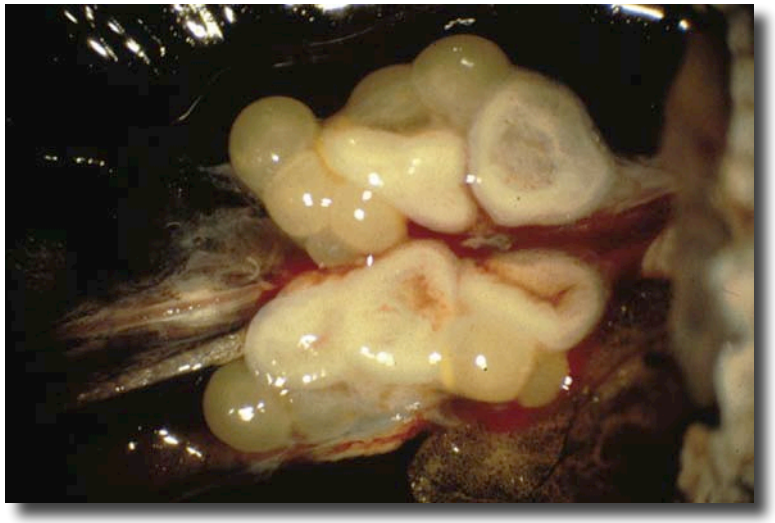
Endocrinology of Pregnancy

Gravidity - oviparous species

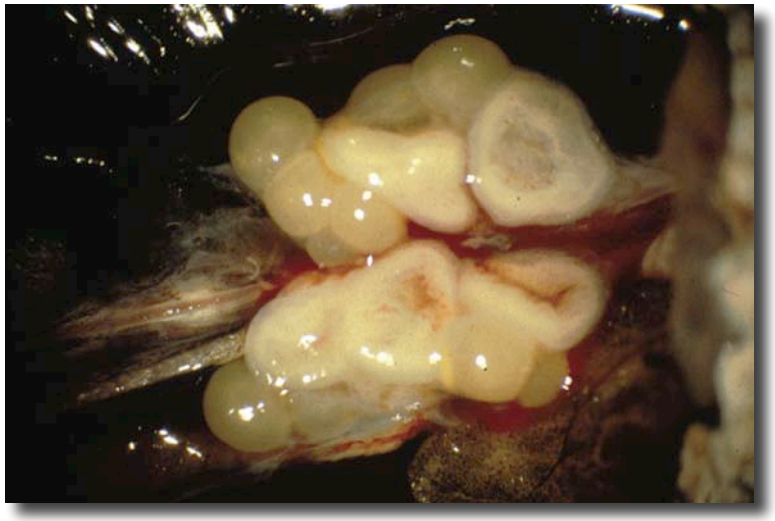
- retain egg for species specific period
- time defined by:
  - length of shelling process
  - oviposition timed to environmental event
- oviposition is under control of mother

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

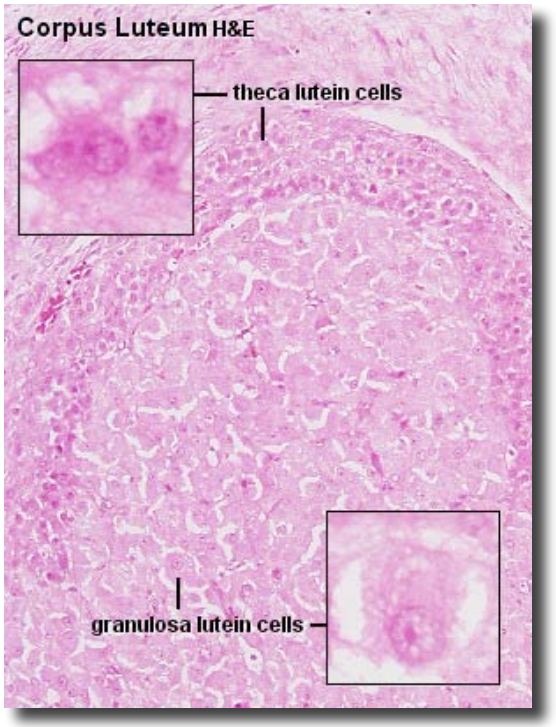


- surge in progesterone observed
  - remains elevated in some species
  - others it is elevated only at ovulation

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 β-adrenergic stimulation
- oviduct contraction then becomes quiescent
  - inhibition of β-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. $PGF_{2\alpha}$
  - potent smooth muscle contractor
  - exogenous injection induces oviposition
  - elevated during natural oviposition
    - sea turtles & tuatara
    - birds

