- Whiff test: occasionally positive

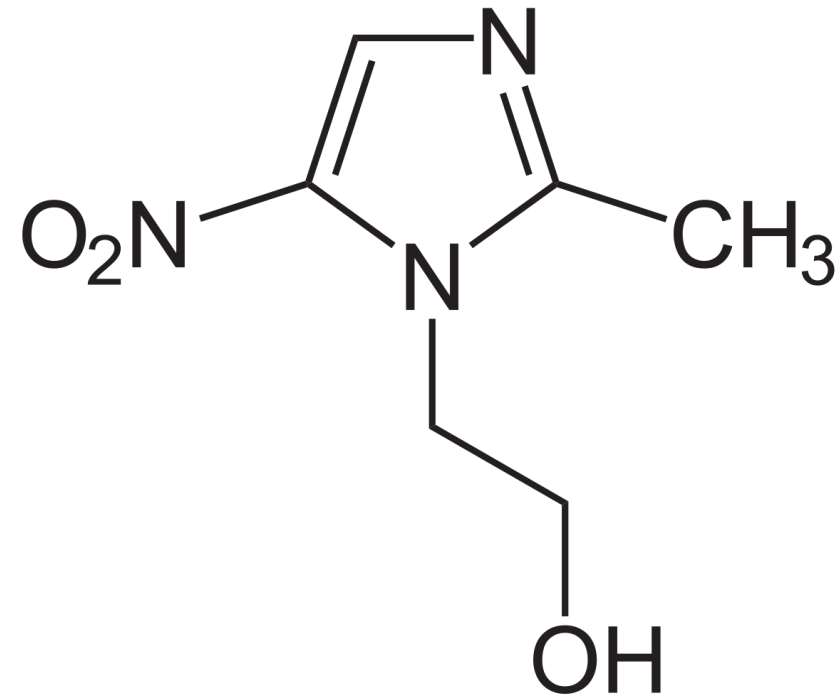
Motile Trichomonads



# Trichomonas Vaginalis

## Treatment

- **Metronidazole** or tinidazole
- Usually 7-day oral course
- Treat patient and partner
- Allergy (rare): desensitization
  - Alternative drugs ineffective



Metronidazole

# Vuvlovaginal Candidiasis

“Yeast infection”

- Overgrowth of Candida species
- Usually *C. albicans* (~ 90% of cases)
- Rarely other Candida species: *C. glabrata* and *C. parapsilosis*
- Candida species part of normal flora in 10 to 20% women

# Vuvlovaginal Candidiasis

## Risk Factors

- **Antibiotic use:** depletion of normal bacterial flora
- Diabetes (consider A1c testing!)
- Immunosuppression

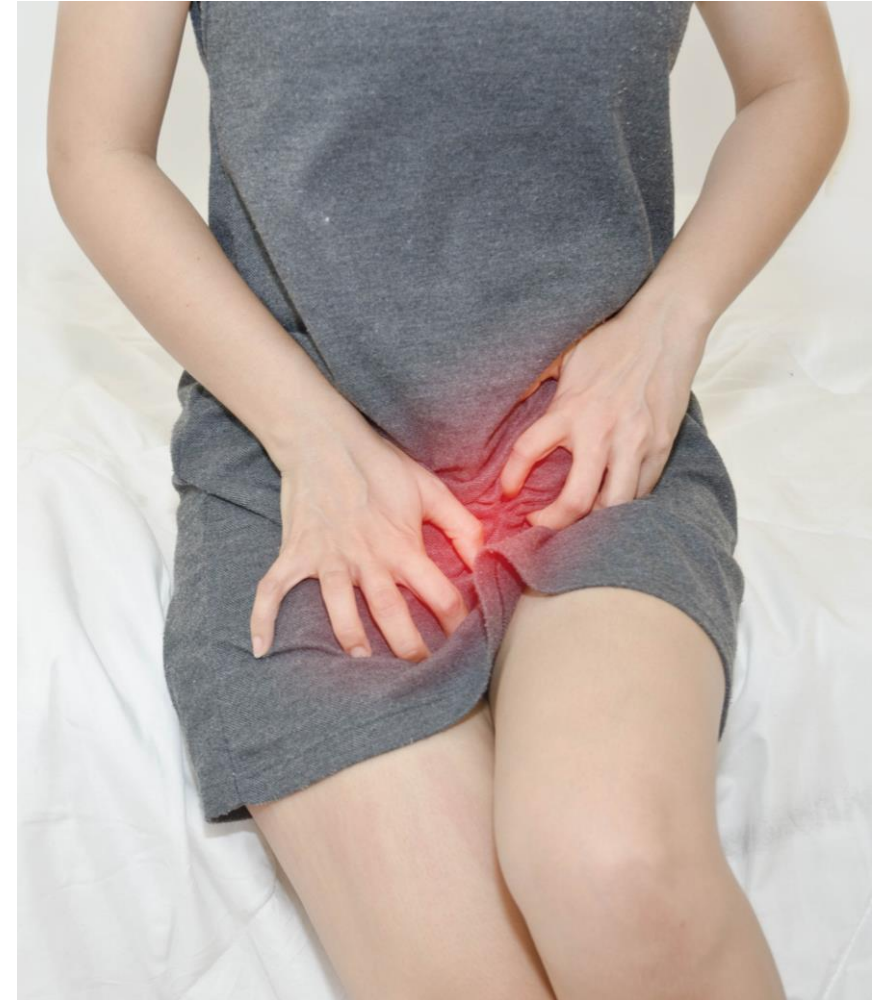




# Vuvlovaginal Candidiasis

## Clinical Features

- Dominant symptom: **pruritus**
- Burning (can cause dysuria)
- Discharge may be minimal or absent
- Classically white, thick, clumpy
- “Curd-like” or “cottage cheese”
- Erythema of the vulva and vaginal mucosa
- Minimal odor



# Vuvlovaginal Candidiasis

## Diagnosis

- Normal vaginal pH: 4.0 to 4.5
- Key test: **potassium hydroxide wet mount**
  - Budding yeast
  - Pseudohyphae
  - Hyphae
- Culture not routinely used
  - Diagnostic uncertainty
  - Persistent or recurrent symptoms

Potassium Hydroxide Wet Mount  
(pseudohyphae)



# Vuvlovaginal Candidiasis

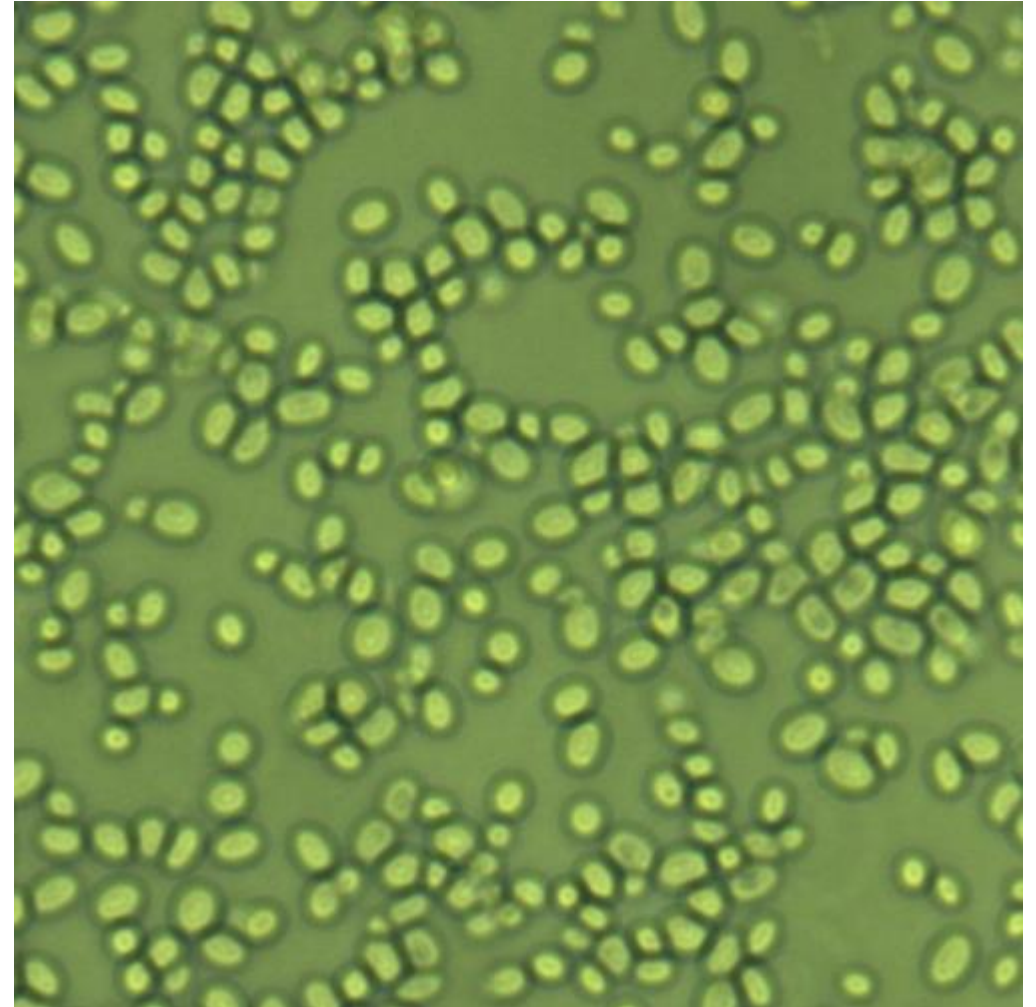
## Treatment

- Uncomplicated infections: single dose **oral fluconazole**
  - Three or less episodes per year
  - Mild to moderate symptoms
  - Immunocompetent
  - Nonpregnant
- Topical azoles
- Some women require long-term suppressive therapy

# Candida Glabrata

- Rare cause of symptomatic infection
- Identified by culture in complex cases
- Poorly responsive to azoles
- Treatment: **intravaginal boric acid**

Candida Glabrata



# Vaginitis

	Bacterial Vaginosis	Trichomoniasis	Vulvovaginal Candidiasis
<b>Microbiology</b>	- Shift in vaginal flora away from lactobacilli, to diverse bacteria including anaerobes - <i>Gardnerella vaginalis</i> predominant	- Protozoan <i>Trichomonas vaginalis</i> infection	- Overgrowth of <i>Candida albicans</i> (part of normal vaginal flora) - Other <i>Candida</i> also possible (ie glabrata)
<b>Risk</b>	- Sexual activity - Frequent douching	- Unprotected sex (passed person-to-person via sexual contact)	- Diabetes mellitus, antibiotic use, immunocompromised states
<b>Clinical</b>	- Odor, increased discharge	- Increased discharge, odor, pruritus, dysuria	- Vulvar pruritus, with possible burning, irritation
<b>Exam</b>	- Homogenous thin gray-white discharge	- Erythema of the vulva and vaginal mucosa - Punctate hemorrhages of upper vagina/ cervix ("Strawberry cervix") - Profuse, malodorous yellow-green discharge	- Erythematous, excoriated vagina - Thick, white, discharge with curdy texture without odor
<b>pH</b>	> 4.5	5.0-6.0	4.0-4.5
<b>Whiff test</b>	Positive	Occasionally positive	Negative
<b>Wet Mount</b>	Clue cells (epithelial cells with bacteria)	Motile trichomonads (bigger than WBC, smaller than epi cells)	Pseudohyphae
<b>KOH Prep</b>	Negative	Negative	Positive (pseudohyphae)
<b>Management</b>	PO Metronidazole (500 mg PO BID 5-7 days) Topical Metronidazole (5 days)  (Vaginal or oral Clindamycin can also be used)	PO Metronidazole or Tinidazole (single dose)  * Partners should also be evaluated and treated	PO Fluconazole (1 time) or topical azoles  * Cases of recurrent disease may require longer PO or topical regimens * Glabrata treated with intravaginal boric acid
<b>Other</b>	Amsel Criteria ( $\geq 3/4$ ): Classic vaginal discharge, elevated pH, clue cells, fishy odor		

# Pelvic Inflammatory Disease

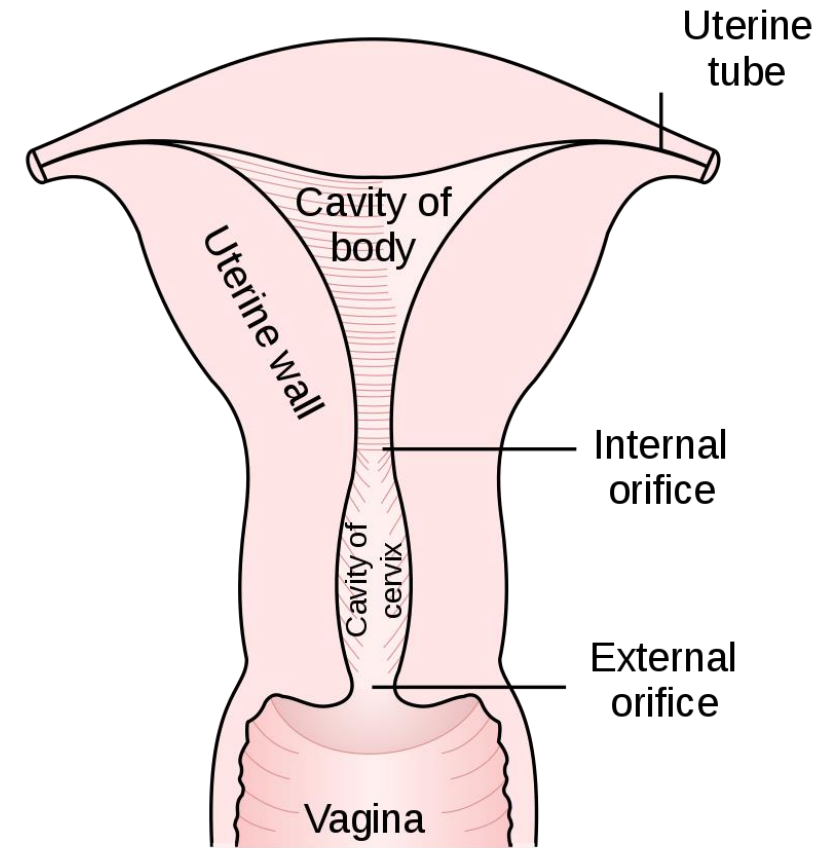
Jason Ryan, MD, MPH





# Pelvic Inflammatory Disease

- Infection of the female **“upper genital tract”**
- Uterus, fallopian tubes or ovaries
- Normal vaginal flora: many pathogenic bacteria
- Upper genital tract normally sterile
- Protected by cervical canal
- Disruption of barrier → ascending infection
- Often due to **cervical infection**

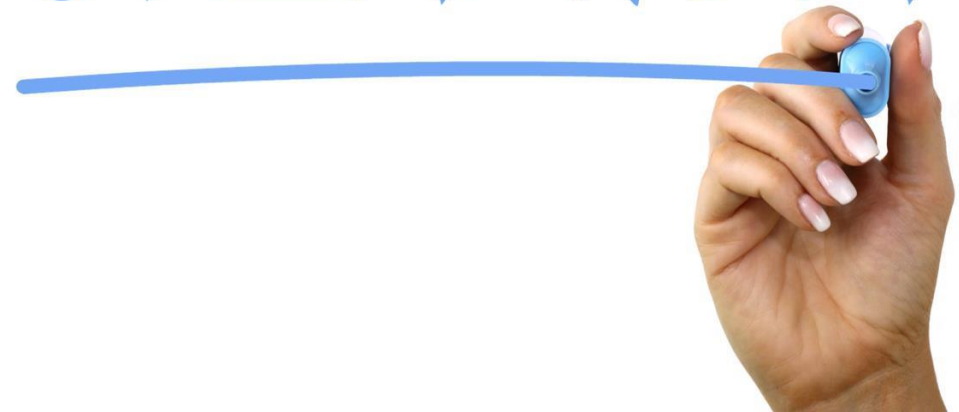


# Pelvic Inflammatory Disease

## Microbiology

- Most common causes: **N. gonorrhoeae** and **C. trachomatis**
  - All sexually-active women under age 25 should have annual screening with PAP test
  - Older women also screened based on sexual activates that contribute to risk
- Mycoplasma genitalium
- Other pathogens

CHLAMYDIA





# Pelvic Inflammatory Disease

## Risk Factors

- Sexual activity
- Multiple partners
- Prior STI or PID
- Lack of barrier protection
- Rare during pregnancy (mucous plug)

# Pelvic Inflammatory Disease

## Clinical Features

- Lower abdominal or pelvic pain
- Cervical motion tenderness (“chandelier sign”)
- Uterine or adnexal tenderness
- Purulent cervical discharge
- Cervical spotting or bleeding
- Systemic symptoms in some cases
- Fever, chills and leukocytosis
- Right upper quadrant pain with perihepatitis

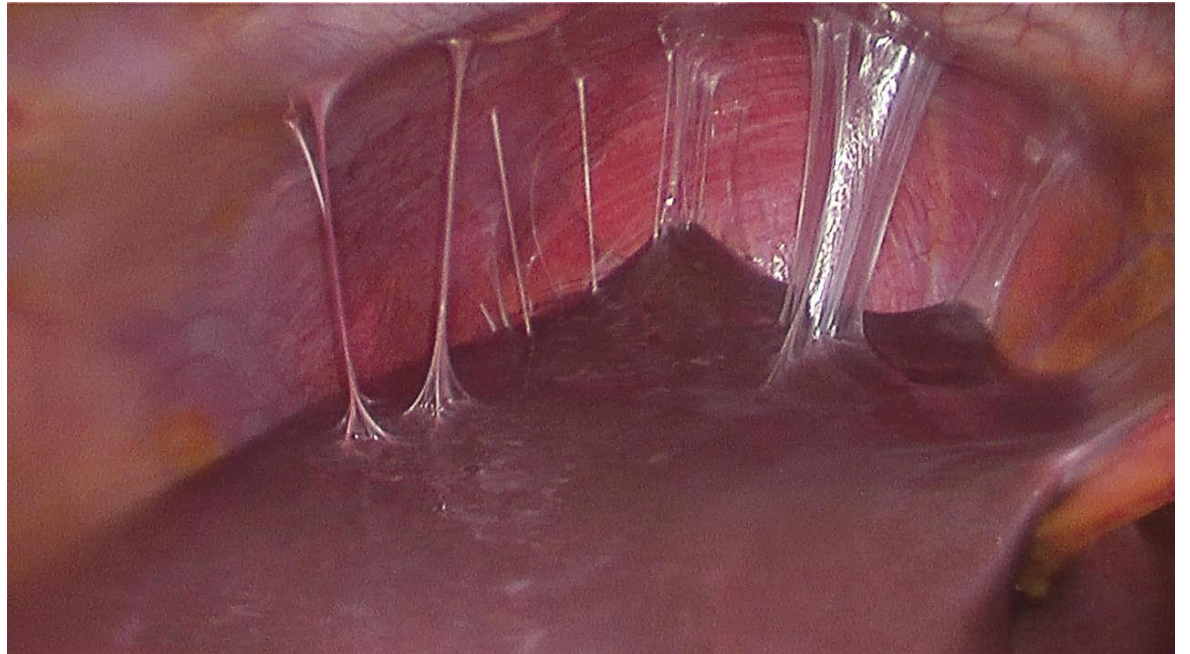


# Perihepatitis

## Fitz-Hugh-Curtis Syndrome

- Inflammation of **liver capsule**
- Caused by spread of infection
- **Right upper quadrant pain**
  - Often pleuritic (worse with inspiration)
  - May radiate to shoulder
- Treatment: same as PID
- Definitive diagnosis: laparoscopy
- “Violin string” adhesions

Perihepatitis



# Pelvic Inflammatory Disease

## Diagnosis

- **Clinical diagnosis**
  - Pelvic or lower abdominal pain
  - Cervical motion tenderness
  - Uterine or adnexal tenderness
- Pelvic imaging not required for diagnosis
- Women with severe disease: **transvaginal ultrasound**
  - High fever, nausea, vomiting, severe pain
  - Women who are hospitalized
  - Exclude tubo-ovarian abscess

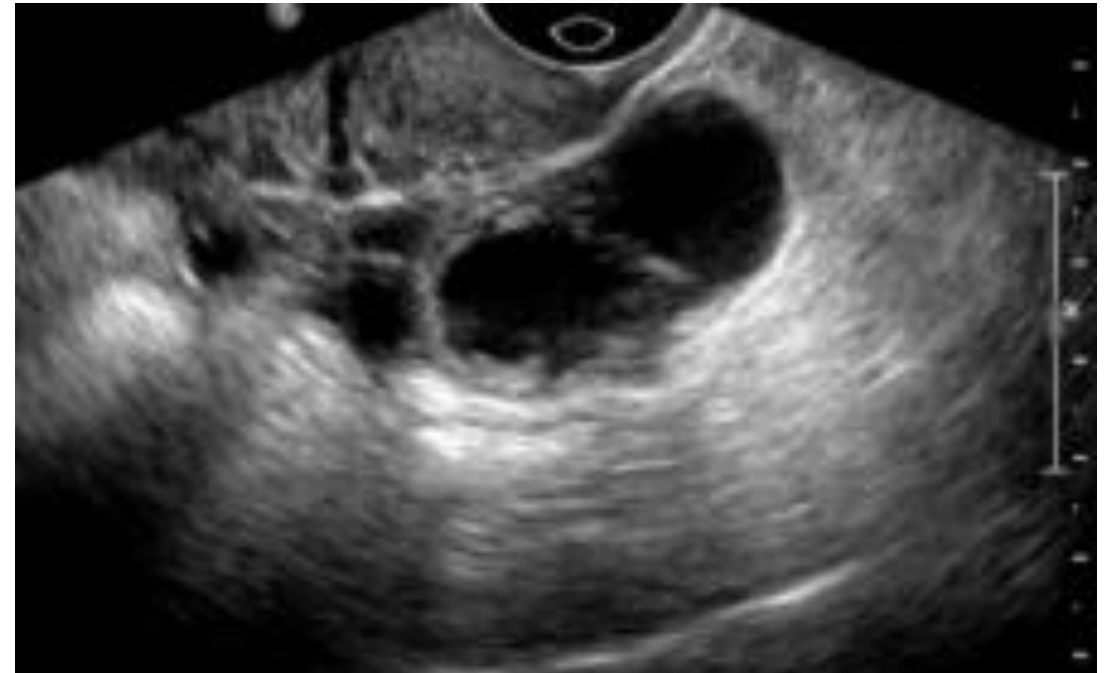
## Transvaginal Ultrasound



# Tubo-Ovarian Abscess

- Complication of PID
- Inflammatory mass in fallopian tubes or ovary
- Similar clinical features to PID
- May rupture → peritonitis
- Diagnosis: **transvaginal ultrasound**

Tubo-ovarian Abscess



# Tubo-Ovarian Abscess

## Management

- **Antibiotics**
  - Same as for PID
  - About 70% of patients improve
- Imaging-guided drainage
  - CT or ultrasound
- Laparotomy





# Pelvic Inflammatory Disease

## Management

- Can be treated as outpatient
- **Hospitalization criteria**
  - High fever
  - Nausea and vomiting
  - Severe pain
  - TOA
  - Pregnancy



# Pelvic Inflammatory Disease

## Management

- **Antibiotics:** usually **cephalosporin plus doxycycline**
- Cover gram-positives, gram-negatives and anaerobes
- Inpatient: cefoxitin IV plus doxycycline PO (“foxy doxy”)
- Outpatient: ceftriaxone IM plus doxycycline PO

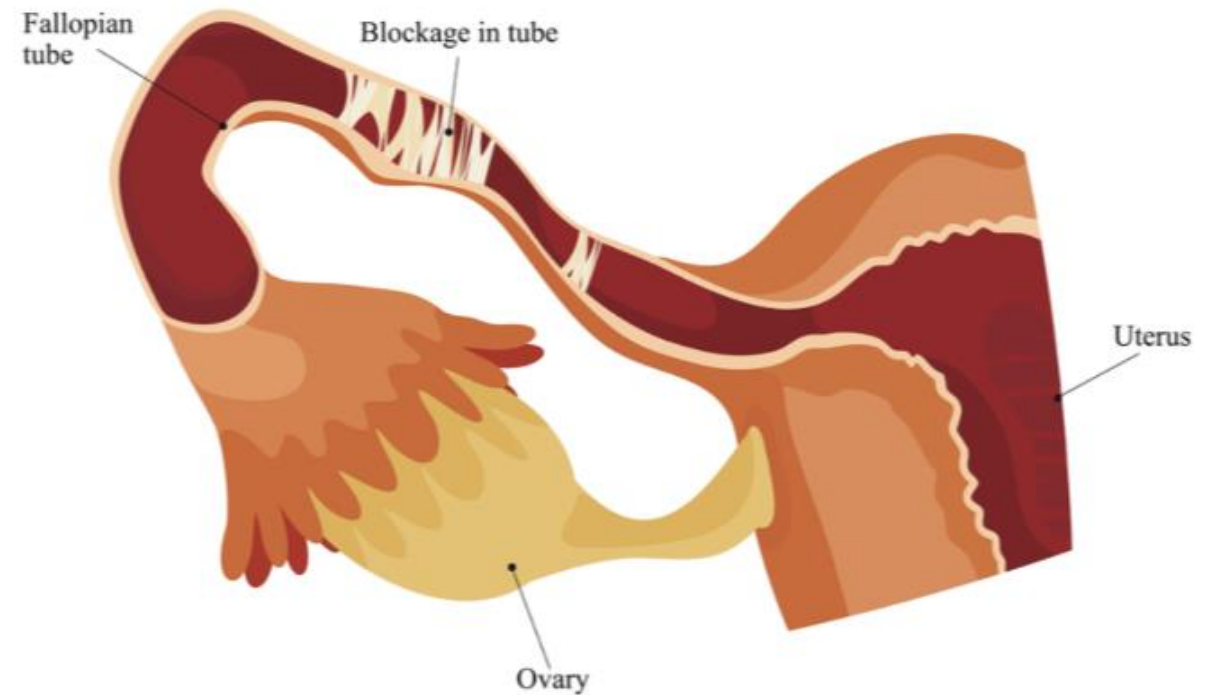


# Pelvic Inflammatory Disease

## Long-term Complications

- Scarring and adhesions
- Uterus or fallopian tubes
- **Infertility**
- **Ectopic pregnancy**

FALLOPIAN TUBE OBSTRUCTION



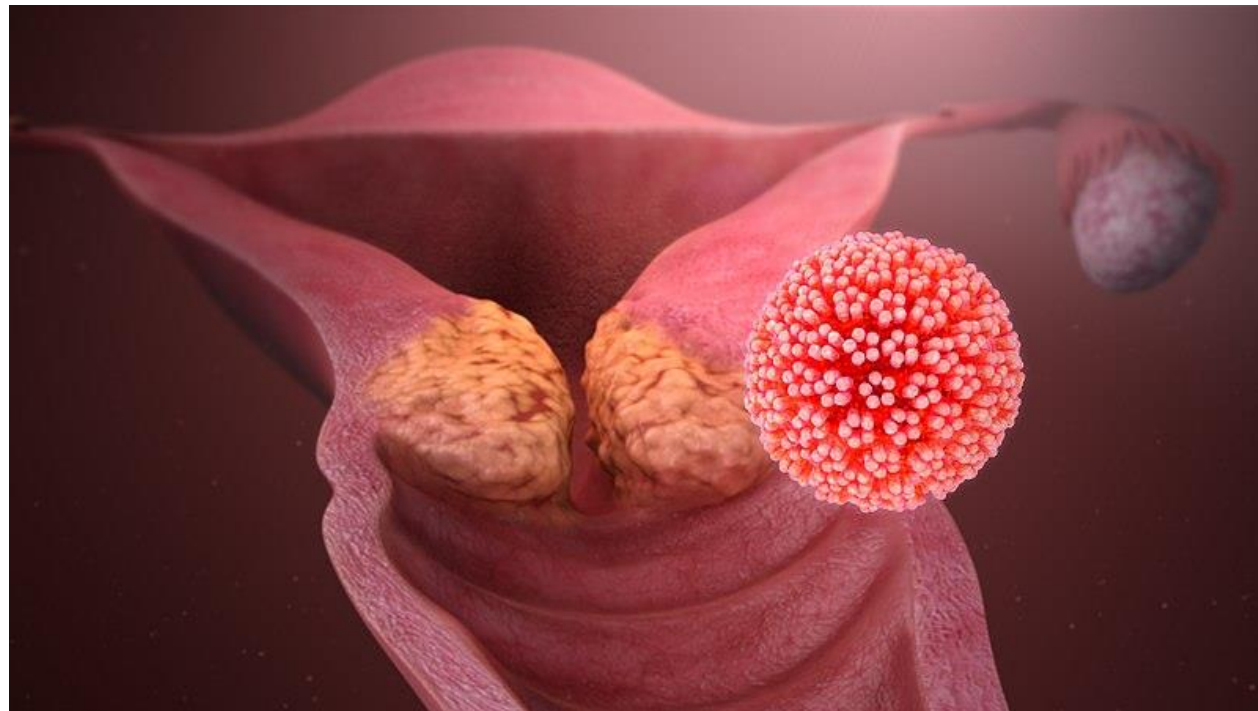
# Cervical Cancer

Jason Ryan, MD, MPH



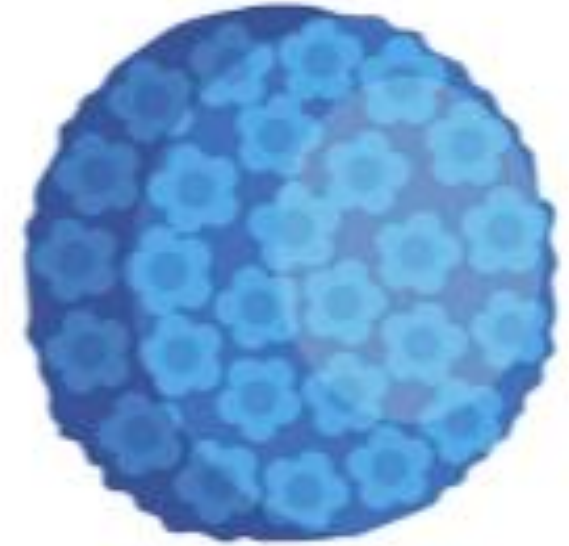
# Cervical Cancer

- Cancer of cervical epithelial cells
- Most cases (97%) associated with **human papilloma virus**



# Human Papillomavirus

- Sexually-transmitted cervical infection
- Multiple subtypes: 1, 2, 6, 11, 16, 18
- Cervical cancer:
  - **HPV 16**: 50% of cases
  - **HPV 18**: 20% of cases
  - Others: HPV 31, 33, 45, 52, and 58
- High prevalence among sexually-active women
  - Most will clear infection within 12 months
  - Some will have infection persist



