ENDOCRINOLOGY OF OBSTETRICS

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LEARNING OBJECTIVES:

- Recognize the actions of placental gonadotropin and placental somatotropins and their relationship to each other.
- List the primary actions of progesterone during pregnancy and delineate the changes in progesterone levels as pregnancy proceeds and parturition is initiated.
- Recognize the placental synthesis and secretion pathway of progesterone and estrogen.
- Name the hormonal changes of pregnancy occurring in the placenta, the fetus, and the mother and whether the compartment relies on another compartment for precursors.
- Recognize how prolactin secretion changes during pregnancy and postpartum.

I. THE PLACENTA AS AN ENDOCRINE ORGAN

The hormonal interactions between the fetus, placenta, and mother control the establishment and maintain of pregnancy, development of the fetus, and initiate parturition. The placenta is an active endocrine organ, as seen by the number of endocrine factors produced during pregnancy. (Table 1). The human placenta is a complex structure that delivers nutrients to the fetus, produces numerous steroid and protein hormones, and removes metabolites from the fetus by delivering them to the maternal compartment. Many of the hormones produced by the placenta may be present in the nonpregnant adult, and therefore, bind to maternal hormone receptors.

Peptides, Steroid Hormones, and Monoamines Produced by the Human Placenta			
Neuropeptides	**Pituitary-like Hormones**	**Steroid Hormones**	**Monoanimes and Adrenal-like Hormones**
CRH	ACTH	Progesterone	Epinephrine
TRH	TSH	Estradiol	Norepinepherine
GnRH	GH	Estrone	Dopamine
Melatonin	PL	Estriol	Serotonin
Cholecystokinin	CG	Estetrol	Adrenomedullin
Met-enkephalin	LH	2-Methoxyestadiol	
Dynorphin	FSH	Alloprenanolone	
Neurotensin	B-Endorphin	Pregnenolone	
Vasoactive intestinal peptide	Prolactin	5α-Dihydroprogesterone	
Calanin	Oxytocin		
Somatostatin	Leptin		
Neuropeptide Y	Activin		
Substance P	Follistatin		
Endothelin	Inhibin		
Renin			
Angiotensis			
Atrial natriuretic peptide			
Urocortine			

Table 1. Peptides, Steroid Hormones, and Monoamines Produced by the Human Placenta (From: Reis FM, Petraglia F. The placenta as a neuroendocrine organ. *Front Horm Res* 27:216, 2001.)

A. Placental Gonadotropin

1. Human Chorionic Gonadotropin (hCG)

HCG is secreted by the syncytiotrophoblast into both the fetal and maternal circulation. It is a 36- to 40-kDa glycoprotein with two non-covalently linked subunits: the common α subunit of glycoprotein hormones and a unique β subunit that resembles LH in structure and action. Used extensively in pregnancy testing, hCG can be detected in maternal serum as early as 6 to 8 days following ovulation. Plasma levels rise rapidly in normal pregnancy and peak between 60 and 90 days of gestation. Thereafter, the concentration of hCG in maternal plasma declines and stays relatively constant until birth. The levels of hCG are higher in multiple pregnancies, in pregnancies associated with Rh isoimmunization, and in pregnant diabetic women. They are highest in pregnancies associated with hydatiform moles or with a tumor known as choriocarcinoma. hCG secretion may be regulated via a paracrine mechanism involving the release of GnRH by the cytotrophoblast. Fetal concentrations of hCG peak at 11 to 14 weeks gestation and thereafter fall progressively until delivery.