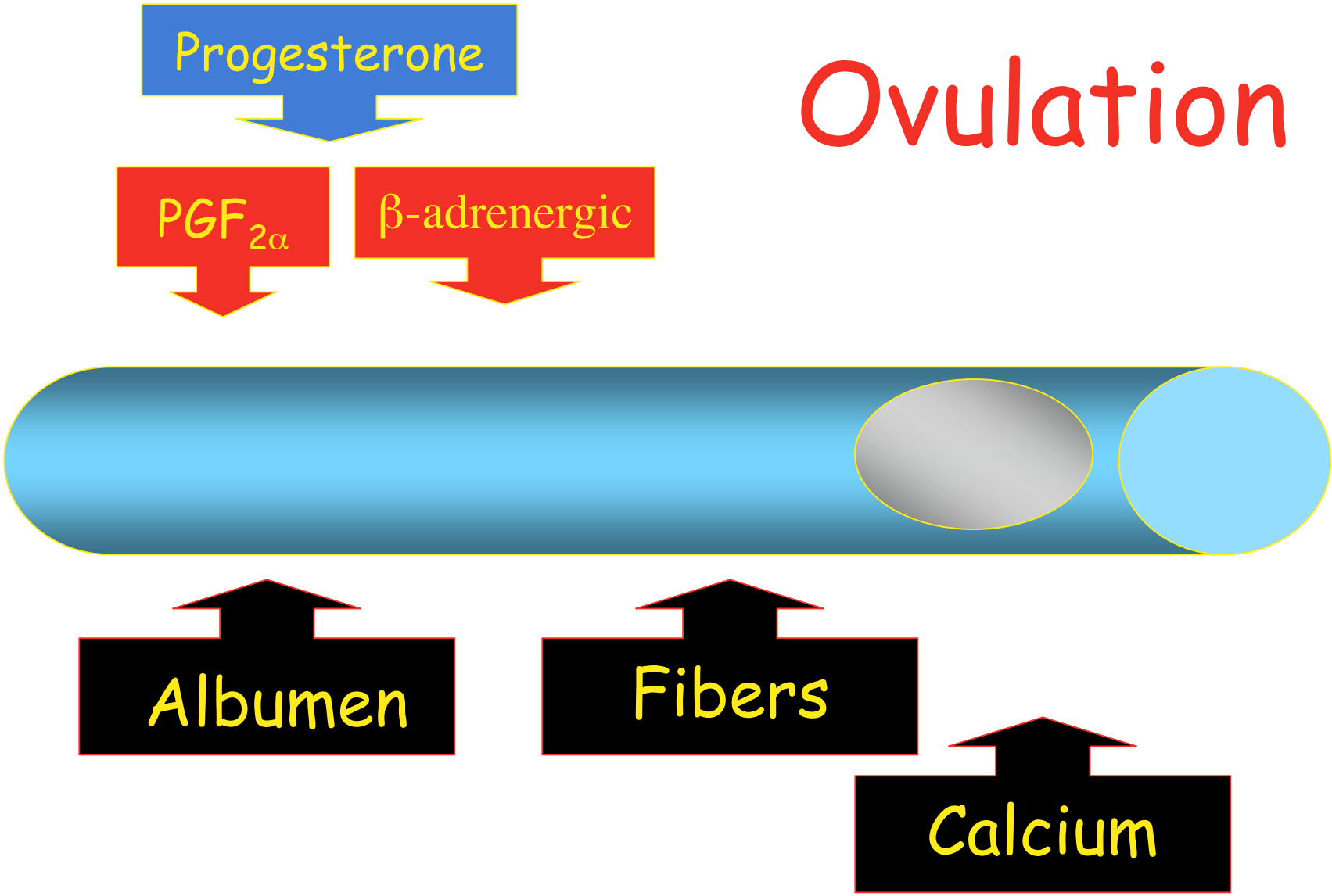
Oviposition III

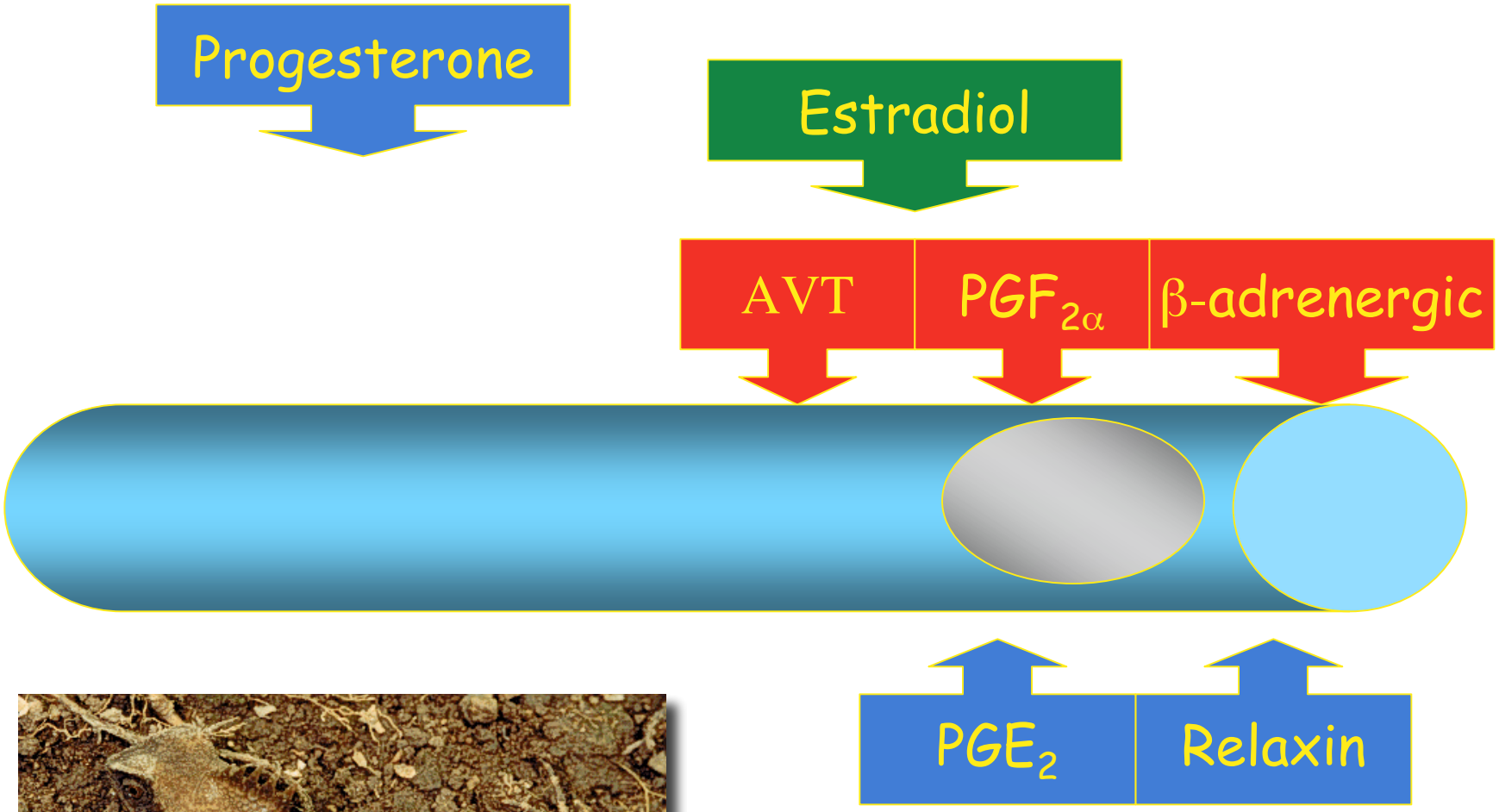
- 2. Arginine Vasotocin (AVT)
  - octapeptide from neurohypophysis
  - potent smooth muscle contractor
  - exogenous injection induces oviposition
  - elevated during natural oviposition
    - sea turtle & tuatara
- 3. β-adrenergic stimulation
  - blockers inhibit oviposition
    - Lizards, birds

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?
- 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



Oviposition

Oviposition or nesting behavior

- observed in many species
- can be induced by $PGF_{2\alpha}$
  - fish spawning behavior
  - lizard oviposition behavior
  - pig "nesting" behavior
  - kangaroo belly licking behavior

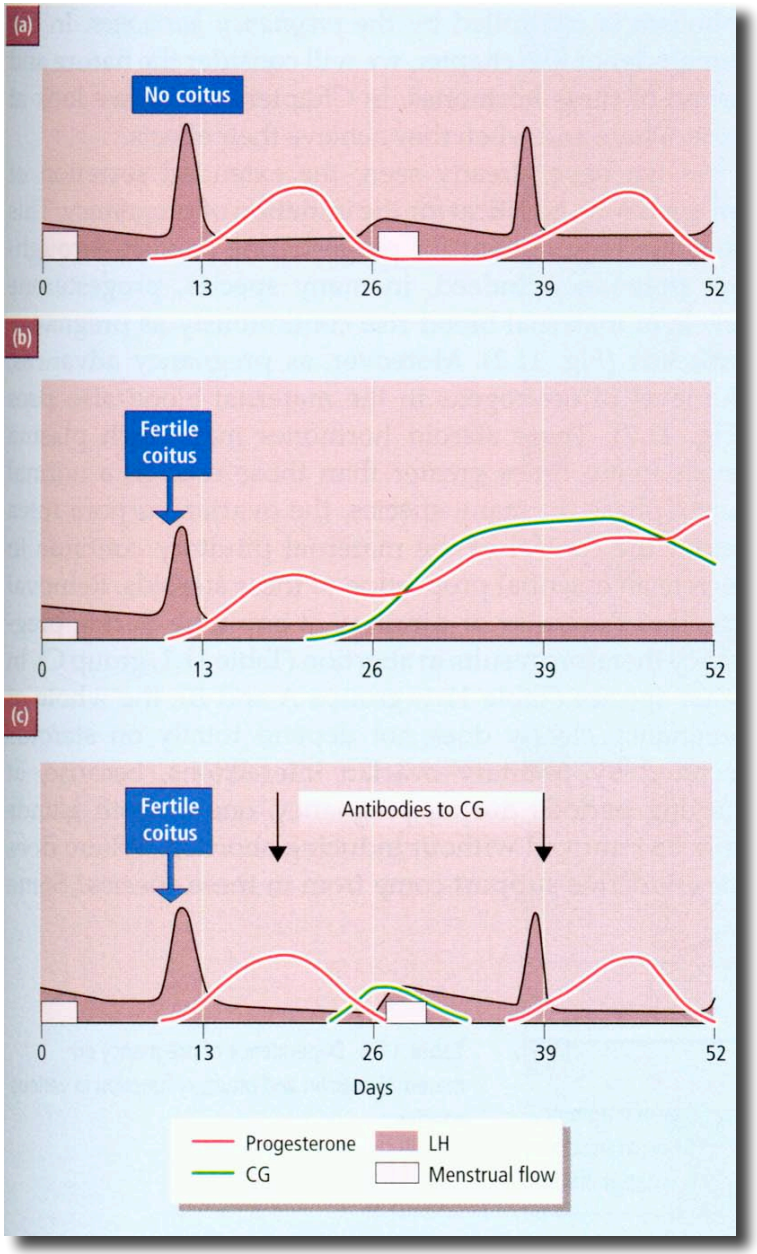
"Birth"

- 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 vitellinus*). A species that broods its young in the stomach. Native to Australian rainforests. Last seen in the wild in 1985; a related species (*R. silus*) has not been seen in the wild since 1981.