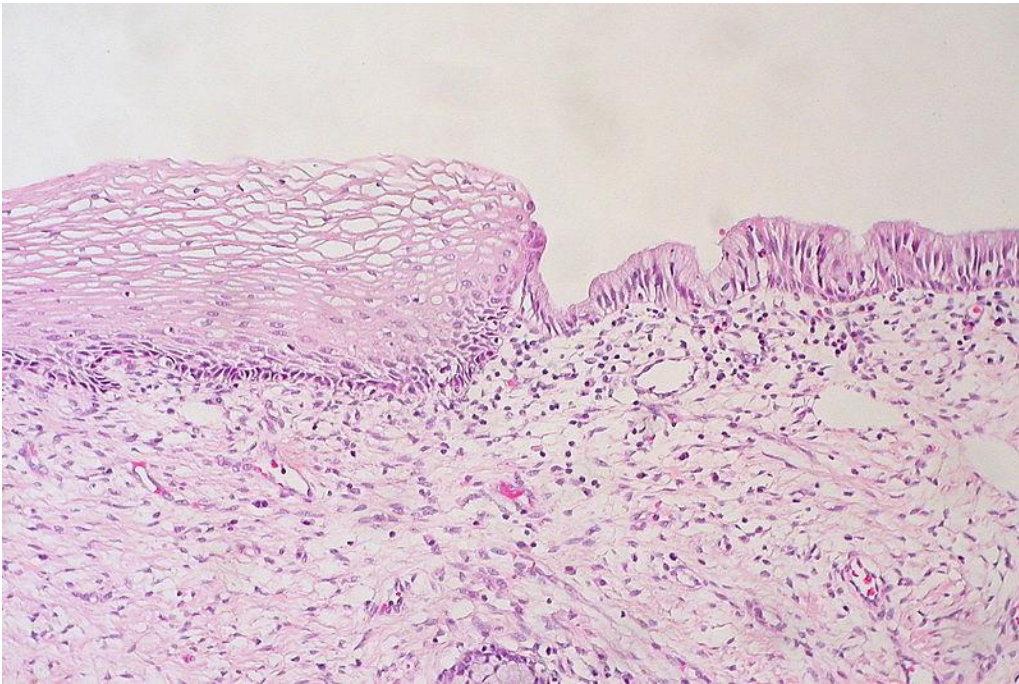
# Cervical Cancer

- **Squamocolumnar junction**
  - Junction between squamous and columnar epithelium
  - Endocervix: columnar epithelium
  - Ectocervix: squamous epithelium
- **Transformation zone**
  - SCJ moves from exposure to hormones
  - TZ: area between original SCJ and new SCJ
  - Most (95%) cancers arise here

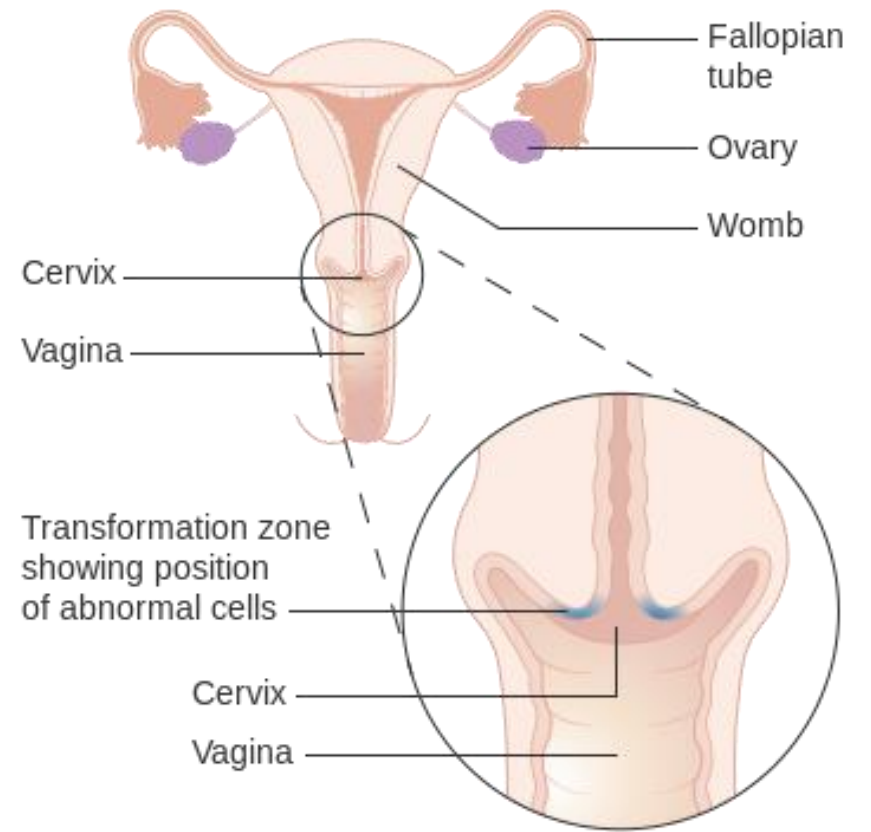
Squamocolumnar Junction



# Cervical Cancer



Ed Uthman/Wikipedia



Cancer Research UK



# Cervical Cancer

## Risk Factors

- Human papillomavirus infection
- Immunodeficiency state
- Cigarette smoking
- Sexual intercourse at a young age
- Multiple sexual partners
- History of STIs



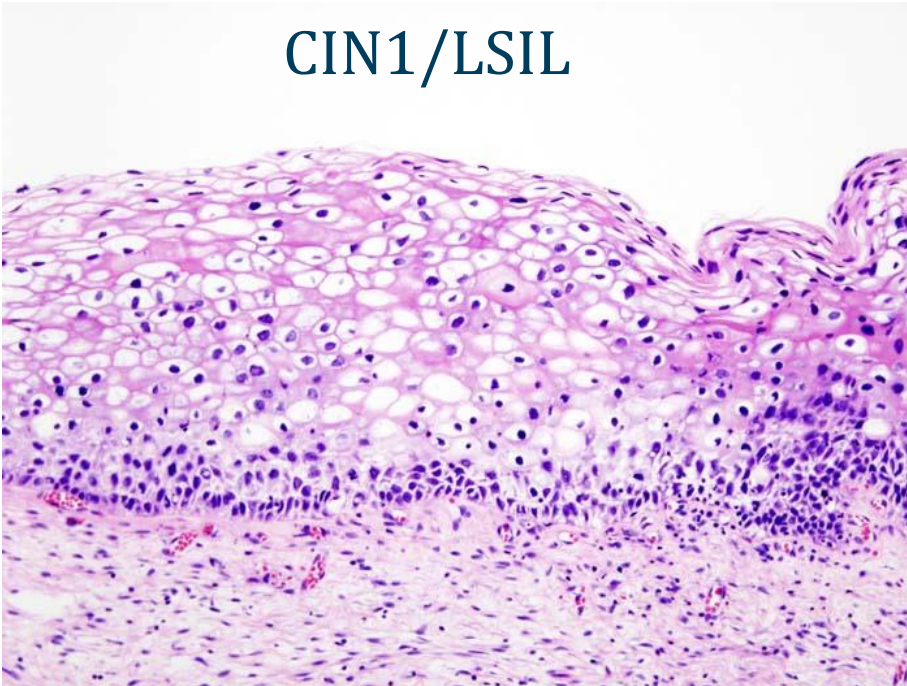
# Cervical Neoplasia

- Progresses slowly through stages to carcinoma
- Average time from HPV exposure to CA 15 years
- Classified based on biopsy findings
- Classified as “cervical intraepithelial neoplasia”
  - CIN1: Low-grade lesion
  - CIN2 and CIN 3: High-grade lesions
- Classified as “squamous intraepithelial lesions”
  - Bethesda system - preferred system but CIN still in wide use
  - Low-grade squamous intraepithelial lesion: LSIL
  - High-grade squamous intraepithelial lesions HSIL

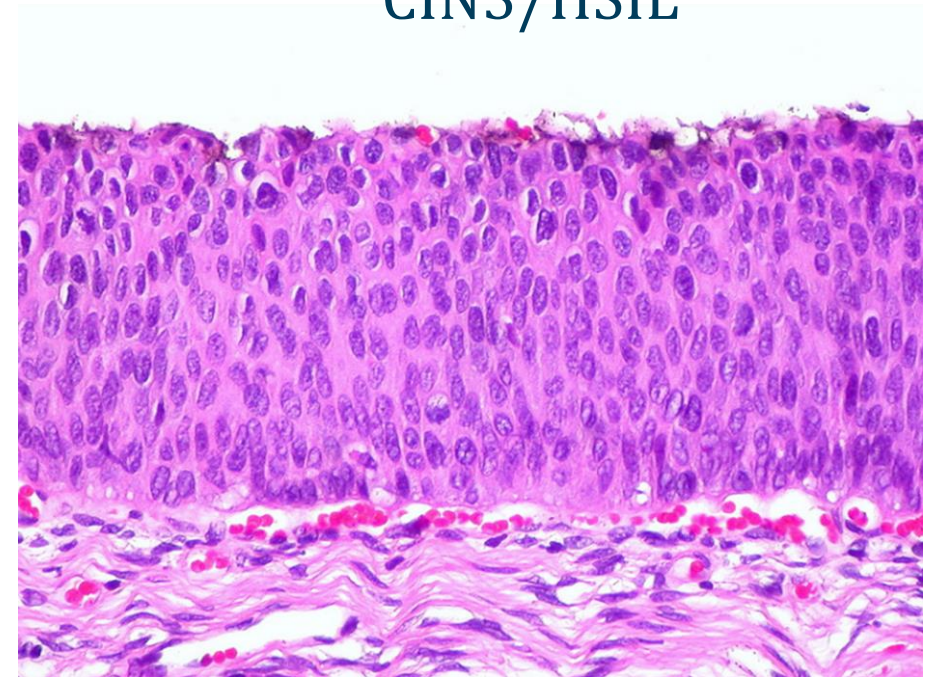


# Cervical Neoplasia

CIN1/LSIL



CIN3/HSIL



# Cervical Carcinoma

- Most commonly **squamous cell carcinoma** (75%)
- Less commonly adenocarcinoma (endocervix origin)
- Almost always in women with HPV infection
- Usually occurs in 40s/50s
- Usually in women not screened



# Cervical Carcinoma

- Usually asymptomatic
- May present as vaginal bleeding
- Irregular/heavy menses
- **Post-coital bleeding**
- Can invade locally: bladder, rectum

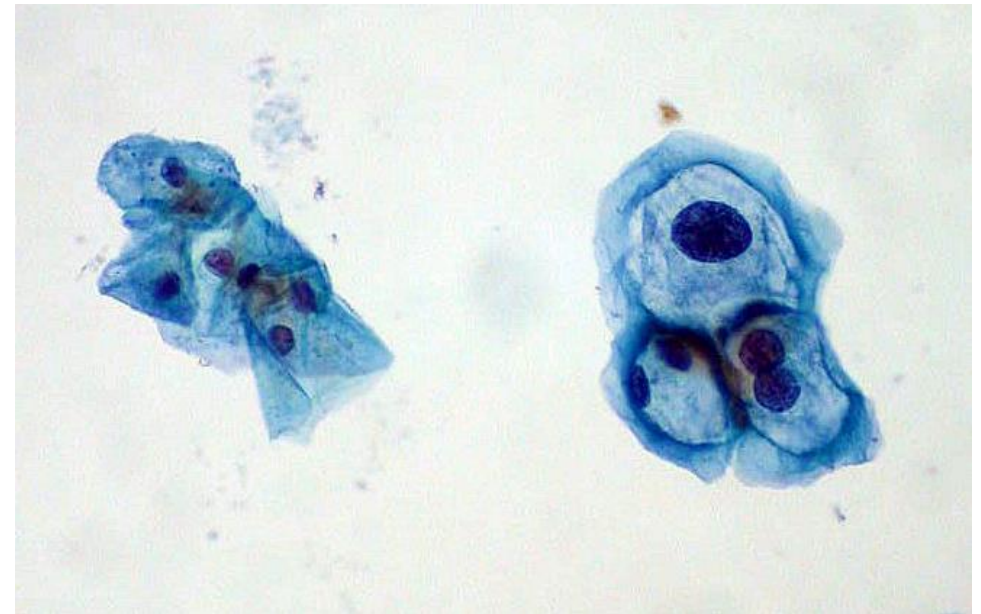


# Cervical Cancer Screening

## PAP Smear

- Analysis of sample of cells from cervix
- Used to detect Koilocytes
- Large, darkened nuclei
- **Epithelial cell changes due to HPV**
- Abnormal studies often followed by colposcopy

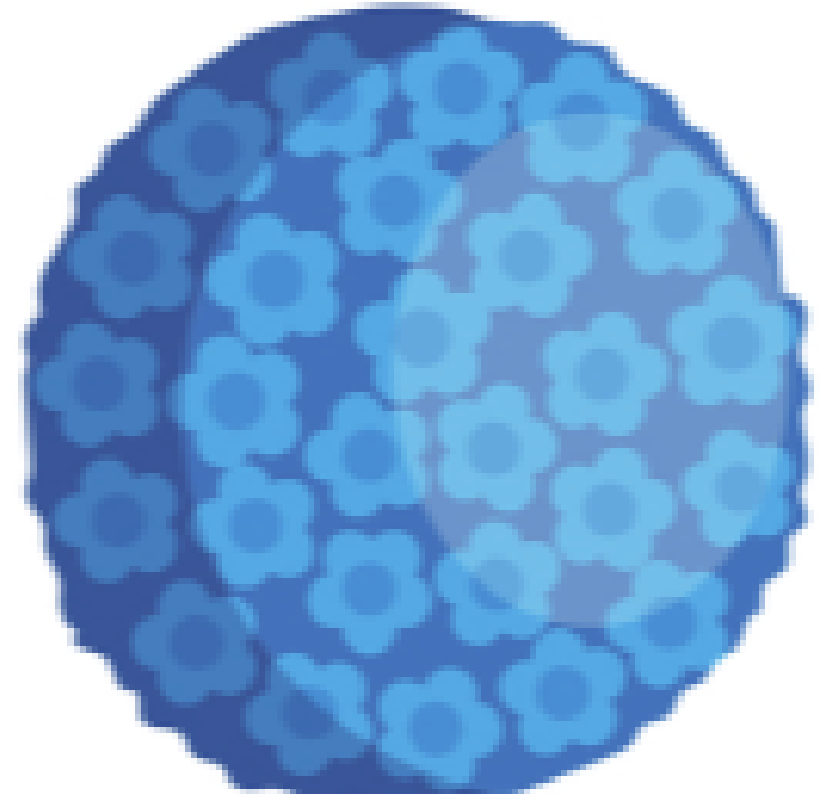
Koilocytes



# Cervical Cancer Screening

## HPV Testing

- Identifies high-risk subtypes of HPV
- Not available in some locations
- **Identifies HPV infection only**
- Does not identify cellular changes
- Primary HPV testing: HPV testing alone (rarely done)
  - Positive test indicates infection only
  - Cellular changes due to infection unknown

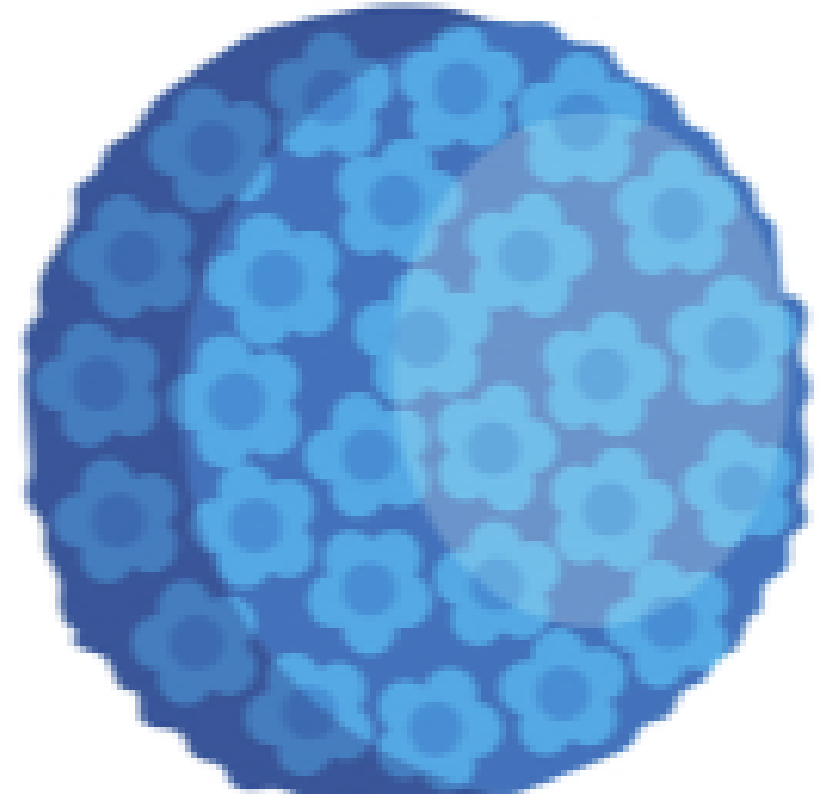




# Cervical Cancer Screening

## HPV Testing

- Co-testing: **HPV plus PAP smear**
- HPV+ and PAP+ = colposcopy
  - Infection plus cellular changes due to HPV
- HPV+ with PAP- = repeat testing in 1 year
  - Infection without cellular changes
  - Can defer colposcopy until abnormal cells



# Cervical Cancer Screening

## Recommendations

Age	Screening
< 21 years	No screening
21 to 29	PAP test every 3 years (age 21)* OR HPV testing every 5 years (age 25)**
30 to 65	PAP test every 3 years OR HPV testing every 5 years OR co-testing every 5 years
> 65	Discontinue screening if 3 normal PAPs or 2 normal co-tests May continue screening if high risk (smokers)

# Cervical Cancer Screening

## Special Populations

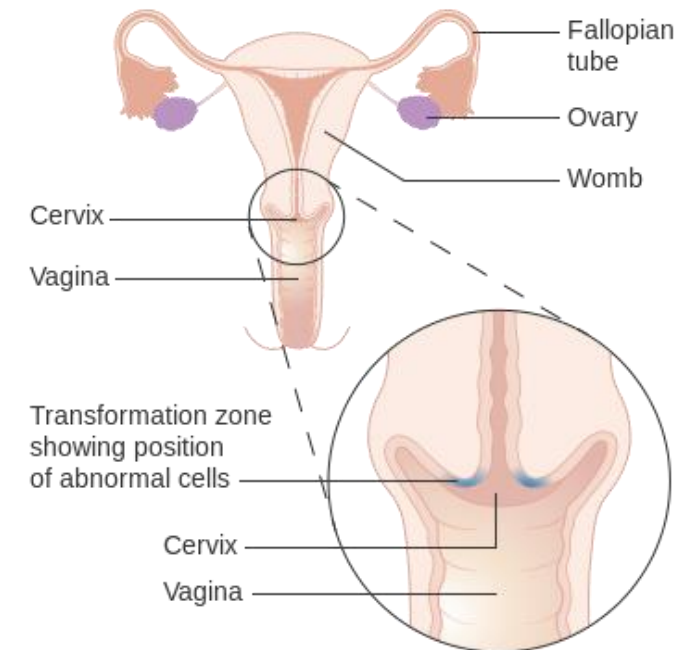
Age	Screening
Immunosuppressed	Begin at onset of sexual activity Continue throughout lifetime (> 65 years) PAP alone: every year then (if 3 normal results q3 years) Co-testing: every 3 years
Total Hysterectomy (cervix removed)	No screening indicated unless prior abnormal result



# Pap Smear

## Interpretation of Results

- **Atypical glandular cells (AGC)**
  - *Glandular* epithelial cells of endocervix or endometrium
  - Often followed with colposcopy and endocervical sampling (curettage)
  - Age > 35 or endometrial cancer risk factors: endometrial biopsy



Cancer Research UK

# Pap Smear

## Interpretation of Results

- **Benign-appearing endometrial cells**
  - Common, benign finding in women < 45 years
  - Finding only reported in women > 45 years
  - May indicate endometrial cancer
  - Premenopausal women: no further workup unless AUB or ↑ risk of endometrial cancer
  - Postmenopausal women: hysteroscopy with endometrial biopsy

# Pap Smear

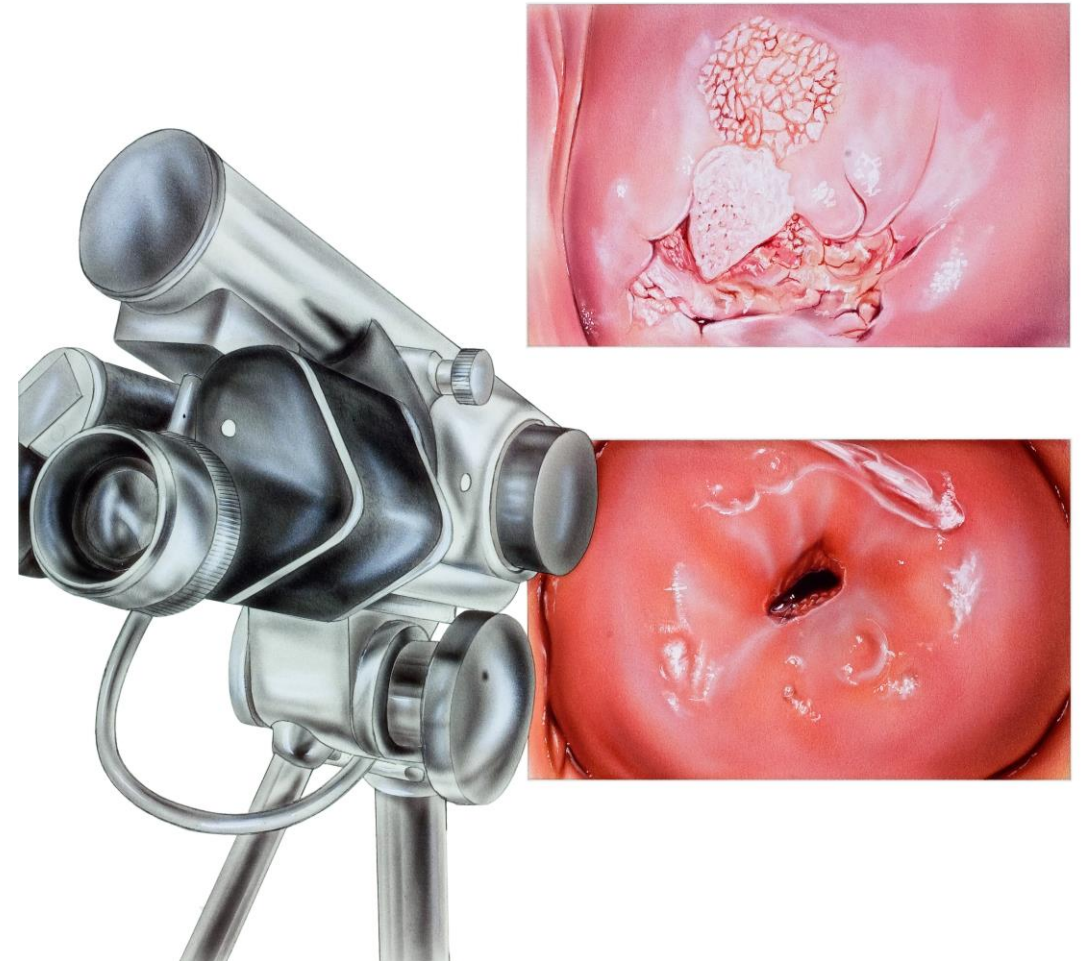
## Interpretation of Results

- Many potential **squamous cell abnormalities**
- Atypical squamous cells (ASC)
  - ASC-US: undetermined significance
  - ASC-H: cannot exclude a high-grade squamous intraepithelial lesion
- Low-grade squamous intraepithelial lesions (LSIL)
- High-grade squamous intraepithelial lesions (HSIL)
- Management based on age and HPV testing (if available)
- High-risk findings followed with **colposcopy**

# Abnormal Screening

## Follow-up Testing

- **Colposcopy with biopsy**
  - Use of a colposcope
  - Illuminated, magnified view of cervix
- Usually after abnormal Pap smear
- Or abnormal findings on pelvic exam
- Cervix washed with **acetic acid**
  - Neoplastic cells appear white
  - Thicker white area = more advanced lesion



# Abnormal Screening

## Follow-up Testing

- Areas consistent with dysplasia are biopsied
- White epithelium
- Abnormal or mosaic vascular patterns
- Punctate or satellite lesions
- Must visualize entire SCJ for satisfactory exam
  - “Inadequate” colposcopy: **endocervical curettage**

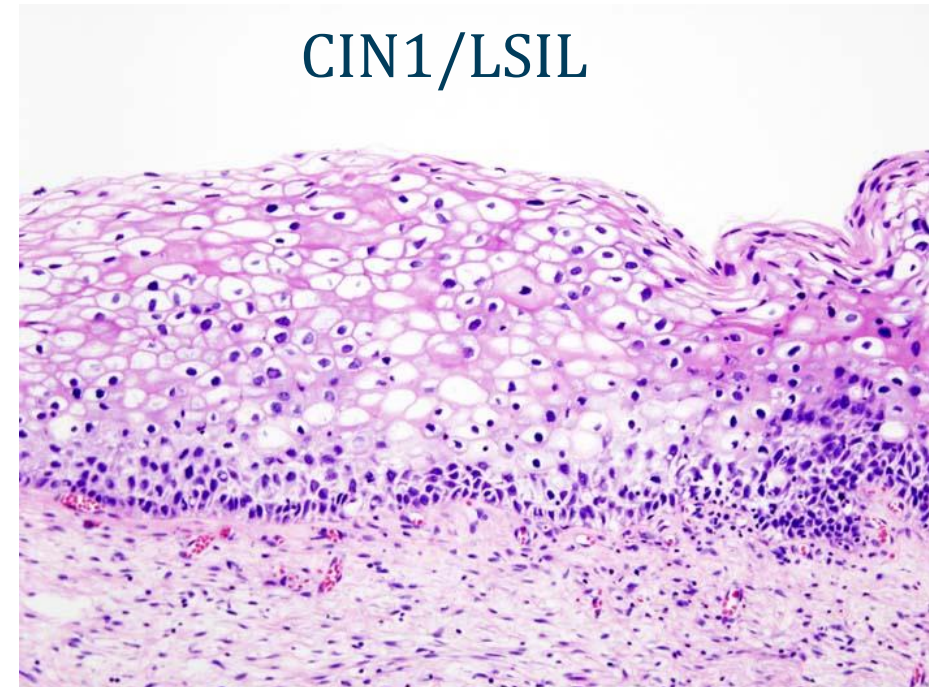
Squamocolumnar Junction



# Cervical Neoplasia

## Management of cervical neoplasia

- All patients: **HPV vaccination**
  - LSIL or HSIL not contraindications
  - Vaccination may prevent progression
- LSIL (CIN I): observation
  - Colposcopy and HPV testing at 1 year
  - Infection may clear
  - Persistent abnormalities → conization

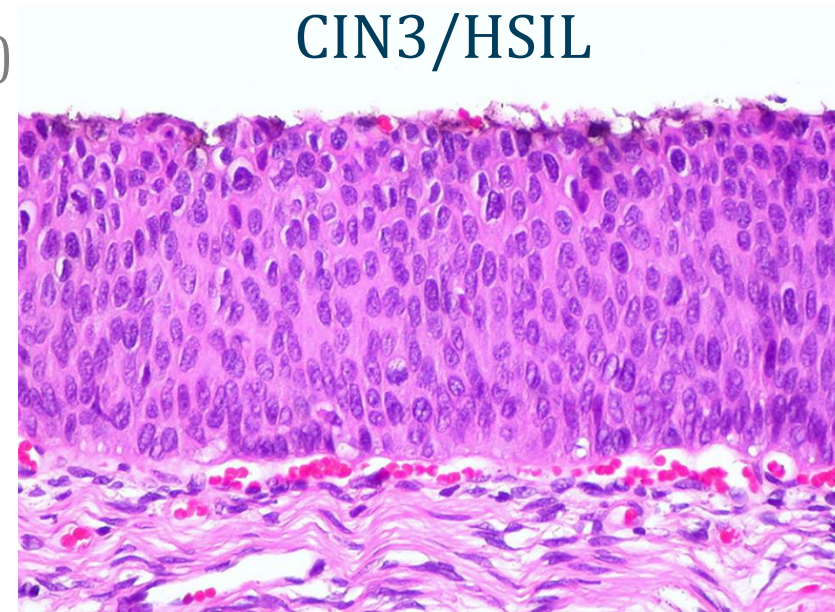




# Cervical Neoplasia

## Management of CIN

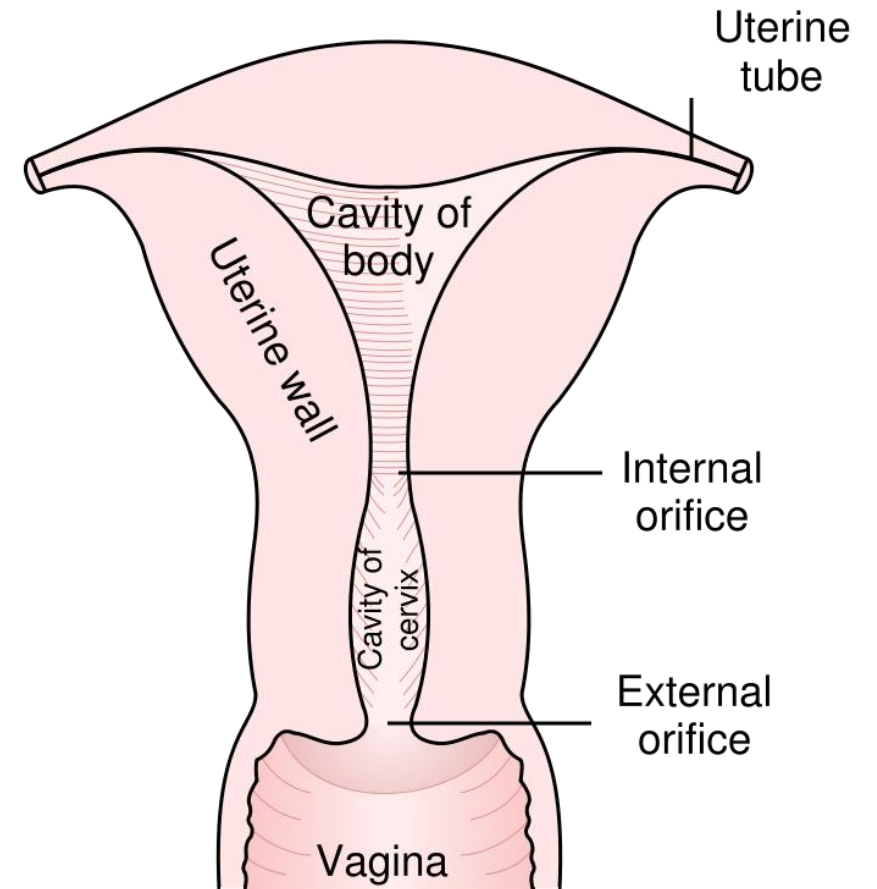
- HSIL (CIN II or CIN III): **cervical conization**
- Removal of a cone-shaped portion of the cervix
- Excision of transformation zone
  - Diagnostic and therapeutic
  - Usually requires general anesthesia
  - Electrocautery (loop electrosurgical excision procedure – LEEP)
  - Scalpel (cold knife biopsy)
  - Laser