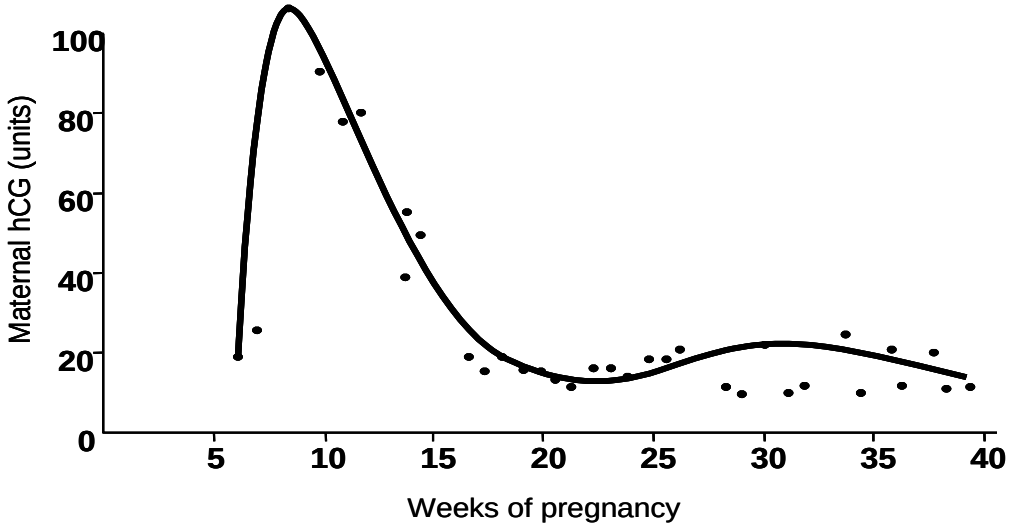

Figure 1. Human chorionic gonadotropin levels during pregnancy.

Various theories have been proposed as to the functional role of hCG in pregnancy. **hCG probably maintains the early CL of pregnancy to ensure continued ovarian progesterone secretion until the trophoblast assumes this function**. The pregnancy will not continue if the embryo cannot gain control of the CL. Therefore, the ability of the embryo to produce sufficient amounts of hCG may represent a selection process of competent embryos.

hCG binds to the thyroid receptor and is responsible for most of the increase thyroid activity during pregnancy. **The primary role of hCG in the fetus probably is to regulate the development and the secretion of testosterone by the fetal testes.** As discussed in other lectures, male sex differentiation occurs at a time in development (~10-14 weeks) when fetal serum hCG levels are high and LH levels are low. Furthermore, hCG may play a role in the decidual response, relaxin production, and relaxation of the uterine smooth muscle.

2. Gonadotropin-Releasing Hormone (GnRH)

Placental GnRH is similar to that produced by the hypothalamus and regulated placental steroidogenesis. The highest amount of GnRH is present early in pregnancy and there is close correlation with hCG levels. In addition, GnRH receptor expression in the cytotrophoblast and syncytiotrophoblast reflects hCG secretion.

3. Inhibin, Activin, and Follistatin

Inhibin-A is the primary inhibin secreted during pregnancy and peaks at 8 weeks gestation

B. Placental Somatotropins

1. Human Placental Lactogen (hPL)

Human placental lactogen (hPL) is a single-chain polypeptide with both lactogenic and growth hormone-like activity (<3% of the growth-stimulating activity of human growth hormone). The structures of hPL, prolactin, and GH are quite similar and they derive from a common ancestral gene. HPL is secreted by syncytiotrophoblast and can be detected in serum by radioimmunoassay as early as the third week after ovulation. Unlike hCG, the plasma level of hPL continues to rise with advancing gestational and is closely correlated with increasing placental weight. The time sequence and peak of hPL secretion differ significantly from that of hCG, which suggests that they are differentially regulated even though both are secreted by the syncytiotrophoblast.