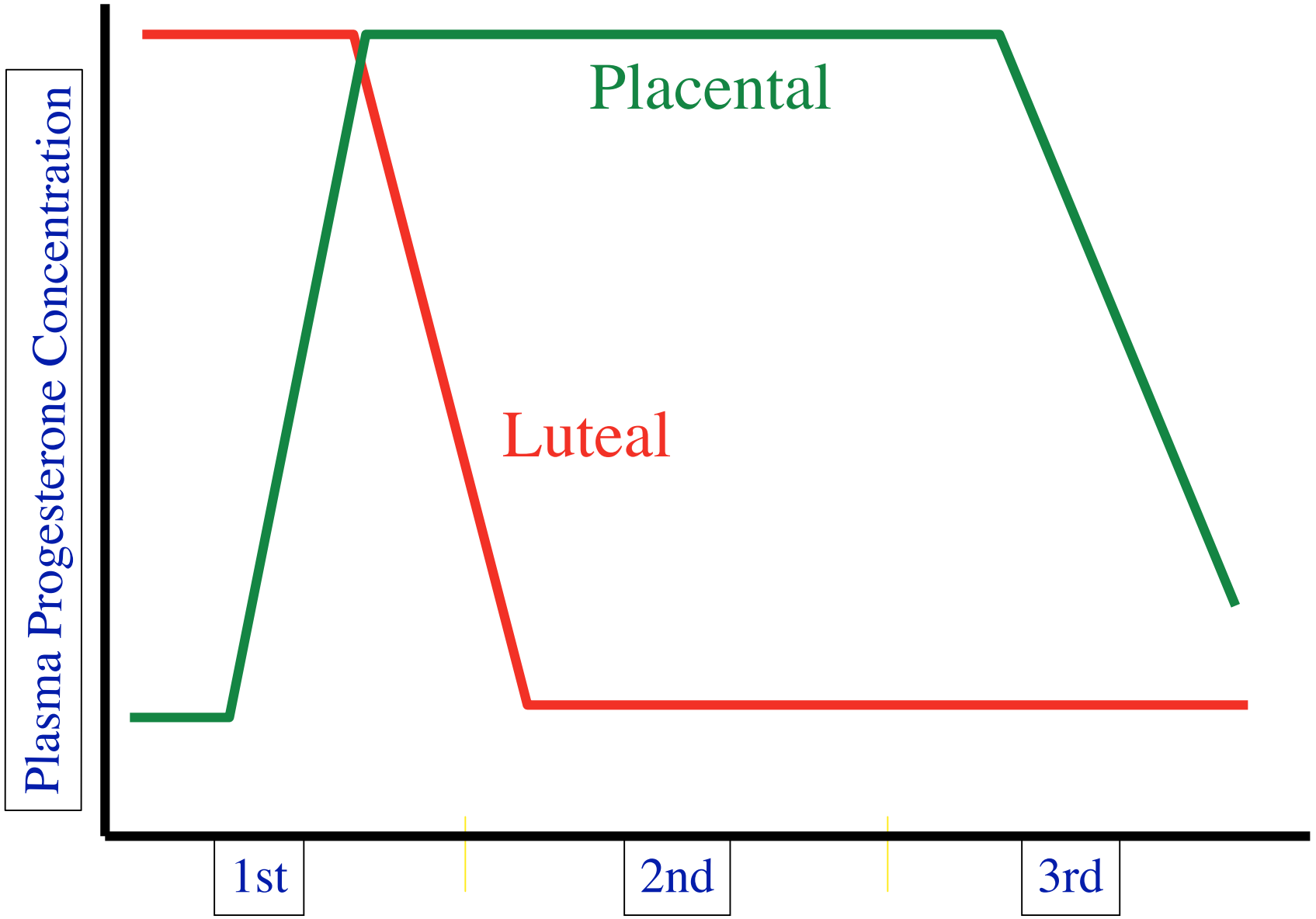
Mammalian Pregnancy

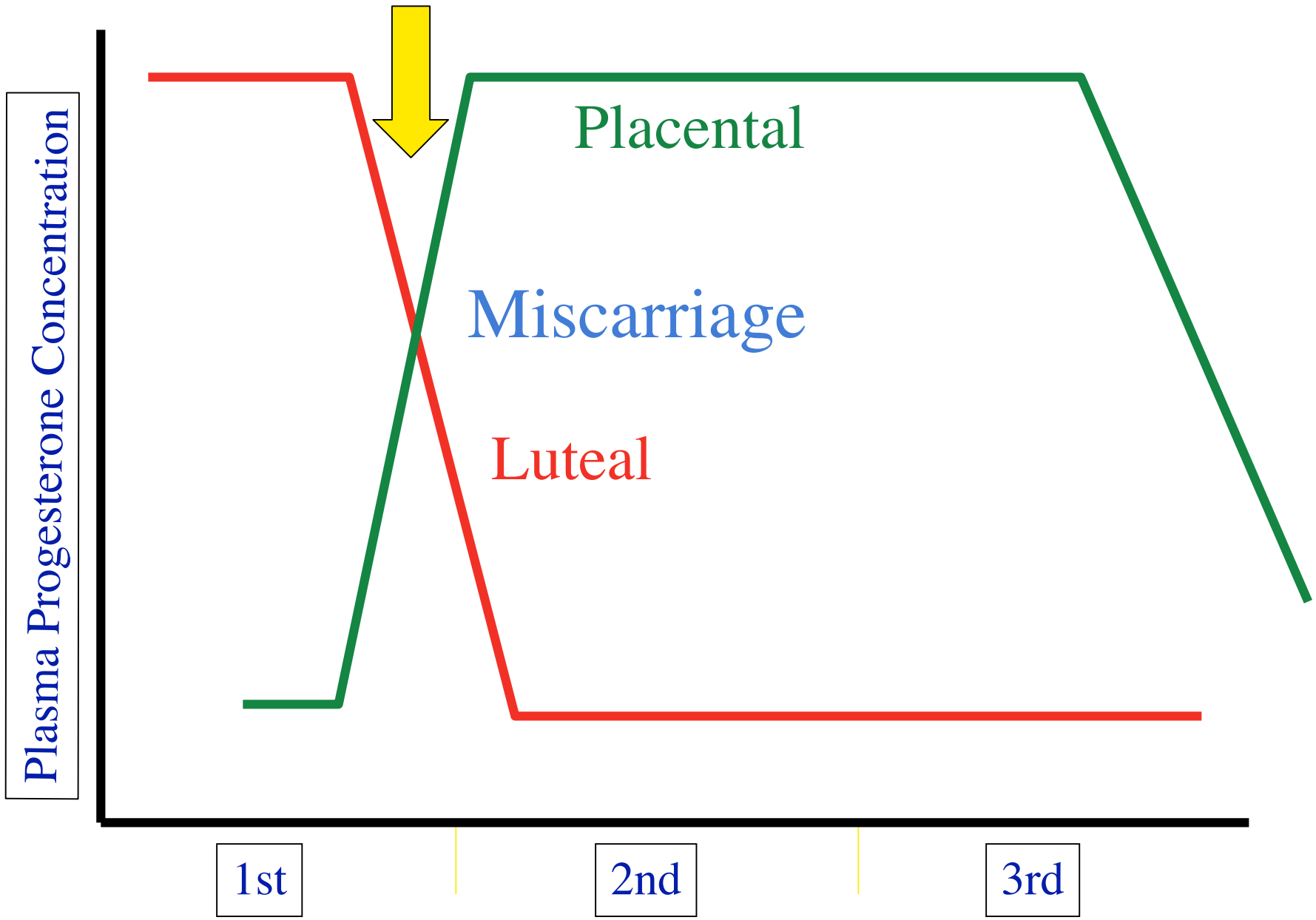
- viviparous eutherian mammal
- unlike oviparous model
  - pregnancy length and establishment due to embryonic signals
- like oviparous model
  - CL plays important role in many species