# Cervical Neoplasia

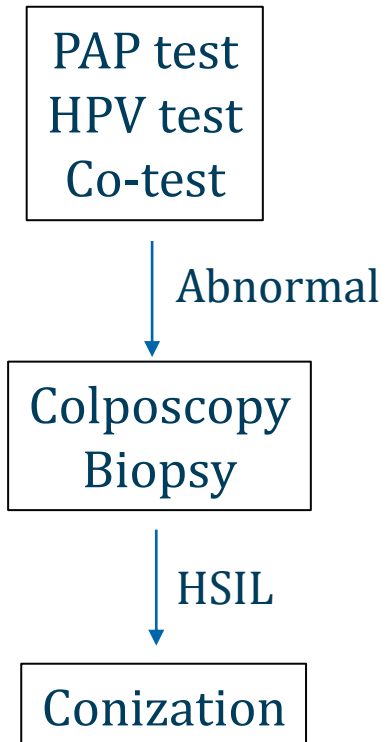
## Management of CIN

- Conization complications
  - **Cervical stenosis**: dysmenorrhea
  - **Cervical insufficiency**: preterm birth
- Post-conization follow-up\*
  - Testing at 6 months
  - Ideally HPV-based testing
  - PAP smear
  - Goal: negative testing after treatment





# Cervical Cancer Workup



# Cervical Carcinoma

## Management

- Staging with CT scan or PET
- Treatment based on stage (local spread, metastasis)
- Surgery, chemotherapy and radiation used

# Cervical Cancer Screening

## Pregnancy

- Screening for cervical cancer as per non-pregnant women
- Abnormal results followed with **colposcopy**
- Biopsy only if lesion appears **high-grade**
  - Raised masses, ulcerative lesions
- Excision only if invasive disease identified



# HPV Vaccine

- 9-valent vaccine available since 2016 in US
  - Types 6, 11, 16, 18, 31, 33, 45, 52, and 58
- ACIP Guidelines: **ages 11 to 12 years**
  - Females (1A) ad males (1B)
- If start before 15 years: **two doses**
  - Second at 6 to 12 months
- If start 15 or later: **three doses**
  - Zero, two and six months



# Uterine Cancer

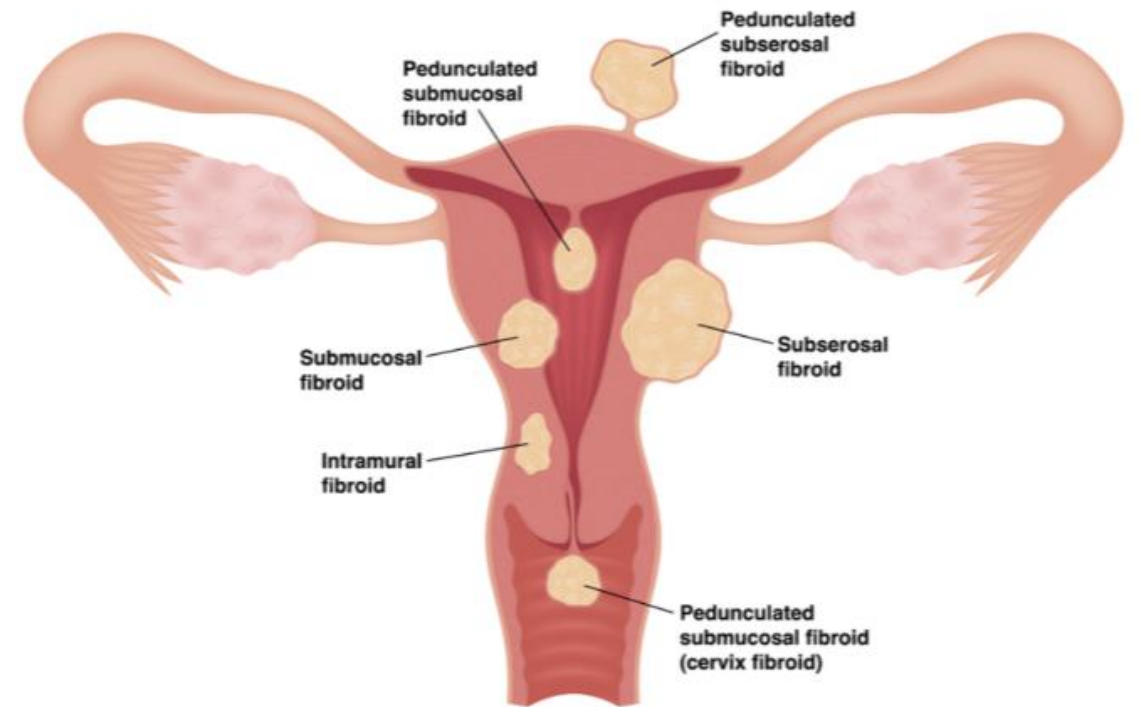
Jason Ryan, MD, MPH



# Leiomyoma

## Fibroid

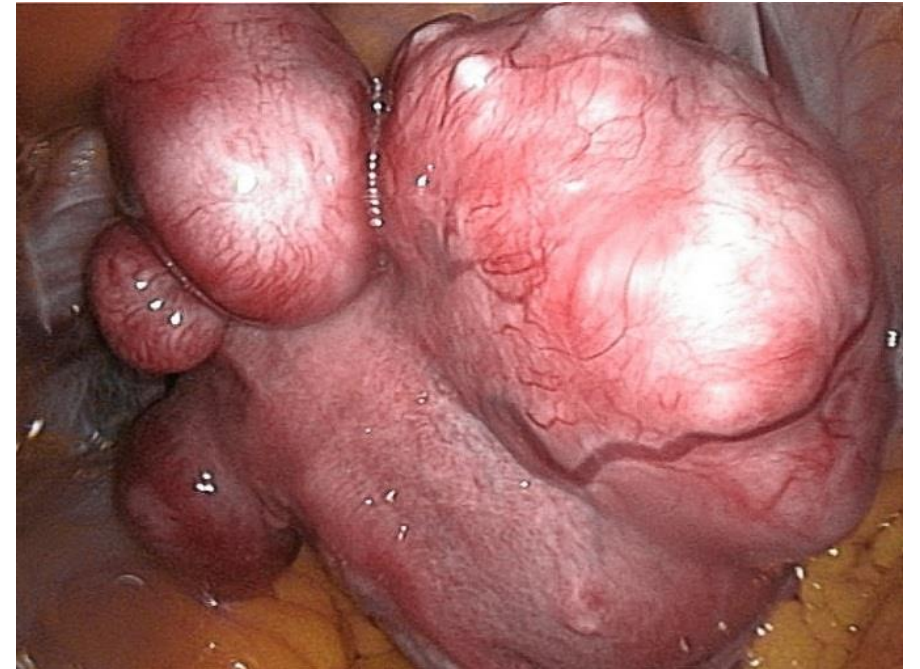
- Benign tumor of myometrial smooth muscle
- Occur in pre-menopausal women
- Growth stimulated by estrogen
- Usually resolve at menopause ( $\downarrow$  estrogen)
- Women commonly have multiple tumors
- Many locations within uterus
- Submucosal: highest AUB risk



# Leiomyoma

## Clinical Features

- Usually asymptomatic
- Bulk symptoms: pelvic-pain, bloating, constipation, urinary frequency/retention
- Abnormal uterine bleeding
- Dysmenorrhea
- Dyspareunia
- Often detected as pelvic mass on exam
- Uterine shape may be irregular
- Rarely can prolapse through cervical os





# Leiomyoma

## Diagnosis

- First-line test: **pelvic ultrasound**
- Hysteroscopy
  - Direct visualization of endometrial cavity
  - Diagnosis of fibroids intruding into uterine cavity
  - May miss subserosal fibroids
- Saline infusion sonography (sonohysterography)
  - Saline injected into uterus during TVUS
  - Detects small fibroids better than TVUS alone

Uterine Fibroid by US





# Leiomyoma

## Size-Date Discrepancy

- Fibroids may be undetected prior to pregnancy
- May lead to uterus **larger than expected**
- High **estrogen** levels lead to rapid fibroid growth
- Uterus larger than normal +/- irregular
- Most fibroids do not affect pregnancy
- Large, multiple fibroids can lead to adverse outcomes
- Fetal loss, placental abruption, preterm birth, malpresentation
- Fibroids will shrink post partum



# Leiomyoma

## Treatment

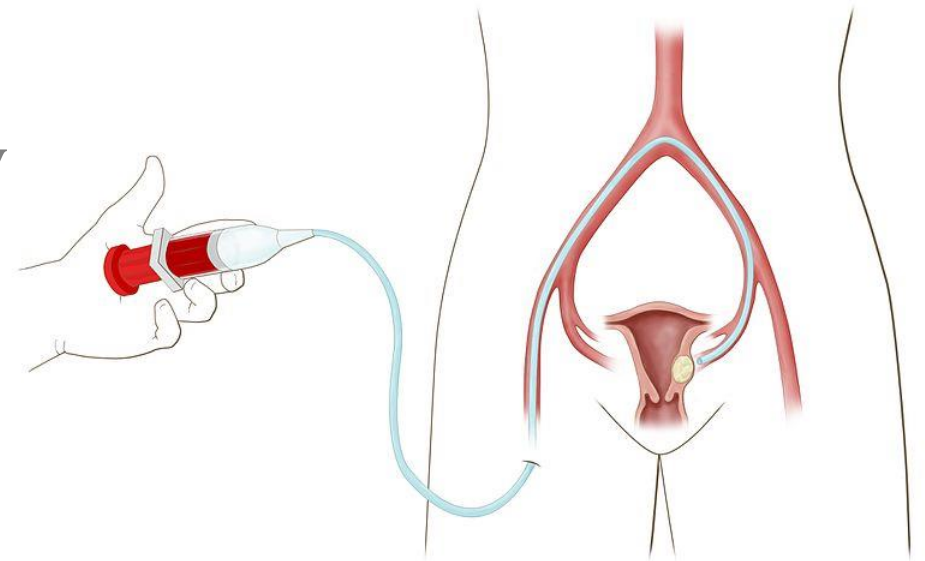
- Medical therapy: may reduce size and bleeding
  - COCs, progestins, LNG IUD or GnRH agonists
- Women who do not desire fertility
  - Hysterectomy
  - Myomectomy
  - Uterine artery embolization
- Women who desire fertility: **myomectomy**
  - Hysteroscopic myomectomy
  - Abdominal myomectomy



# Leiomyoma

## Uterine artery embolization

- Minimally-invasive option for treatment
- Improved bleeding and bulk symptoms
- Used in pre-menopausal women only
  - Most fibroids shrink after menopause
  - Enlarging fibroids after menopause → surgery
- Generally not used in women who desire fertility
  - Poor uterine perfusion limits pregnancy
  - Post-UAE pregnancies are possible however



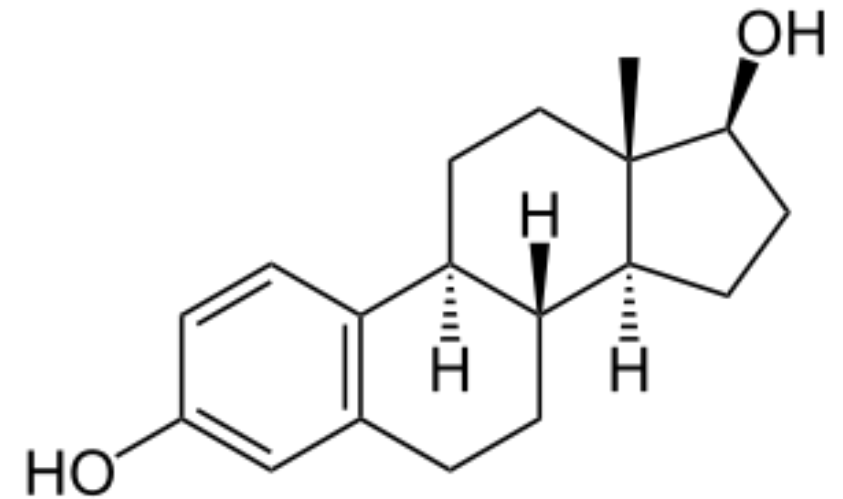
# Uterine Sarcoma

- Rare, malignant smooth muscle tumor of uterus
- Usually occurs in post-menopausal women
- Usually a single large mass
- May cause bulk symptoms
- May cause post-menopausal bleeding
- Increased risk with tamoxifen

# Endometrial Malignancy

## Estrogens

- Exposure drives endometrial growth
- Growth opposed by progesterone
- Excessive **unopposed estrogen** → abnormal growth
- Uterine polyps
- Endometrial hyperplasia
- Endometrial carcinoma



Estradiol

# Endometrial Malignancy

## Unopposed estrogen sources

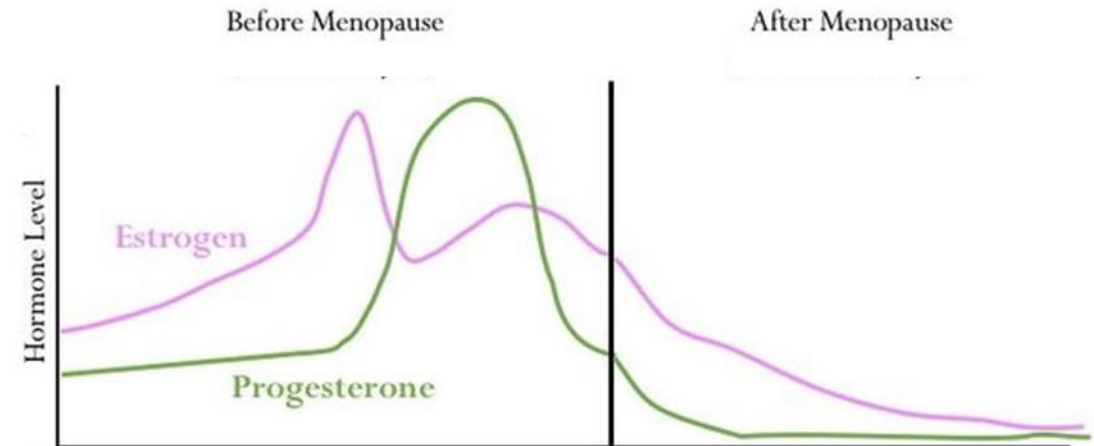
- **Obesity**
  - Androgens to estrogens in adipose tissue
- Tamoxifen
- Anovulation
  - Ovaries produce estrogen not progesterone
  - Common in PCOS
  - Common near menopause
- Estrogen-secreting tumors
- Hormone replacement



# Endometrial Malignancy

## Unopposed estrogen sources

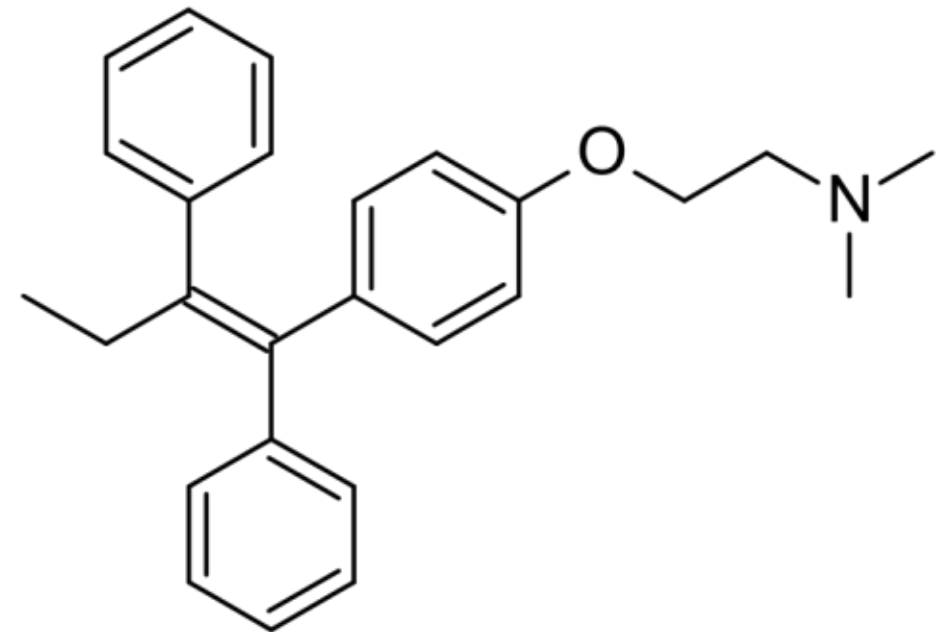
- Pre-menopause
  - Most estrogen from ovaries
  - Occurs as part of menstrual cycle
  - Opposed by progesterone
- Post-menopause
  - Ovarian estrogen declines and eventually stops
  - Most estrogen from **adipose tissue**
  - Unopposed by progesterone



# Tamoxifen

- Selective estrogen receptor modulator (SERM)
- Competitive antagonist of **breast estrogen receptor**
  - Used in ER positive (ER+) breast cancer
- **Estrogen agonist** in other tissues (bone/uterus)
- Partial agonist to endometrium
- Endometrial proliferation
  - Polyp formation (up to 36% of women)
  - Hyperplasia
- Associated with endometrial cancer and sarcoma

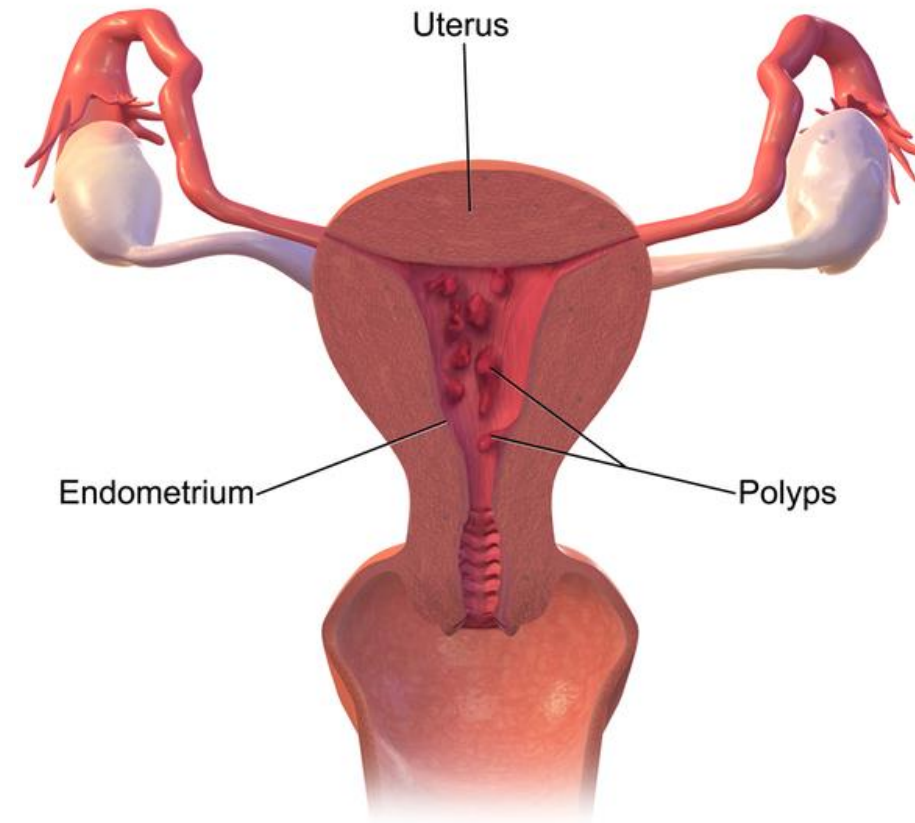
Tamoxifen





# Endometrial Polyps

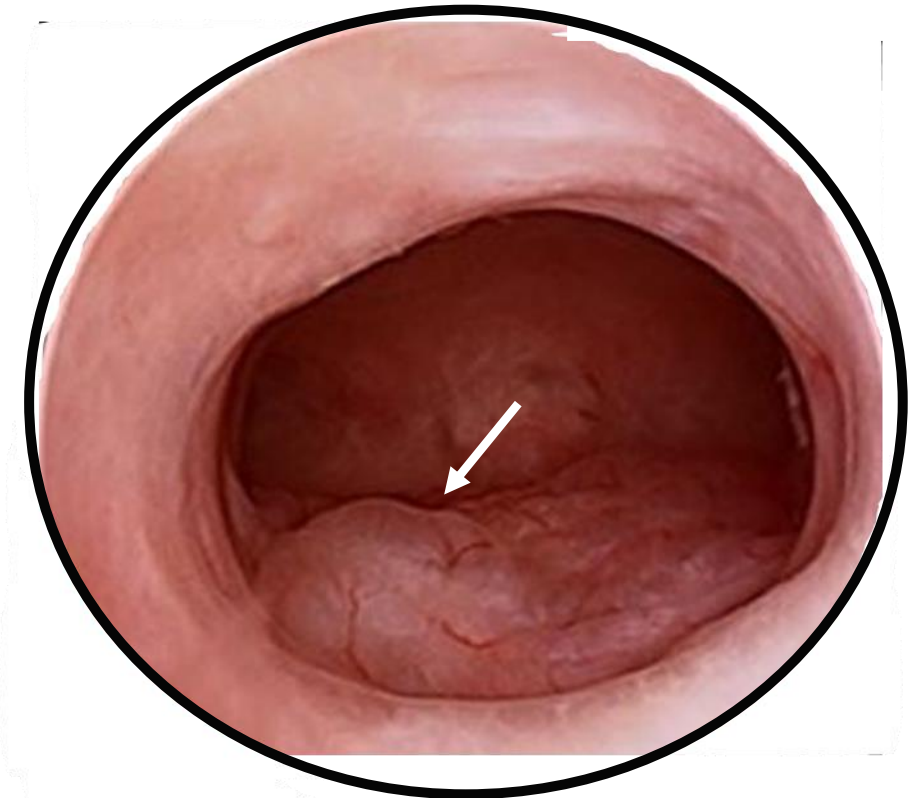
- Hyperplastic growth of glands and stroma
- Most benign (95%)
- Small risk of malignancy, especially post menopause
- Project from endometrium (“exophytic mass”)
- Often asymptomatic
- May cause painless uterine bleeding



# Endometrial Polyps

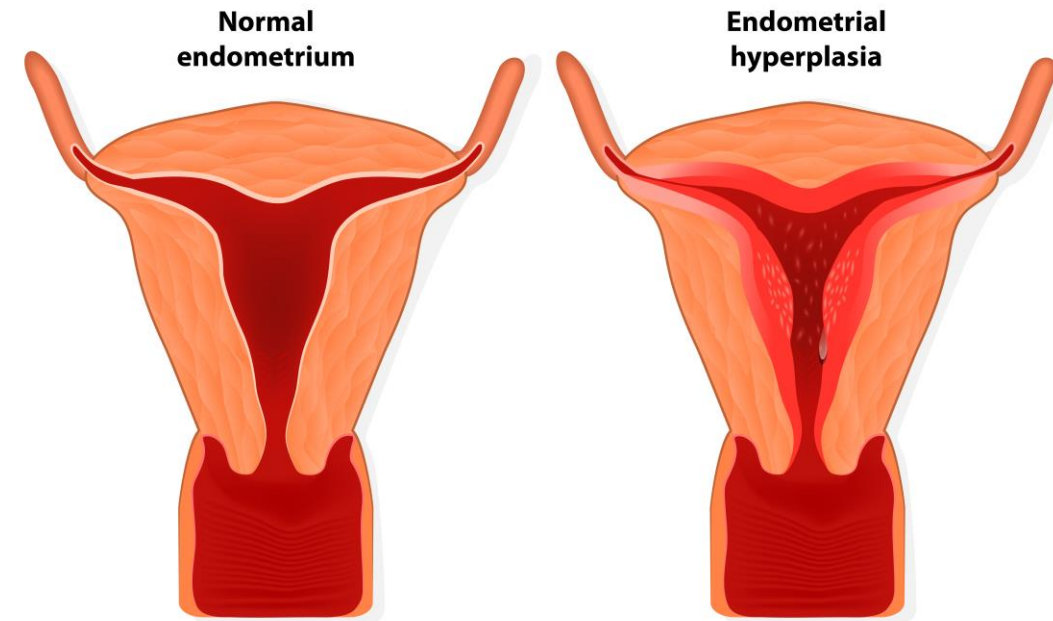
- Associated with **unopposed estrogen**
- Diagnosis: TVUS or hysteroscopy
- Can be removed in office during hysteroscopy
- Premenopausal women: removal for bleeding
  - Or high-risk patient for cancer
- Postmenopausal women: polypectomy for all

Endometrial Polyp



# Endometrial Hyperplasia

- Stimulation of endometrial growth by unopposed estrogen
- Absence of progesterone stimulation/withdrawal
- Often occurs in **peri/postmenopausal women**
  - Menstruation has slowed or stopped
  - Anovulation → no progesterone from ovary
  - Any estrogen source → hyperplasia

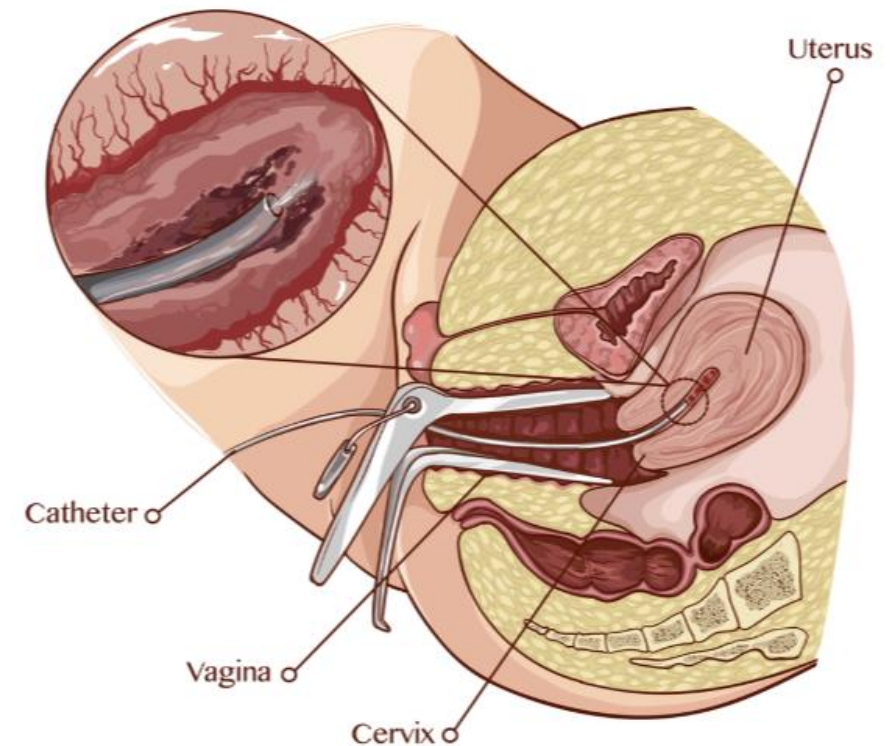


# Endometrial Hyperplasia

## Clinical Features

- **Abnormal uterine bleeding**
- Same presentation as endometrial carcinoma
- Same risk factors as endometrial carcinoma
- Diagnosis: **endometrial biopsy**
  - Performed in all women with AUB and risk factors
- Pap smear: may show endometrial cells
  - Atypical glandular cells or endometrial cells
  - Followed by endometrial biopsy in high-risk cases

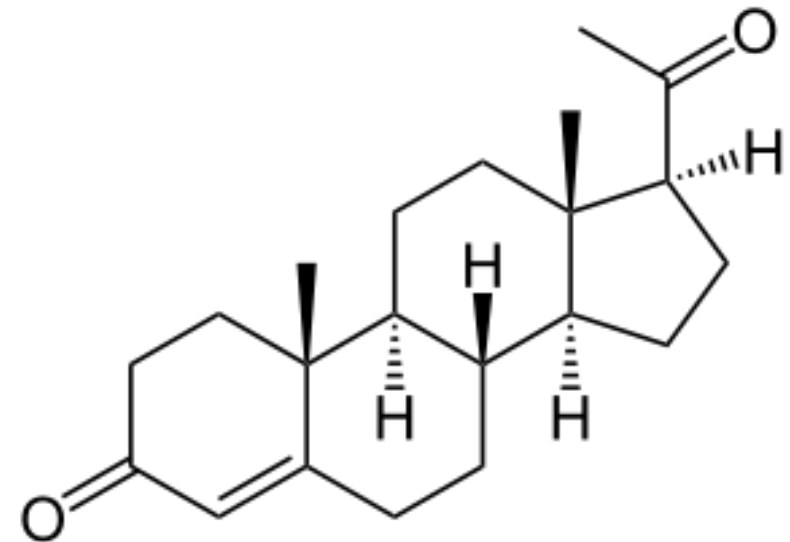
## Endometrial Biopsy



# Endometrial Hyperplasia

## Treatment

- Treat source of estrogen if possible
  - Anovulation
  - Obesity
- Low risk forms: **progestins**
  - Often levonorgestrel IUD
  - Oppose estrogen effects
  - Reverse hyperplasia
  - Improve bleeding
- High risk forms: hysterectomy



Progesterone

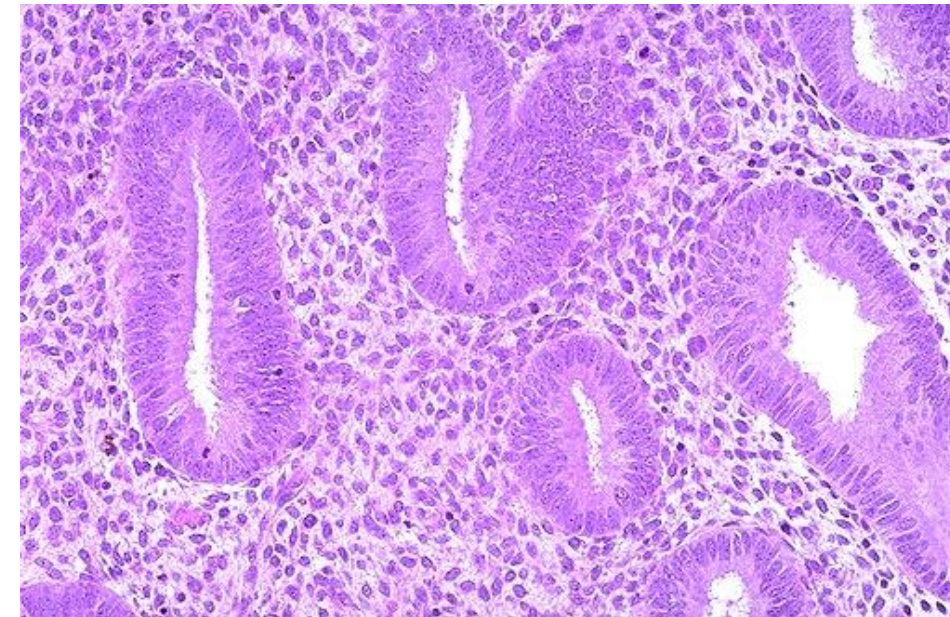


# Endometrial Hyperplasia

## Interpretation of Biopsy Results

- **Proliferative endometrium**
  - Not a form of endometrial hyperplasia
  - Endometrium similar to proliferative menstrual phase
  - Treatment based on patient symptoms (e.g., bleeding)

