Teaching Script: Maternal-Fetal Physiology

Clinical Case Applicability:
Early pregnancy nausea and other common physical complaints in pregnancy, Routine prenatal care monitoring with concern for maternal and fetal tolerance of pregnancy

Learning Objectives:
1) Describe the maternal endocrine changes that provide an adaptive environment for the developing fetus.
2) Identify the physiologic changes of pregnancy that allow the mother to tolerate a symbiotic relationship
3) Explain how the physiologic adaptation of the fetus and placenta allow the fetus to thrive

Clinical Presentation:
New obstetric patient who is well-conditioned athlete with annoying signs/symptoms attributable to physiologic changes in pregnancy

How do maternal endocrine changes in pregnancy and the fetal-placental unit provide an adaptive environment for the developing fetus?

- **General Principles**:
  - The fetus is a master parasite whose fetal-placental unit is able to influence the maternal physiology to its advantage
  - Most common endocrine function tests are significantly altered in pregnancy due to true physiologic changes, to ↑ liver production of binding globulins, or ↓ serum albumin due to dilutional effects of volume expansion
  - Maternal endocrine changes also mediated by ↑ renal glomerular filtration, ↓ hepatic clearance, or metabolic clearance of hormone by placenta
- **Maternal Endocrine Changes**
  - *Pituitary gland*: ↑ size mainly due to lactotroph hyperplasia stimulated by high estrogen (E) levels; Prolactin progressively ↑ up to delivery in preparation for lactation. FSH/LH are almost undetectable.
  - *Thyroid gland:* enlarges in first trimester; hCG and TSH alpha-subunits similar, thus elevated hCG has thyrotropic effect. Total serum thyroxine ↑ due to increase thyroid binding globulin. Free T3 and T4 unchanged.
  - *Parathyroid glands*: hyperplasia to ↑ parathyroid hormone production, and meet calcium needs of fetal bone formation; maternal calcium concentration nadirs early 3rd trimester due to dilutional hypoalbuminemia and fetal consumption.
  - *Pancreas*: hyperplasia of insulin-secreting beta cells. Hyperinsulinemic with ↑ resistance to peripheral metabolic effects. Insulin responsible for intracellular transport of nutrients, but does not itself cross the placenta; insulin regulates the availability of metabolites for placental transport.
  - *Adrenal Cortex*: total serum cortisol is ↑, mostly due to estrogen-stimulated ↑ in cortisol binding globulin (CBG); ↑ cortisol may contribute to insulin resistance and development of striae.
  - *Androgens*: production is ↑, but buffered by ↑ sex hormone binding globulin (SHBG) and by metabolism of DHEAS to estrogens in the fetal-placental unit.
- **Fetal-Placental Unit**
  - Initially, the placenta functions autonomously to provide communication between fetus and mother. By end of first trimester, fetal endocrine system functioning to provide hormone precursors to the placenta (ex. DHEAS)
  - *Placental Peptide Hormones:*
    - *Human Chorionic Gonadotropin (hCG)* is first marker of trophoblastic differentiation, peaking maternal blood established in intervillous space
    - *Human Placental Lactogen (hPL*) is a placental polypeptide hormone produced by early trophoblasts and is diabetogenic and lactogenic, alters maternal glucose metabolism and mobilization of free fatty acids, stimulates pancreatic islet insulin secretion causing hyperinsulin response to glucose loads, and contributes to peripheral insulin resistance. Production is proportional to placental mass.
    - *Chorionic Peptides* – placental growth factor (PIGF) and vascular endothelial growth factor (VEGF) play a role in placental angiogenesis, fetal growth, and preeclampsia.
  - *Placental Steroid Hormones:*
    - *Corpus Luteum(CL)* produces progesterone(P), 17-hydroxyprogesterone (17-OHP), relaxin, estradiol; not needed after 7th gestational week as placenta produces progesterone
    - *Progesterone* steadily rises to delivery, while 17-OHP peaks and then declines as CL no longer needed. Maternal cholesterol is substrate for placental P production. Progesterone acts synergistically with relaxin to promote uterine quiescence, and inhibits T-cell mediated allograft rejection so may aid in uterine tolerance of the trophoblastic tissue.
    - *Estrogen* placental production depends on maternal and fetal precursors (mostly fetal adrenal DHEA). 17α-hydroxysteroid dehydrogenase protects fetus from exposure to potent estrogens by converting estradiol to estrone. Most of the DHEA is converted to estriol, which ↑ dramatically in the maternal serum during pregnancy and reflects fetal and placental function.