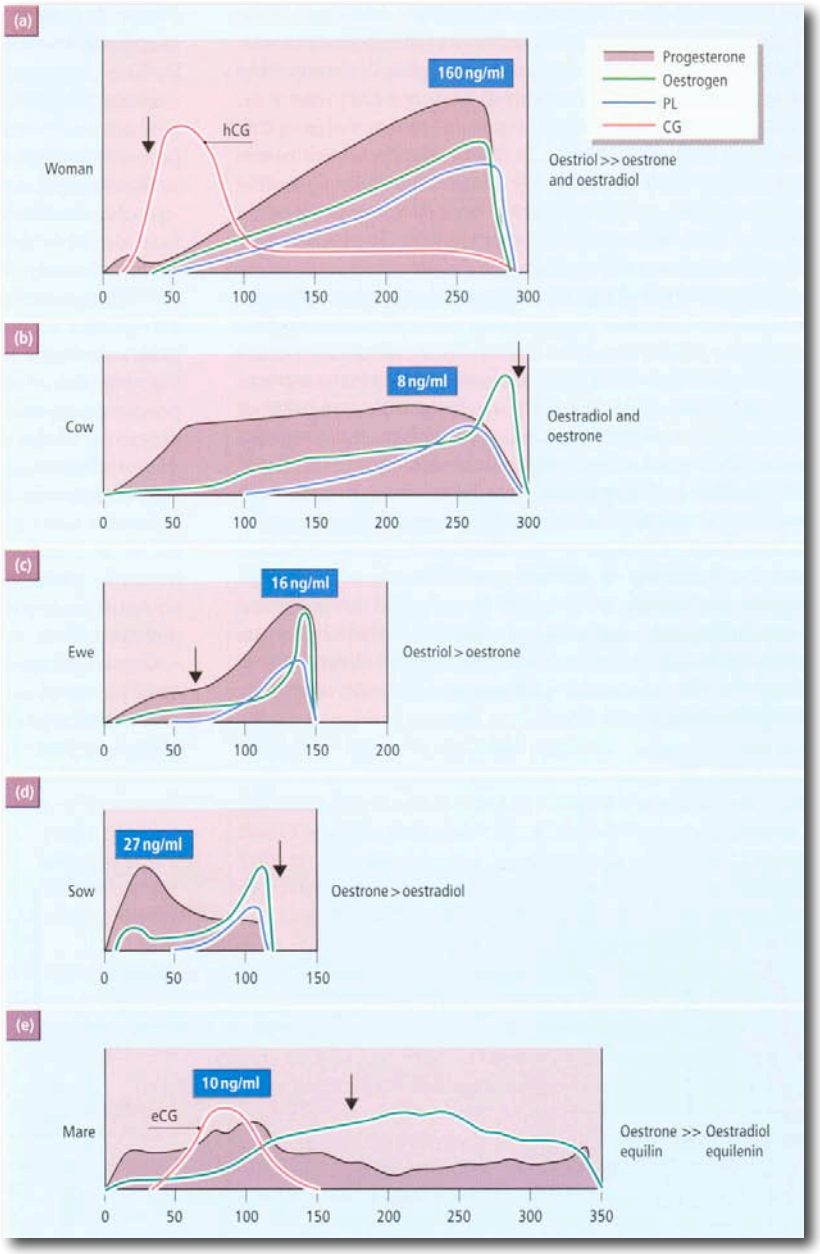
In humans

- 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
1st
2nd
3rd


Plasma Progesterone Concentration
Placental
Miscarriage
Luteal
1st
2nd
3rd

- 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

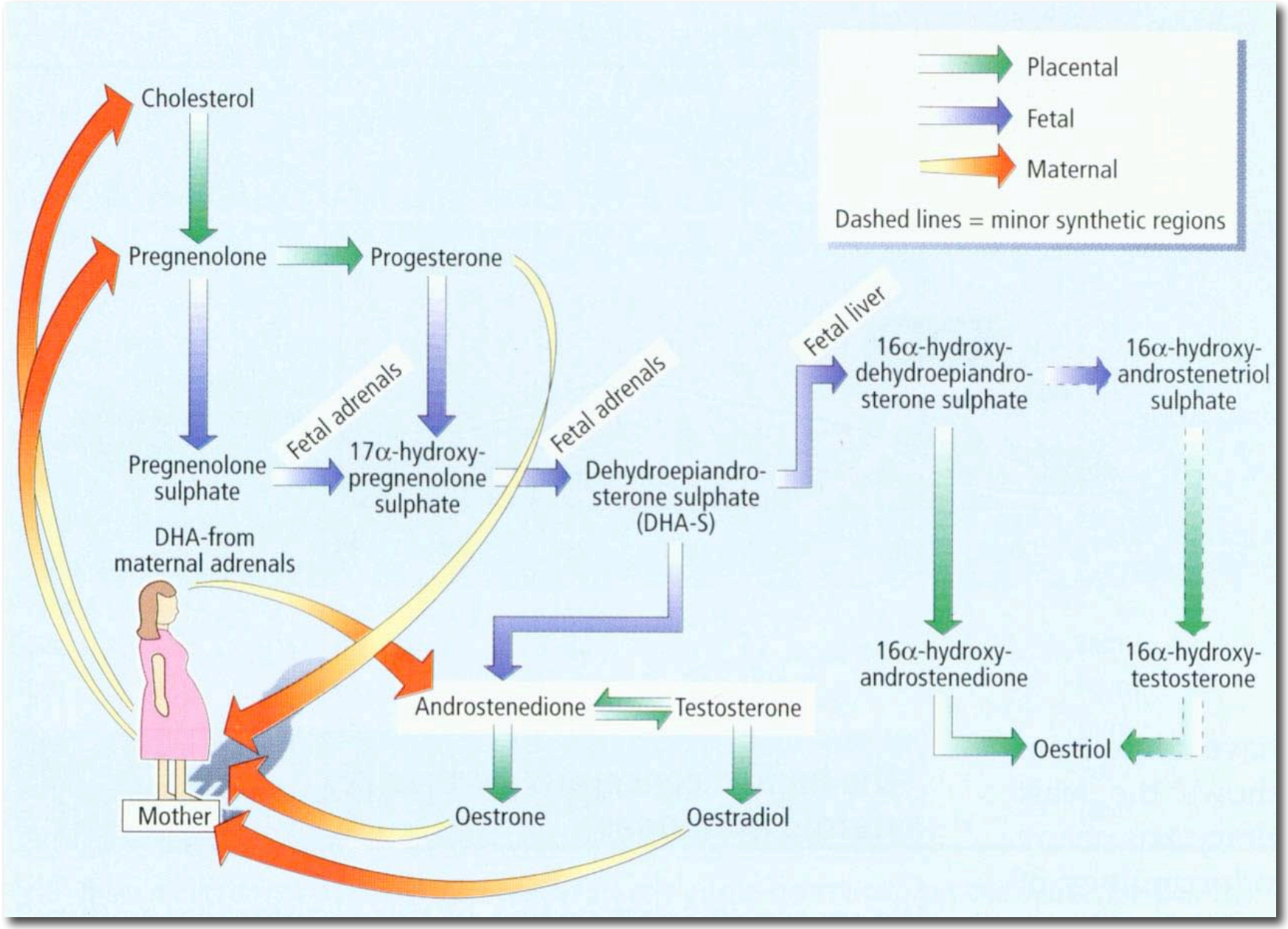
- progesterone circulates in fetus to its adrenal glands
  - fetus has special region of adrenal
  - fetal zone
    - very large region compared to other regions
    - disappears soon after birth

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

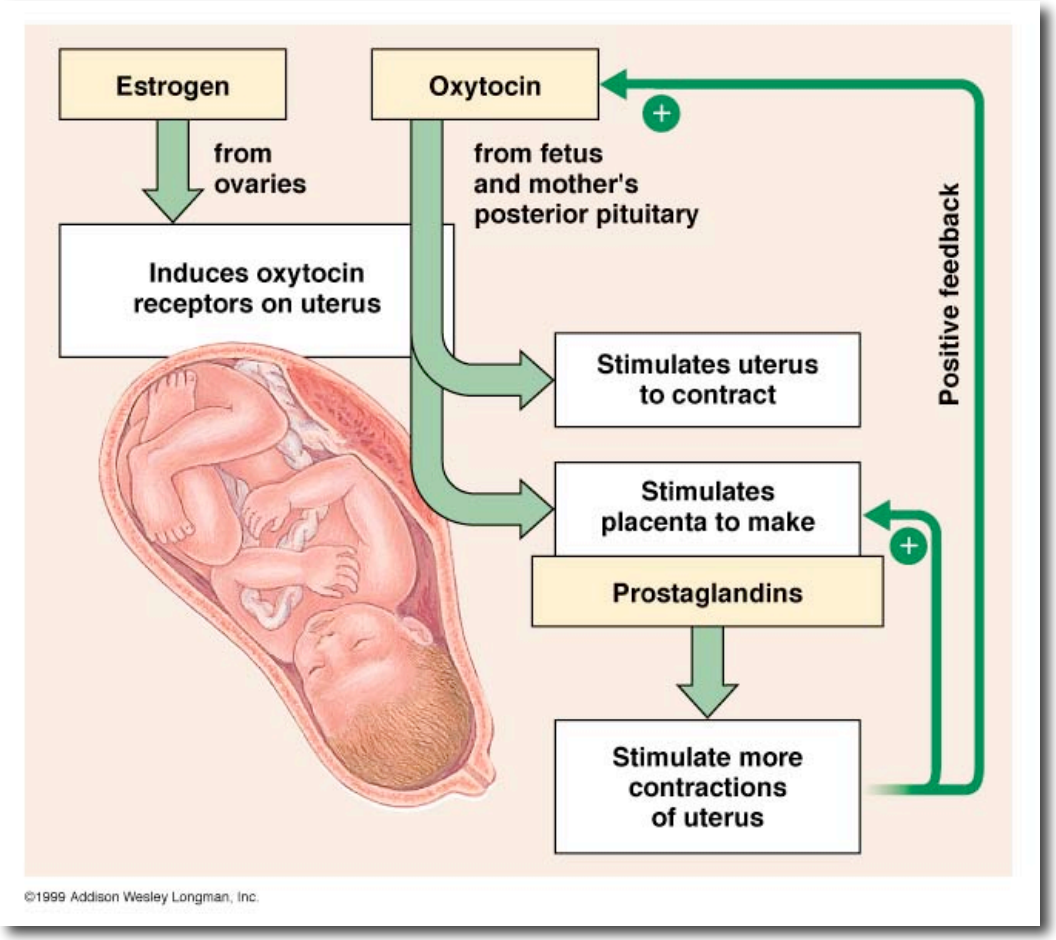
- fetal zone also secretes cortisol
  - glucocorticoid hormone - steroid
  - important in timing of birth