Proliferative Endometrium

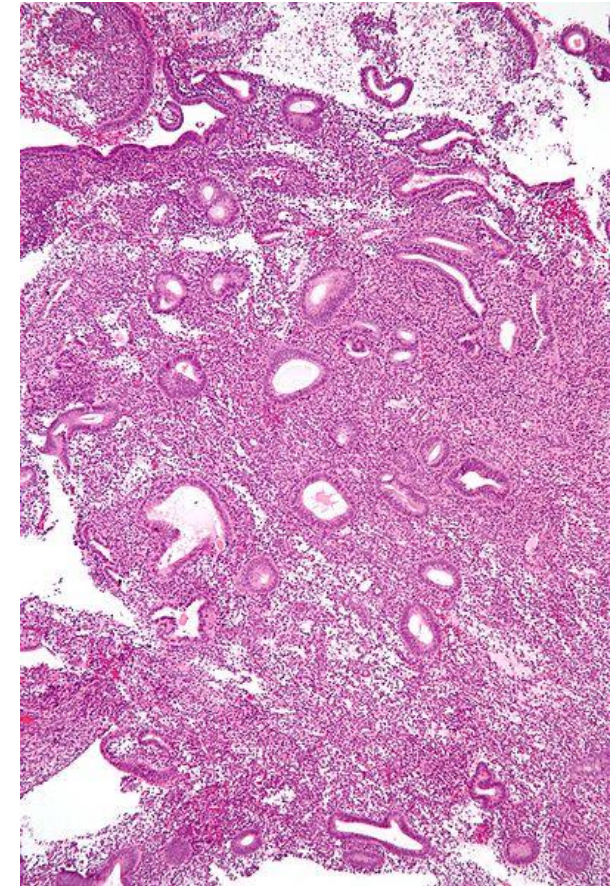


# Endometrial Hyperplasia

## Interpretation of Biopsy Results

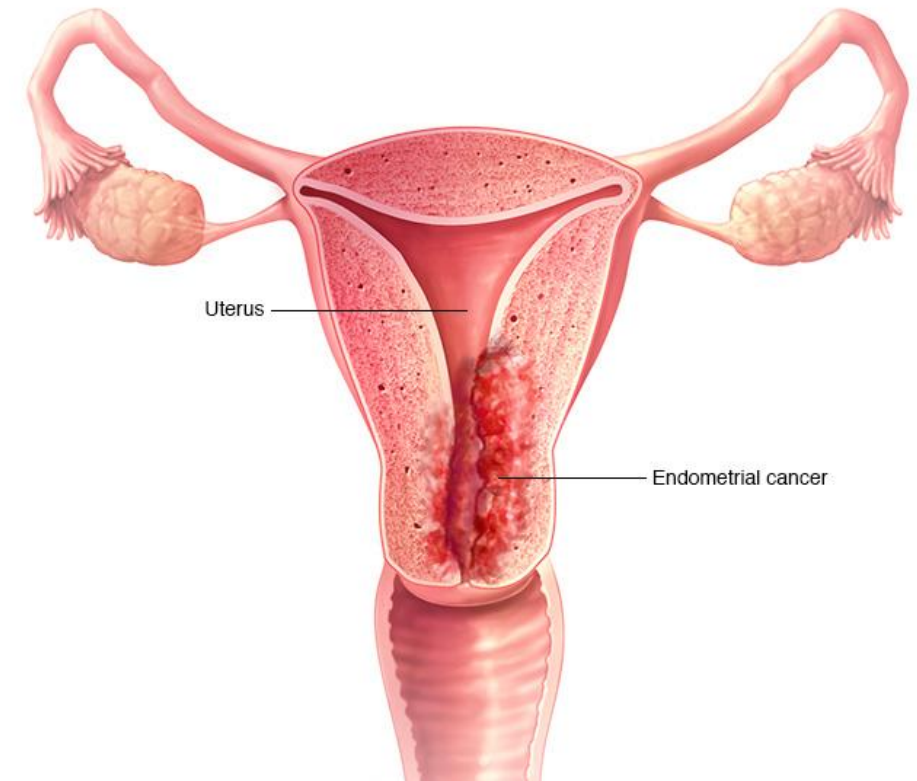
- **EH without atypia\***
  - Low cancer risk
  - Premenopause: observation or progestins
  - Postmenopause: progestins
- **EH with atypia\*: hysterectomy**
  - Represents malignant neoplasm
  - Managed with progestins until childbearing completed
  - Treated with hysterectomy if childbearing not desired

EH without atypia



# Endometrial Carcinoma

- Most common gynecologic cancer
- Most common in **post menopausal women**
  - Average age of diagnosis ~60 years old
  - Menopause: anovulation → ↑ unopposed estrogen
- Classic presentation: **abnormal uterine bleeding**



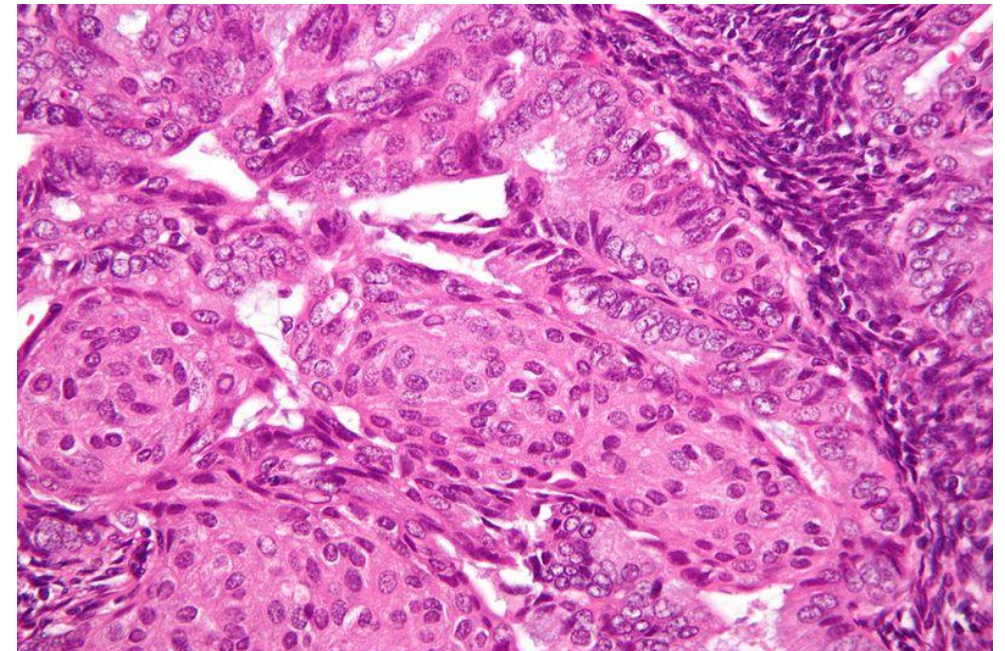


# Endometrial Carcinoma

## Major Subtypes

- Endometrioid subtype (type I)
  - Estrogen-dependent hyperplasia
  - Resembles endometrium (“Endometrioid”)
- Serous subtype (type II)
  - Estrogen independent
  - Arise from atrophic endometrium post-menopause
  - Strong association with p53 mutations
  - Tumor suppressor gene
  - Mutated in 90% tumors
  - Poor prognosis (more aggressive type)

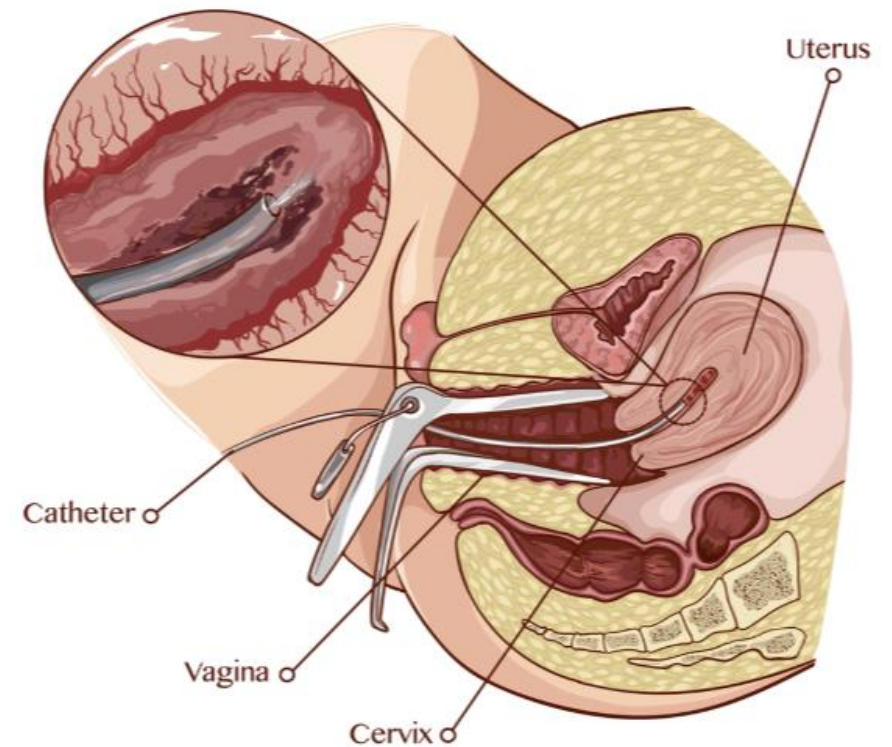
Endometrioid Subtype



# Endometrial Carcinoma

- Diagnosis: endometrial biopsy
- Standard treatment: **total abdominal hysterectomy**
  - Radiation for locally invasive disease
  - Chemotherapy and radiation for metastatic disease
- Progestins sometimes used in low risk forms
  - Often in young nulliparous patients
  - May induce remission in some cases

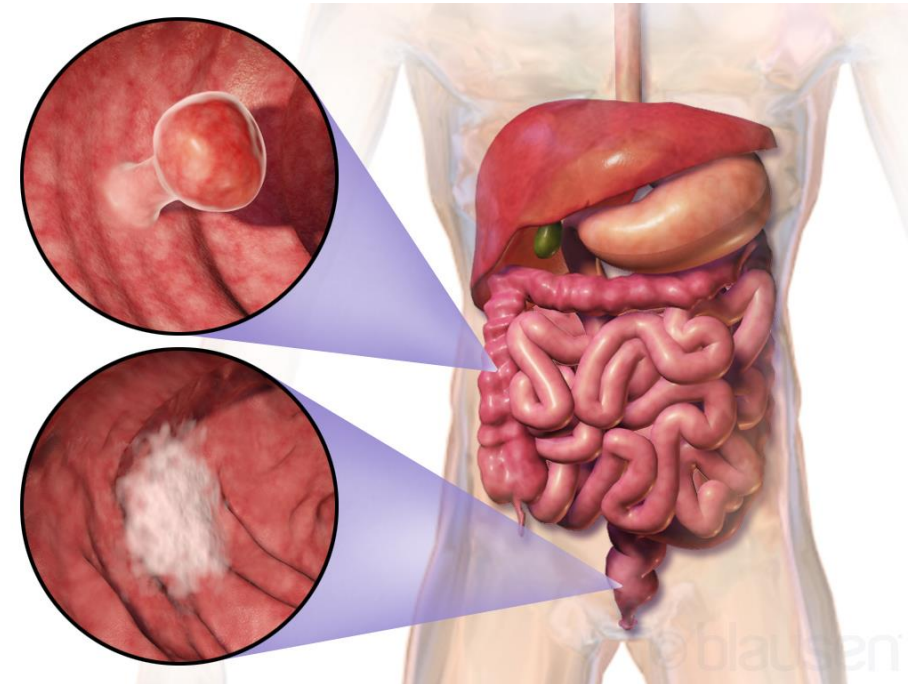
Endometrial Biopsy



# HNPPC

## Hereditary Non-Polyposis Colorectal Cancer/Lynch Syndrome

- Germline mutation in DNA mismatch repair genes
- Leads to colon cancer
- Also increased risk of **endometrial cancer**
  - Most common non-colon malignancy
- Regular endometrial sampling
  - Guidelines vary
  - Beginning age 30 to 35
  - Or 10 years prior to earliest family cancer diagnosis



# Adnexal Masses

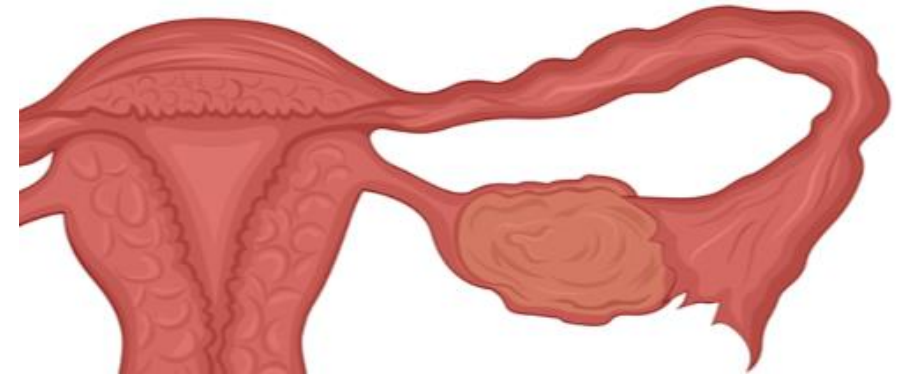
Jason Ryan, MD, MPH



# Adnexal Mass

- Adnexa: appendages of uterus
- Ovary, fallopian tubes, ligaments
- Adnexal mass: common gynecologic problem
- Many ovarian causes: cysts, benign masses, malignancy
- Endometrioma
- Tubo-ovarian abscess
- Ectopic pregnancy
- Bowel disorders

Uterus and Ovary



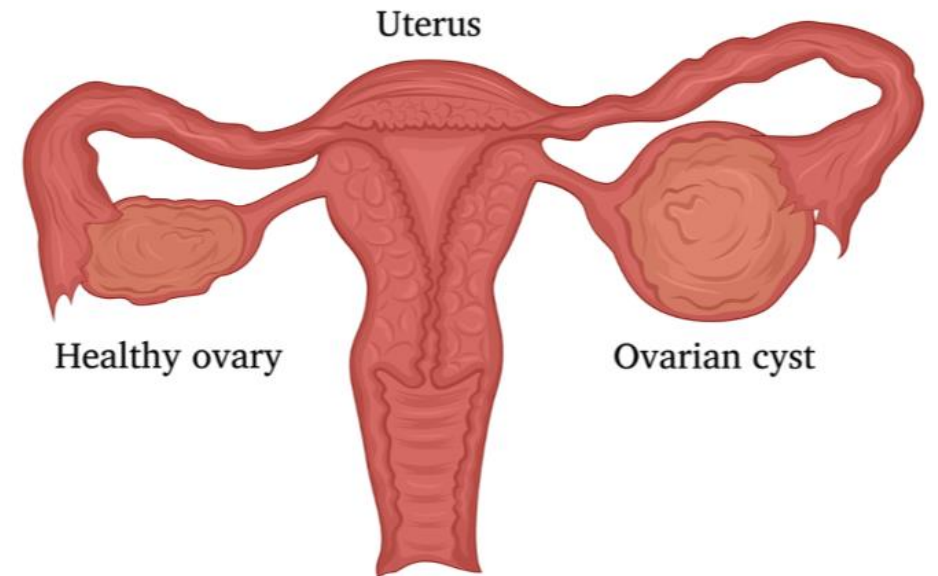


# Ovarian Masses

## Basic Principles

- May cause pelvic pain
- May be detected by physical exam
- Common cause: functional ovarian cyst
  - Derive from follicles or corpus luteum
- Major concern: malignant neoplasm

## Ovarian cyst

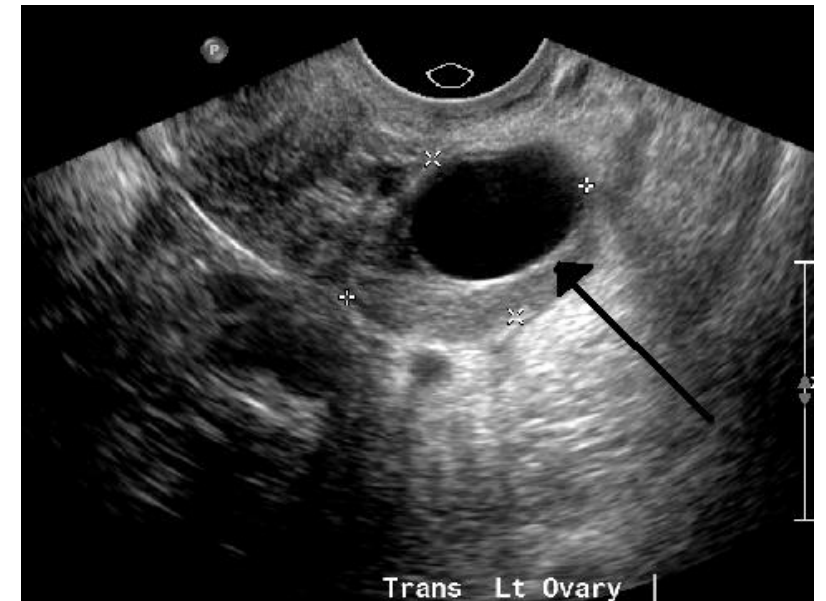


# Ovarian Masses

## Basic Principles

- Best first-test: **pelvic ultrasound**
  - MRI used in unclear cases
- Benign US findings: reassurance +/- follow-up imaging
- Concerning US findings: surgical removal

Ovarian Cyst



# Follicular Cysts

- Common cause of ovarian mass in young women
- Derive from an ovarian follicle (1<sup>st</sup> half cycle)
- Failure of ovarian follicle to rupture or rupture/reseal
- Filled with estrogen
- May release estrogen → endometrial growth
- May cause **pain plus irregular bleeding**
- Thin-walled, fluid-filled, no vascularity
- No specific treatment - usually self-limited



James Heilman, MD/Wikipedia

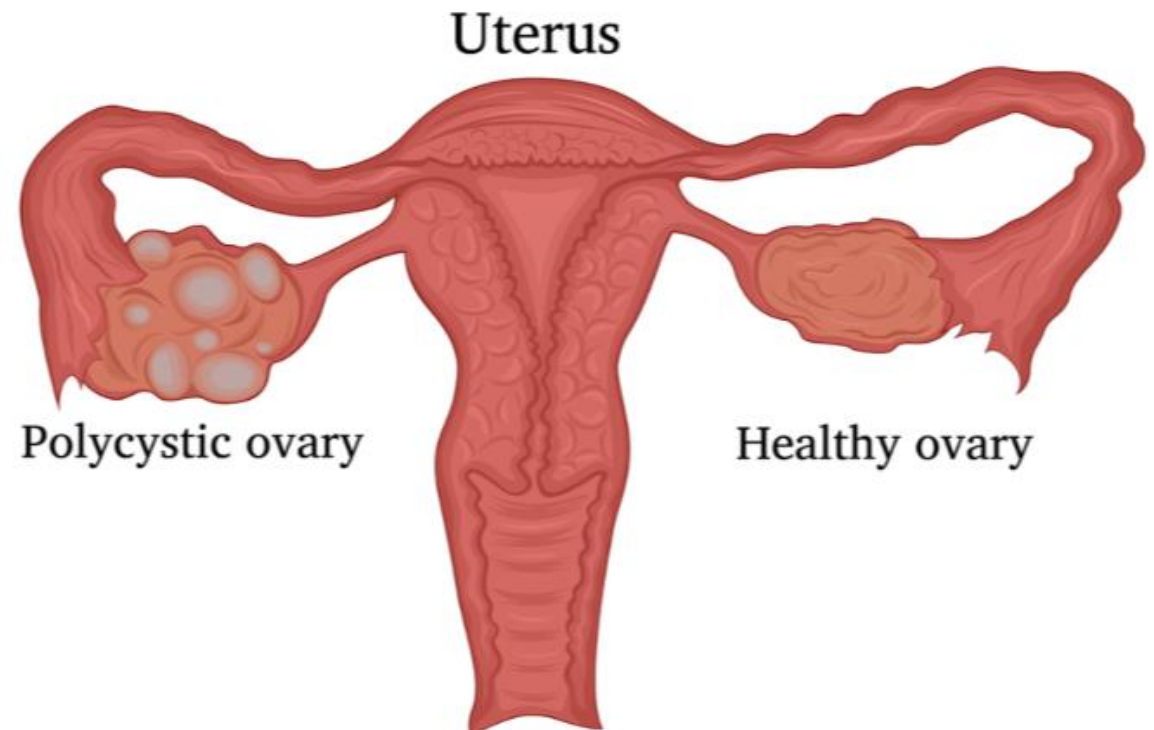


# PCOS

## Polycystic Ovarian Syndrome

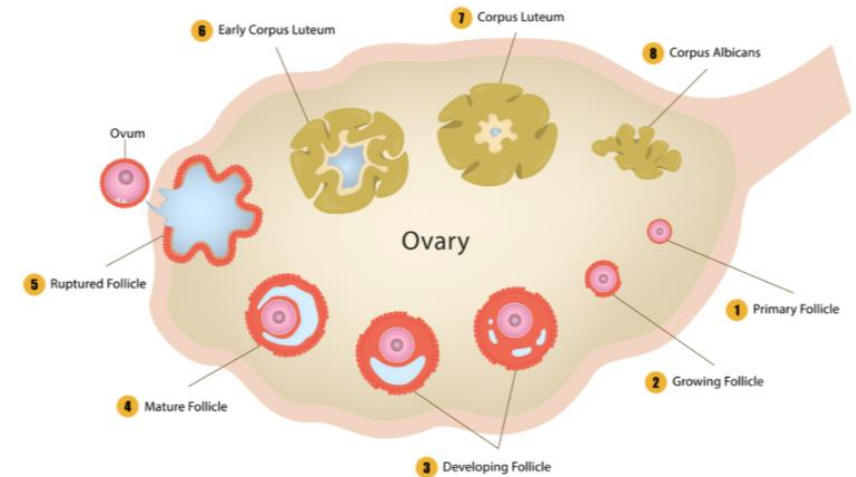
- **Multiple follicular cysts**
- Chronic anovulation (amenorrhea)
- Excess androgens
- Insulin resistance/diabetes

## Polycystic ovary



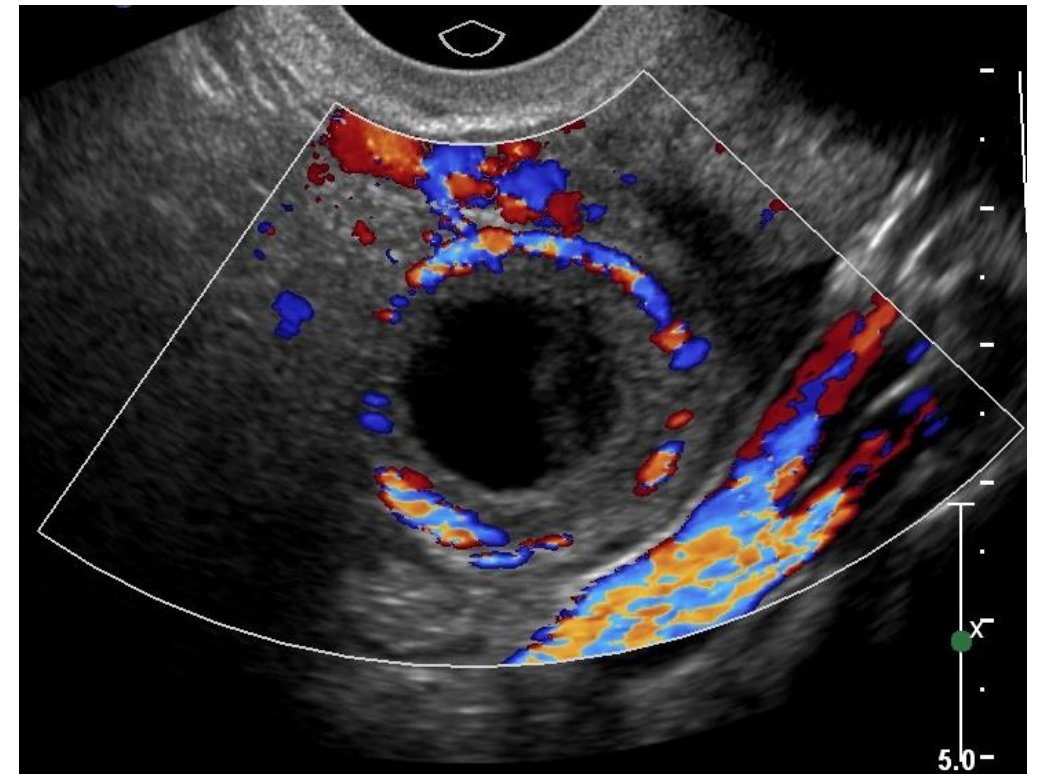
# Corpus Luteal Cyst

- Corpus luteum forms 2<sup>nd</sup> half of menstrual cycle
- Failure to involute → cyst
- May continue producing progesterone
- May delay menstruation
- Classic presentation: pain, missed period, mass
- Can mimic ectopic pregnancy (check hCG)
- Thick-walled with peripheral vascularity
- No specific treatment: self-limited
- Recurrent cysts: COCs



# Ring of Fire Sign

- Identified by color Doppler during US exam
- Indicates peripheral hypervascularity
- Seen in **corpus luteal cysts**
- Also seen with **ectopic pregnancy**

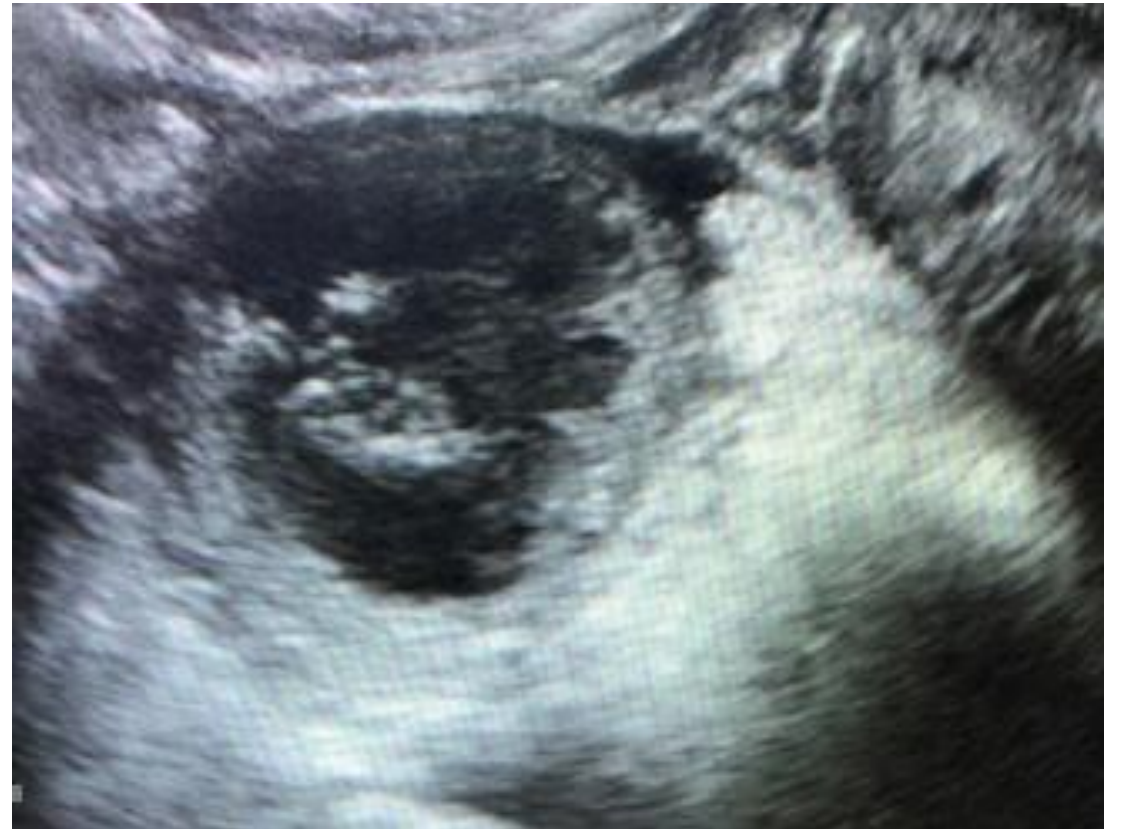


# Luteal-Phase Cyst

Corpus Hemorrhagicum or Bleeding Corpus Luteum

- Rare form of corpus luteal cyst
- Spontaneous hemorrhage
- Rapid enlargement of cyst
- Acute onset of pain
- May rupture → peritonitis

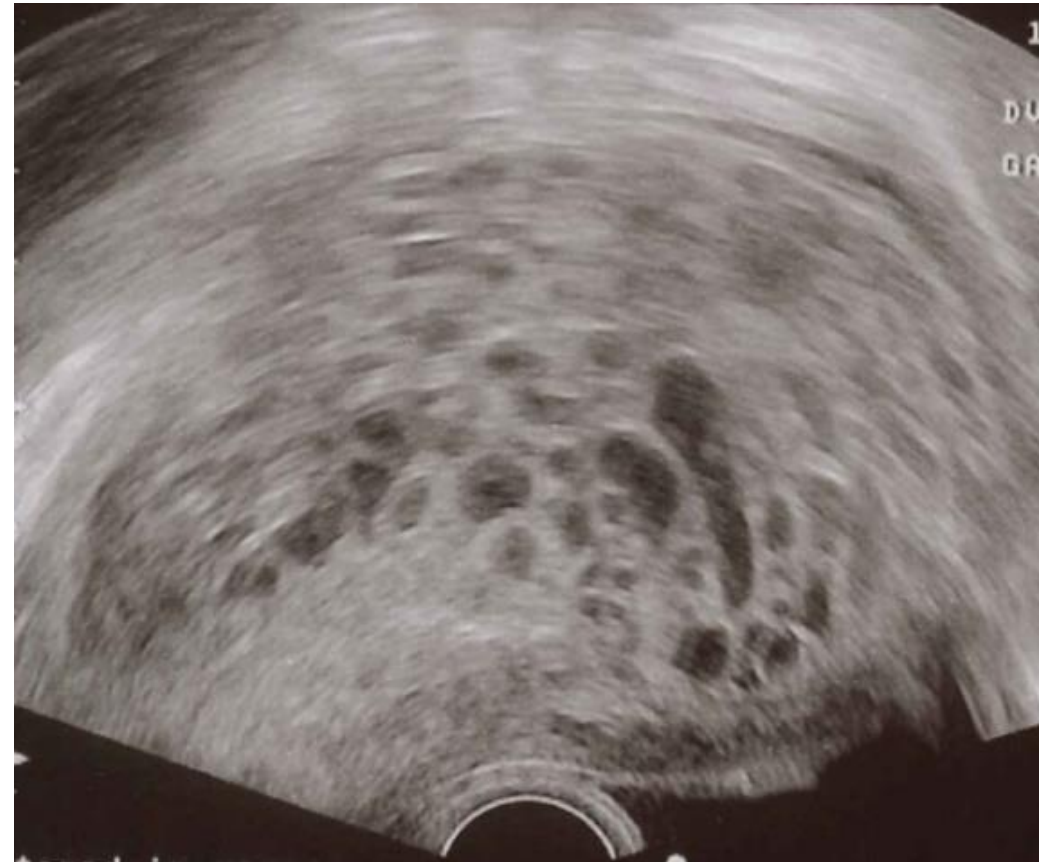
Complex Hemorrhagic Cyst



# Theca-Lutein Cysts

- Usually **bilateral**, multiple cysts
- Associated with high  **$\beta$ -hCG levels**
  - Twins
  - Molar pregnancy
- Luteinized theca cells with edema
  - Hyperplasia of theca cells
- Benign
- Usually regress

