The Endocrinology of Pregnancy

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Objectives

- Understanding pregnancy polypeptide hormones
- Feto-placental steroid production
- The role of hCG and clinical utility of measurement
- Clinical utility of progesterone measurements
- Role of hormones in pregnancy maintenance
The fertilized ovum reaches uterus 4 days after conception.

The blastocyst implants at 6-7 days.

The trophoblast divides into 2 layers by 10 days:

- Cytotrophoblast: well-demarcated cell borders, single nucleus, ability to undergo DNA synthesis and mitosis.
- Syncytiotrophoblast: amorphous cytoplasm without cell borders, multiple nuclei.
  - Produces steroid and protein hormones.
Drawing of sections through implanted blastocysts. A. At 10 days. B. At 12 days after fertilization. This stage is characterized by the intercommunication of the lacunae filled with maternal blood. Note in (B) that large cavities have appeared in the extraembryonic mesoderm, forming the beginning of the extraembryonic coelom. Also note that extraembryonic endodermal cells have begun to form on the inside of the primitive yolk sac. (Adapted from Moore, 1988.)
- Functional lifespan of 14 days (no pregnancy).
  - Maximal activity 7-8 days after LH peak.
  - Leuteolysis 2-3 days before menses.
- Maintenance of function mandatory for pregnancy continuation before 7 weeks EGA.
  - Produces estrogen and progesterone, preparing endometrium for implantation.
  - Progesterone production necessary for decidual development until placental production begins.
  - hCG (syncytiotrophoblast) = leutotropic in pregnancy.

Corpus Luteum
Corpus luteum

Ultrasonography of the ovary showing a corpus luteum.

*Courtesy of Judith Adams, DMU.*
Formed by the invading trophoblast by 10 days post-conception.

Thought to provide stem cells from which syncytiotrophoblasts can further develop.

*Hypothalamic-like placental proteins:*
- CRH
- GnRH
- TRH
- Line the fetal surface of the intervillous space.
- Contains rough ER, Golgi complexes, mitochondria (machinery for hormone synthesis).
- Principal site of placental steroid and protein hormone biosynthesis.
- **Pituitary-like hormones:**
  - ACTH, GH, FSH, LH, TSH, hCG, hPL.
- Interact directly with maternal blood to secrete placental proteins directly into circulation.
Maternal Decidua

Syncytiotrophoblast

Cytotrophoblast

Decidua

Maternal Blood

Mature Granule (Polypeptide)

Early Granule

Rough Endoplasmic Reticulum

Ribosome

Cytotrophoblast

Fetal Capillary

Fetal血
There is no direct communication between fetal and maternal blood.

- Fetal blood in capillaries of intervillous space.
- Maternal blood in intervillous space.

This “barrier” adjusts the amount and rate of substrate transfer.
Extravillous trophoblasts are found outside the villus and can be subdivided into endovascular and interstitial categories. Endovascular trophoblasts invade and transform spiral arteries during pregnancy to create low-resistance blood flow that is characteristic of the placenta. Interstitial trophoblasts invade the decidua and surround spiral arteries.
Early Pregnancy factor (EPF)
Placental Proteins
Decidual Proteins
Fetal Proteins
Other

Pregnancy Proteins
Present in maternal circulation almost at time of conception.

Platelet activating factor (PAF) - like substance evident almost immediately.