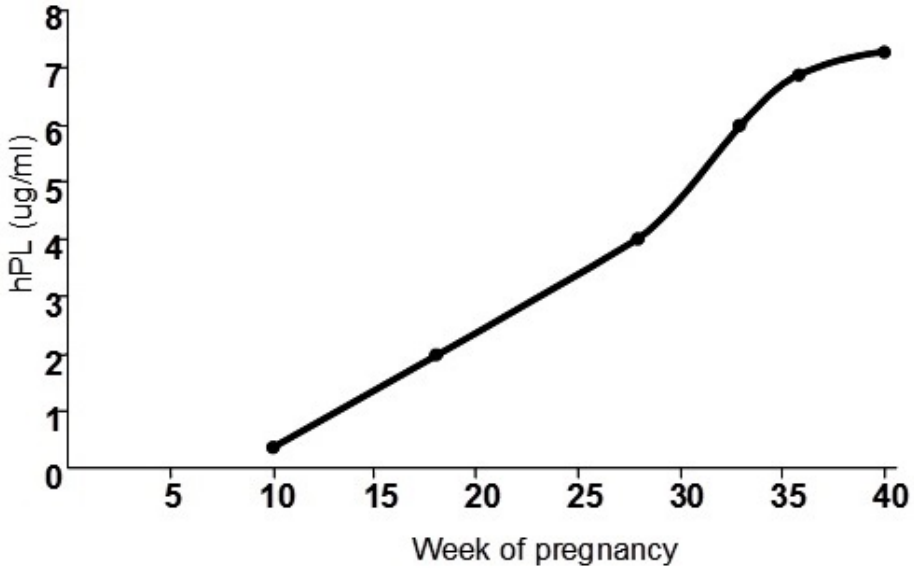

Figure 2: Human placental lactogen levels during pregnancy

hPL is secreted primarily into the maternal circulation, rather than the fetal circulation, and its potential physiological roles likely reflect action(s) in maternal tissues. **It has been suggested that hPL exerts metabolic effects in pregnancy similar to those of GH, stimulating lipolysis to increase circulating free fatty acids and inhibiting glucose uptake in maternal tissues. The net effect of these metabolic effects favors supply of glucose and amino acids to the fetus**.

2. Human Placental Growth Hormone (hPGH)

Placental growth hormone is 22-kDa and differs from pituitary GH by 13 amino acids. In early pregnancy maternal pituitary GH is dominant, but after 15-20 weeks gestation, hPGH production increases and replaces pituitary GH. hPGH is secreted into the maternal and not the fetal circulation. hPGH production responds inversely to glucose and insulin levels, allowing for glucose availability for the fetus.

C. Relaxin

Relaxin is a member of the insulin/IGF family of hormones and has dissimilar A and B chains linked together by two disulfide bonds. Relaxin activates a G-coupled protein receptor (GPCR) that is homologous to those for the glycoprotein hormones LH, FSH, and TSH. While structurally similar to insulin, there is neither amino acid homology nor biologic cross-reactivity. The CL synthesizes relaxin throughout pregnancy, with peak expression between weeks 8 and 12. Levels gradually stabilize at a slightly lower concentration for the rest of the pregnancy. In addition to relaxin synthesis by the CL, the placenta, endometrium, and decidua also synthesize this peptide hormone. Relaxin is not required for pregnancy but has a role in softening of the cervix and relaxation of the connective tissue between the pelvic bones in preparation for parturition.

D. Steroid hormones

Steroidogenesis in pregnancy requires integration of multiple organs – the fetus, the placenta and the mother. These organ systems must depend on one another, as each does not possess all the necessary enzymes for steroidogenesis. The placenta expresses cholesterol side-chain cleavage and 3β-hydroxysteroid dehydrogenase, but lacks 17α-hydroxylase/17,20-lyase. Therefore, progesterone cannot be metabolized further. Androgens, mainly DHEA from the fetal adrenal, serve as the substrate for placental aromatase to produce estrogens (**Figure 3**).

1. Progesterone

The main source of progesterone during pregnancy is the placenta. **The CL is the major source of progesterone secretion during the first 6 to 8 weeks of gestation.** It is believed that the developing trophoblast takes over as the major source of progesterone secretion by early gestation, since removal of the CL