Molar Pregnancy



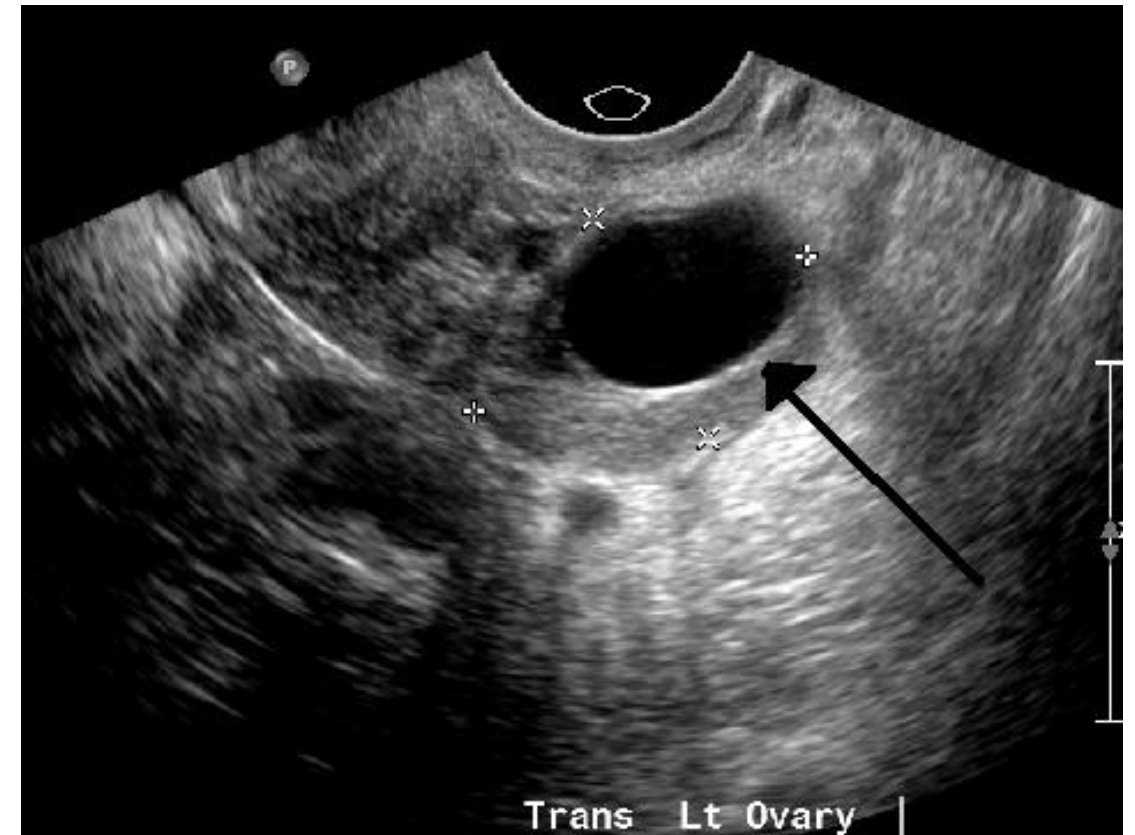


# Adnexal Mass

## Workup

- Best first test: pelvic ultrasound
- **Simple cysts**
  - Round or oval
  - Thin walls
  - Anechoic (dark) fluid
- **Complex cysts**
  - Thick septations
  - Soft tissue elements
  - Projections (“excrescences”)
  - Mounds of tissue in cyst (“papillations”)

Ovarian Cyst



# Adnexal Mass

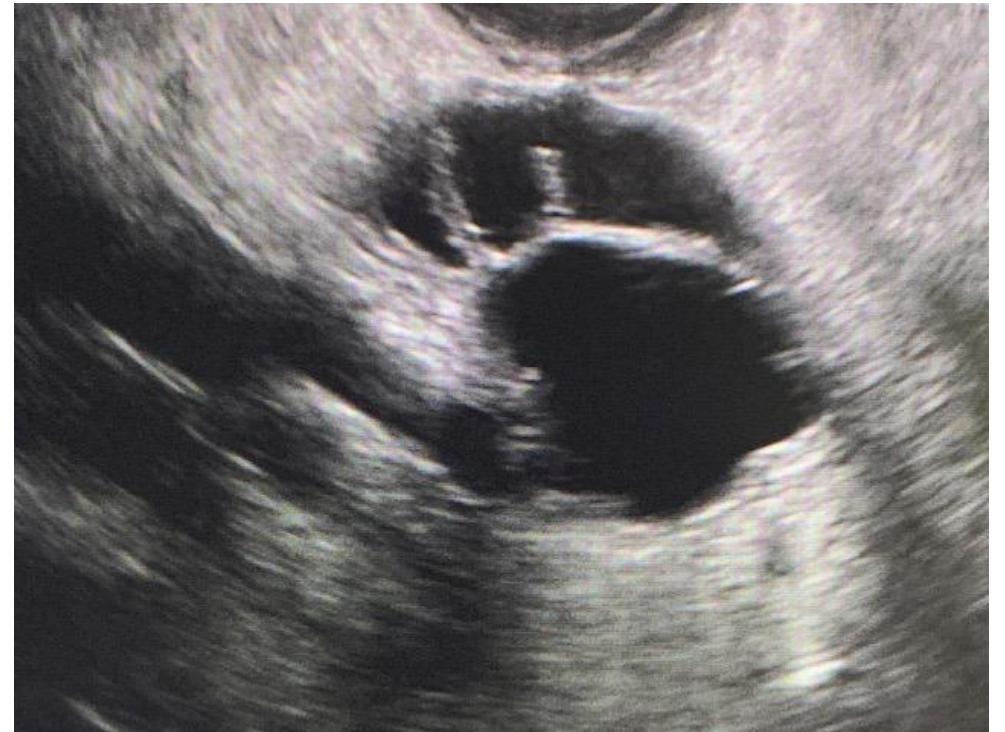
## Workup

Simple Cyst



James Heilman, MD/Wikipedia

Complex Cyst



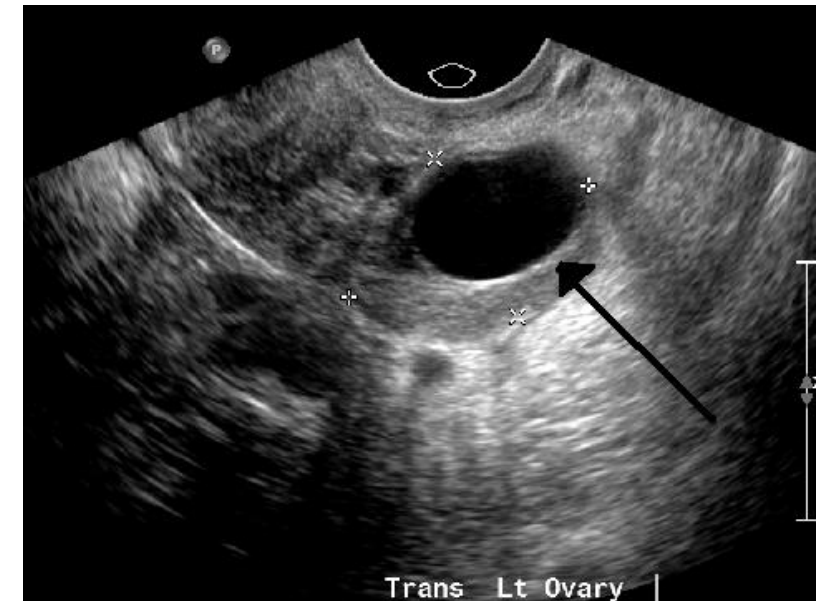
Public Domain

# Ovarian Cysts

## Management

- **Simple cysts: premenopausal women**
  - Cysts less than 5 cm normal finding
  - Larger cyst followed for resolution
- **Simple cysts: postmenopausal women**
  - Small risk of malignancy if > 3 cm
  - Less than 3cm: check CA-125
  - Larger than 3cm: follow-up imaging
- **Complex cysts:** surgical removal
- All symptomatic cysts followed for resolution

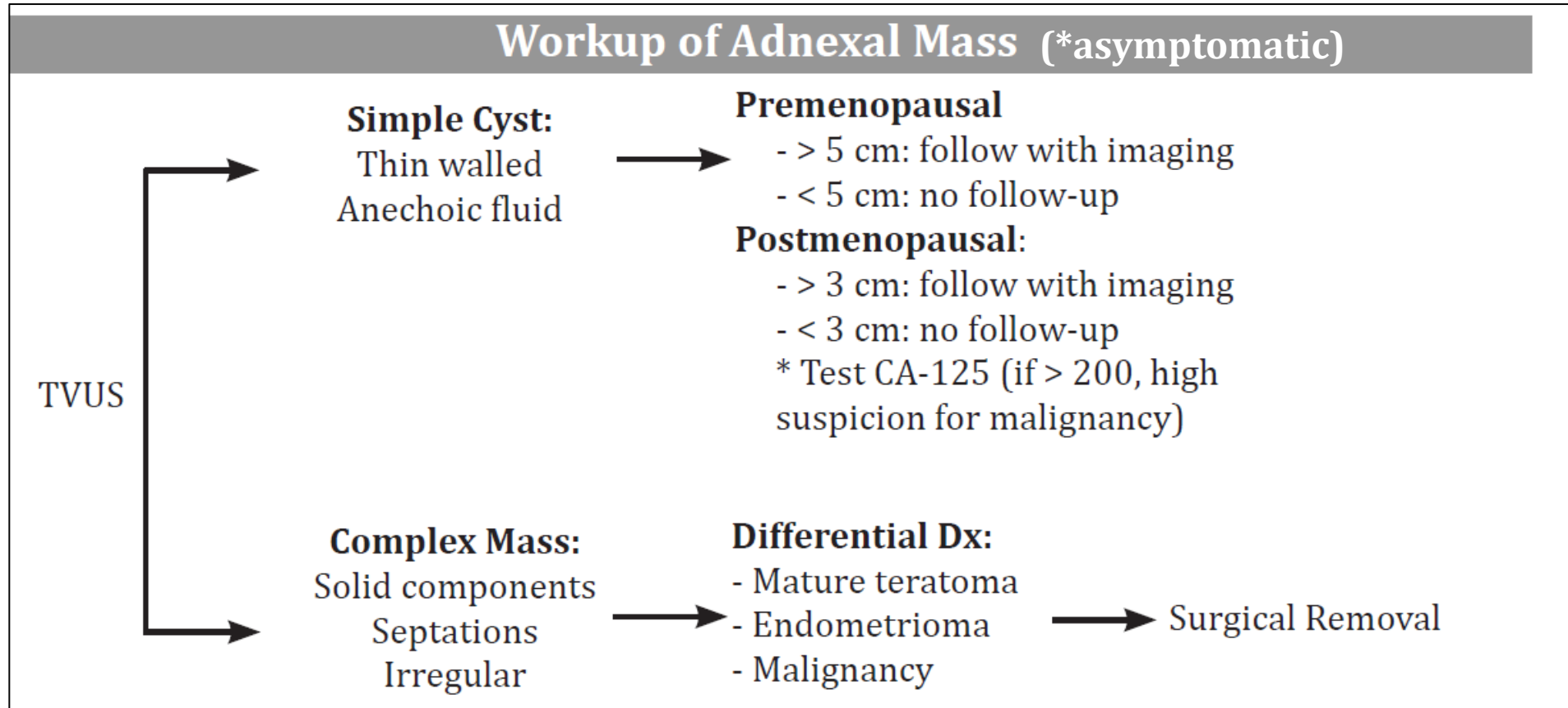
Ovarian Cyst





# Adnexal Mass

## Workup



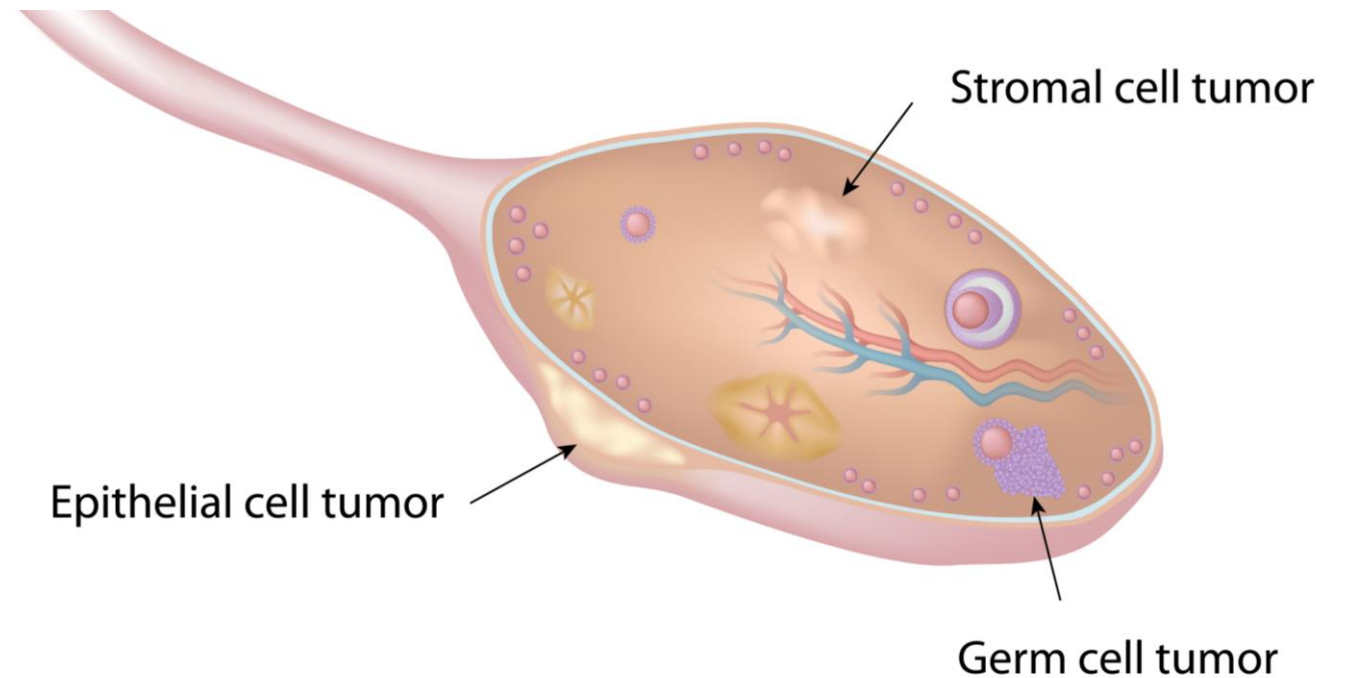
# Ovarian Neoplasia

Jason Ryan, MD, MPH



# Ovarian Neoplasia

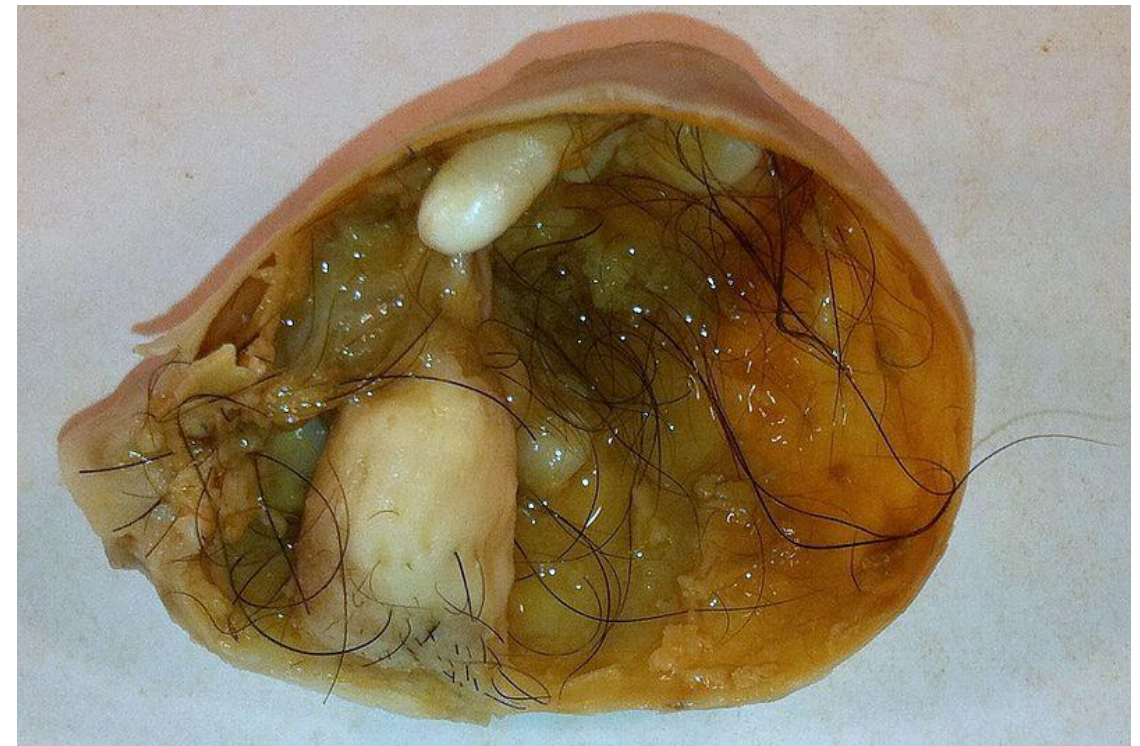
- Classified by ovarian cell type of origin
- Stromal tumors (connective tissue)
- Germ cell tumors
- Epithelial cell tumors



# Teratoma

- Most common overall germ cell tumor
- Cells from all three germ layers
  - Ectoderm (skin, hair follicles)
  - Endoderm (lung, GI)
  - Mesoderm (muscle, cartilage)
- Benign form: dermoid cyst
- Malignant form: immature teratoma

Benign Cystic Teratoma



# Dermoid Cyst

## Benign Cystic Teratoma

- “Dermoid” = skin like
- Contain hair, squamous cells, sebaceous (oily) material
- Walls may contain calcification, tooth-like material
- Usually asymptomatic and detected on exam
- Up to 20% bilateral → must evaluate both ovaries
- Characteristic features on ultrasound

Dermoid Cyst



# Dermoid Cyst

## Benign Cystic Teratoma

- High fat content makes tumors mobile
- Commonly lead to **ovarian torsion**
- May also rupture → peritonitis
- Small risk (< 1%) of malignant transformation
  - Elements may become malignant
  - Skin malignancies common
  - Squamous cell carcinoma most common
- Usually **removed surgically** to avoid complications



# Benign Stromal Cell Tumors

- Granulosa cell tumors
  - Produce estrogens
  - May cause **precocious puberty** in girls
  - Endometrial hyperplasia or carcinoma
  - Abnormal uterine bleeding
- Sertoli-Leydig cell tumors
  - Produce androgens
  - **Hirsutism**
  - Acne
  - Oligomenorrhea or amenorrhea
  - Breast atrophy

Hirsutism





# Ovarian Fibroma

- Benign tumors of fibroblasts
- Solid, white tumor
- Usually unilateral
- No hormone activity
- Occur in postmenopausal women
- Usually present as a pelvic/adnexal mass
- Two classic clinical associations
  - Ascites
  - Meigs syndrome



# Ascites and Meigs Syndrome

- Ascites occurs in 40% cases of ovarian fibroma
- **Meigs syndrome**
  - Ovarian fibroma
  - Ascites
  - Pleural effusion
- Etiology unclear
- Probably related to capillary leak from tumor factors
- Removal of tumor resolves ascites and effusion

Pleural Effusion

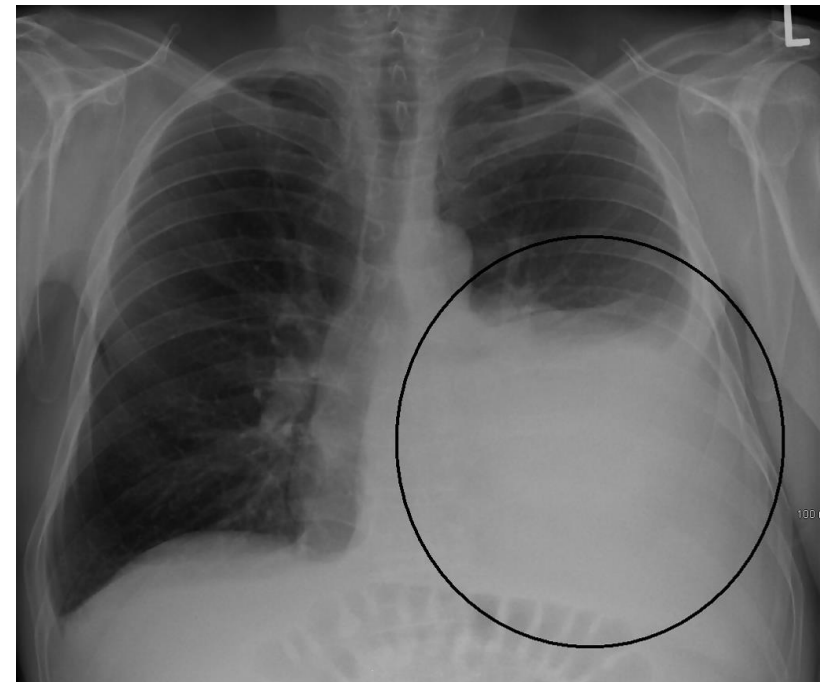
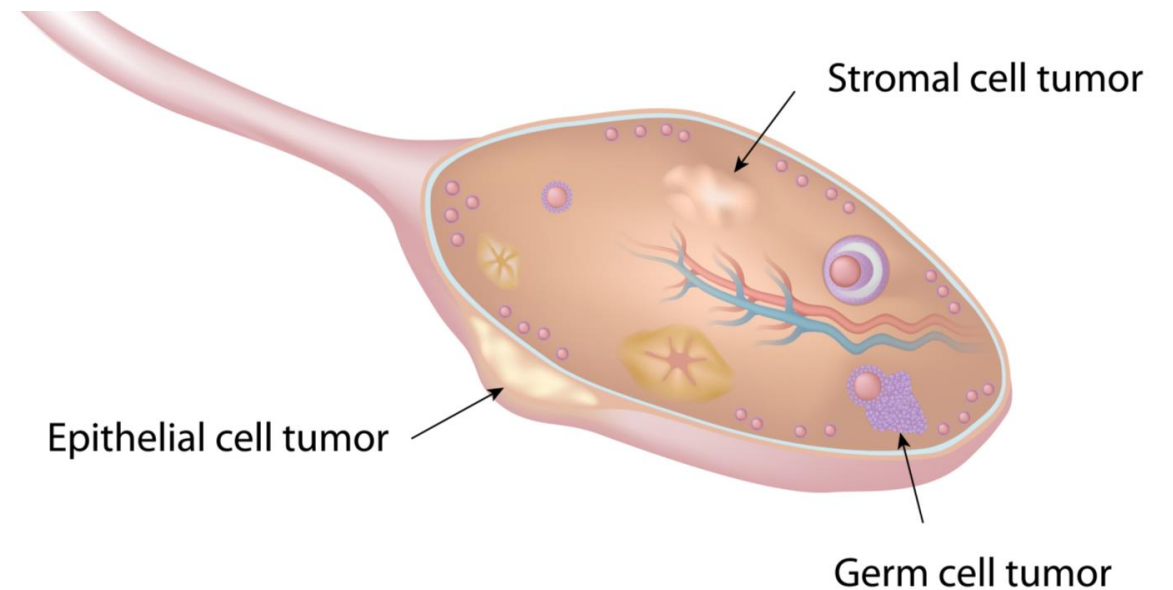


Image courtesy of James Heilman, MD

# Epithelial Cell Tumors

- Most common ovarian cancer
- Derive from ovarian epithelial lining
- Often spread directly into peritoneum
- Classic presentation is adnexal mass
- May cause vague abdominal symptoms
  - Bloating
  - Early satiety
  - Pelvic/abdominal pain
- Average age at diagnosis: 63 years old

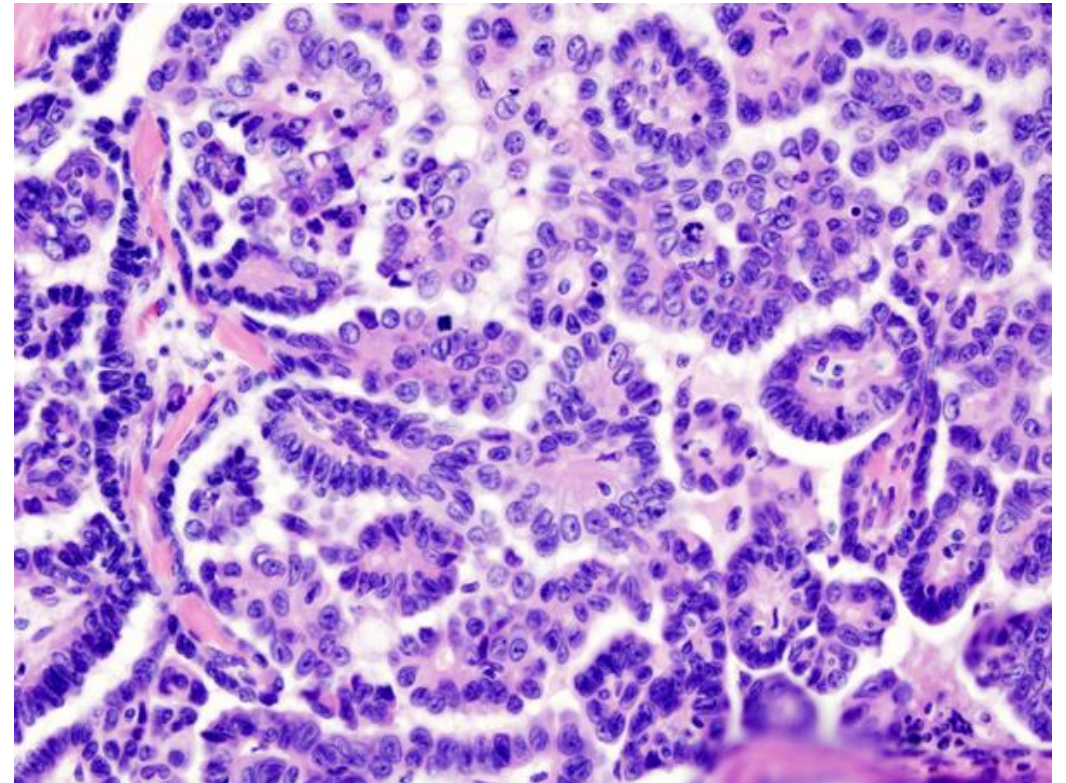


# Epithelial Cell Tumors

## Subtypes

- Determined by examination of removed ovary
- Serous (40%) – most common
  - Secrete serum (water)
- Mucinous (25%)
  - Secrete mucous
- Endometrioid (10%)
  - Similar to endometrium
  - Good prognosis
  - Sensitive to chemotherapy

Serous Cystadenocarcinoma



# Epithelial Cell Tumors

## Subtypes

- Occur as benign precursor lesions or malignant tumors
- Benign tumor identified → consider removal of other ovary
- Possible malignant transformation in remaining ovary

Benign	Malignant
Serous cystadenoma	Serous cystadenocarcinoma
Mucinous cystadenoma	Mucinous cystadenocarcinoma

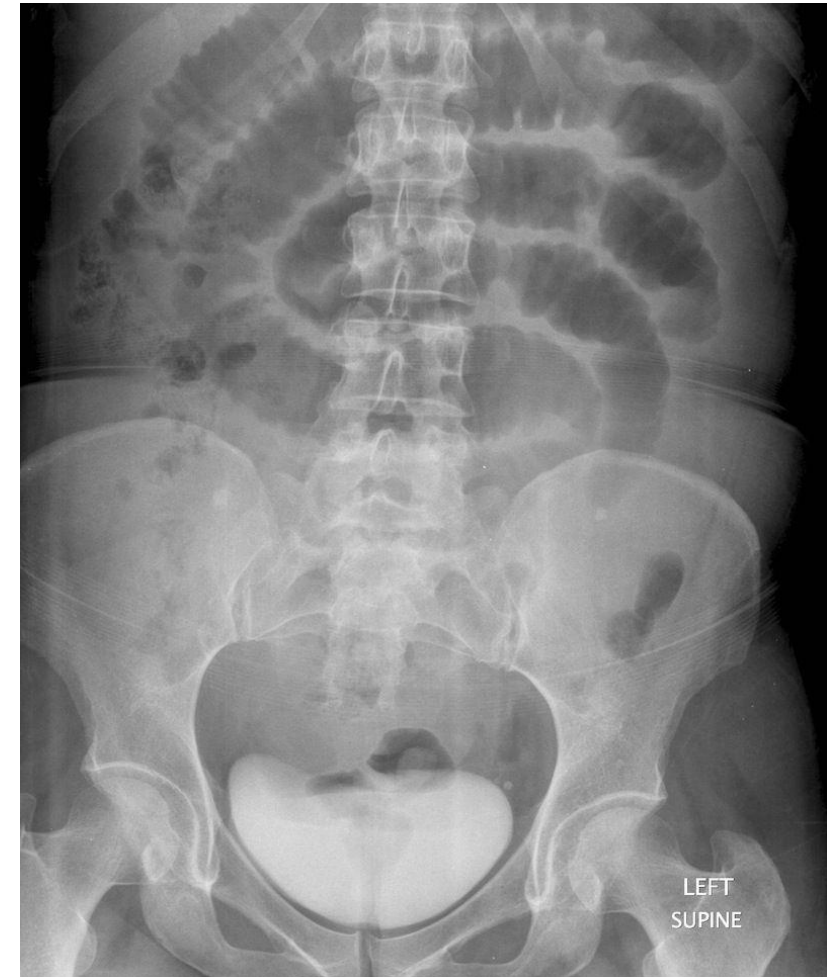


# Epithelial Cell Tumors

## Clinical Features

- Usually vague abdominal symptoms
- Rarely can present with acute symptoms
- Often in advanced disease
- Often from peritoneal spread
- Bowel obstruction
- Ascites
- Malignant pleural effusion
- Venous thromboembolism

Small Bowel Obstruction



# Pseudomyxoma Peritonei

- “Mucinous ascites”
- Gelatinous material (mucin)
- Accumulates in abdomen/pelvis
- Bowel obstruction may occur
- Also seen in cancer of appendix





# Epithelial Cell Tumors

## Risk Factors

- More ovulation associated with more risk

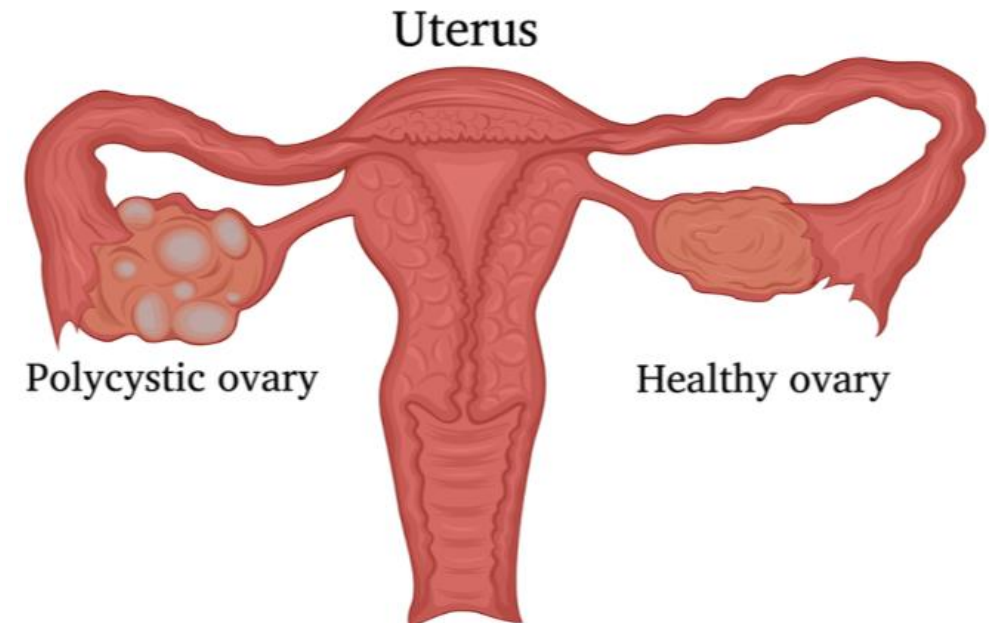
More Risk	Less Risk
Advanced age Early Menarche Late Menopause Nulliparity	Pregnancy Breast Feeding Oral Contraceptive Pills

