Endocrinology of Pregnancy
Gravidity - oviparous species

- retain egg for species specific period
- time defined by:
  - length of shelling process
  - oviposition timed to environmental event
- oviposition is under control of mother
Oviparous reptiles

- Egg retention associated with corpus luteum activity
  - remove CL early in gravidity and spontaneous oviposition (e.g., lizards, snakes)
- at ovulation, CL formed by luteinization of granulosa and thecal cells
CL & Progesterone

- surge in progesterone observed
  - remains elevated in some species
  - others it is elevated only at ovulation
Post-ovulation

• movement of egg down reproductive tract associated with synthesis of PGF$_{2\alpha}$
  - activity present for short period
  - period of albumen and shell fiber secretion
  - associated with $\beta$-adrenergic stimulation

• oviduct contraction then becomes quiescent
  - inhibition of $\beta$-adrenergic stimulation
  - PG synthesis
Oviposition I

- egg retention can last
  - a few days
  - or months
- oviposition preceded by/associated with luteolysis
  - PGF$_{2\alpha}$ induces luteolysis in two lizard species
Oviposition II

• uterine contraction associated with:
  • 1. \( \text{PGF}_2\alpha \)
    • potent smooth muscle contractor
    • exogenous injection induces oviposition
    • elevated during natural oviposition
      - sea turtles & tuatara
      - birds
Oviposition III

2. Arginine Vasotocin (AVT)
   - octapeptide from neurohypophysis
   - potent smooth muscle contractor
   - exogenous injection induces oviposition
   - elevated during natural oviposition
     • sea turtle & tuatara

3. $\beta$-adrenergic stimulation
   - blockers inhibit oviposition
     • Lizards, birds
Cervical Relaxation

• Relaxin - peptide hormone from CL
  - augments timing of uterine contraction in turtle
  - removal of CL late in gravidity inhibits oviposition
  - in birds and reptiles - role unknown?

• \( \text{PGE}_2 \)
  - synthesis increases just prior to oviposition
  - exogenous injection does not induce oviposition
    • Elevated at oviposition in sea turtle, tuatara, birds
Ovulation

Progesterone

PGF$_{2\alpha}$  β-adrenergic

Albumen  Fibers  Calcium
Progesterone

Estradiol

AVT  PGF$_2\alpha$  β-adrenergic

PGE$_2$  Relaxin

Oviposition
Oviposition or nesting behavior

• observed in many species
• can be induced by $\text{PGF}_2\alpha$
  - fish spawning behavior
  - lizard oviposition behavior
  - pig "nesting" behavior
  - kangaroo belly licking behavior
“Birth”

- **Gastric brooding frog** (extinct 1980s)
  - swallow fertilized eggs
  - embryo and tadpoles synthesize PGE$_2$
  - inhibits gastric secretion during time in stomach!

- **Gastrotheca** - marsupial frog
  - AVT induces 'birth'
  - Induces female leg movements which include wiping-out the pouch

Northern gastric-breeding frog (*Rheobatrachus silus*), a species that broods its young in the stomach. Native to Australian rainforests. Last seen in the wild in 1985; a related species (*R. viola*) has not been seen in the wild since 1981.
Mammalian Pregnancy

• viviparous eutherian mammal
• unlike oviparous model
  - pregnancy length and establishment due to embryonic signals
• like oviparous model
  - CL plays important role in many species
In humans

- CL dies after 10-14 days unless rescued
- CL rescued by
  - human chorionic gonadotropin (hCG)
  - Synthesized / released by embryo
  - rescue called "maternal recognition of pregnancy"
- hCG related to FSH and LH
Plasma Progesterone Concentration

- **Placental**
- **Luteal**

**Axes:**
- **Y-axis:** Plasma Progesterone Concentration
- **X-axis:** 1st, 2nd, 3rd
Plasma Progesterone Concentration

1st

2nd

3rd

Placental

Miscarriage

Luteal
• after 5 weeks of pregnancy
  - placenta begin secreting estrogens
    - estradiol, estrone and mostly estriol
  - and progesterone
  - under hCG stimulation
  - levels secreted increase thru out pregnancy
    • support uterus and breast
    • inhibit ovulation
Feto-placental unit