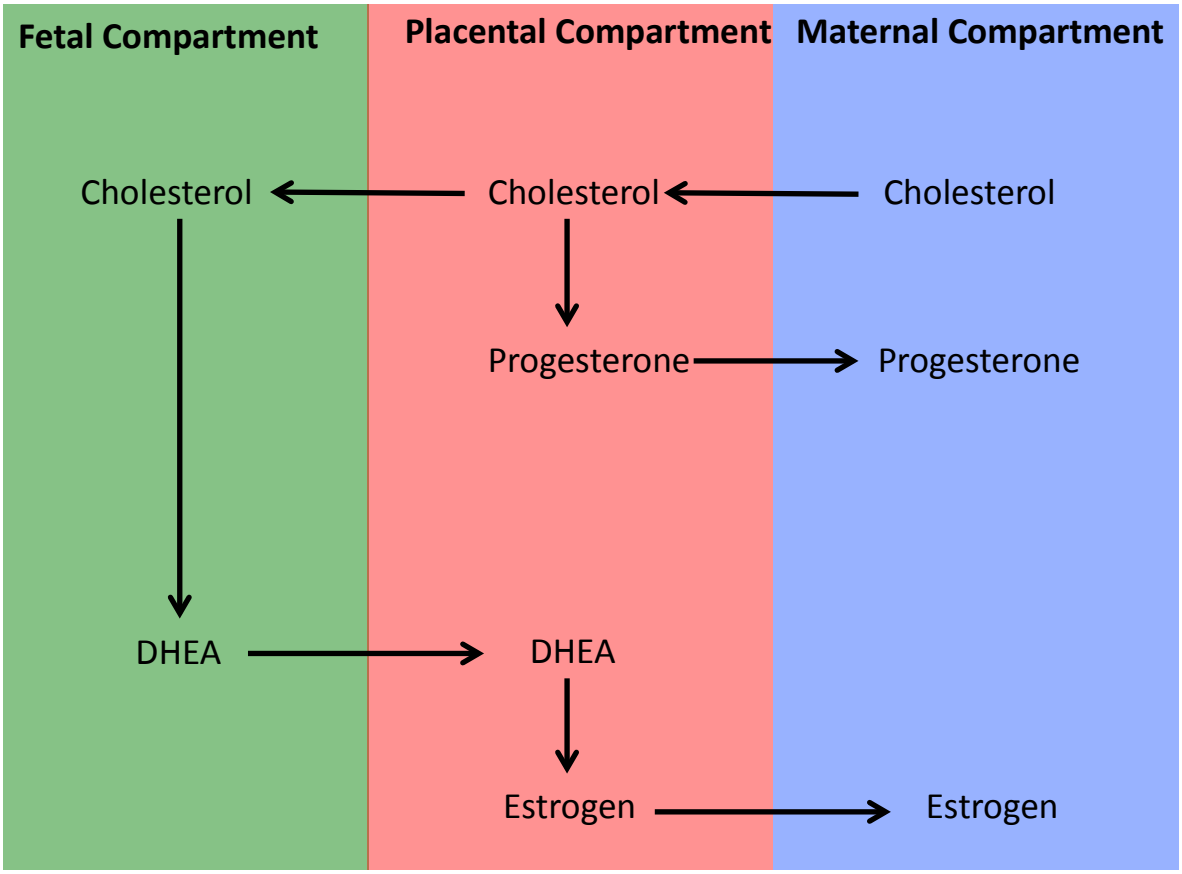

Figure 3. Production of progesterone and estrogen by the human placenta.

before, but not after, this time leads to spontaneous abortion or miscarriage. **After 8 weeks gestation the CL continues to secrete progesterone, but the amount of progesterone secreted is only a fraction of that secreted by the placenta.** Placental progesterone secretion is regulated in part by GnRH stimulated secretion of hCG by the cytotrophoblast. The hCG binds its receptor on the syncytiotrophoblast in an autocrine fashion, resulting in increased progesterone secretion by the syncytiotrophoblast. The placenta at term produces approximately 250 mg of progesterone each day, an enormous amount of steroid. Maternal progesterone plasma levels rise from 25 ng/ml during the late luteal phase to 150 ng/ml at term (Figure 4-A). Most progesterone secreted by the placenta enters the maternal compartment. The placenta has very limited capacity for de novo cholesterol biosynthesis, and the cholesterol required for progesterone synthesis therefore comes from maternal LDL taken up via the LDL receptor on the trophoblast. Unlike the classic steroidogenic cells (e.g., adrenocortical, theca, and Leydig cells), the steroidogenic acute regulatory protein is not essential for placental steroidogenesis.

A functioning fetal circulation is not important for the regulation of progesterone levels in the maternal unit. **In fact, fetal death, ligation of the umbilical cord, and anencephaly, all of which are associated with a decrease in placental estrogen production (see below), have no significant effect on progesterone levels in the maternal compartment.**

Progesterone binds to receptors in uterine smooth muscle, thereby inhibiting smooth muscle contractility leading to myometrial quiescence and prevention of uterine contractions. Progesterone inhibits cyclooxygenase 2 (COX-2), an enzyme involved in prostaglandin synthesis, thus preventing uterine contractility. **Progesterone is essential for the maintenance of pregnancy in all mammals,** possibly due to its ability to inhibit T lymphocyte cell-mediated responses in graft rejection. Since the fetus is a foreign body within the uterus, the high local levels of progesterone may block cellular immune responses to foreign antigens and may be important for providing immunological privilege to the pregnant uterus.