What are physiologic changes of pregnancy that allow mother to tolerate this symbiotic relationship?
Peptide and steroid hormones produced by the fetal-placental unit are able to influence physiologic changes in nearly every maternal organ system with the purpose to maximize blood flow to the placenta *and* allow mom to tolerate the changes of pregnancy:

- **Cardiovascular**: changes to maximize oxygen delivery
  - Diaphragm elevation and rib cage changes elevate and rotate heart; eccentric hypertrophy resulting from expanded blood volume and increased afterload.

        - Cardiac output increase early gestation; peak ↑ 30-50%; result of ↑ blood volume, heart rate, and stroke volume; most shunted to uterus, placenta and breasts
        - Blood pressure and systemic vascular resistance ↓ with mid-pregnancy nadir; due to P-mediated smooth muscle relaxation and relative unresponsiveness to angiotensin II and norepinephrine in pregnancy.
        - Venous pressure rises in lower extremities with obstruction of inferior vena cava by enlarging uterus, lead to LE edema and varicose veins, hemorrhoids, and increased risk of deep vein thrombosis.
        - ↑ risk of pulmonary edema due to ↓ systemic/pulmonary vascular resistance and ↓ colloid osmotic pressure
        - Creatinine kinase ↑ with uterine contractions, but troponin levels are not affected by pregnancy
        - Cardiac function crescendos in labor and immediately postpartum; must manage autotransfusion after delivery
    - **Pulmonary:**
        - Mild dyspnea compatible with daily living activities and related to ↑ inspiratory muscle effort
        - Elevation of diaphragm ↓ resting lung volumes—total lung capacity and functional residual capacity
        - Tidal volume and inspiratory capacity ↑, as well as minute ventilation – driven by ↓ P leading to chronic hyperventilation. This results in ↑ PaO_2 and ↓ $PaCO_2$ – chronic respiratory alkalosis; partial compensation with ↑ renal excretion of bicarbonate to maintain maternal pH
        - Maternal oxygen consumption rises due to maternal organ and fetal-placental consumption
    - **Hematologic:**
        - Blood volume ↑ by 40-50% starting with plasma volume ↑ at 6 weeks, and later red cell volume
        - Physiologic anemia nadirs at 28-34 weeks due to plasma volume expansion > red cell mass; 3-fold ↑ erythropoietin causes erythroid hyperplasia in bone marrow; protective against possible hemorrhage
        - Iron requirements ↑; 50% used for ↑ RBC production, 30% transported to fetus, 20% daily maternal loss
        - Platelet count ↓ (hemodilution and ↑ destruction; and aggregability ↑ to maintain hemostasis)
        - White blood cells ↑, particularly neutrophils and granulocytes, possibly due to elevated estrogen and cortisol
        - 5-fold ↑ risk thromboembolism due to estrogen stimulation of liver to produce procoagulants, and ↓ of natural coagulation inhibitors and fibrinolytic activity
    - **Gastrointestinal:**
        - ↑ gastroesophageal (GE) reflux due to esophageal dysmotility and ↓ pressure of GE sphincter caused by P, and gastric compression by enlarged uterus.
        - Reduced risk of peptic ulcer disease may be due to ↑ placental histaminase lowering maternal histamine levels, ↑ gastric mucin production to protect mucosa, ↓ gastric acid secretion, and enhanced immunologic tolerance of H. Pylori in pregnancy.
        - ↓ intestinal motility due to E-induced nitric oxide relaxation of GI smooth muscle, and P influence.
        - ↑ portovenous pressure contribute to hemorrhoids
        - Slowed emptying of gallbladder due to P, along with ↑ biliary cholesterol saturation and ↓ chenodeoxycholic acid levels favors gallstone production
    - **Renal:**
        - P-mediated smooth muscle relaxation leads to dilated ureters and renal pelvis
        - ↑ bladder vascularity may lead to microscopic hematuria
        - ↓ bladder capacity due to enlarging uterus
        - Renal plasma flow and glomerular filtration rate ↑, leading to hyperfiltration and ↑ creatinine clearance (thus a fall in serum creatinine), glucose excretion, urinary protein and albumin excretion, tubular sodium reabsorption
    - **Gestational weight gain** (GWG) – 35-60% GWG is placenta, fetus, and amniotic fluid; maternal contributions include ↑ blood volume, uterine/breast mass, extracellular fluid, and fat mass (mostly subcutaneous, some visceral fat).
- **Increase in total body water** one of most significant adaptations – maternal plasma volume, fetus, placenta and amniotic fluid; chronic volume overload with active sodium and water retentions due to changes in renin-angiotensin system and osmoregulation.
- **Microbiome during pregnancy** may help maintain pregnancy, prepare for parturition, and establish neonatal microbiome
    - E-induced glyiogen ↑ metabolized to lactic acid by lactobacillus and ↓ pH of vagina, allowing further growth of Lactobacillus species, important to the colonization of the neonatal gut.
    - Maternal gut microbiome resembles proinflammatory / prodiabetogenic state; may promote energy storage for fetal growth
- **Immunologic Adaptions**
    - Maternal immune system not altered
    - Placenta is the
        - Key to maternal tolerance of antigenically different fetal allograft
        - Interface between maternal and fetal vasculature
        - Produces E, P, hCG, and hPL which may contribute to suppression of maternal immune response
        - Placenta blocks or masks antibodies; IgG is the only immunoglobin that can cross placenta
    - Maternal IgG provides passive immunity to fetus and early neonate
    - Fetal immune system gradually develops with lymphocyte production beginning at 6 weeks; IgG/IgM/IgE/IgD produced at 12 weeks gestation allowing for mature immune system, plus maternal IgG, at birth