• synthesis of steroids a joint operation of embryo and mother
• cooperative synthesis called
• feto-placental unit
  - placenta:
    • cholesterol > progesterone
    • fetus can not do this conversion
  - progesterone passes to fetus
Feto-placental unit II

- progesterone circulates in fetus to its adrenal glands
  - fetus has special region of adrenal
  - fetal zone
    - very large region compared to other regions
    - disappears soon after birth
Feto-placental unit III

- fetal zone
  - converts progesterone to dehydroepiandrosterone sulfate (DHEA-S)

- DHEA-S then goes to fetal liver and converted there to 16-OH-DHEA-S

- 16-OH-DHEA-S then goes back to placenta and converted to estriol
Feto-placental unit III

- fetal zone also secretes cortisol
  - glucocorticoid hormone - steroid
  - important in timing of birth
other placental hormones

• human placental lactogen (hPL)
  - rise late in pregnancy
  - can control maternal blood sugar concentrations
  - energy for embryo needs
  - primes breast for lactation

• prolactin

• chorionic corticotropin

• chorionic thyrotropin

• relaxin

• endorphins
  - opiate-like natural pain killers
Labor and Parturition

timing due to embryonic signals and fetoplacental unit activity
The key - CRH

• placental release of corticotropin-releasing hormone (CRH) into maternal and fetal circulation

• CRH level is "placental clock"
  - high levels early in pregnancy (week 16-20) higher risk of early birth
  - those with lower levels delayed birth
CRH

- CRH from fetal brain and the placenta
- CRH stimulates cortisol synthesis by fetal adrenal
  - cortisol stimulates maturation of lungs
- CRH also stimulates adrenal DHEA sulfate
  - DHEA sulfate converted to estrogens in placenta
Estrogens - late pregnancy

- rise during pregnancy & stimulates **CONNEXINS**
  - connexins are cell surface proteins
  - link myometrial cells for rapid, coordinated electrical signals
- **OXYTOCIN** receptors
  - oxytocin related to AVT
  - potent smooth muscle contractor
  - stimulates uterine contraction during birth
- **PROSTAGLANDIN** synthesis
  - degradation of collagen fibers
  - PGE$_2$ softening of cervix with RELAXIN
Connexins

[Diagram of Connexin molecules]
A lesson from sheep

• in pregnant sheep that ate plant *Veratrum californicum*
  - plant contains alkaloid that passes across placenta
  - harms pituitary and adrenal gland of fetus
  - delays or precludes birth
• thus a hint at what times birth
  - Adrenal required for birth
Induction of Birth

• as cervix softens, baby drops down onto cervix - **lightening**
  - about 2 weeks prior to birth - first pregnancy
  - can occur at labor in subsequent pregnancies

• **a few hours prior to birth**
  - "engagement of the presenting part" occurs
  - head of baby drops down into pelvic girdle
Fetal Ejection Reflex

• mechanical stimulation of cervix by head stimulates a neuroendocrine reflex
  - stimulating release of oxytocin from neurohypophysis
  - Oxytocin stimulates uterine contractions
• mechanical stimulation of contractions stimulates PGF$_{2\alpha}$ synthesis
• relaxin released as well as PGE$_2$ and birth is on its way!
Hypothalamus

Paraventricular nucleus
Supraoptic nucleus

Hypothalamo-hypophyseal tract. Increased firing rate after reproductive tract stimulation causes increased oxytocin secretion

Posterior pituitary

Brainstem

Blood

Oxytocin release

Uterus

Cervix

Vagina

Anterolateral columns (ipsi- and contra-lateral routes)

Spinal cord

Dorsal horn

Paraventricular nucleus
Supraoptic nucleus

Medial forebrain bundle

Hypothalamo-hypophyseal tract. Increased firing rate after reproductive tract stimulation causes increased oxytocin secretion

Blood

Anterolateral columns (ipsi- and contra-lateral routes)

Brainstem

Uterus

Cervix

Vagina

Dorsal horn
Estrogen

from ovaries

Induces oxytocin receptors on uterus

Oxytocin

from fetus and mother's posterior pituitary

Stimulates uterus to contract

Stimulates placenta to make Prostaglandins

Stimulate more contractions of uterus

Positive feedback
Signs of pregnancy

• Missed menstrual period
• Increased urination
• Cervix softens ~6 weeks post conception
  – (Hegars Sign)
• Later in pregnancy
  – fetal movement and heartbeat apparent
Pregnancy tests (2): Antibody