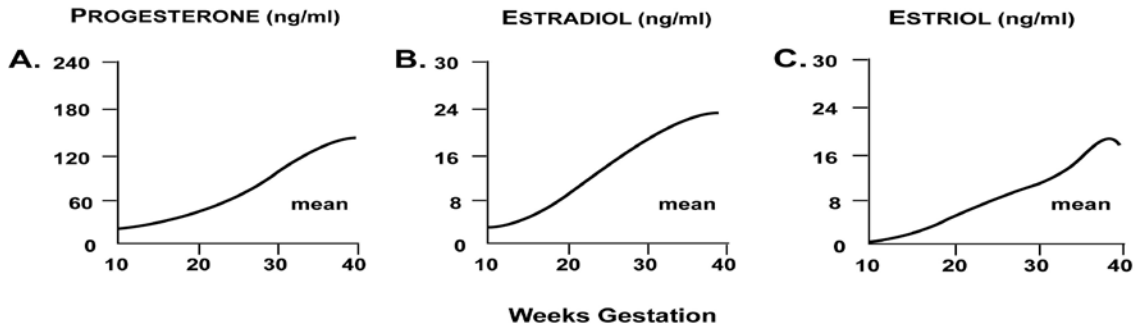

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Figure 4. The mean values of (A) progesterone, (B) estradiol-17β, and (C) estriol in maternal plasma as a function of weeks of gestation.

2. Estrogen

Estrogen production and the estrogen level in plasma increase markedly during pregnancy (Figure 4-B and C). Urinary estriol increases 1000-fold during pregnancy. The CL is the principal source of estrogen during the first few weeks of pregnancy, but thereafter nearly all of the estrogen derives from the trophoblast of the placenta. The placenta cannot convert progesterone to estrogens because it lacks the enzyme 17□-hydroxylase (CYP17), which carries out both 17α-hydroxylation and cleavage of the C17,20 bond. Thus, **the placental relies on preformed androgens produced in the maternal and fetal adrenal glands.** Estradiol-17β and estrone are synthesized by the placenta via conversion of dehydroepiandrosterone sulfate (DHEA-S) derived from both maternal and fetal compartments.

The placenta metabolizes DHEA-S to estrogens via the following enzymes: placental sulfatase, 3β-hydroxysteroid dehydrogenase (3β-HSD), and aromatase (CYP19). Estriol is synthesized by the placenta from 16α-hydroxydehydroepiandrosterone sulfate formed in fetal liver from circulating DHEA-S secreted by the fetal adrenal gland. **At least 90% of urinary estriol is ultimately derived from the fetal adrenal gland.** The sources of estrogen biosynthesis in the maternal-fetal-placental unit are presented in Figure 4. The major source of fetal adrenal DHEA-S is LDL cholesterol circulating in fetal blood.

Historically, the measurement of urinary estriol was used to monitor fetal well-being in high-risk pregnancies. There are several disorders in addition to fetal distress that lead to low urinary excretion of estriol by the mother; t**he most notable is placental sulfatase deficiency, also known as steroid sulfatase deficiency syndrome, which is an X-linked disorder characterized by decreased maternal estriol production due to deficient placental sulfatase**. In this disorder, the placenta is unable to cleave the sulfate moiety from DHEA-S and consequently, the levels of maternal estrogens, particularly estriol, are quite low. Placental sulfatase deficiency is also associated with prolonged gestation and difficulty in cervical dilatation at term, often requiring cesarean section. Steroid sulfatase deficiency occurs in 1 of every 2,000 to 6,000 newborns. The male offspring are, of course, sulfatase deficient and they have a characteristic skin condition termed ichthyosis, which is first apparent after the first few months in life.

Estrogen plays a role in regulating progesterone production, uteroplacental blood flow, development of the mammary gland, and fetal adrenal function.

The ultimate destination of most of the estrogen and progesterone secreted by the placenta is the maternal compartment, where estrogen may regulate or fine-tune the events leading to parturition (see below).

II. ENDOCRINOLOGY OF PARTURITION

Parturition, the process of labor, requires two changes in the female reproductive tract. **First, the uterus must be converted from a quiescent structure with dyssynchronous contractions to an active, coordinately contracting organ**. **Second, the cervical connective tissue must undergo profound changes to allow dilatation and passage of the fetus through the birth canal.** These events can be divided into distinct phases (**Figure 5**).