Placental
Fetal
Maternal
Dashed lines = minor synthetic regions
Cholesterol
Pregnenolone
Progesterone
Pregnenolone sulphate
Fetal adrenals
17α-hydroxy-pregnenolone sulphate
Fetal adrenals
Dehydroepiandro-sterone sulphate (DHA-S)
Fetal liver
16α-hydroxy-dehydroepiandro-sterone sulphate
16α-hydroxy-androstenetriol sulphate
DHA-from maternal adrenals
16α-hydroxy-androstenedione
16α-hydroxy-testosterone
Androstenedione
Testosterone
Oestriol
Mother
Oestrone
Oestradiol

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 feto-placental 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

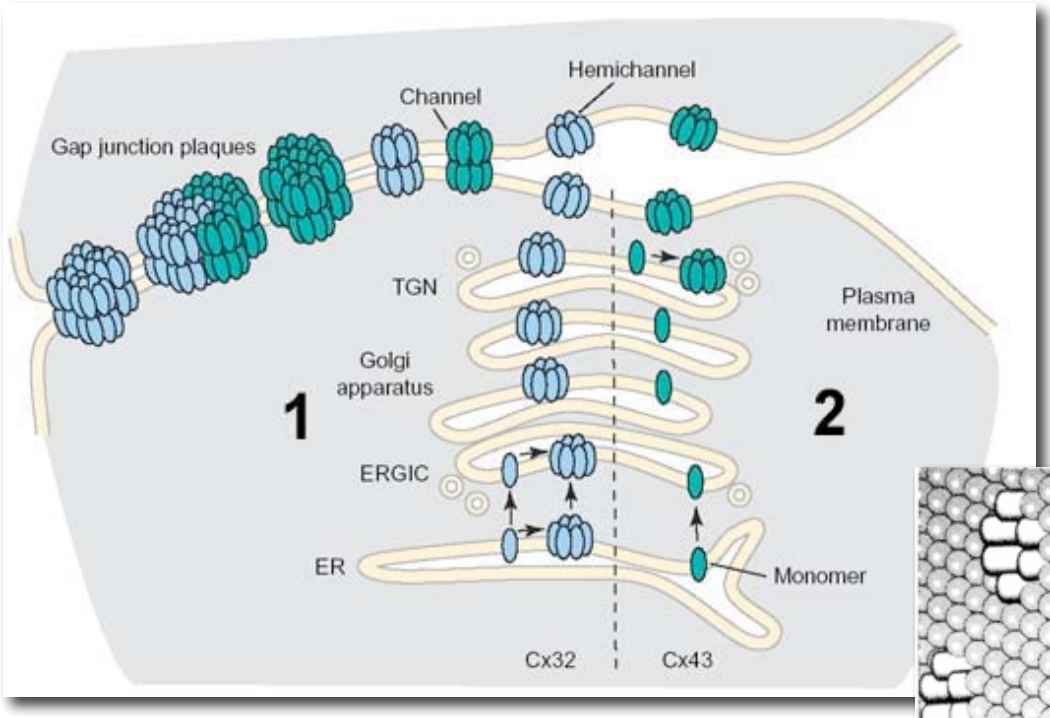
CRH

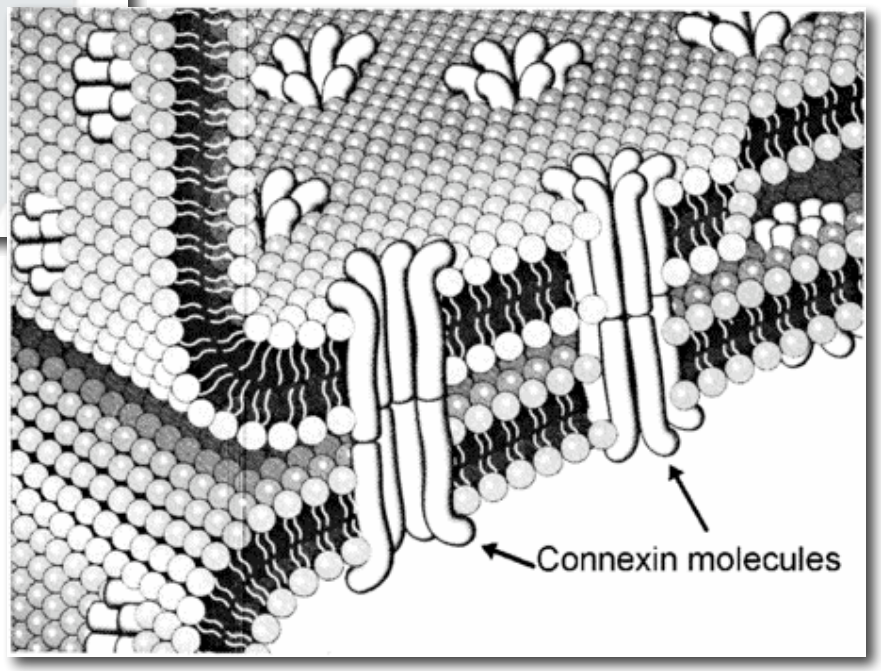
- CRH from fetal brain and the placenta
- CRH stimulates cortisol synthesis by fetal adrenal
  - cortisol stimulates maturation of lungs
- CRH also stimulates adrenal DHEA sulfate
  - DHEA sulfate converted to estrogens in placenta

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


Hemichannel
Channel
Gap junction plaques
TGN
Plasma membrane
Golgi apparatus
1
2
ERGIC
ER
Monomer
Cx32
Cx43


