Objectives

• Understand the molecular mechanisms responsible for onset of labor at term
• Appreciate why these mechanisms fail leading to preterm or post-term birth
• Discuss rationale behind interventions designed to prevent and/or treat abnormalities of labor

What is labor?

• The physiological process by which products of conception are passed from uterus to the outside world, and is common to all viviparous species
• Labor is a clinical diagnosis characterized by:
  ➢ Regular painful uterine contractions
  ➢ Progressive cervical effacement and dilatation
  (or an initial examination of ≥80% effacement, or ≥ 2 cm dilatation in a nulliparous patient)
The reproductive tract changes in pregnancy

- The uterus undergoes a dramatic increase in weight and volume due to an increase in cell number and an increase in fibers, connective tissue, blood vessels, and lymphatics.
- In the latter half of pregnancy, the uterus undergoes thinning of the uterine wall, forming the lower uterine segment.
- The increase in size is accompanied by a 10-fold increase in uterine blood flow, with 80-90% of uterine blood flow going to the placenta.
- This increase parallels the increase in placental size and decrease in placental vascular resistance.
- In contrast to the uterus, the cervix is composed of fibrous connective tissue containing an extracellular matrix.

The cervix undergoes extensive remodeling during pregnancy:

- At 20 weeks, the cervix is firm and closed.
- At term, the cervix is soft and relaxed, ready for labor.

What causes labor?

“The fetus in the womb”
Leonardo Da Vinci, circa 1510
Labor timing

- In most mammalian species the fetus is in control of the timing of labor
- Mechanical approach to labor
- Endocrine events
- Paracrine/autocrine events

Species-specific obstacles to reproduction

SP-A from the fetal lungs causes activation and migration of AM macrophages into uterus leading to ↑ IL-1β, NF-κB activation and labor

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It is fetal 16-hydroxy-DHEAS that serves as a substrate for estrogen production in the human placenta and not progesterone as in other animal species. This explains why there is no systemic withdrawal of progesterone levels prior to the onset of labor in humans.

Levels of progesterone measured in the maternal circulation one week prior to the onset of labor in humans is similar to that during labor. However, circulating progesterone levels are not an accurate reflection of progesterone activity at the level of the uterus and there is mounting evidence to suggest that withdrawal of progesterone activity at the level of the uterus is a prerequisite for parturition in the human.

This is supported by evidence showing that the administration of a pro-receptor agonist at term leads to increased uterine activity and cervical ripening.

Moreover, maternal supplementation with progesterone from 16 to 20 weeks gestation through 34-36 weeks has been shown to reduce the rate of preterm birth in some women at high risk.

Regardless of whether the trigger for parturition begins with the fetus or the placenta, it leads in the tissues of the maternal uterus, leading to regular phasic uterine contractions and cervical effacement and dilatation.
Cardinal movements

A. Before engagement
B. Engagement, flexion, descent
C. Descent, rotation
D. Complete rotation, early extension
E. Complete extension
F. Restitution
G. Anterior shoulder delivery
H. Posterior shoulder delivery

Cardinal movements

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Is there a genetic predisposition for PTB?

Indirect evidence

- Horse-donkey crossbreeding studies show intermediate gestational length

- Familial clustering of PTB
  - PGDH deficiency may account for 15% of PTB

Indirect evidence (cont.)

- Racial predisposition to PTB
  - 2- to 4-fold ↑ risk in African-American women
  - Disproportionate ↑ risk of PTB < 28 weeks in African-American women

References:

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PTB in the U.S. is highest for African-Americans
>> Native Americans > Hispanics > Whites, Asians

Indirect evidence (cont.)

- High rate of recurrent PTB
  - If the first delivery was at 20-31 weeks, the risk of a similar recurrent PTB was 13.4% (African-American) and 8.2% (Caucasian)
  - If the first delivery was at 32-36 weeks, the risk of a similar recurrent PTB was 3.8% (African-American) and 1.9% (Caucasian)

Indirect evidence (cont.)

- Twin studies of pregnancy outcomes suggest the heritability of PTB to be around 17-36%

Unlikely to be an example of simple Mendelian genetics

Complex genetic model

- Primarily a single gene disorder
  - Variable penetrance of the gene
  - Genetic background (gene-gene interactions)
  - Gene-environment interactions
- Multiple genes involved
- Epigenetic factors
  - DNA methylation/histone acetylation
  - siRNA

Gene-environment interaction and PTB

- A disproportionate ↑ in IL-1β over IL-1ra in vaginal secretions of pregnant women with altered vaginal microflora is assoc with PTB
  

- Maternal carriers of SNP in intron 2 of IL-1ra is assoc. with ↓ pro-inflammatory IL-1β response to abnormal vaginal flora and ↓ rate of spont. PTB (6% vs. 18%, P = 0.02)
  
Gene-environment interaction and PTB (cont.)

- Also ↓ spontaneous PTB rate with maternal carriage of 896 A>G SNP in TLR4 gene
  - Maternal carriers have ↑ in vaginal pH, 10-fold ↑ in *Gardinerella vaginalis* and gram negative rods, and an alteration in vaginal IL-1β and IL-1ra levels
  

Gene-environment interaction and PTB (cont.)

- Maternal carriers of -308 G>A SNP in TNFα promoter are assoc. with ↑ risk of PTB (OR, 2.7; 95% CI, 1.7-4.5), which was further ↑ in presence of BV (OR, 6.1; 95% CI, 1.9-21.0)
  
  

- ...and in African-American women (OR = 17)
  

When labor goes right

Photo by Diane Arbus
Preterm birth

Why all the fuss?