A. Human Parturition

In phase 1 (pregnancy or quiescence), the myometrium is in a relaxed state and relatively insensitive to oxytocin and prostaglandins. The uterine cervix is closed and rigid. This phase is controlled by pro-pregnancy factors such as progesterone, prostacyclin, relaxin, CRH, and nitric oxide. At term, there is a transition from phase 1 to phase 2 (transformation) in which the myometrium becomes more responsive to uterotonics and develops the capacity to contract. **Uterine transformation and activation occurs in response to functional inactivation of progesterone action, uterine stretch, and activation of contractile associated proteins (CAPs).** Some CAPs include connexins, ion channels, and enzymes for uterotonic synthesis. In phase 3, the activated uterus can be stimulated to contract by uterotonins (e.g., prostaglandins and oxytocin). In addition, the cervix begins to efface and become more compliant. The contractions move the fetus toward the birth canal and the force of the fetus against the lower uterine segment dilates the softened cervix to allow for the fetus and placenta to pass through. Phase 4 (hemostasis and involution) begins after delivery of the placenta. Myometrial contractions continue to constrict the spiral arteries leading to hemostasis and uterine involution. The uterus will return to its nonpregnant size in the following weeks.

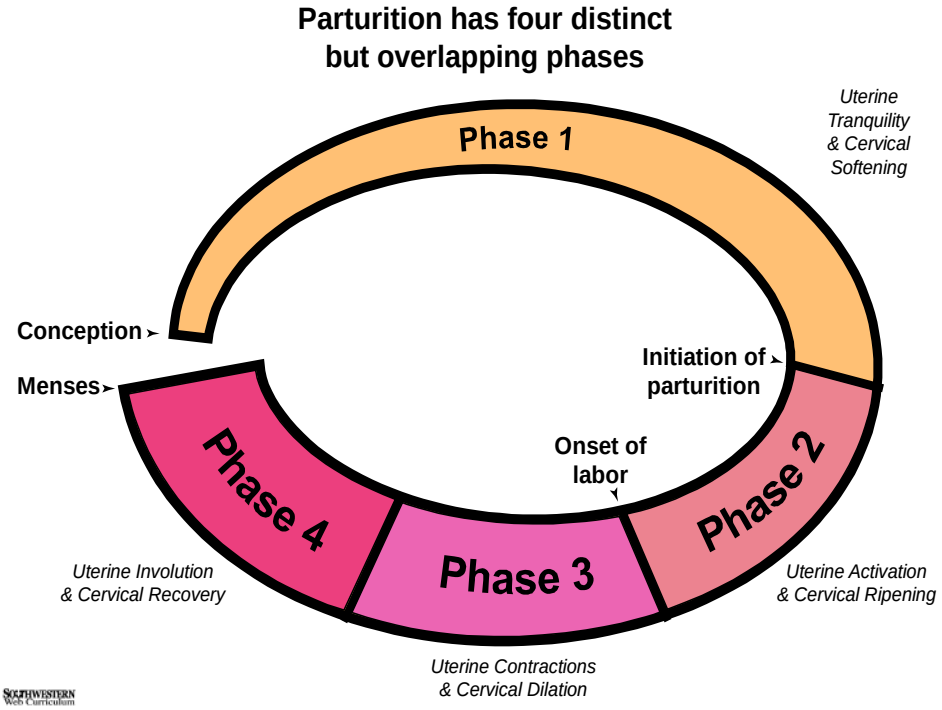

Figure 5. Parturition has four distinct but overlapping phases. The transition from phase 1 to phase 2 is the initiation of parturition. This transition is mediate in part by endocrine signals that include 1) function inactivation of progesterone action, 2) increase in maternal estrogen levels, and 3) increase synthesis of peptide hormones such as relaxin and fetal derives signals.

B. Regulation of Parturition

1.Progesterone

Throughout pregnancy vast quantities of progesterone are synthesized by the CL and then the placenta to maintain uterine quiescence. In most species, a sharp reduction in the rate of progesterone formation heralds the initiation of parturition, suggesting that the transition from phase 1 to phase 2 is the result of progesterone "withdrawal". A decline in progesterone synthesis by the placenta does not occur in humans, thus blood levels of progesterone remain high up to and during labor and decline only after delivery of the placenta. **The idea that a functional "withdrawal" of progesterone action facilitates human parturition is supported by studies that identify increased progesterone metabolism, changes in progesterone receptor isoforms, and decreased levels of progesterone receptor coactivators as a means of eliminating progesterone action**.