• Immunoassay pregnancy test
• Anti-hCG and urine mixed → color change

Problems:
3%: color change in absence of hCG
20%: Negative result in newly pregnant women
  - not sensitive enough until 15 days after conception
Pregnancy tests (3): Radioimmunoassay

- Very sensitive to hCG
- Detection within a few days of conception

- Problem:
  - More expensive
  - Many clinics do not run this test
Problems with hCG tests

• Misleading results can occur
• Hydatidiform moles
• Ectopic pregnancies
Hydatidiform moles

- Implantation of swollen chorionic villi & no embryo
  - 2N → all paternal chromosomes
  - 3N → partial hydatidiform condition, dead embryo
- Become malignant and secrete large amounts of hCG
- 1/1000 pregnancies

[Link to MOOンドラゴン・オガイン・マンドリーガット]
Ectopic pregnancy

- Blastocyst implants outside of the uterus
- May not produce detectable hCG
- Dangerous if not detected!
- 1% of pregnancies
  - 96% in oviduct (tubal pregnancy)
  - 4% abdominal pregnancies

www.psc.uc.edu/hs/HS_ectopic_pregnancy.htm
Tubal pregnancy

- Embryo develops in restricted area
- Oviduct walls thin and vascular
- Pain/hemorrhage
- Require surgical removal
- 10% of all maternal deaths

www.psc.uc.edu/hs/HS_ectopic_pregnancy.htm
Abdominal pregnancy

- Fetus develops in abdominal cavity
  - Often dies
  - Can be surrounded by calcium
- Rare cases cesarean section → healthy infant

www.psc.uc.edu/hs/HS_ectopic_pregnancy.htm
Why doesn’t mother’s immune system reject fetus?

One possibility:
1) Zona pelucida protects blastocyst from immunologic rejection
2) After implantation, ZP shed
3) Antibodies produced that suppress immunological rejection

How?
How? Possibility #1?

- Embryo stimulates production of a specific progesterone receptor on the surface of lymphocytes ("attacking cells")

Progesterone $\rightarrow$ binds lymphocyte $\rightarrow$ stimulates secretion of protein that prevents miscarriage
How? Possibility #2?

hCG coats trophoblast $\rightarrow$ protects against rejection

Supported by fact that certain tumors are coated by hCG $\rightarrow$ protects against immune rejection
How? Possibility #3?

Fetal cells have been shown to enter mother’s blood during early pregnancy
- Remain for at least 27 years
- May play a role in the maternal tolerance of the embryo
Fetal disorders (1)

• Rh incompatibility
  - Inherited phenomenon
  - Affects fetus of future pregnancy

  R-dominant  r- recessive

  Rh+ = RR or Rr
  Rh- = rr
Rh incompatibility

- Rh- mother and Rh+ father
  - ~10% of marriages
- If mother Rh- carries an Rh+ fetus, possible to have an immune response if blood mixes during labor
- Mother forms antibody to fetal Rh+ cells
Rh incompatibility (2)

2\textsuperscript{nd} Rh+ fetus leads to:

- (maternal) Immune system attack on mature red blood cells of fetus

- Fetus:
  - Juandice from accumulation of billirubin
    - Breakdown product of RBCs
    - Toxic $\rightarrow$ brain damage
  - High number of immature RBCs
    - Inefficient transport of O2
    - Anemia
Rh incompatibility (3)

Treatment:
1) Complete blood transfusion
2) Inject mother with Rhogam (Rhoimmune)
   1) Antibody to Rh factor
   2) Needs to be injected within 2-3 days of delivery or miscarriage of 1st Rh+ infant
   3) Prevents the formation of maternal Rh antibodies to future fetus
Damage to fetus

### Critical Periods in Human Development

<table>
<thead>
<tr>
<th>Period</th>
<th>Age of Embryo (in weeks)</th>
<th>Fetal Period (in weeks)</th>
<th>Full Term</th>
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<td>1</td>
<td>0-2</td>
<td>3-4</td>
<td>5-8</td>
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<tr>
<td>2</td>
<td>period of dividing zygote, implantation &amp; bilaminar embryo</td>
<td>C.N.S.</td>
<td>central nervous system</td>
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- **Heart**
- **Upper Limbs**
- **Eyes**
- **Lower Limbs**
- **Teeth**
- **Palate**
- **External Genitalia**
- **Ear**