Connexin molecules

A lesson from sheep

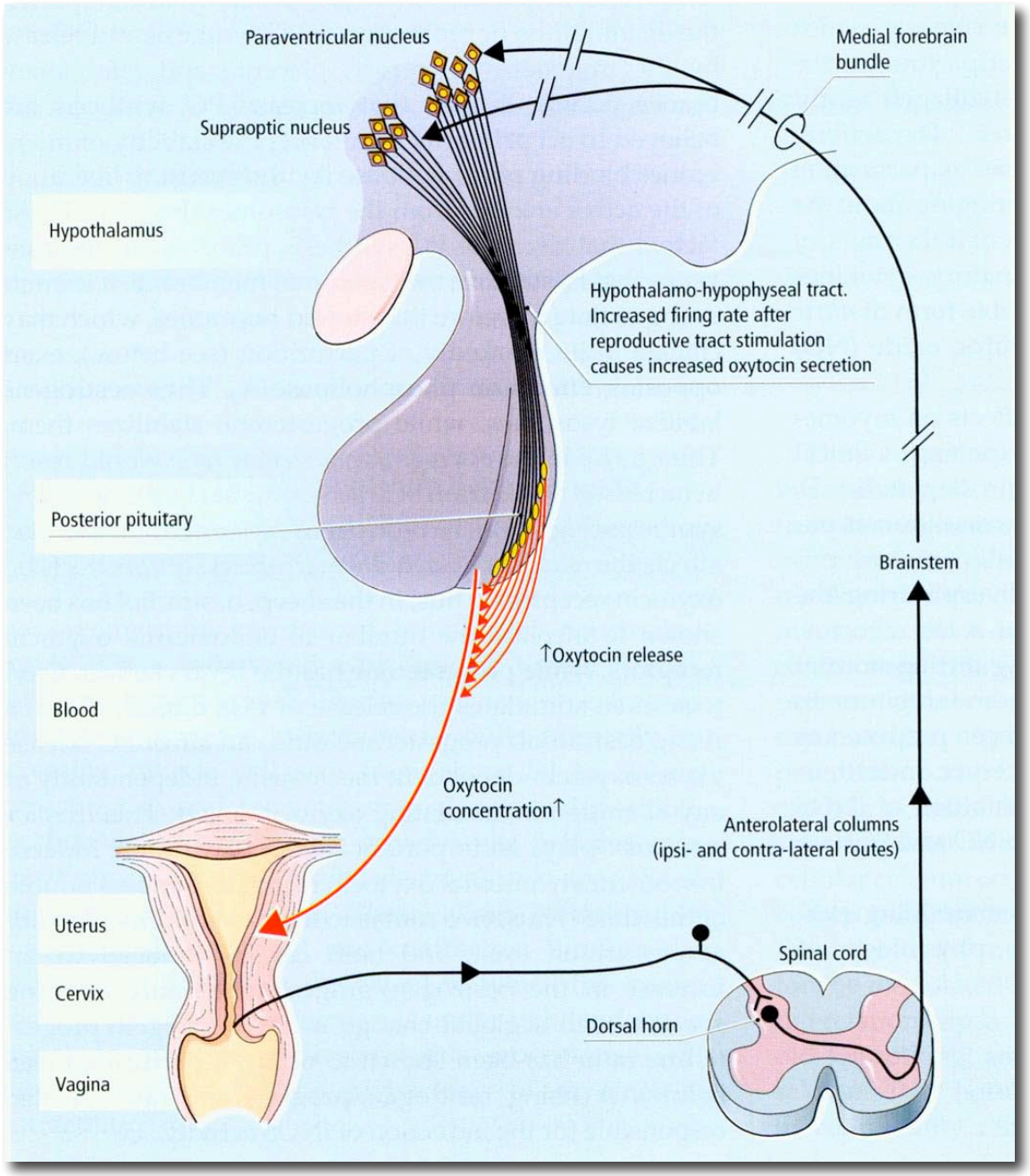
- in pregnant sheep that ate plant *Veratrum californicum*
  - plant contains alkaloid that passes across placenta
  - harms pituitary and adrenal gland of fetus
  - delays or precludes birth
- thus a hint at what times birth
  - Adrenal required for birth

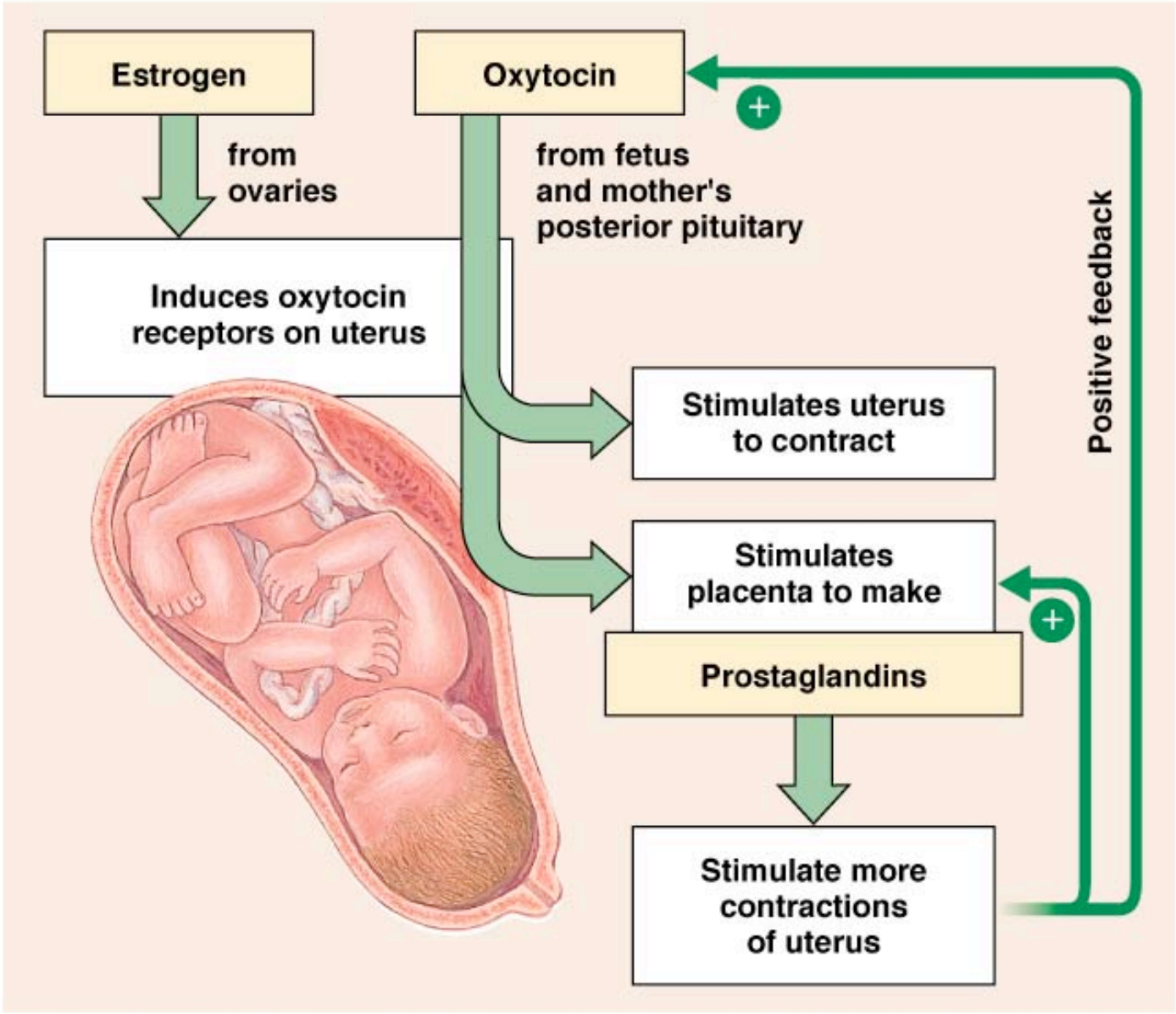
Induction of Birth

- as cervic 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!


Paraventricular nucleus
Medial forebrain bundle
Supraoptic nucleus
Hypothalamus
Hypothalamo-hypophyseal tract. Increased firing rate after reproductive tract stimulation causes increased oxytocin secretion
Posterior pituitary
Brainstem
↑Oxytocin release
Blood
Oxytocin concentration↑
Anterolateral columns (ipsi- and contra-lateral routes)
Uterus
Cervix
Vagina
Spinal cord
Dorsal horn

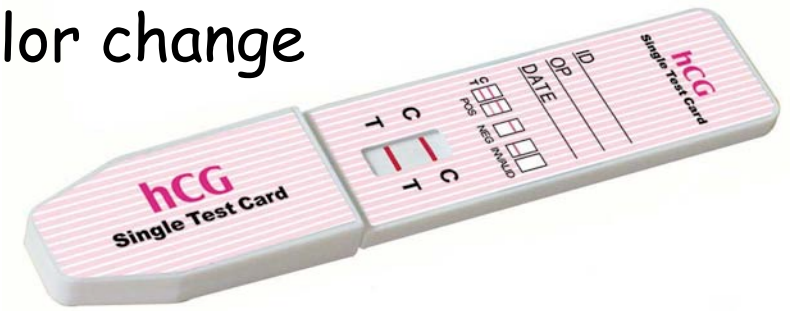


Signs of pregnancy

- 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

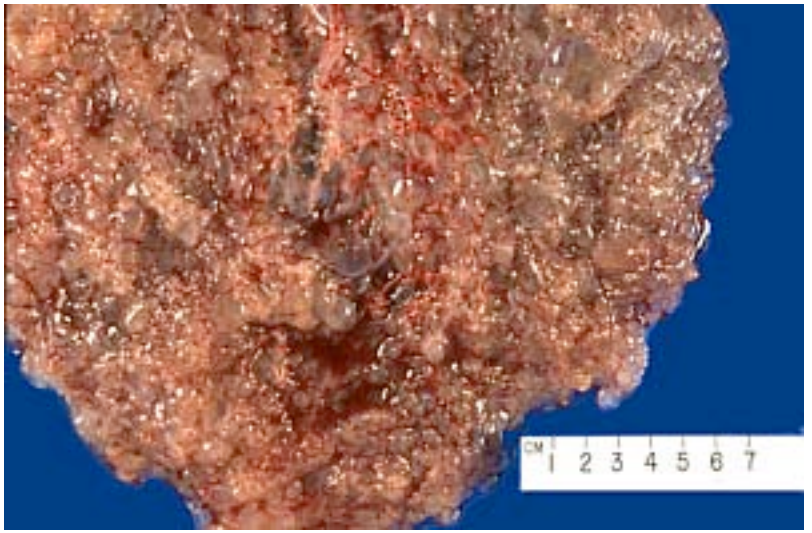
- Problem:
  - More expensive
  - Many clinics do not run this test