2. Estrogen

The predominant destination of estrogen secreted by the placenta is the maternal compartment. At parturition, increases in estrogen facilitate events leading to increased uterine contractility, such as changes in the resting membrane potential, the formation of gap junctions between myometrial cells, and increase the production and release of prostaglandins. In the cervix, estrogens stimulate proteolytic enzymes necessary to degrade the extracellular matrix for cervical dilation. **Estrogen may regulate or fine-tune the events leading to parturition, since pregnancies are often prolonged when estrogen levels in maternal blood and urine are low, as in placental sulfatase deficiency or in association with anencephaly.**

3. Prostaglandins

Prostaglandins are synthesized from arachadonic acid by two prostaglandin synthases, cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2). Three main lines of evidence suggest a role of prostaglandins, PGE_2 and $PGF_{2\square\square}$ in the onset of labor. **During parturition, there is an increase in the concentration in PGE_2 and $PGF_{2\square}$ in amniotic fluid and of their metabolites in maternal plasma and urine. Administration of COX inhibitors (e.g., aspirin and indomethacin) suppresses uterine activity and may prolong the length of pregnancy. Finally, exogenously administered prostaglandins stimulate myometrial contractility and cervical ripening, and prostaglandin analogs are used clinically for this purpose**.

4. Oxytocin

Oxytocin is a nonapeptide synthesized by hypothalamic magnocellular neurons located in the supraoptic and paraventricular nuclei. Its classical **effects include promoting myometrial contractility during parturition and stimulating milk release (let down) in lactation**. Receptors for oxytocin are increased in the myometrium during phase 2 of parturition. Synthesis of oxytocin receptors is stimulated by estrogen and inhibited by progesterone. While oxytocin infusion into near term pregnant women brings about the orderly commencement of labor (i.e., labor induction), its primary function more likely is in postpartum uterine involution and lactation. Oxytocin levels in maternal blood do not increase until phase 2 of parturition is in progress. Blood levels remain high during the immediate postpartum period and increase further when the infant suckles. **Oxytocin causes contractions of the uterus immediately after delivery, thereby helping to stop postpartum hemorrhage and facilitating events required for involution of the uterus to its prepregnant state**.

5. Fetal signals

The timing of birth may be regulated by signals from the developing fetus. Maternal plasma CRH levels (derived from the placenta) increase exponentially as pregnancy advances, peaking at the time of delivery. In women who deliver preterm, the exponential increase is rapid while women who deliver post-term have a slower rise in CRH levels, suggesting that a placental clock determines the timing of delivery. CRH may lead to an increase in fetal cortisol concentration, which in turn activates a cascade of events that stimulate parturition.

III. ENDOCRINOLOGY OF LACTATION

Mammals are separated from other classes by the function of the breast to produce milk to nurture newborns. The breast consists of glandular, adipose and connective tissue. The breast lobule is lined by milk-secreting epithelial cells (acini) that connect to intralobular ducts that empty into the 15 – 20 lobes that make up the glandular tissue of the breast.

The breast is responsive to sex steroid hormones. Estradiol stimulates growth of the ductal system and progesterone influences the growth of the acini. However, several other hormones and growth factors are required for complete growth and development. Exposure to estradiol, progesterone, prolactin, cortisol, insulin, thyroid hormone, and hPL is necessary for lactation. During the first trimester, proliferation of the breast is greatest followed by differentiation and secretion later in pregnancy.

A. Lactation

Prolactin is single-chain polypeptide similar in structure to GH an hPL. In the nonpregnant woman, prolactin levels are <25 ng/mL. In the third trimester, prolactin levels are 200 to 450 ng/mL. The increase in prolactin parallels the increase in estrogen beginning at 7-8 weeks gestation. At term hPL levels reach 6,000 ng/mL and also exert a lactogenic effect. During pregnancy, progesterone prevents lactogenesis. After delivery, estradiol and progesterone levels decrease, but prolactin remains elevated leading to an increase in production of milk components. Colostrum (epithelial cells and transudate) is produced during the first days following delivery. Milk production is established 2 to 5 days after the decrease in estradiol and progesterone.

In the first week postpartum, prolactin levels decrease to approximately 50% (100 ng/mL). Suckling stimulates a large increase in prolactin secretion. Basal prolactin levels remain at 40-50 ng/mL at 3 months postpartum until lactation ends. The increased prolactin sustains secretion of casein, fatty acids, lactose and the volume. Suckling also causes the release of oxytocin that contracts the myoepithelial cells leading to emptying of the alveoli (let-down).