# Epithelial Cell Tumors

## Risk Factors

- Family history of ovarian cancer
- Infertility due to any cause
- Polycystic Ovarian Syndrome (PCOS)
- Endometriosis
- Tubal ligation: protective (↓ risk)
  - Possibly related to fallopian tube factors → cancer

## Polycystic ovary



# BRCA1 and BRCA2

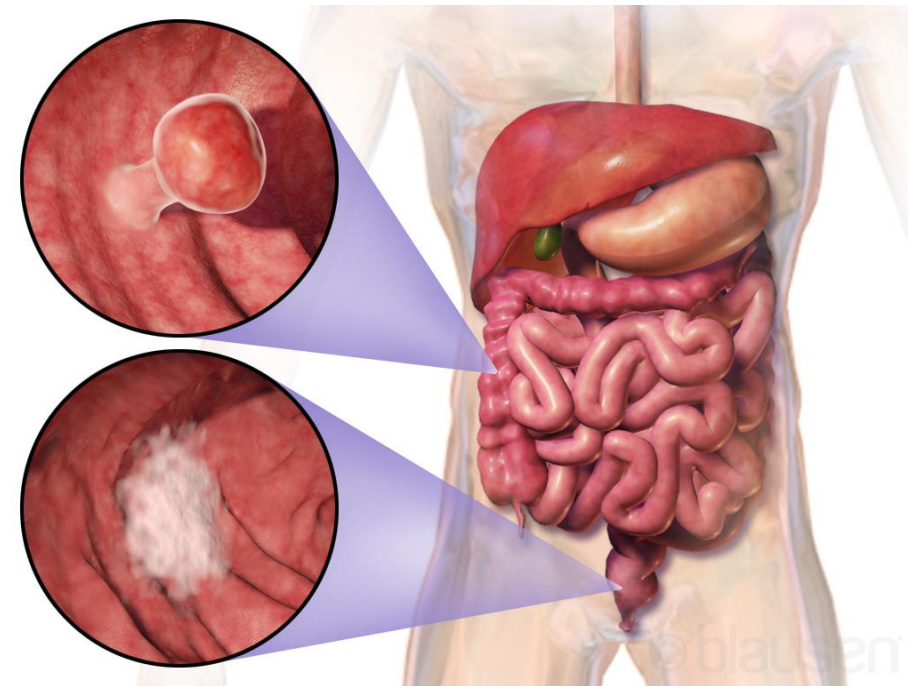
- BRCA1/BRCA2 genes → DNA repair proteins
- Gene mutations associated with breast and **ovarian cancer**



# HNPPCC

## Hereditary Non-Polyposis Colorectal Cancer/Lynch Syndrome

- Germline mutation in DNA mismatch repair genes
- Leads to colon cancer
- Also increased risk of:
  - Endometrial cancer (most common non-colon malignancy)
  - Ovarian cancer (epithelial serous)



# CA-125

## Cancer Antigen 125

- Biomarker for epithelial ovarian cancer
- Poor performance for screening
- Useful in evaluating **adnexal mass**
- Over 35 units/mL is abnormal
- Over 200 units/mL concerning for malignancy
- Useful in monitoring **response to treatment**
- Serial measurement for follow-up

# Ovarian Epithelial Cancer

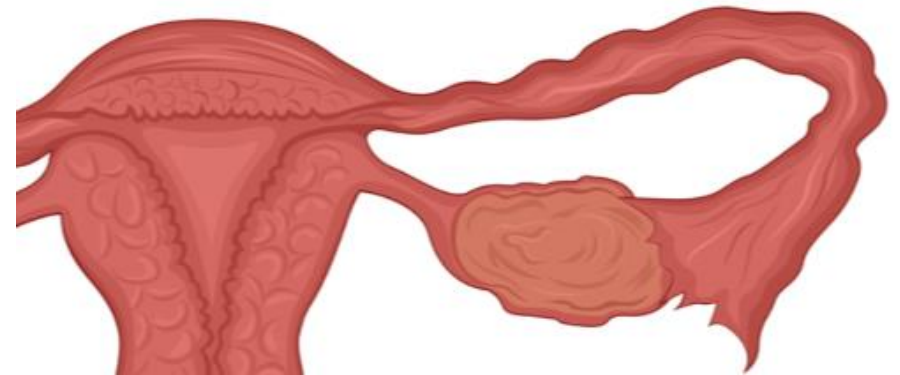
## Management

- **Total hysterectomy with salpingo-oophorectomy**
- Cytoreductive surgery (“tumor debulking”)
  - Tumor removal from peritoneal cavity and structures
  - Chemotherapy more effective with less tumor mass
- Adjuvant chemotherapy
- Usually “platinum-based” chemotherapy
- Common regimen: paclitaxel plus carboplatin or cisplatin

# Ovarian Torsion

- Rotation of ovary around suspensory ligaments
- Leads to **ischemia and necrosis** of ovary
- Acute onset pelvic pain with adnexal mass
- Classically waves of nausea and vomiting
- Major risk factor: ovarian mass
- Especially if greater than 5 cm
- Associated with ovulation induction
  - Can lead to large cysts

Uterus and Ovary





# Ovarian Torsion

- Best test: **pelvic ultrasound**
  - Ovarian mass
  - Limited Doppler flow
- Treatment: **surgical emergency**
  - Detorsion versus oophorectomy
  - Depends on viability of affected ovary



# Breast Masses

Jason Ryan, MD, MPH



# Breast Masses

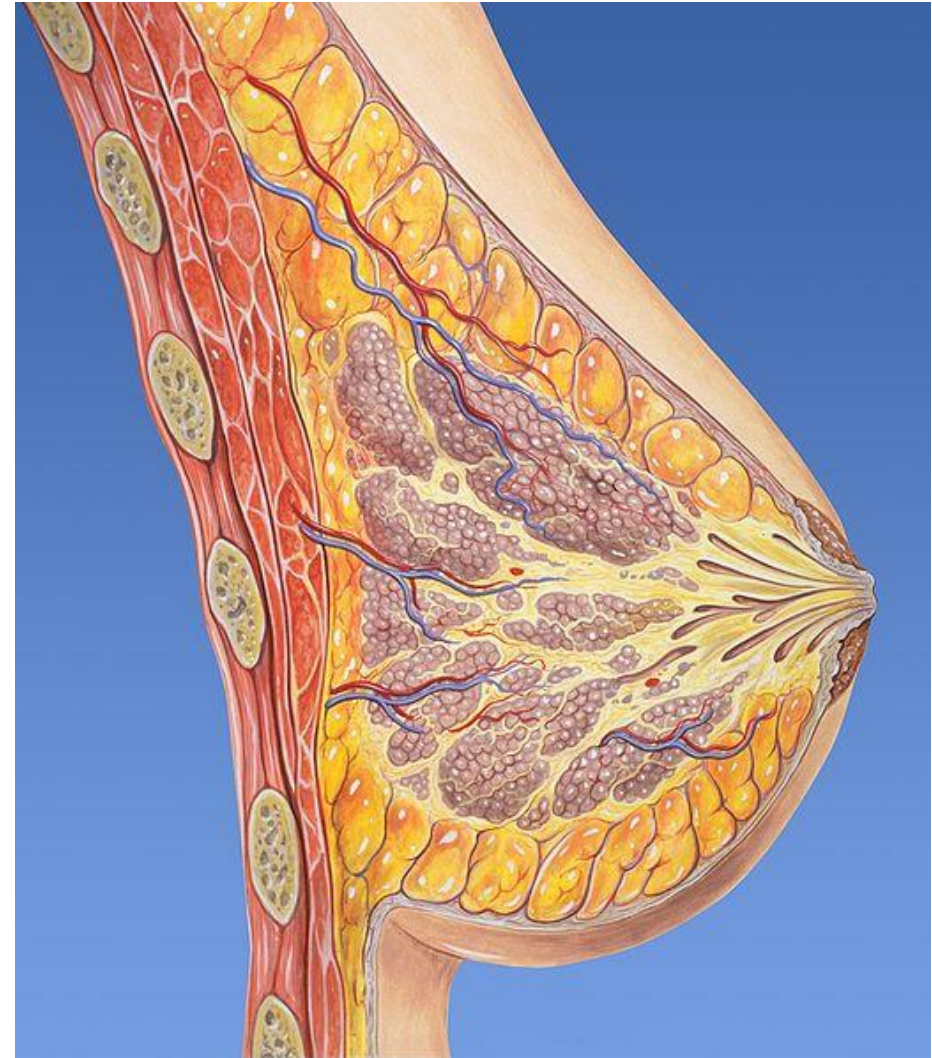
- Commonly detected on **self-exam** or **clinical exam**
  - Breast self-exam no longer recommended for average risk women
- May represent benign breast disease or malignancy



# Breast Masses

## Evaluation

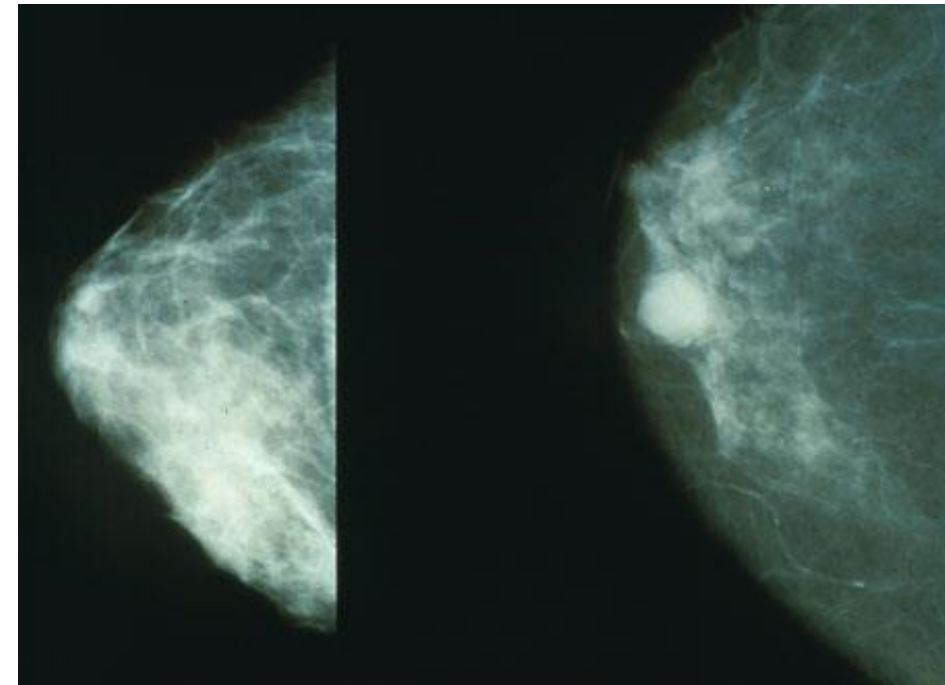
- Biopsy
- Clinical features
  - Change with menstrual cycle
  - Discharge
- Mammography
- Ultrasound
- Breast MRI (rarely used)



# Mammography

## Breast mass evaluation

- Detects **micro-calcifications**
- Occur in malignant lesions
- Also seen in some non-malignant lesions
- Screening mammography: asymptomatic women
- Diagnostic mammography: breast mass workup
  - “Targeted ultrasound”: US of mammogram lesion
  - Further characterizes abnormality




# BI-RADS

## Breast Imaging Reporting and Data System

- American College of Radiology standard format for mammography reports

Increasing  
Cancer  
Risk



BI-RADS Score	Interpretation	Follow-up
1	Negative	Routine
2	Benign finding	Routine
3	Probably benign finding	Repeat imaging
4	Suspicious abnormality	Biopsy
5	Highly suggestive of malignancy	Biopsy
6	Biopsy-proven malignancy	--

# Breast Ultrasound

## Breast mass evaluation

- Differentiate **solid** and **cystic masses**
- Simple cysts: may be drained
  - Usually no further workup needed - low risk of cancer
- Solid masses may have benign or malignant features by US





# Breast Masses

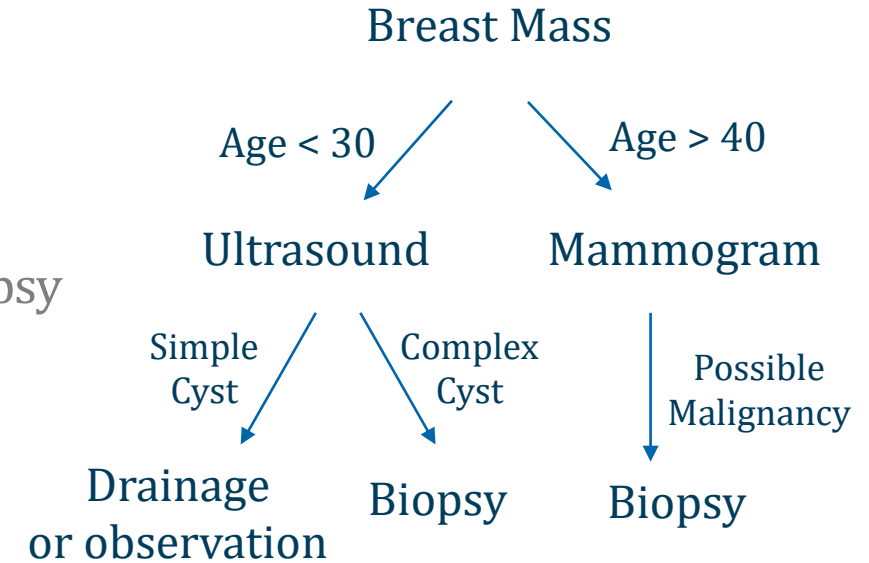
## Biopsy Types

- **Core needle biopsy (CNB)**
  - Obtains a “core” of tissue
  - Can be done with imaging guidance (often ultrasound)
- Fine needle aspiration (FNA)
  - Obtains cells for analysis
  - Simpler procedure with less risk of complications than CNB
  - No tissue – cannot distinguish **in situ from invasive disease**
- Surgical biopsy
  - Usually not done as initial biopsy
  - Used when CNB is non-diagnostic

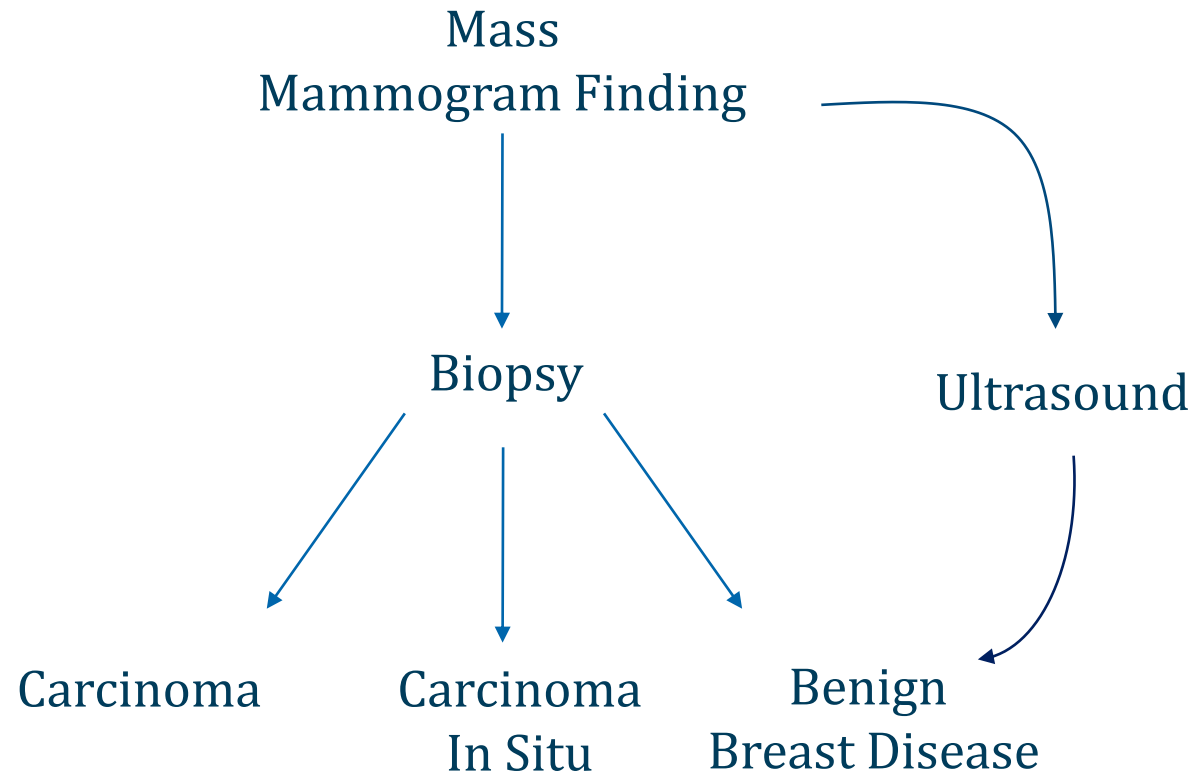
# Breast Masses

## Preferred Initial Imaging Modalities

- Women less than 30 years of age: **ultrasound**
  - High likelihood of breast cyst
  - Non-cystic lesions may be followed with mammogram or biopsy
- Women over 40 years of age: **mammography**
  - Low BI-RADS score: ultrasound for possible cyst
  - High BI-RADS score: biopsy or excision
- Women 30 to 39: either modality acceptable



# Breast Lesions



# Benign Breast Lesions

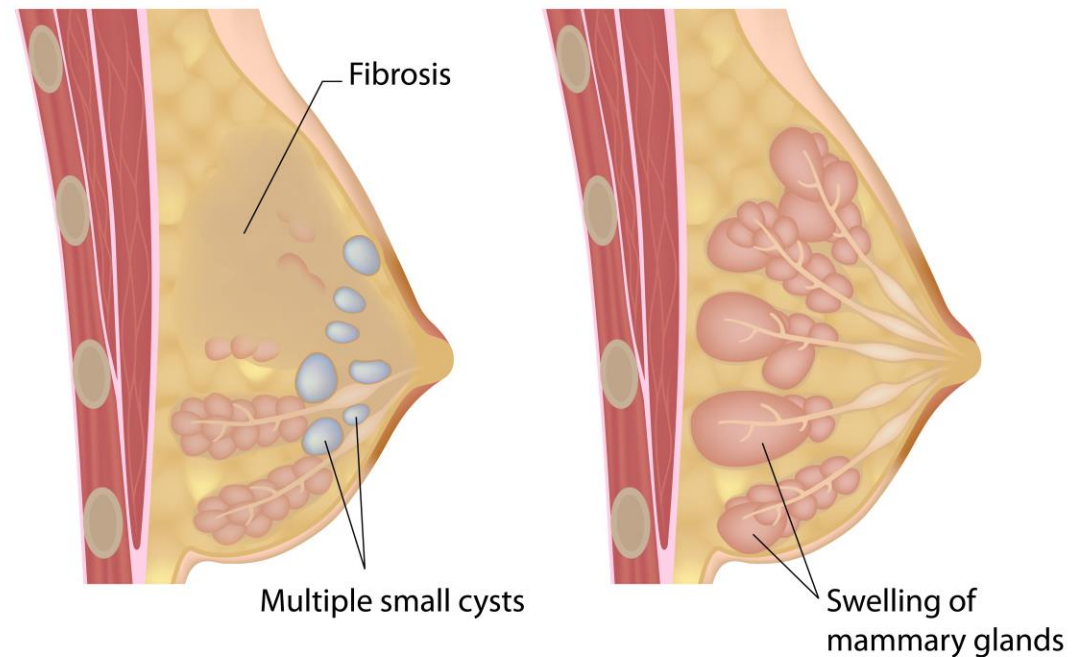
- Classified histologically into three categories:
  - Nonproliferative lesions
  - Proliferative without atypia
  - Atypical hyperplasia
- Some associated with increased risk of subsequent breast cancer

# Nonproliferative Breast Lesions

## Fibrocystic Breast Changes

- Group of breast changes/lesions
- Not associated with increased risk of cancer
- Occur in premenopausal women
- Present as “lumpy, bumpy” breasts
- Must be distinguished from breast cancer
- May cause breast pain (mastalgia)
- Often **cyclical pain** week prior to menses
- Mastalgia often relieved by COCs

## Fibrocystic Breast Changes



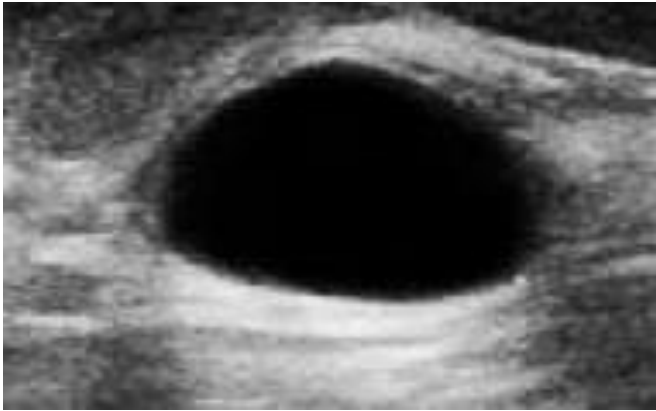
# Nonproliferative Breast Lesions

## Other Lesions

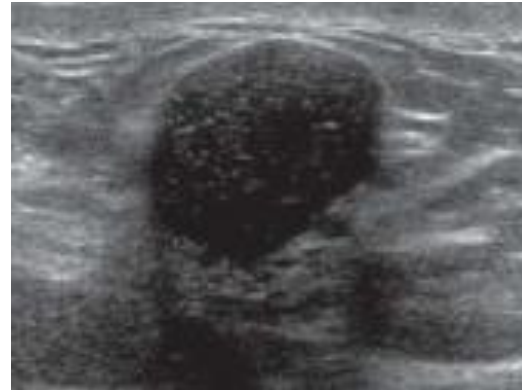
- Simple cysts - most common
- Papillary apocrine change
- Epithelial-related calcifications
- Mild hyperplasia of the usual type
- Apocrine metaplasia

# Breast Cysts

- Simple: smooth, thin walls; completely filled with fluid
  - **Posterior acoustic enhancement:** back wall brighter due to fluid-filled cavity
- Complex: irregular borders, thick walls; solid areas or debris
- Complicated: intermediate category - low-level internal echoes



Simple



Complicated



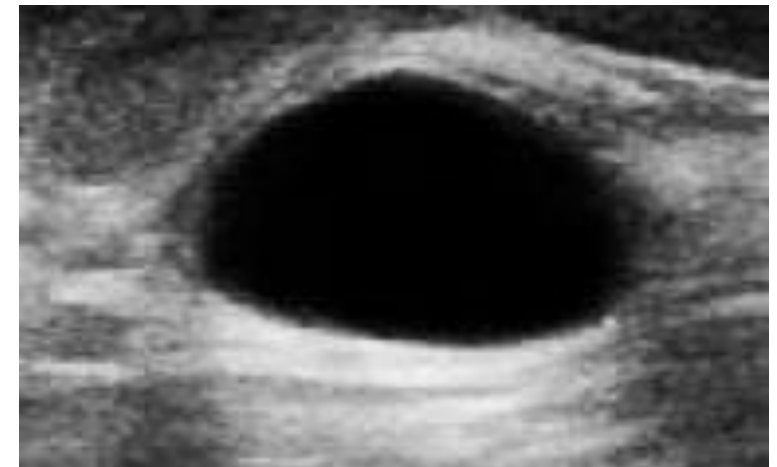
Complex



# Simple Breast Cysts

- Smooth, firm masses
- May be tender
- Physical exam *cannot* distinguish simple cysts from malignancy
- Ultrasound: well-circumscribed, anechoic (black), posterior enhancement
- Mammogram (not required): BI-RADS 2

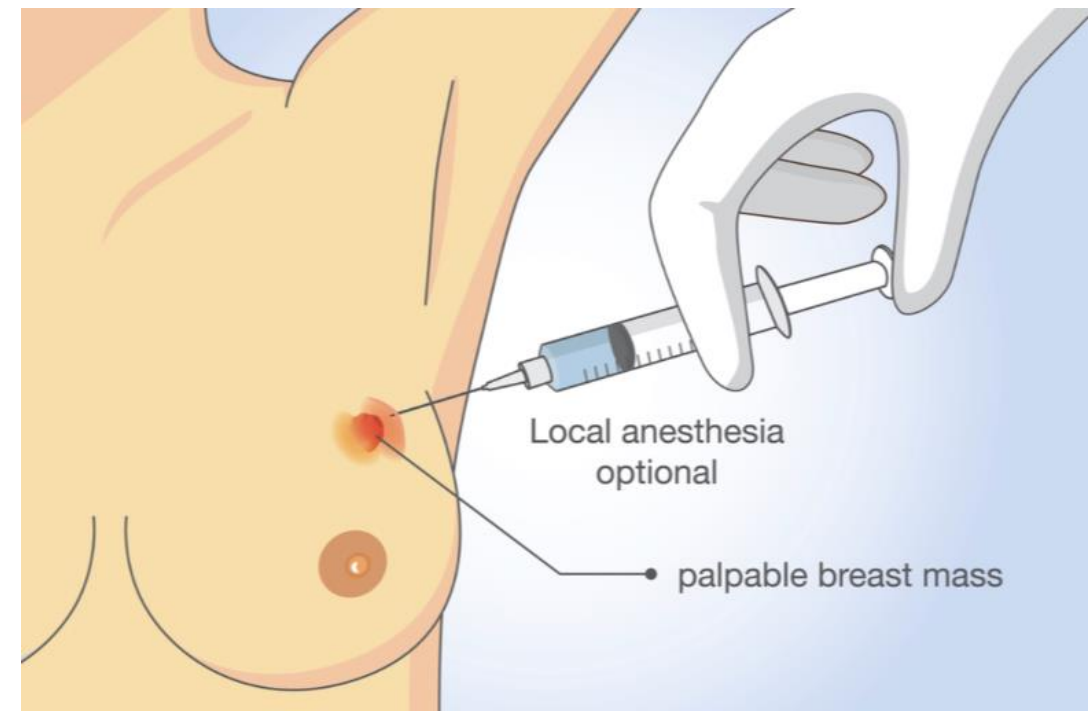
Simple Breast Cyst



# Simple Breast Cysts

## Management

- Asymptomatic: no further workup required
  - Non-simple cysts may require additional workup
- Symptomatic: **fine need aspiration**
  - Resolves cyst
  - Should yield clear yellow fluid
  - Sometimes green or bloody (still usually benign)
- Cysts may recur after aspiration
  - Follow-up exam in 2 to 4 months

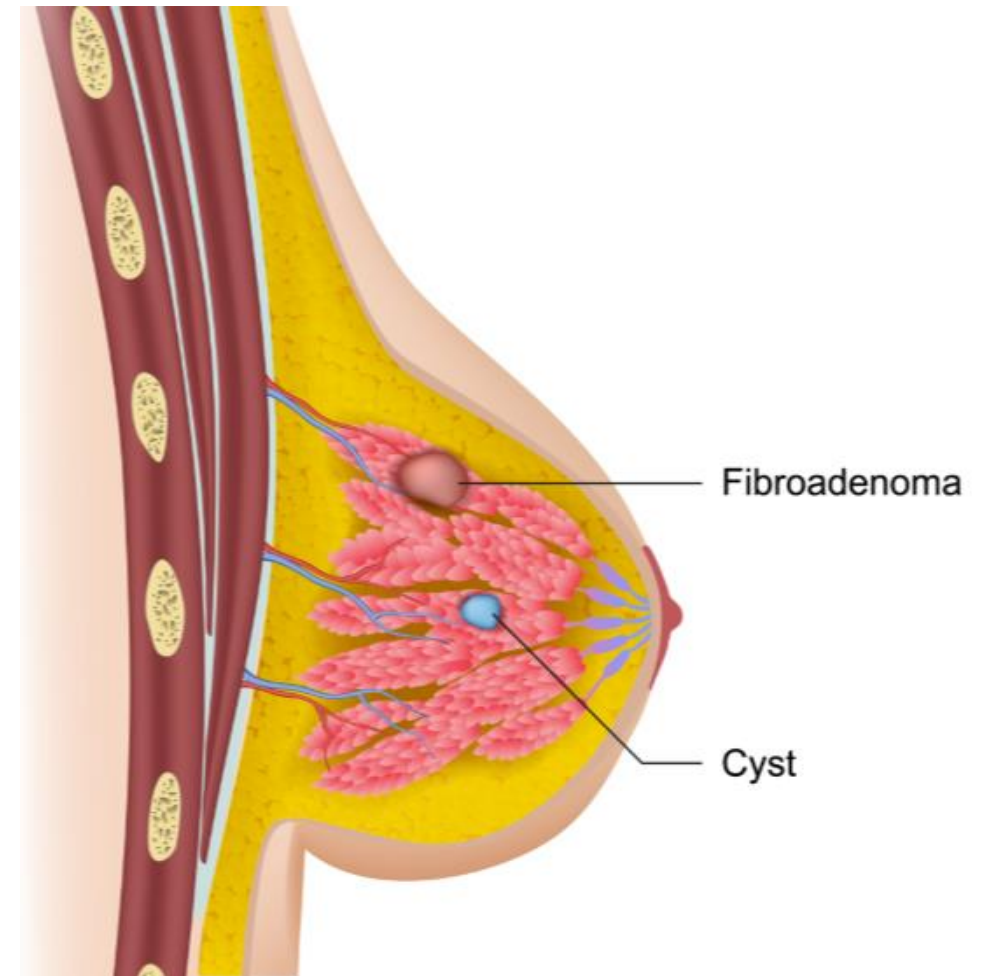


# Proliferative Breast Lesions without Atypia

- Proliferation of breast tissue cells without atypia (all normal cells)
- **Small increase in risk of breast cancer**
- Many subtypes
- Fibroadenoma
- Intraductal papilloma
- Epithelial hyperplasia
- Sclerosing adenosis

# Fibroadenoma

- Most common benign breast tumor
- Mass of fibrous and glandular tissue
- Histologically similar to fibroids (often find both)
- Occurs in **premenopausal women**
- Hormone sensitive
  - Increase in size during menstrual cycle/pregnancy
  - Decrease in size after menopause
- Well-defined, solid mobile mass