Human chorionic gonadotropin (hCG):
- Detectable in blastomeres of 8 cell embryos at 2 days
- Found in maternal serum after implantation (8-11 days after conception)

Pregnancy Proteins
Early Pregnancy Factor (EPF)

- Produced by the ovaries and blastocyst.
- Immunosuppressive role.
- Undetectable in many abnormal pregnancies.
- Clinically useful assay unavailable at this time.
**Pituitary-like:**
- Produced by the *syncytio* trophoblast:
  - ACTH, hCG, hPL, TSH, LH, FSH, GH

**Hypothalamic-like:**
- Produced by the *cyto* trophoblast:
  - CRH, GnRH, TRH

Pregnancy Proteins

16
hCG
Human Chorionic Gonadotropin

- Maintains the corpus luteum.
- Stimulates adrenal and placental steroidogenesis, is increased with placental hypertrophy-hypoxia.
- Modulates maternal immunologic response to pregnancy.
- Stimulates fetal testis.
- Stimulates maternal thyroid gland.
- Promotes vascular dilation and uterine relaxation.
3 - 9 weeks EGA
- Rises rapidly due to proliferation of villi.

10 - 18 weeks EGA
- Declining levels due to reduction in proliferation of villi.

20 weeks - term
- Gradual increase due to increased placental mass.

hCG
Human Chorionic Gonadotropin
Mean serum hCG levels in normal pregnancy.
Glycoprotein

Produced in syncytiotrophoblast

hCG

Human Chorionic Gonadotropin

Alpha and Beta chains
hCG
Human Chorionic Gonadotropin
Clinical Utility

- Expect a 66% rise in 48 hours.
- 15% of normal pregnancies have an "abnormal" rise.
- 15% of ectopics have "normal" rise.

- Ultrasound Correlation
  - Visualization of the gestational sac:
    - 6500 mIU/ml with transabdominal scan.
    - 1500 mIU/ml with transvaginal scan.
First detectable 8 - 11 days post-conception.

- Half-life is about 24 hours.

Days to Resolution:
- Normal delivery: 16 days
- Therapeutic abortion: 27 days
- Ectopic pregnancy: 24 days
- Molar pregnancy: 115 days

hCG
Human Chorionic Gonadotropin
Clinical Utility
Higher levels in multiple gestations, molar pregnancies.

Higher levels in trisomy 21 (Down syndrome).
- Placenta less mature as a function of gestational age.

**hCG**

Human Chorionic Gonadotropin

Clinical Utility
Single chain polypeptide.
Closely related to growth hormone.
Derived from syncytiotrophoblast.
Rises steadily until 36 weeks (placental mass).

Metabolic actions:
- Antagonizes insulin action (diabetogenic factor).
- Protects transfer of glucose and amino acids to the fetus.
- Mobilizes free chain fatty acids from maternal fat depots.

Human Placental Lactogen
hPL
- Human chorionic thyrotropin (hCT)
- ACTH
- β-lipoprotein
- β-endorphin
- β₁-glycoprotein
- PAPP-A
- PAPP-B

Other protein hormones and substances of the trophoblast
Largely produced by the corpus luteum until 10 weeks.

Transition period (7-10 weeks): CL placenta.

Synthesized from maternal LDL-cholesterol.

**Minimal dependence on fetal precursors.**
Steroid Hormones

- Progesterone
- Estradiol
- Estrone
- Estriol
- Pregnenolone
- Decreases tubal motility/uterine contractions.
- Immunosuppressive role.
- Antagonizes estrogen augmented blood flow.
- Antagonizes estrogen in parturition process.

**Progesterone Functions**
<5 ng/ml predicts abnormal pregnancy.

>25 ng/ml rules out 98% of ectopic gestations.

Progesterone
Clinical Utility
Placental Progesterone Biosynthesis

Maternal

Acetate
\[ \downarrow \]
LDL-cholesterol
\[ \downarrow \]
Pregnenolone-S
Progresserone

Placental

Cholesterol
\[ \downarrow \]
Pregnenolone
\[ \downarrow \]
Progesterone

Fetal

LDL-cholesterol
\[ \downarrow \]
Pregnenolone-S
\[ * \]
Progesterone
\[ \downarrow \]
Corticosteroids

* 3 β-OH dehydrogenase block
Key Points

- Placenta does not metabolize progesterone to 17-OH progesterone nor 17-OH progesterone to androstenedione.
- Lacks:
  1. 17-hydroxylase
  2. 17,20-desmolasease

Steroid Production

Progesterone
Key Points

- The fetus lacks 3 β-OH dehydrogenase.
- Borrows progesterone from the placenta to synthesize important corticosteroids.
- In return, fetus supplies placenta with what it lacks: 19-carbon compounds to serve as estrogen precursors.