What are the unique physiologic adaptations of the fetus and placenta that allow the fetus to grow and develop?

- **Amniotic Fluid and Water Balance**
    - Normal amniotic fluid volume is produced by intramembranous flow from placenta, fetal urine, and lung fluid, and is absorbed through intramembranous flow and fetal swallowing.
    - Water and electrolyte homeostasis primarily mediated by placental exchange, also substances normally excreted by the liver and kidney

- **Fetal Cardiovascular Adaptations**
  - Review fetal cardiac physiology in APGO Educational Topic #8 Video on Maternal-Fetal Physiology
  - Fetal-placental circulation resistant to vasoconstrictive pressor agents, so umbilical flood flow is preserved unless cardiac output ↓ – also allowing maintenance of umbilical flood flow over a wide range of oxygen tensions.
  - At birth, major vascular distribution changes – with alveolar expansion during first breaths, ↑ alveolar capillary O2 tension, ↓ pulmonary microvascular resistance occurs – causes:
    - ↓ right atrial afterload and right atrial pressure
    - ↑ pulmonary flow ↑ venous return to left atrium and ↑ left atrial pressure; physiologic closure foramen ovale
    - ↓ right atrial pressure augmented when cord clamped and venous return ↓
  - Fetal sympathetic system develops before parasympathetic system; combine to regulate fetal heart rate and variability, cardiac contractility and vascular tone. Early mismatch of sympathetic and parasympathetic influence may explain difference in variability between extremely preterm and term fetuses. Peripheral chemoreceptors also regulate the fetal cardiac activity in response to hypoxia.
- **Fetal Metabolic Adaptations**
  - Aerobic metabolism with PaO2 20-30mmHg without metabolic acidosis. Adequate tissue oxygenation maintained by:
    - Higher fetal cardiac output (higher heart rate)
    - Preferential shunting to vital organs
    - Higher hemoglobin concentration (higher RBCs/hematocrit)
    - Fetal hemoglobin has ↑ oxygen-carrying capacity and oxygen affinity
  - Glucose, derived from the placenta, is the main substrate for fetal oxidative metabolism (especially in the fetal brain) to produce energy and tissue growth; other substrates include lactate and amino acids.
  - Fat tissue growth is a result of conversion of carbohydrates to lipids and placental fatty acid uptake
  - 20% fetal oxygen consumption is used to grow new tissue.
  - Central acidosis sensed by central medullary respiratory chemoreceptors and stimulates breathing, alkalosis results in apnea. However, marked hypoxemia will inhibit these centers and ↓ fetal breathing activity
- **Fetal Endocrinology Adaptations**
  - Higher insulin levels increase fetal body, heart, and liver weights; insulin-like growth factor I (IGF-1) performs similarly
  - Corticosteroids important for fetal growth and organ maturation, with fetal levels increased at parturition. Fetal growth actually slows simultaneously, perhaps through suppression of IGF-1
  - Adrenal gland is stimulated by fetal ACTH and produces cortisol, DHEAS and mineralocorticoids.
  - Fetal thyroid begins to function after 12 week when the hypothalamus begins to release thyrotropin-releasing hormone.
- **Fetal Immune Adaptations**
  - Mature immune system, plus maternal IgG, at birth allows newborn to defend against infectious disease