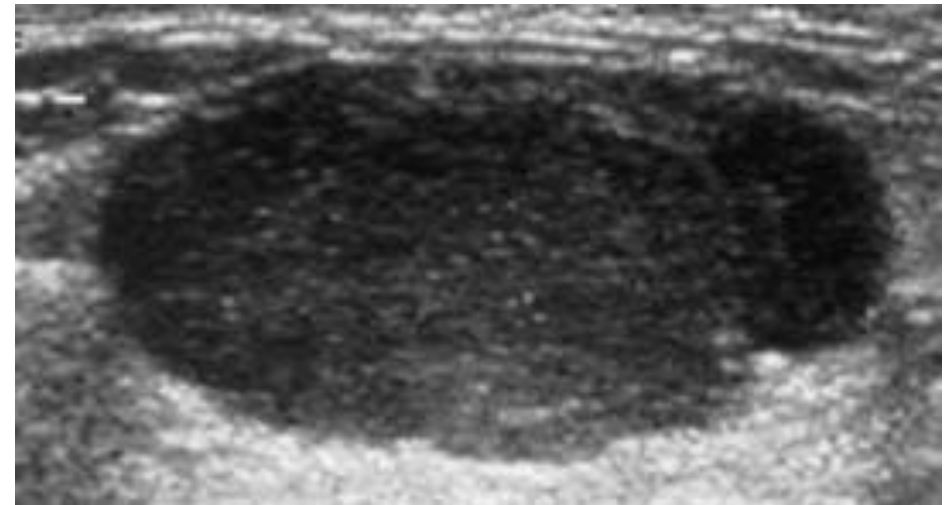


# Fibroadenoma

## Workup and Management

- Adults
  - Ultrasound: hypoechoic (gray) mass
  - CNB if diagnosis unclear
  - Can be followed clinically
  - Do not require excision

### Fibroadenoma Ultrasound

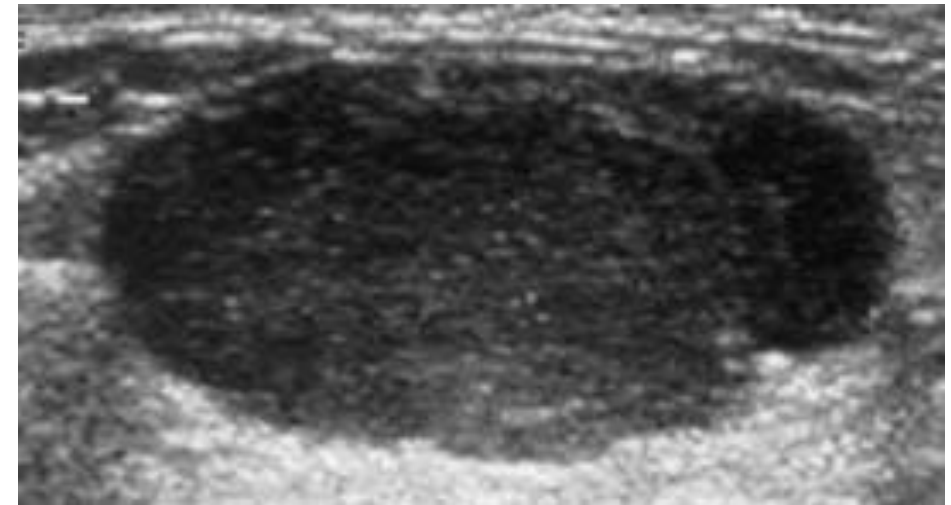


# Fibroadenoma

## Workup and Management

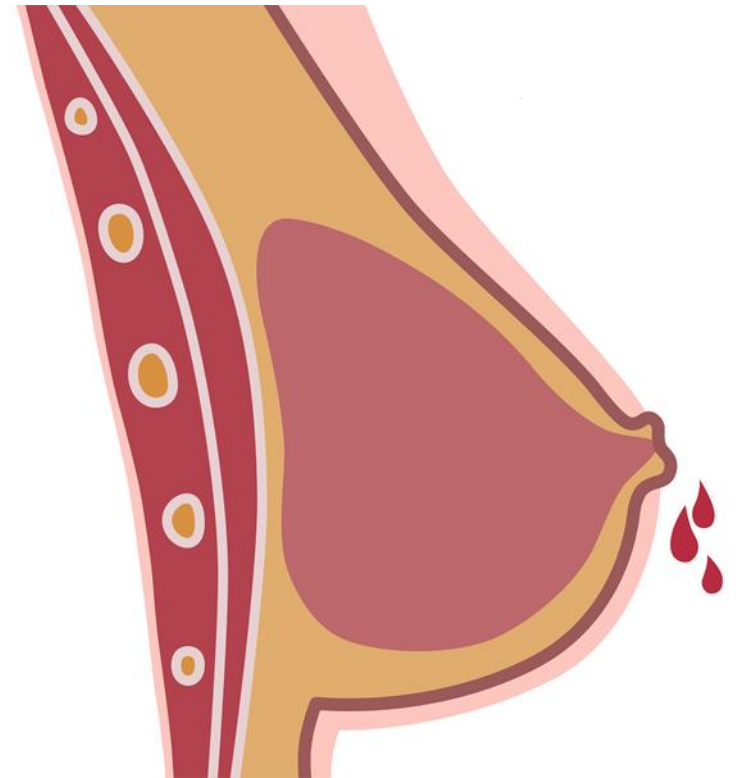
- Adolescents
  - Most common breast mass
  - Can be diagnosed **clinically**
  - Well-defined, solid, mobile mass
  - Premenstrual tenderness
  - Decreases in size after menses
  - Equivocal cases: ultrasound, FNA or CNB

### Fibroadenoma Ultrasound



# Intraductal Papilloma

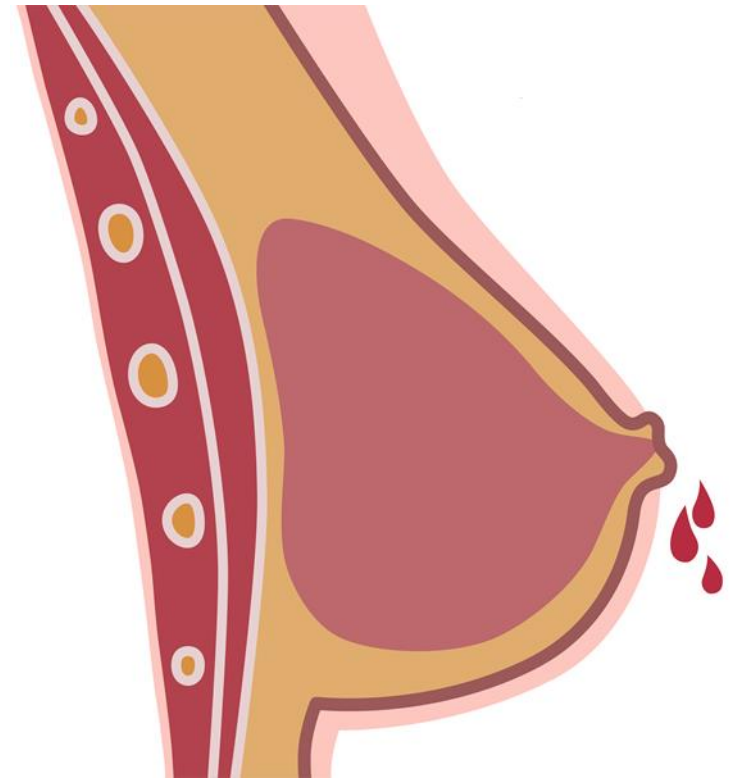
- Benign breast tumor
- Classic cause of **unilateral bloody nipple discharge**
- Associated with a small mass that *may be nonpalpable*
- Growth of normal ductal epithelial cells
- Cells grow in “finger-like” projections
- Must exclude malignancy
- Workup: mammography and ultrasound
- Diagnosis: core needle biopsy





# Nipple Discharge

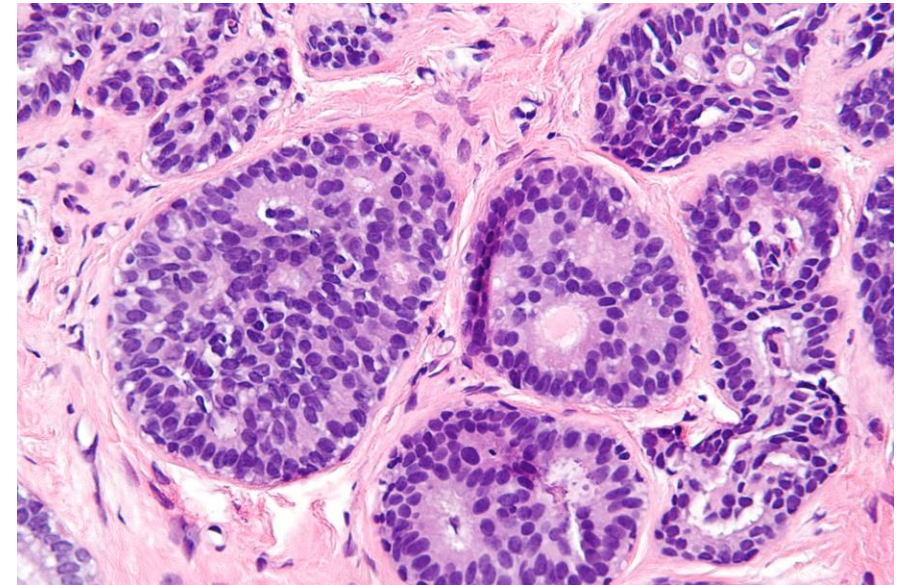
- Physiologic discharge: **bilateral**, clear or milky
  - Due to **hyperprolactinemia**
  - Pregnancy test (hCG), prolactin, TSH
  - Pituitary MRI if prolactin elevated
- Pathologic features:
  - **Unilateral**
  - Bloody/serous discharge
  - Associated with a **breast mass**
  - Possible malignancy
  - Workup: mammogram or ultrasound similar to breast mass
  - Most common cause: intraductal papilloma



# Atypical Hyperplasia

- Atypical ductal hyperplasia (ADH)
- Atypical lobular hyperplasia (ALH)
- Often an incidental finding on biopsy for other reasons
- **Substantial increase** in risk of subsequent breast cancer
- Risk reduction strategies
  - Annual mammogram
  - Twice-yearly breast exams
  - Stop oral contraceptives and avoid HRT
  - Consider SERM or aromatase inhibitor

Atypical Ductal Hyperplasia



# Atypical Hyperplasia

- Core needle biopsy followed by **surgical excisional biopsy**
  - Exclude possibility of associated higher-grade lesion
  - Up to 30% of cases will be “upgraded”



# Atypical Hyperplasia

## Management

- No additional surgery after surgical excision
- Increased surveillance for breast cancer
- Often yearly mammography and twice-yearly breast exams
- Stop oral contraceptives
- Chemoprophylaxis: tamoxifen (SERM), aromatase inhibitors

# Phyllodes Tumor

- Stromal breast tumor
  - Phyllodes = Greek word “leaf like”
  - Leaf-like growths of stroma
- Usually benign
  - Low grade forms similar to fibroadenomas
  - High grade variants can metastasize
- Presents as growing mass
- Usually occur in **older women (> 60 years)**
- Diagnosis: ultrasound and CNB
- Usually treated with **surgical excision**

Phyllodes Tumor

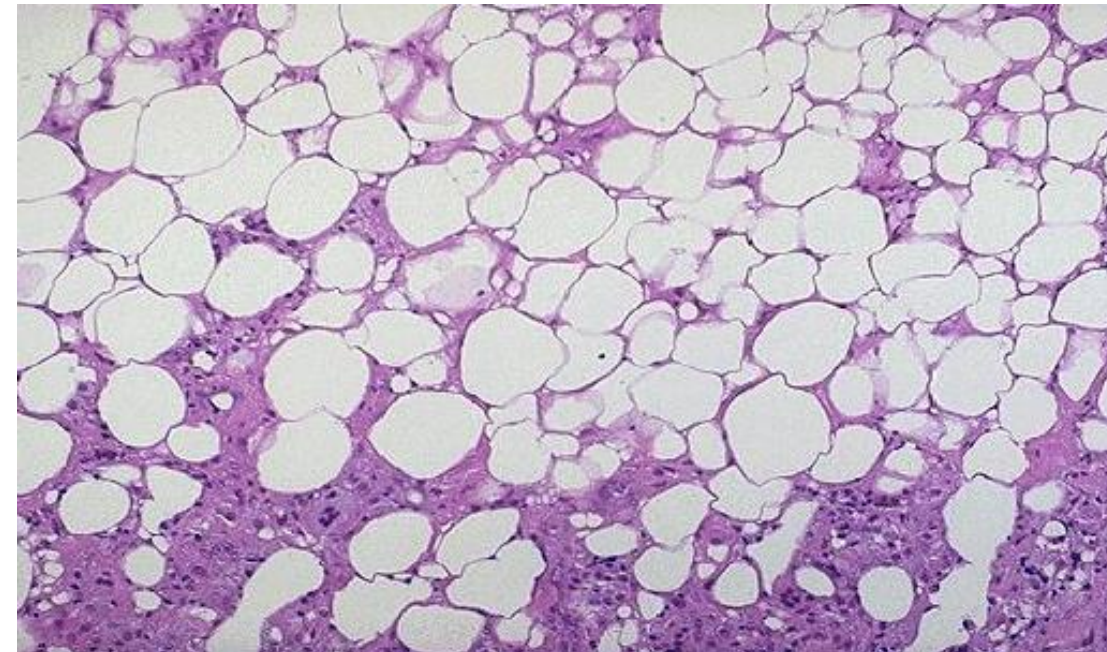




# Fat Necrosis

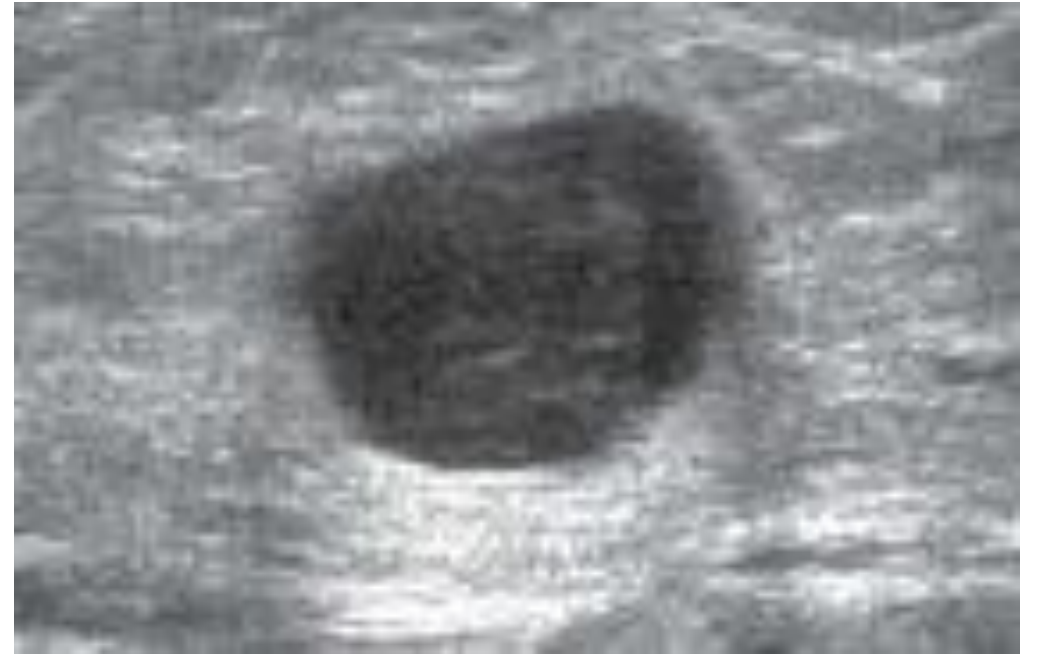
- Benign, inflammatory breast process
- Results from **trauma**
  - **Often biopsy, surgery**
  - Sports injury, seatbelt injury
  - Many women do not recall a specific trauma
- Often mimics breast cancer
  - May present as painless mass in breast
  - Calcifications on mammogram
- Biopsy: fat necrosis with inflammatory cells
- No further treatment indicated

## Fat Necrosis



# Galactocele

- Milk retention cyst
- Often occur in breastfeeding women
- Caused by obstructed milk ducts
- Ultrasound: complex cyst
- FNA: milky substance
- No specific treatment
- No increased risk of breast cancer





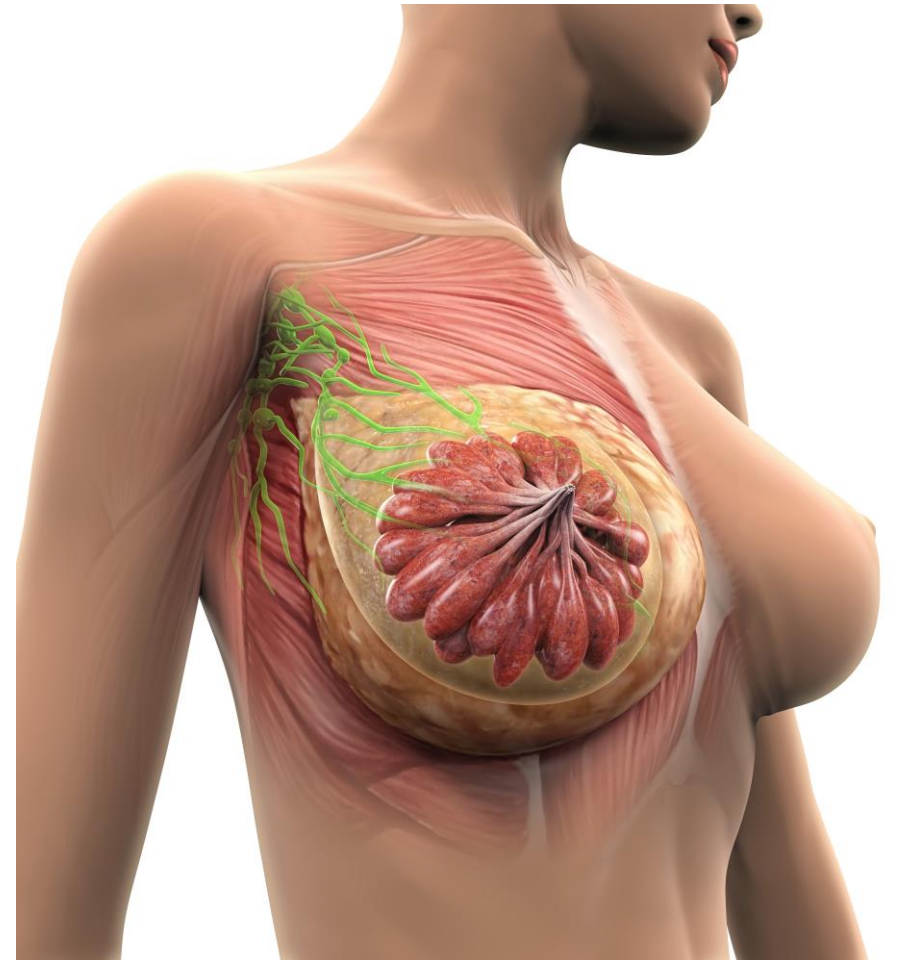
# Breast Cancer

Jason Ryan, MD, MPH



# Breast Carcinoma

- Most common cancer in women
- Usually **adenocarcinoma** from epithelial cells
- 2<sup>nd</sup> leading cause of cancer death in US women
- Mostly a disease of older women
  - Rare before age 25
  - Incidence increases after age 30
  - Median age at diagnosis: 62 years
- Can rarely occur in men



# Breast Carcinoma

## Risk Factors

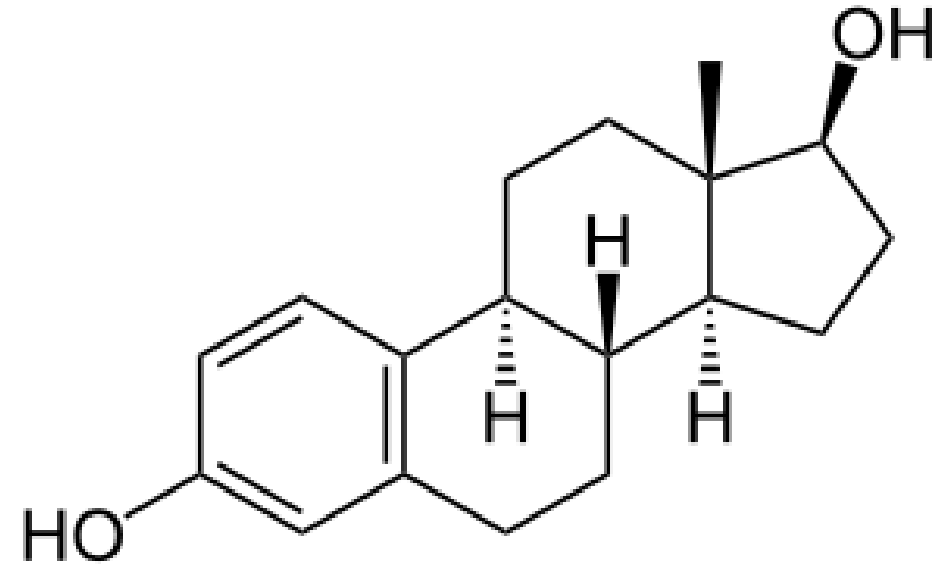
- **Female sex** (99% of cases)
- 1<sup>st</sup> degree relative with breast cancer
- Age
- Alcohol
- Smoking



# Breast Carcinoma

## Risk Factors

- **Increased estrogen exposure**
  - Early menarche
  - Late menopause
  - Obesity
  - Breast feeding = protective
- **Age at first live birth**
  - Young (< 20) = protective
  - Older (> 35) = higher risk



Estradiol

# Breast Carcinoma

## Modifiable Risk Factors

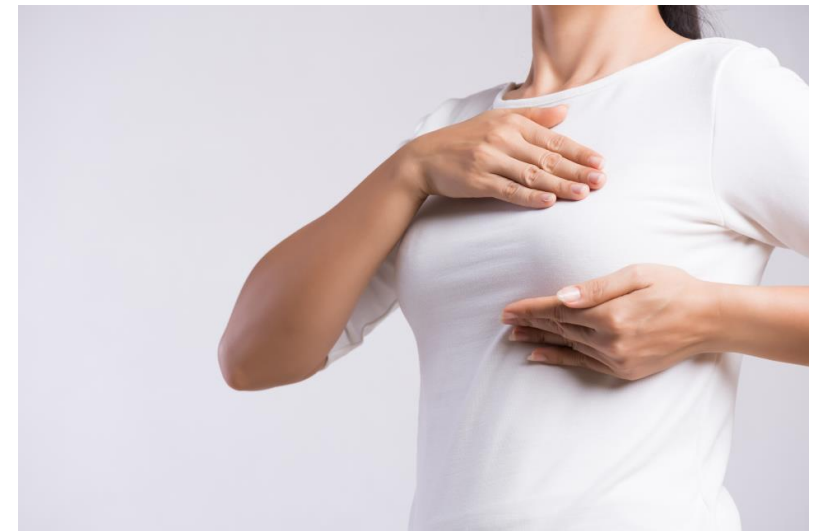
- **Obesity**
- **Alcohol consumption**
- **Smoking**
- Physical inactivity
- Hormone replacement therapy
- Reproductive history



# Breast Carcinoma

## Clinical Features

- Often identified in asymptomatic stage by screening
- Early disease: **breast mass**
- Classic features: hard, immobile mass with irregular borders
- Late disease findings: axillary adenopathy or skin findings





# Peau d'orange

## Inflammatory Breast Carcinoma

- Erythema, swelling of breast
- Dimpling of skin similar to orange rind
- May be itchy or painful
- May mimic infection with **no response to antibiotics**
- Tumor invasion of dermal lymphatic vessels
- Often high-grade malignancy
- Usually poor prognosis
- Next step: diagnostic mammography +/- ultrasound





# Paget Disease

- Erythema at nipple due to underlying malignancy
- May cause bloody nipple discharge
- Can be mistaken for eczema or contact dermatitis
- Diagnosis: **skin biopsy** showing **Paget cells**
  - Intraepithelial adenocarcinoma cells



# Paget Disease

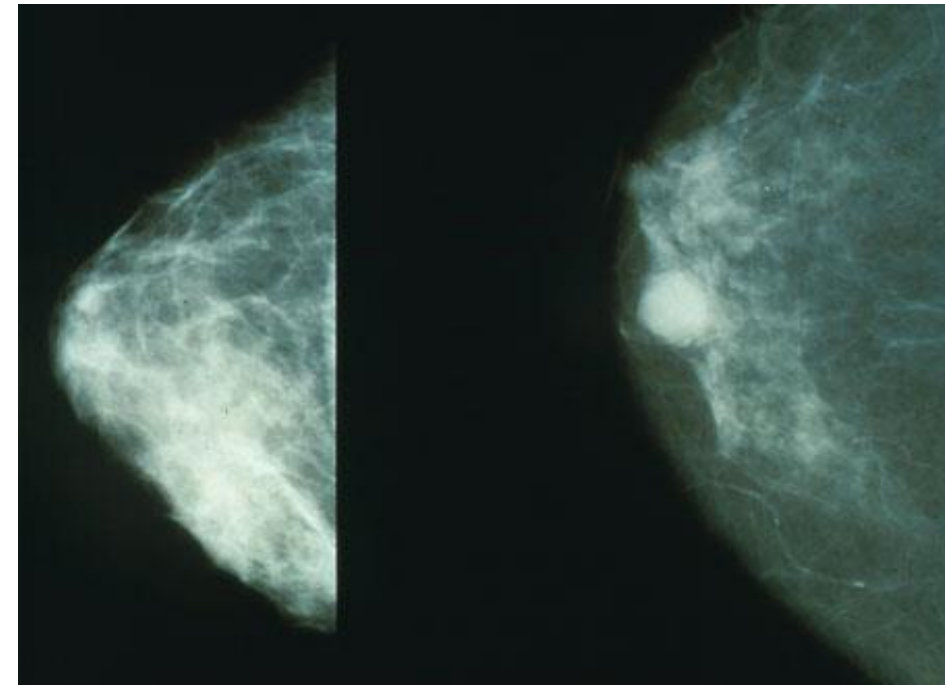
- About 50% cases have palpable mass
- Follow-up testing: **mammography**
- About 50% cases have lesion on mammogram
- Standard work-up for mass or mammogram lesion
- If no mass/lesion: mastectomy or breast-conserving therapy
  - Most have DCIS
  - About 25% have invasive cancer



# Breast Cancer Screening

## Mammography

- Detects **micro-calcifications**
- Occur in malignant lesions
- Also seen in some non-malignant lesions
  - Fat necrosis and sclerosing adenosis
- Screening mammography: asymptomatic women
- Diagnostic mammography: breast mass workup



# Breast Cancer Screening

## Guidelines

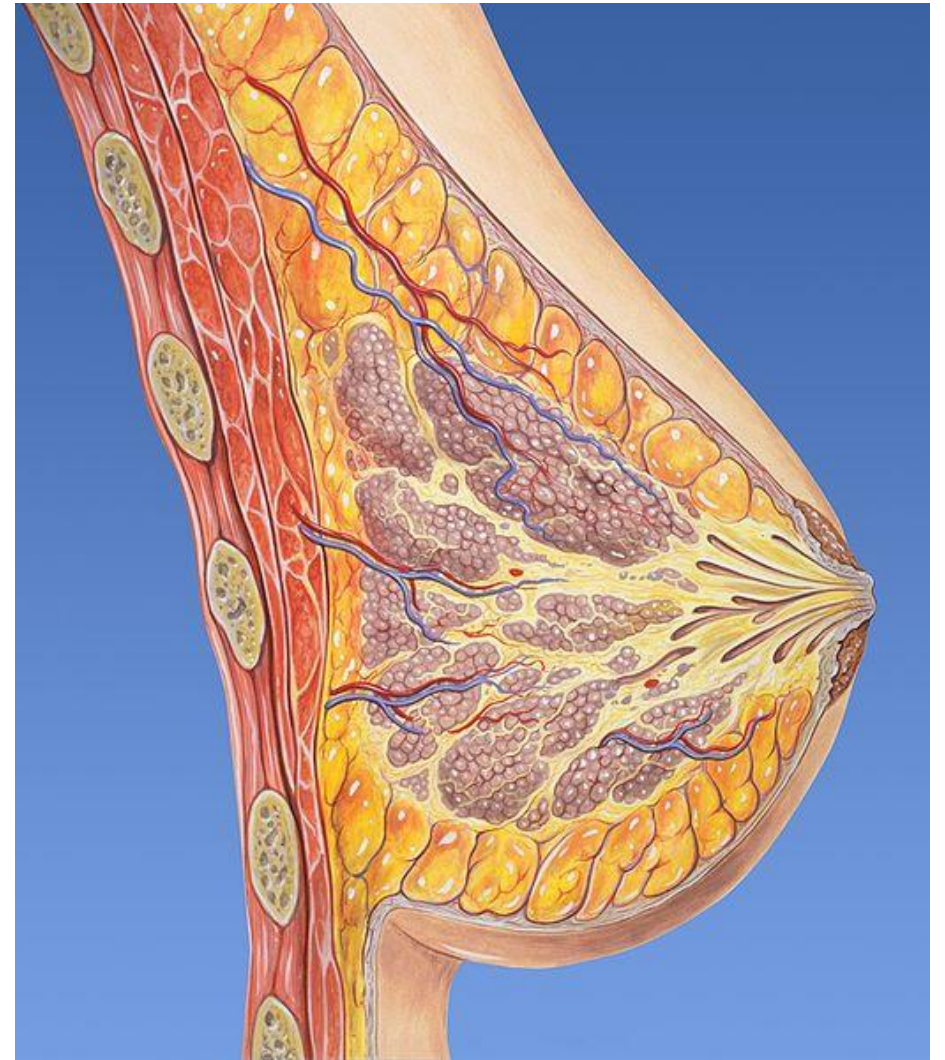
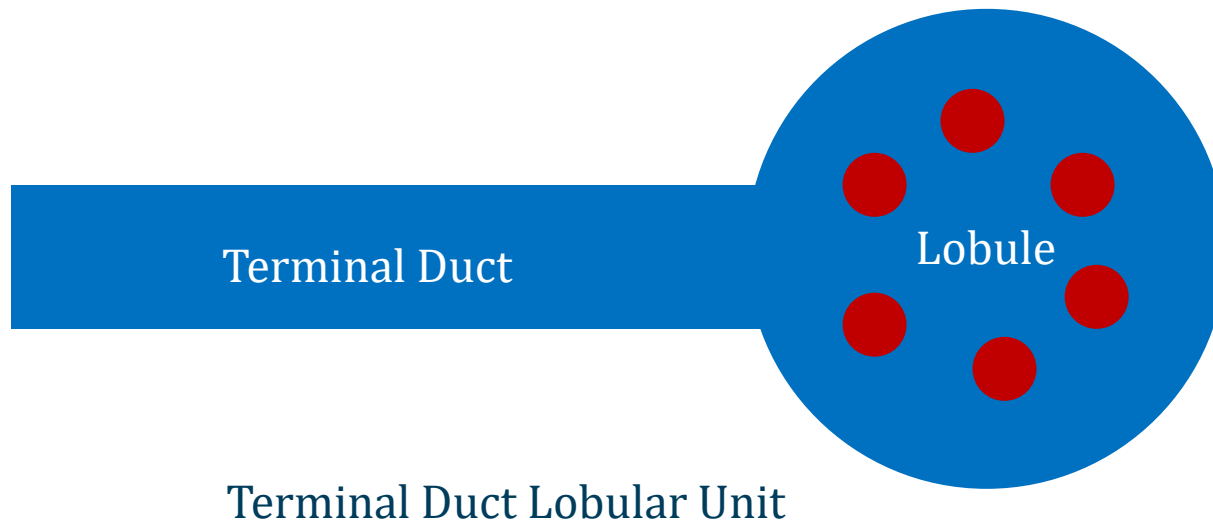
### Screening for Breast Cancer