- Preterm birth complicates 8-12% of all deliveries
- Leading cause of perinatal mortality and morbidity
- There has been no decrease in the incidence of preterm birth over the past 30 years

Preterm births, 1990-2004

March of Dimes Perinatal Data Center, 2006; www.marchofdimes.com
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Preterm birth is a syndrome

Spontaneous
- Preterm PROM
- Intra-amniotic infection
- Idiopathic preterm labor

Iatrogenic
- Preterm births for maternal or fetal indication
  - Diabetes
  - IUGR
  - Preeclampsia
  - Placenta previa
  - Placental abruption


Preterm birth is a syndrome

Spontaneous

Iatrogenic

Intrauterine infection/inflammation

Excessive uterine stretch

Maternal and/or fetal stress

Hemorrhage

Preterm labor

Risk factors

- Prior preterm birth
- African-American race
- Age < 18 or > 40 years
- Poor nutrition
- Anemia
- Low pre-pregnancy weight
- Low socioeconomic status
- Absent prenatal care
- Bacteriuria or UTI
- Genital/gingival infection

- Cigarette smoking
- Illicit drug use
- Cervical injury or anomaly
- Uterine anomaly or fibroids
- Excessive uterine activity
- Premature cervical dilatation
- Overdistended uterus (twins)
- Vaginal bleeding
- Strenuous work
- High personal stress

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Markers
- Activin/inhibin
- Follistatin
- Ferritin
- CRP
- Interleukin-6
- CRH
- Progesterone
- Estrogens
- Metalloproteinases
- Collagenase
- Relaxin
- Fibronectin

Biochemical/endocrine markers

Source
- Blood
- Serum
- Saliva
- Amniotic fluid
- Vagina
- Cervix


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Fetal fibronectin (fFN)

- Amnion
- Chorion
- Fetal fibronectin
- Decidua


Positive fFN
- Cervical length < 25 mm
- Previous SPTB
- BMI < 19.8
- Vaginal bleeding
- Bacterial vaginosis
- Pelvic infection
- Black race
- RR of spont PTB < 32 weeks

Risk factors for preterm birth

- Contraction
- Black race
- Pelvic infection
- Bacterial vaginosis
- Vaginal bleeding
- BMI < 19.8
- Previous SPTB
- Cervical length < 35 mm
- Positive fFN

Effective strategies for prevention of preterm birth

- Prevention of multifetal pregnancies
- Cervical cerclage, if indicated
- Early diagnosis and treatment of genitourinary infections and STDs
- Stop smoking and substance abuse
- Progesterone supplementation (?)
Preventive strategies without proven benefit

- Intensive prenatal care
- Bed rest, flexible workforce policies
- Screening asymptomatic women for genital tract/gingival infections
- Broad-spectrum antibiotics
- Uterine tocolytic therapy (?)
What is the definition of post-term pregnancy?

- % of all deliveries
  - Gestational age (weeks)
  - Term
  - Post-term (prolonged)
  - EDC

10% (range, 3-14%)
4% (range, 2-7%)

What is the definition of post-term pregnancy?

- Accurate dating
  - Menstrual history is often inaccurate
    ➢ Especially if irregular cycles, on hormonal contraception, or intermenstrual bleeding
  - Routine early ultrasound will ↓ incidence of post-term pregnancy from 10% to 1.5-5%
    ➢ Not currently recommended in the U.S.

- Can we identify parturients at risk of post-term pregnancy?
  - Risk factors for post-term pregnancy ...
    ➢ Primiparity
    ➢ Prior post-term pregnancy
    ➢ Fetal anencephaly (without polyhydramnios)
    ➢ Congenital adrenal hypoplasia (CAH)
    ➢ Placental sulfatase deficiency (rare)
    ➢ Male fetus
  - The majority of post-term pregnancies have no known cause
## Risks to the Fetus

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal death (stillbirth)</td>
<td>4-fold ↑ at 43 wks and 5 to 7-fold ↑ at 44 wks (vs. 40 wks)</td>
</tr>
<tr>
<td>Fetal macrosomia</td>
<td>2.5-10% (vs. 0.8-1% at 40 wks)</td>
</tr>
<tr>
<td>Meconium</td>
<td>30-38% (vs. 17% at 40 wks)</td>
</tr>
<tr>
<td>“Fetal distress”</td>
<td>8% (vs. 5% at term)</td>
</tr>
<tr>
<td>Uteroplacental insufficiency</td>
<td>20-40%</td>
</tr>
</tbody>
</table>

## “Antepartum fetal deaths account for more perinatal deaths than do complications of prematurity or sudden infant death syndrome (SIDS)”


## Infant mortality and Stillbirth

Also increased risk of perinatal morbidity

- Post-term pregnancy is a risk factor for:
  - Apgar score < 4 at 5 min (OR 3.6; 95% CI, 1.5-8.7)
  - Neonatal convulsions (OR 3.4; 95% CI, 1.5-7.6)
  - Meconium aspiration (OR 3.0; 95% CI, 2.6-3.7)

- Also an independent risk factor for newborn encephalopathy (OR 13.2; 95% CI, 5.03-34.83)

Conclusions

- The timing of labor and birth is a critical determinant of perinatal outcome
- The factors responsible for the onset of labor at term remain poorly understood
- A better understanding of the factors responsible for labor will improve our ability to manage abnormalities of labor

“Children are one third of our population and all of our future”
Select Panel for the Promotion of Child Health
U.S. Dept of Health and Human Services
Washington, DC, 1981