Steroid Production

Progesterone
Steroid Production

Progesterone

Maternal Plasma Progesterone

ng/mL

200

150

100

50

Weeks of pregnancy
Placental Androgen Metabolism

Maternal

Pregnenolone-S

DHEA-S

Placental

Pregnenolone

* 17 Hydroxylase Block

DHEA

Androstenedione

Testosterone

Estrone

Estradiol

Fetal

Pregnenolone-S

DHEA-S

Placental Androgen Metabolism

* 17 Hydroxylase Block
Fetoplacental Estrogen Production

**Maternal**
- DHEA-S
- Estrone
- Estradiol

**Placental**
- DHEA
- Estrone
- Estradiol
- 16α-OH DHA
- 16α-OH Androstenedione
- Estriol

**Fetal**
- DHEA-S

**Adrenal**
- Liver

* 3β-OH dehydrogenase block
- Augment uterine blood flow.
- Regulates progesterone synthesis by availability of LDL precursors.
- Role in parturition:
  - Increases uterine contractions
  - Ripens cervix
- Estriol Measurements:
  - Previously used as a test of placental function and fetal well-being
  - Low estriol = increased risk of trisomy 18
Prime the endometrium for conceptus.

Increase uterine blood flow:

- **Estradiol**: initially from maternal ovaries, then from placenta.
- **Estrone**: initially from maternal ovaries, adrenals, and adipose, then from placenta.
- **Estriol**: from placenta.

**Steroid Hormones - Estrogens**
“The fetal adrenal cortex and placenta are incomplete but complimentary steroidogenic organs.”

At term the fetal adrenals are adult size:

- 80% cortical mass “fetal zone.”
- Involutes postpartum.

Lacks 3 β OH dehydrogenase

- Unable to make progesterone or estrogens.
Regulate intrauterine maturation

Control glycogen storage

Induce various enzymes

Steroid Hormones

Adrenocorticoids
Conceptus secretes estrogen and progesterone.
Decidua secrets cortisol.
Corpus luteum secretes progesterone and other hormones.
The placenta takes over for corpus luteum starting at 7 weeks.
The fetal adrenal cortex functions at 7 weeks:
  By the 2nd trimester the placenta and fetal adrenals produce more steroids than any other human tissue!

Steroid Hormones-
Summary
- Peaks in the fetus between 10-13 weeks.
- Peaks in maternal serum around 28 weeks.
- Increases in maternal serum due to increased placental permeability.
- Regulates intravascular volume.
- Elevated with neural tube and abdominal wall defects.
- Decreased in pregnancies with trisomy 21.

**Alpha-Fetoprotein**
Both estradiol and progesterone are involved.

100X rise in estradiol:
- Stimulates uterine growth (myometrial hypertrophy = 10X weight, 500X volume).
- Increases uteroplacental blood flow.
- Increases hepatic protein synthesis.
- Suppresses FSH and LH at the hypothalamic-pituitary level.
- Enhances uterine muscle excitability.

Maintenance of Pregnancy
Progesterone:

- Blocks cellular immune response to fetal (foreign) antigens - decreased maternal cellular mediated immunity.
- May play role in preventing maternal rejection of trophoblast.
- Decreased response to oxytocin.
Relaxin:
- Originates in the corpus luteum, and probably in decidua and myometrium.
- Stimulates prostacyclin synthesis (PGI$_2$) = relaxation of uterine muscle.
- High levels in early pregnancy are likely to maintain pregnancy (cortisol may have opposite effect).
- Leads to increase pubic shear due to effect on ligaments.

Maintenance of Pregnancy