Age	Screening Recommendation
< 40	- Not indicated for average risk women
40-50	- Guidelines vary by expert group - Overall, an individualized "shared decision making" model is encouraged
50-75	- Screening recommended for all (q2 years) - Note: Frequency is debated and varies between expert groups (q1-2 years)
>75	- Not indicated, unless life expectancy >10 years

# Breast Carcinoma

## Major Types

- Ductal versus lobular
  - Ductal = resemble duct cells
  - Lobular = resemble lobules
  - Both types from TDLU
- In situ versus invasive
  - In situ = limited by basement membrane



# Premalignant Lesions

- “Proliferative lesions with atypia”
- Associated with significantly increased risk of subsequent breast cancer
- Ductal carcinoma in situ
- Lobular carcinoma in situ
- Atypical hyperplasia

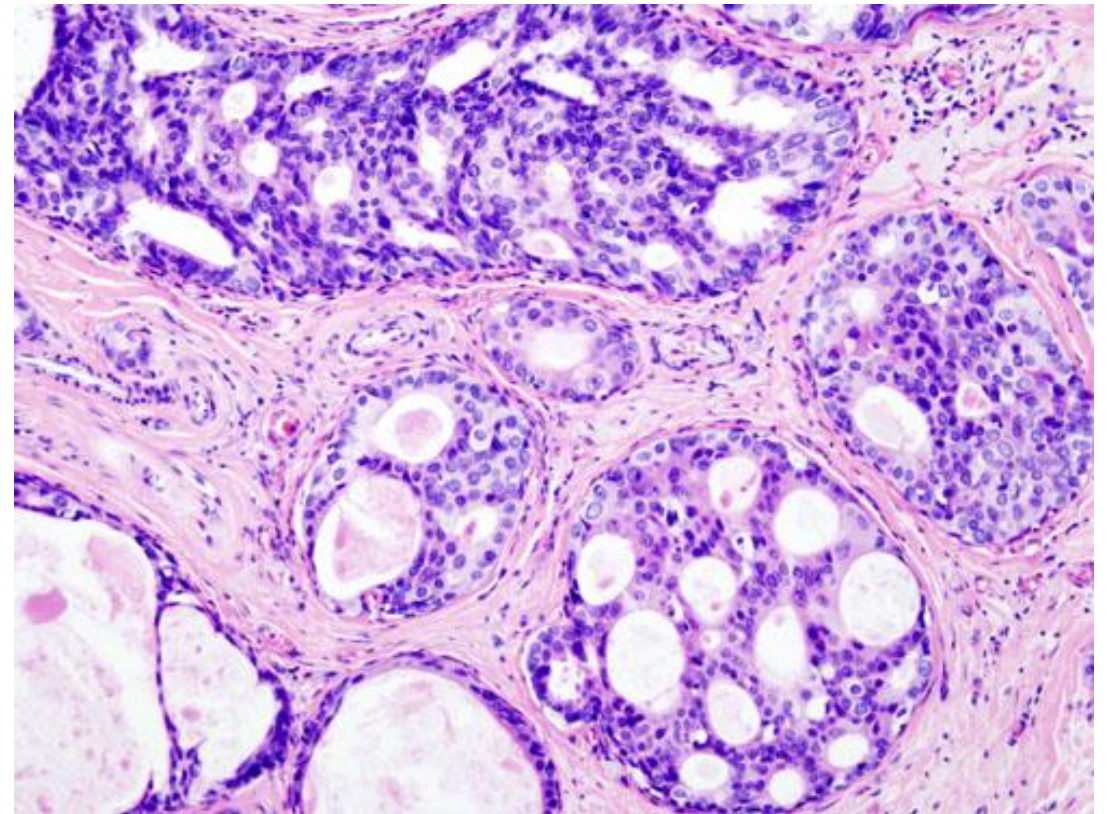


# DCIS

## Ductal Carcinoma In Situ

- Malignant growth of epithelial cells of TDLU
- Fills ductal lumen
- Limited by intact basement membrane
- Forms **microcalcifications**
- Usually detected by mammography
- Many subtypes based on histology

**Cribriform DCIS**





# DCIS

## Management

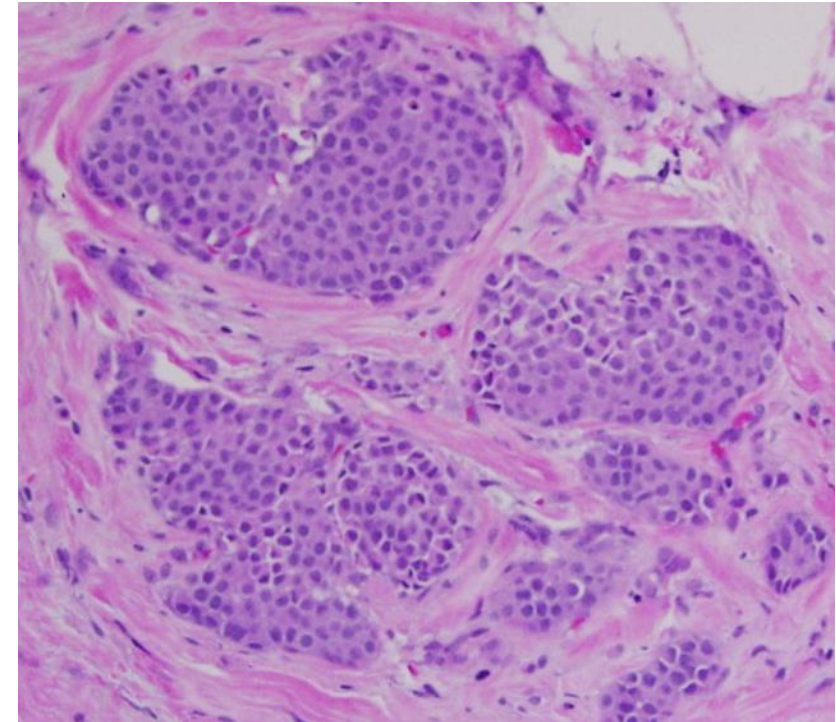
- **Mastectomy** or **breast-conserving therapy**
- Mastectomy: removal of entire affected breast
- BCT: lumpectomy plus radiation therapy
  - Lumpectomy with sentinel node biopsy
  - Positive margins require re-excision
- ER-positive cases: chemoprevention

# LCIS

## Lobular Carcinoma In Situ

- Proliferation of cells in ducts/lobules
- Limited by intact basement membrane
- “Discohesive growth:” loose intercellular connections
- Loss of adhesion protein E-cadherin
- Round cells clumped together
- Does not lead to micro-calcifications
- Usually an **incidental finding** on biopsy
- Often bilateral
- May be multi-focal

Lobular Carcinoma In Situ



# LCIS

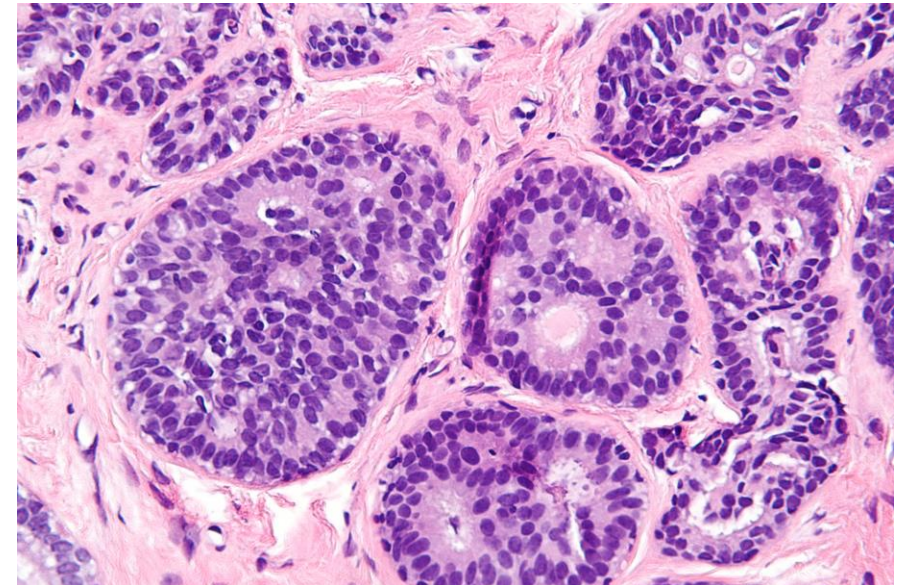
## Management

- **Risk factor** for invasive carcinoma
  - Non-invasive lesion
  - Increased risk of carcinoma in both breasts
- Classic and non-classic forms by histology
- Classic form: **surveillance and chemoprevention**
  - Annual mammograms
  - Twice-yearly breast exams
  - Stop oral contraceptives and avoid HRT
  - SERMs or aromatase inhibitors
- Non-classic forms: surgical excision

# Atypical Hyperplasia

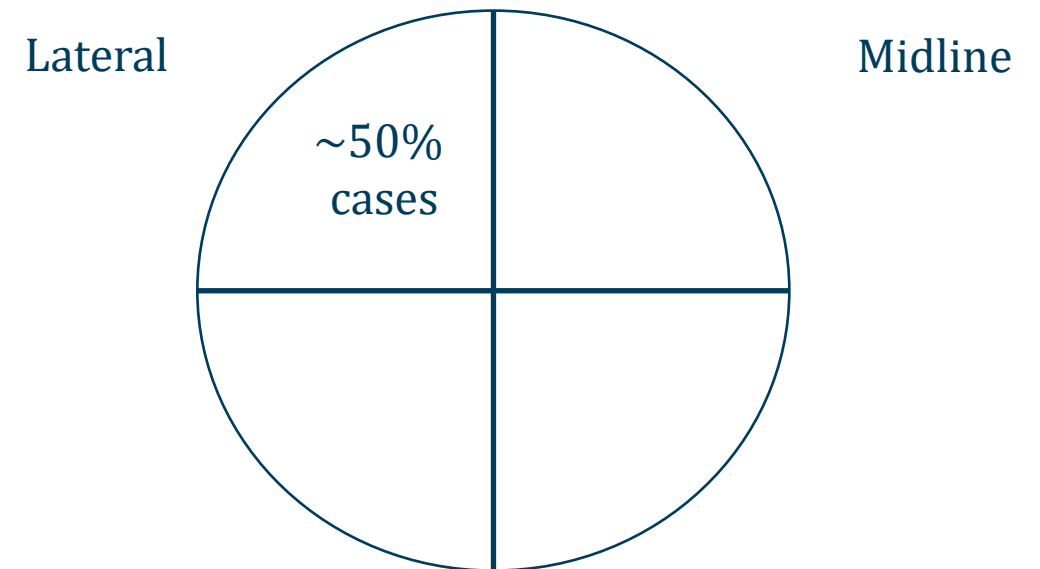
- Atypical ductal hyperplasia (ADH)
- Atypical lobular hyperplasia (ALH)
- Often an incidental finding on biopsy for other reasons
- **Substantial increase** in risk of subsequent breast cancer
- Risk reduction strategies
  - Annual mammogram
  - Twice-yearly breast exams
  - Stop oral contraceptives and avoid HRT
  - Consider SERM or aromatase inhibitor

Atypical Ductal Hyperplasia



# Invasive Ductal Carcinoma

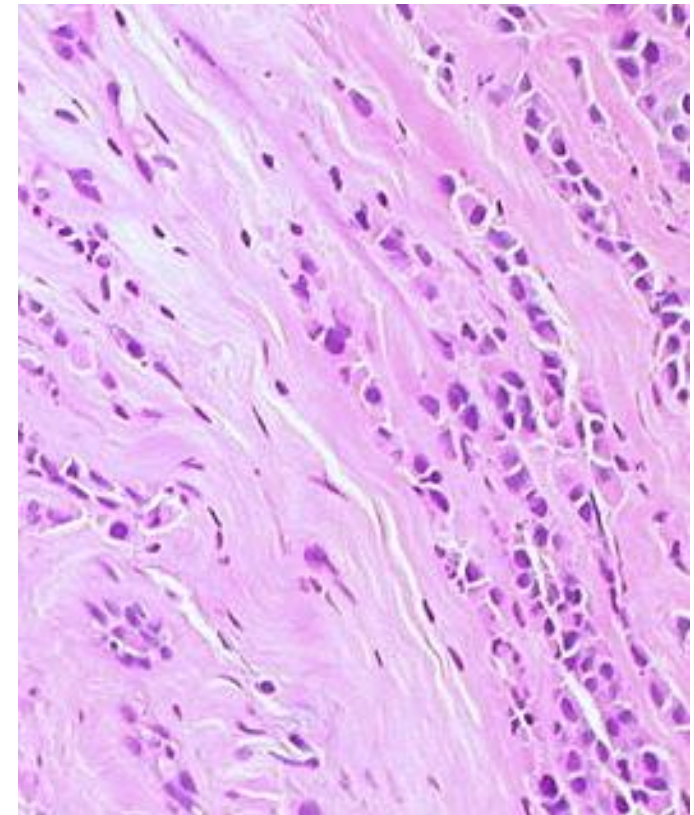
- Most common type (~ 80%) invasive carcinoma
- Biopsy: duct cells with stroma
- Most commonly in outer quadrant of breast
- More breast tissue
- Treatment based on TNM stage
- Surgery, chemotherapy, hormone therapy



# Invasive Lobular Carcinoma

- Cells grow in “single file”
- Lack of E-cadherin adhesion protein expression
- Cells cannot stick together in clumps
- Often bilateral with multiple lesions
- Treatment based on TNM stage
- Surgery, chemotherapy, hormone therapy

Lobular Carcinoma

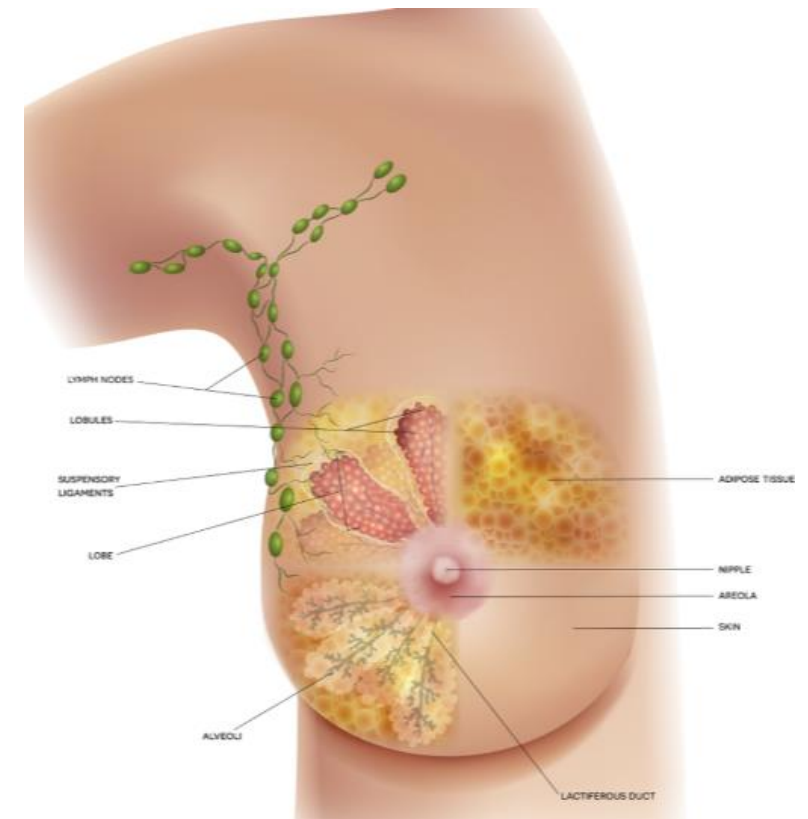




# Breast Carcinoma

## Prognosis

- Axillary lymph node metastases
- Most important prognostic factor
- Detected by biopsy
- Sentinel node biopsy often performed





# Breast Carcinoma

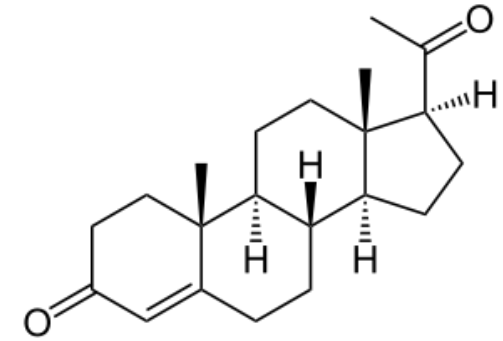
## Staging

- Tumor, Node, Metastasis (TNM) staging system
- Example: IA = T1 N0 M0
- Stage IV carries worst prognosis

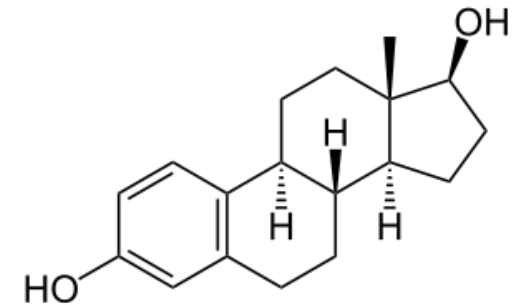
Stage	Tumor Size	Nodes	Metastases
IA			None
IB			None
IIA	Larger	More	None
IIB		Nodes	None
IIIA			None
IIIB			None
IIIC			None
IV	Any	Any	Detectable

# Tumor Markers

- Important for prognosis and therapy
- Less important than TNM stage
- Estrogen receptor positivity (ER+)
- Progesterone receptor positivity (PR+)
- Human epidermal growth factor receptor-2 (HER2)



Progesterone



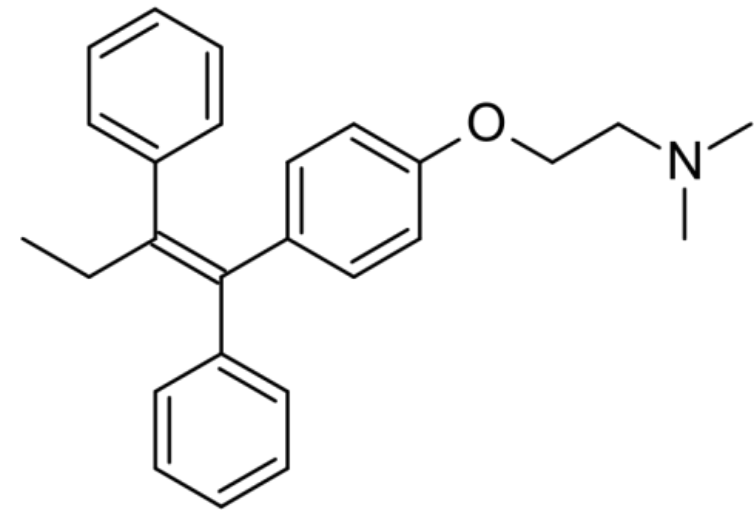
Estradiol

# Tumor Markers

- ER+ and PR+ tumors: **chemoprevention** (“endocrine therapy”)
  - Oral drugs
  - Tamoxifen: selective estrogen receptor modulator (SERM)
  - Aromatase inhibitors
- HER2+ tumors: may respond to **trastuzumab**
  - Infusion therapy
  - Monoclonal antibody targeting HER2
- “Triple negative” tumors
  - Highly aggressive
  - More common in women under 40

# Tamoxifen

- Selective estrogen receptor modulator (SERM)
- Competitive antagonist of breast estrogen receptor
- Used in ER positive (ER+) breast cancer
- Estrogen *agonist* in other tissues (bone/uterus)
- Preferred in **premenopausal women**
  - Aromatase inhibitors not effective in this group

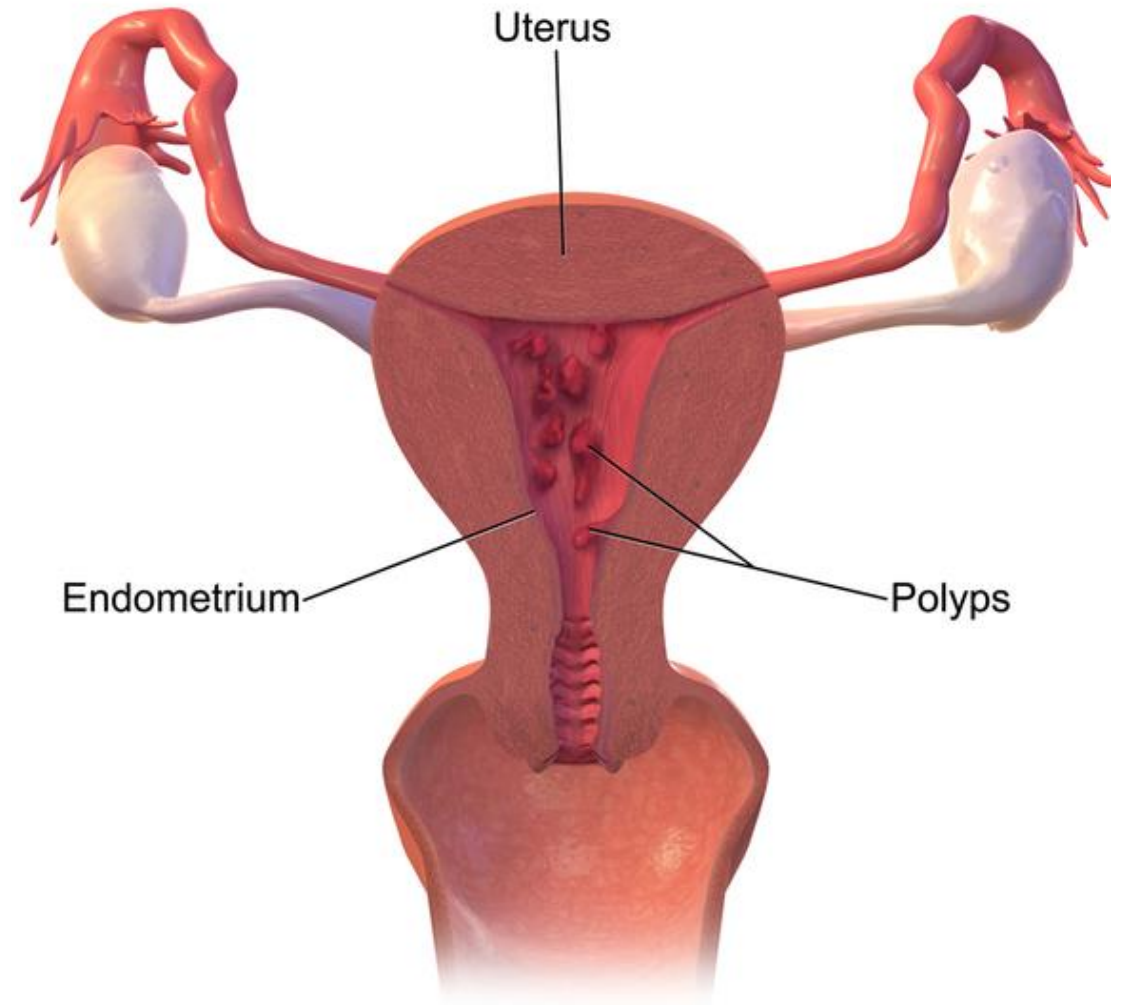


Tamoxifen

# Tamoxifen

## Adverse Effects

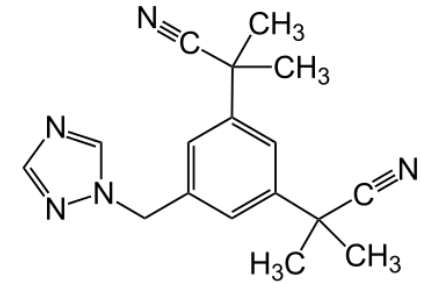
- Commonly causes **hot flashes**
- Increased risk of DVT/PE
- Partial agonist to endometrium
  - Endometrial proliferation
  - Hyperplasia
  - Polyp formation (up to 36% of women)
  - Associated with endometrial cancer



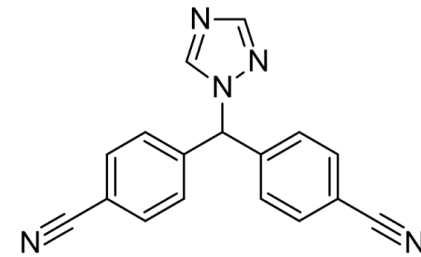
# Aromatase Inhibitors

Anastrozole, Letrozole, Exemestane

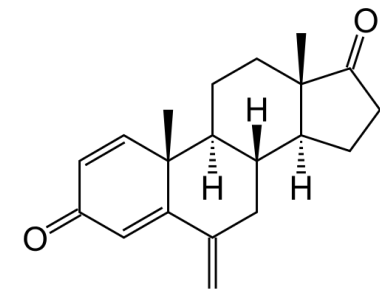
- ER+ breast cancer among **postmenopausal women**
- More effective than tamoxifen in clinical trials
- Block peripheral conversion of androgens to estrogen
- **Not used premenopause**: no impact in high estrogen states
- Increased risk of osteoporosis from loss of estrogen
- Increased risk of fracture



Anastrozole



Letrozole

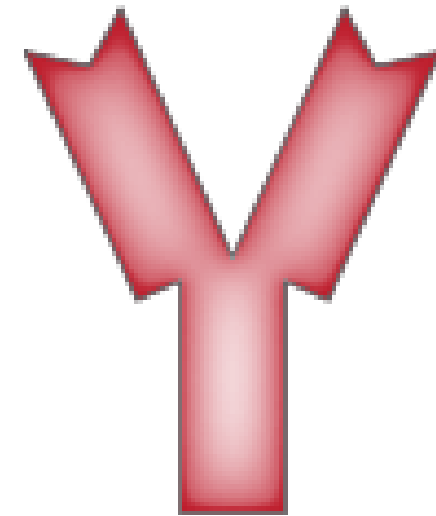


Exemestane

# Trastuzumab

## Herceptin

- Monoclonal antibody to **HER-2**
  - Surface receptor
  - Activation → cell growth and proliferation
  - Overexpressed by cancer cells
- Improves survival in HER-2+ breast cancer



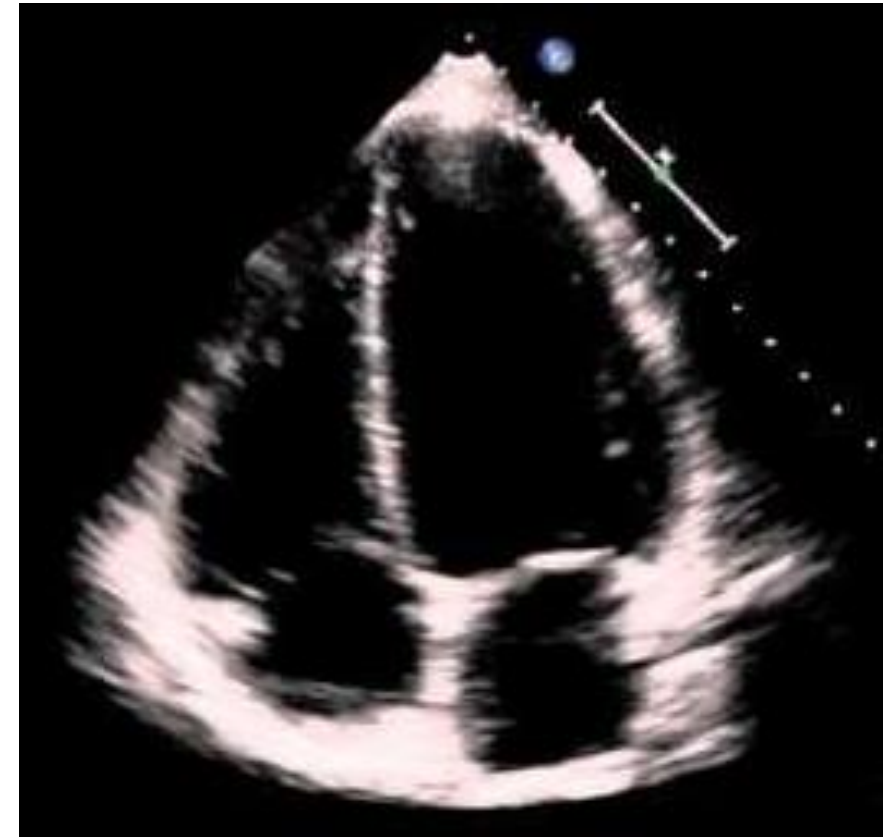


# Trastuzumab

## Toxicity

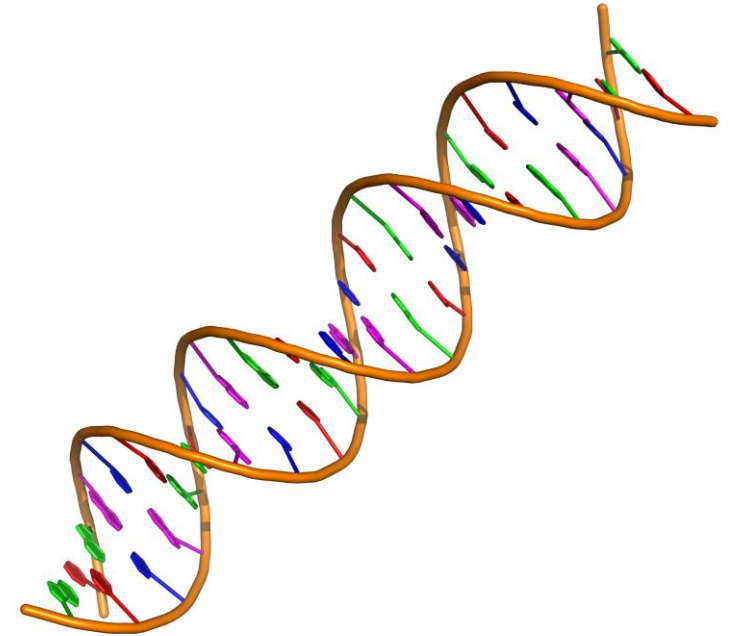
- **Cardiomyopathy**
- Usually asymptomatic ↓ LVEF
- Rarely causes heart failure symptoms
- Monitoring: serial **echocardiography**
- Different from anthracycline cardiotoxicity
  - Not dose dependent
  - **Often reversible** when drug discontinued
  - Re-challenge often tolerated after LVEF recovery

Echocardiogram



# Familial Breast Cancer

- Cause about 10% of breast cancers
- **BRCA1 and BRCA2 gene mutations**
  - Genes code for DNA repair proteins
  - Both gene mutations associated with breast cancer
- Also associated with other malignancies
- BRCA1: ovarian cancer
- BRCA2: male breast cancer and pancreatic cancer
- Autosomal dominant with incomplete penetrance
- Not all individuals with disease mutation develop disease



# Male Breast Cancer

- Incidence 1% compared to women
- Usually occurs 60 to 70 years of age
- Usually presents as subareolar mass +/- discharge
  - Most breast tissue in males near nipple
- Key associations:
  - Klinefelter syndrome (3 to 8% cases)
  - BRCA2 gene mutations (4 to 14% cases)