*Red indicates highly sensitive periods when teratogens may induce major anomalies.*
Thalidomide

- Tranquilizer to treat morning sickness + stop bleeding
- 1950’s-1960’s
- Fetal exposure between 4-7 weeks of development leads to phocomelia:
  - Phoke-seal / melos- limb
  - hands and feet with no arms or legs

www.thalidomide.ca/en/information/brochure1.html
DES (Diethylstibestrol)

- Synthetic estrogen
- Thought to prevent miscarriage (1940’s-1970’s)
- 2 million women in the U.S.
- Daughters:
  - Increased miscarriages & premature births
  - Increased cervical and vaginal cancer
- Sons:
  - Undescended testicles
  - Low sperm count
Fetal alcohol syndrome

• During pregnancy:
  - 2 drinks/week: increased risk of miscarriage

• Chronic / 3 oz. Alcohol daily →
  - fetal alcohol syndrome 30-45% of time
  - infants with small heads
  - 1-2 oz/day constricts umbilical blood vessels

• 3 drinks / day →
  - lowers IQ test performance @ 4 years of age
Tobacco Smoke

- Nicotine constricts blood vessels in placenta and fetus
  - Poor delivery of O2 and glucose
- Carbon monoxide can build up in fetal RBCs
- Lower vitamin C levels in fetus
- Hearing difficulties and lower performance on IQ tests
Fetal evaluation

- Amniocentesis
- Ultrasound
Amniocentesis

- 14th-16th week of pregnancy
- Needle inserted to sample amniotic fluid
- 40 genetic abnormalities (or many more?) can be detected

Problems:
- Kills 1.5% of fetuses?
- Several weeks for results

http://www.fetalmaternal.org/images/Amniocentesis.jpg
http://ici.cegep-ste-foy.qc.ca/profs/gbourbonnais/biotlm/genetiquetl/m/imagesgenet/amniocentesis.gif
Ultrasound

- Uses high frequency sound
- Dense tissues reflect waves that are detected by a receiver
- Thought to be minimally invasive

[Image: Ultrasound scan]

keystone.stanford.edu/.../nph-photos?q=prenatal
Maternal nutrition

• Energetic demands to support developing fetus
  • ~ 25 lb. Should be gained by average mother
    - 11 lb Fat
    - 3 lb increased uterine and breast size
    - 2 lb growing placenta
    - 1 lb amniotic fluid
    - 1 lb increase in maternal blood volume
    - 7 lb fetus weight
Adaptive value of morning sickness?

First 2-8 weeks of pregnancy
- 75% of women
- Food aversion, nausea, vomiting
- Traditionally treated with drugs
  - Thalidomide

Not treated any more
Adaptive value of morning sickness? (2)

Prevent pregnant females from eating substances that could harm/abort embryo?
- nausea, vomiting in response of substances
- bitter, pungent odors
- Lower rates of miscarriage in women who do not have symptoms
Adaptive value of morning sickness? (3)

Chemicals evolved in plants to prevent being eaten
- Many will cause sickness/induce abortion

**Phytoestrogens**
(clover, willow, alfalfa)
Can cause miscarriage in farm animals
Some cultures use to induce abortions

http://www.lifequestherbs.com/images/alfalfa.jpg

www.english.ubc.ca/.../trail3/plants/photos.htm
Adaptive value of morning sickness? (4)

Native Americans of Western U.S.
Brew pine needle tea
- phytoestrogens + toxins
- induce abortion
Adaptive value of morning sickness? (5)

Greeks
- Stalks and seeds of plants from genus Ferula
  - (fennel, Queen Anne’s Lace)
    - Cause abortion when chewed or brewed as tea
    - Have strong aroma
    - Component of many steak sauces produced today

Active chemicals block progesterone synthesis
- vital for implantation and pregnancy

www.heorot.dk/woden-notes.html
Adaptive value of morning sickness? (6)

Other plants that can induce abortion:
- Pennyroyal, sage, myrrh, rue, papyrus, dates, and mustard

Morning sickness occurs in all cultures studied

Adaptive origin

www.hcfnps.org/miscellaneous/onlyinflorida.htm