Figures:

Figure 1

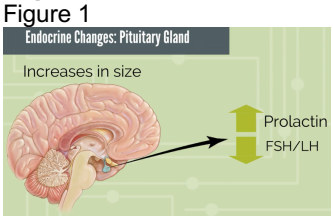


Figure 2

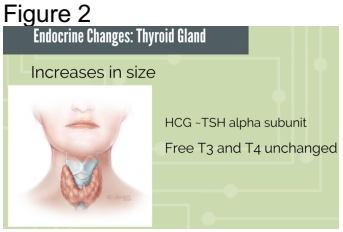


Figure 3

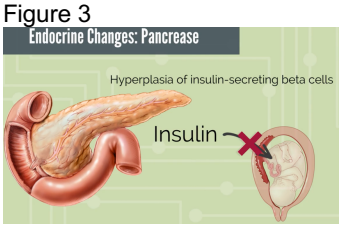
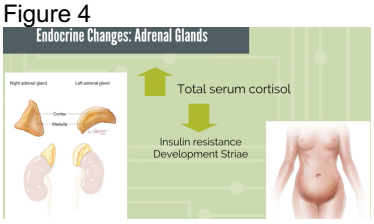


Figure 4



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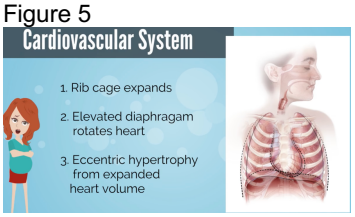

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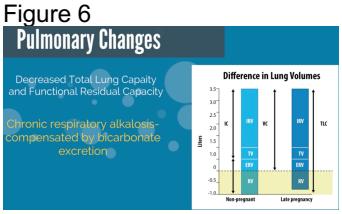

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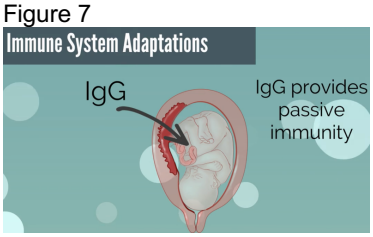
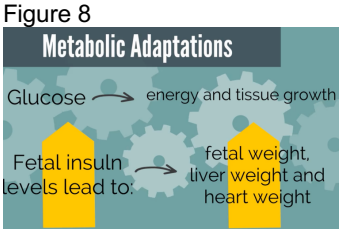


Figure 8



References:

- Beckmann, CRB, et al. Obstetrics and Gynecology. 8th edition. Baltimore, MD: Lippincott, Williams, and Wilkins, 2018.
- Taylor, RN and Badell, ML. Chapter 16 Endocrinology of Pregnancy. Greenspan's Basic & Clinical Endocrinology, 9th edition. McGraw-Hill, 2011.
- Gabbe, SG, et al. Obstetrics: Normal and Problem Pregnancies, 7th Edition. Elsevier, 2016