Problems with hCG tests

- Misleading results can occur
- Hydratidiform moles
- Ectopic pregancies

Hydratidiform moles

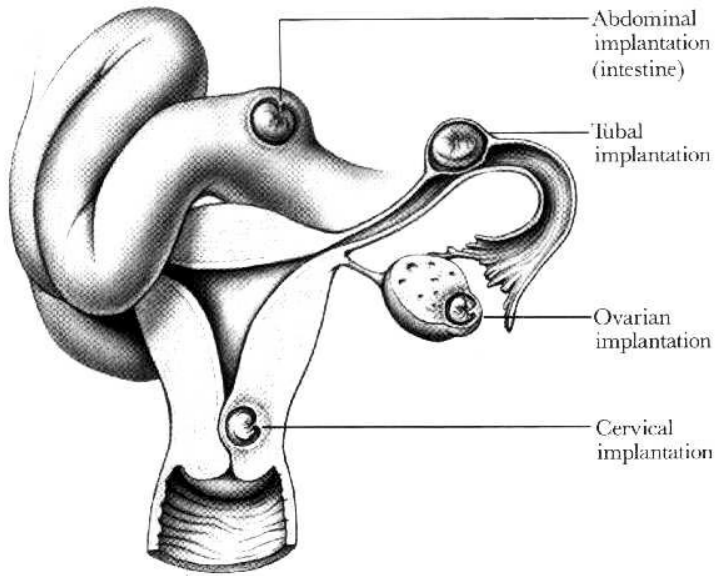
- Implantation of swollen chorionic villi & no embryo
  - 2N → all paternal chromosomes
  - 3N→ partial hydratidiform condition, dead embryo
- Become malignant and secrete large amounts of hCG
- 1/1000 pregnancies



www.moondragon.org/obgyn/pregnancy/molar.html

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

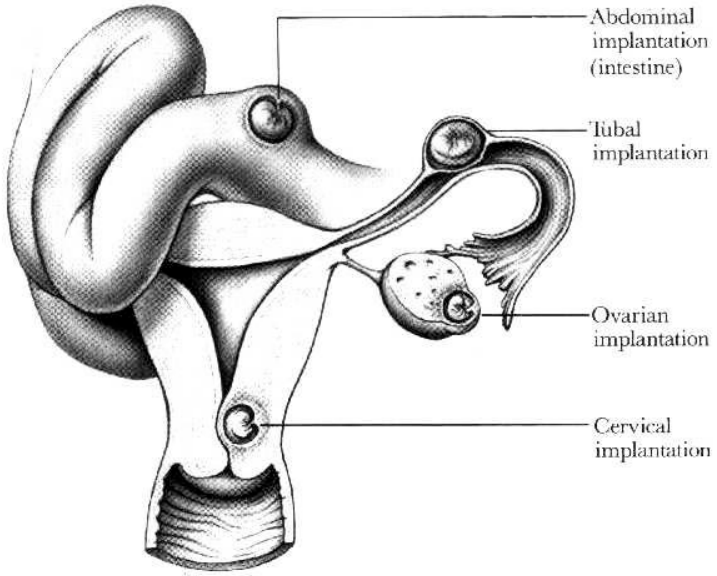


Ectopic Pregnancy

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

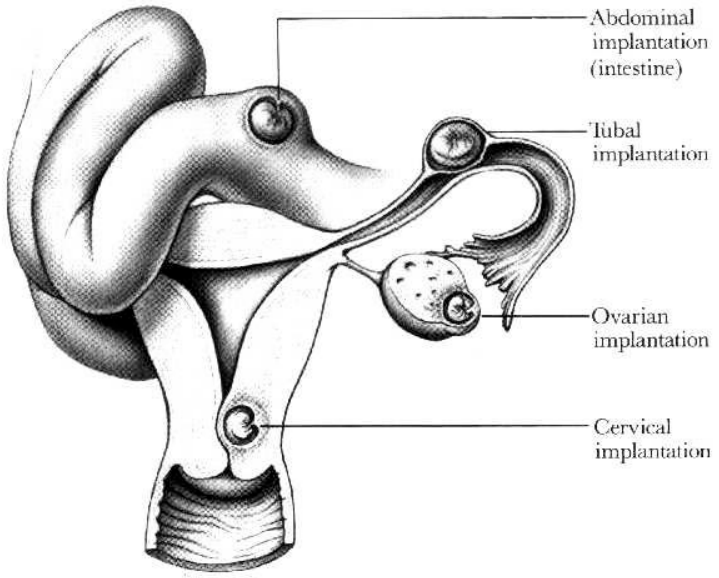


Ectopic Pregnancy

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



Ectopic Pregnancy

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 → binds lymphocyte → stimulates secretion of protein that prevents miscarriage

How? Possibility #2?

hCG coats trophoblast → protects against rejection

Supported by fact that certain tumors are coated by hCG → 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

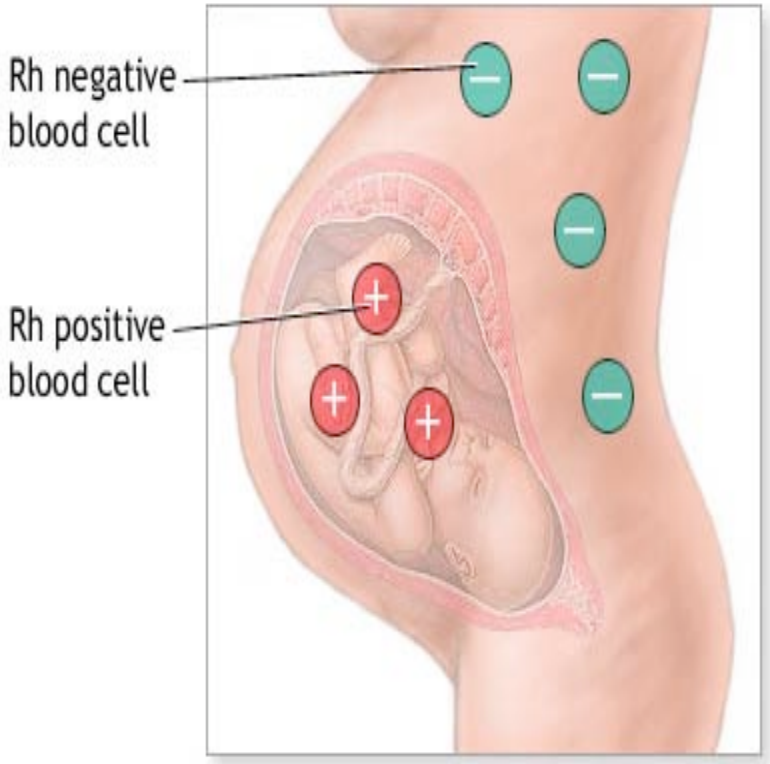
  R-dominant r- recessive

  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
- <u>Mother forms antibody to fetal Rh+ cells</u>



Rh incompatibility (2)

2nd Rh+ fetus leads to:

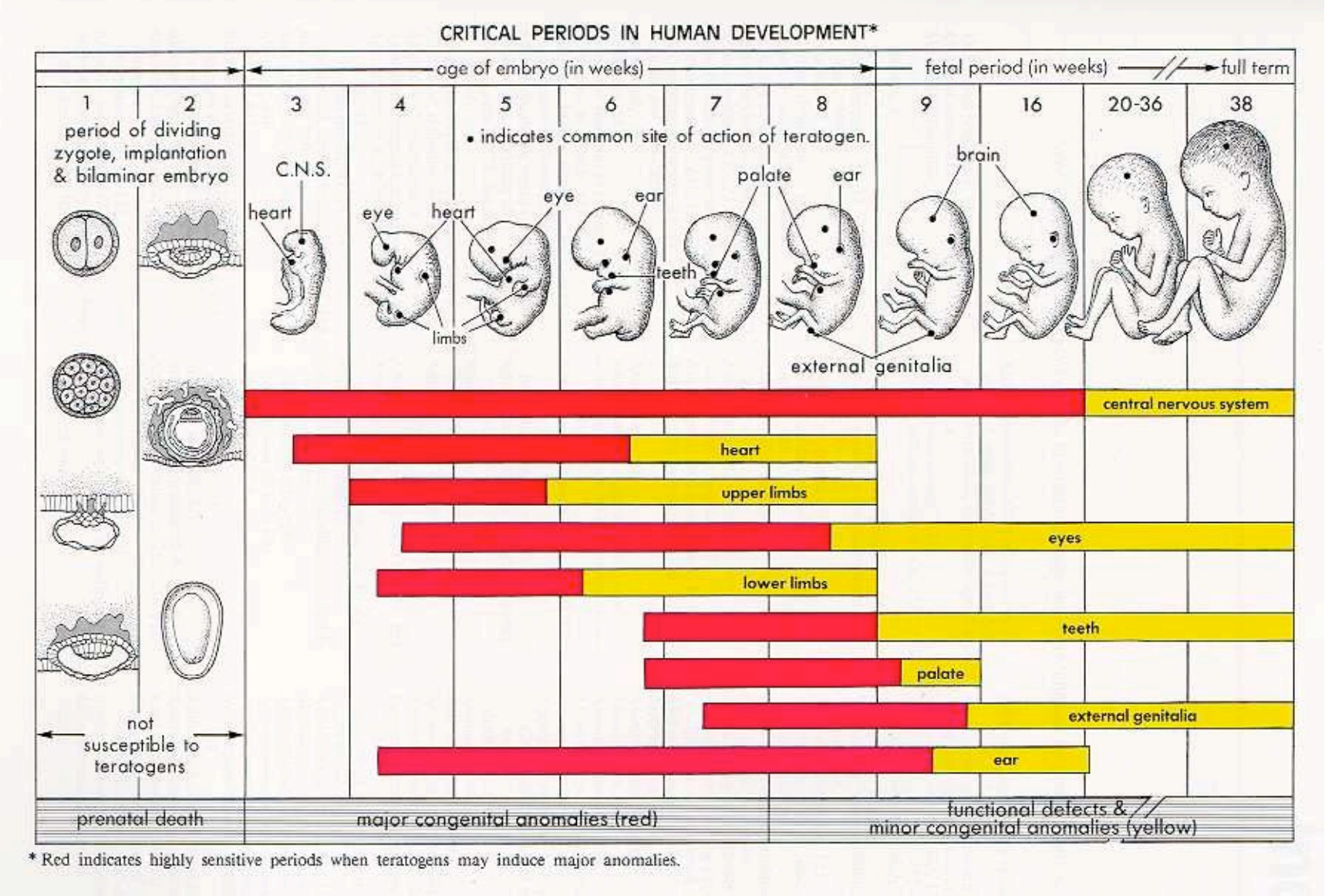
- (maternal) Immune system attack on mature red blood cells of fetus
- Fetus:
  - Juandice from accumulation of billirubin
    - Breakdown product of RBCs
    - Toxic→ brain damage
  - High number of immature RBCs
    - Inefficient transport of O2
    - Anemia

Rh incompatibility (3)

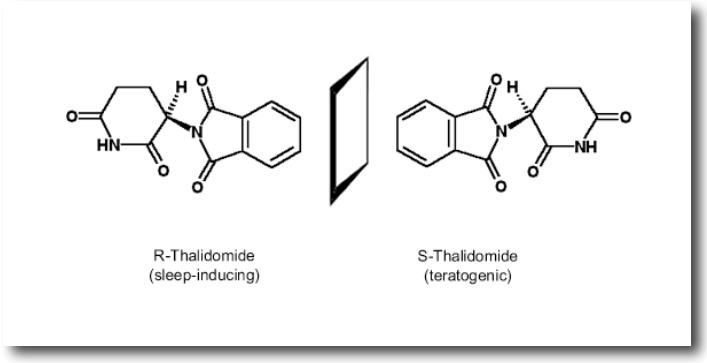
Treatment:

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

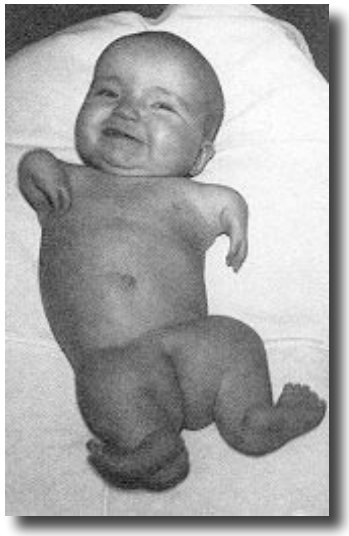
Damage to fetus



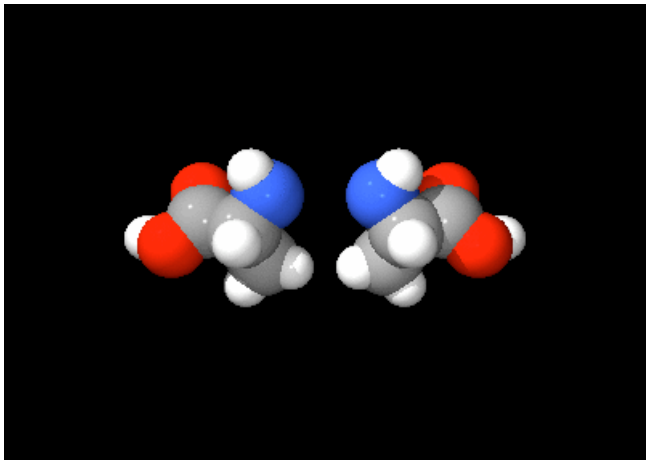
* Red indicates highly sensitive periods when teratogens may induce major anomalies.



Thalidomide



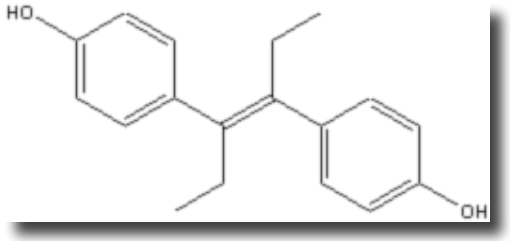
- Tranquilizer to treat morning sickness + stop bleeding
- 1950's-1960's
- Fetal exposure between 4-7 weeks of development leads to phocomelia:
  - Phoke-seal / melos- limb
  - hands and feet with no arms or legs



Two enantiomers of a generic amino acid

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

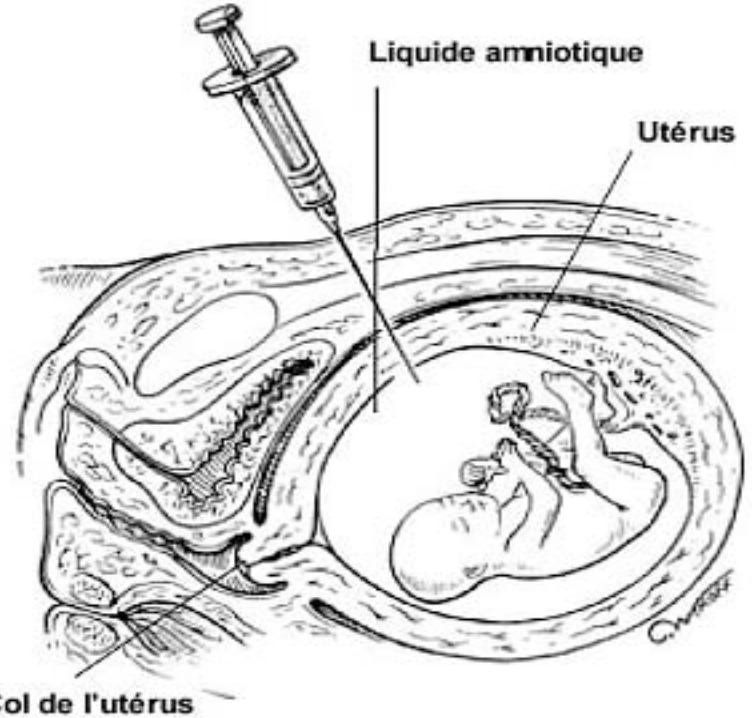
Amniocentesis

http://www.fetalmaternal.org/images/Amniocentesis.jpg

- 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://ici.cegep-ste-foy.qc.ca/profs/gbourbonnais/biotlm/genetiquetlm/imagesgenet/amniocentesis.gif

Ultrasound

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

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

www.english.ubc.ca/.../trail3/plants/photos.htm

<u>Phytoestrogens</u>

(clover, willow, alfalfa)

Can cause miscarriage in farm animals

Some cultures use to induce abortions

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

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