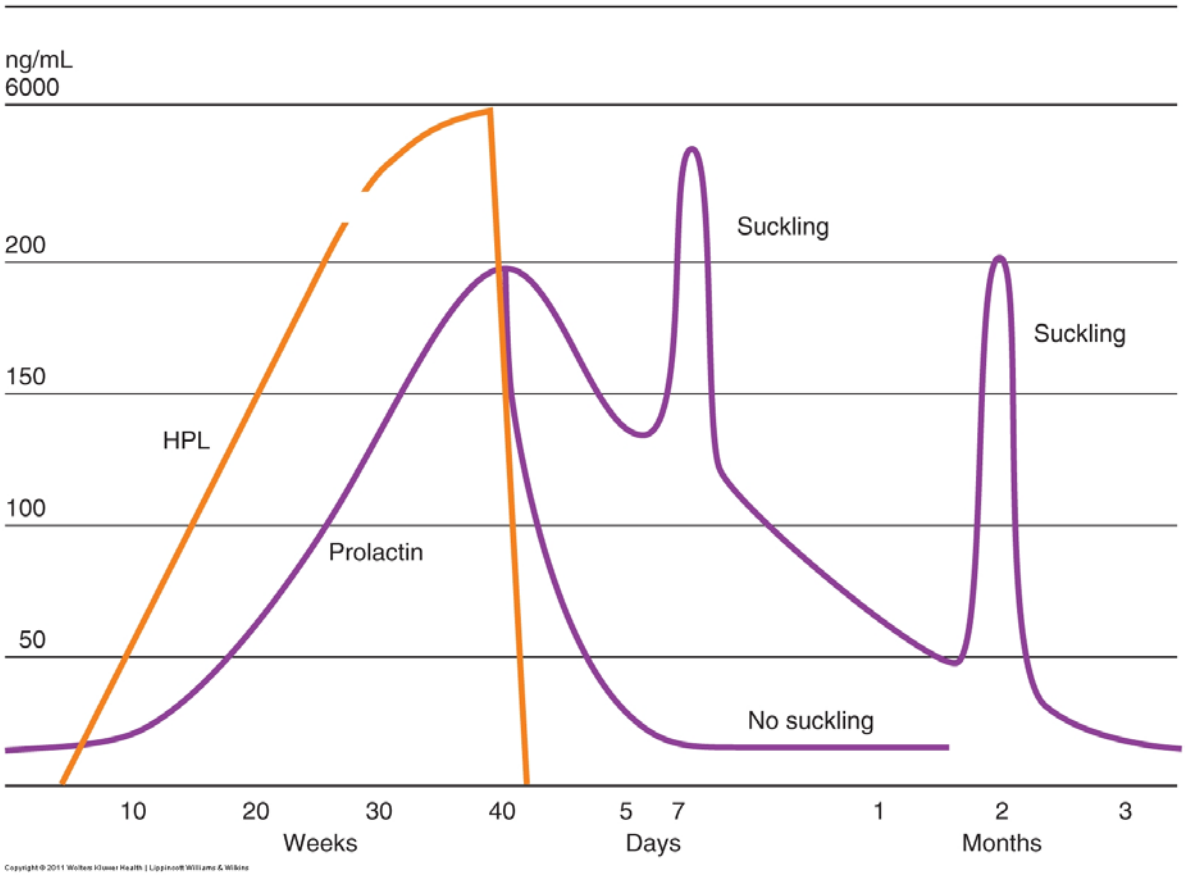

Figure 6. Prolactin production during pregnancy and postpartum. (From: Fritz MA and Speroff L. *Clinical Gynecological Endocrinology and Infertility 8th edition.*)

B. Lactation and Contraception

Lactation can provide a moderate contraceptive effect. Elevated prolactin levels inhibit GnRH secretion; FSH and LH are in the low-normal range. There is not follicular development or estrogen secretion in the ovary. Only amenorrheic women who exclusively breastfeed at regular intervals for the first 6 months have contraceptive protection similar to oral contraceptive pills. Total protection in exclusively breastfeeding women only occurs for the first 10 weeks. Therefore, contraception counseling is important. High doses of estrogen and progestins suppress lactation. The combination pill containing 30 μg ethinyl estradiol may reduce daily milk production by 40%, whereas the progestin-only pill reduces daily milk volume by 15%. The combination of lactation and the progestin-only pill will likely cause prolonged amenorrhea.

B. Lactation Suppression

Prolactin secretion is critical to maintain lactation. Lactation can be suppressed by discontinuing suckling and minimizing stimulation of the breast and nipple. Without suckling there is loss of oxytocin production and milk let-down. After a few days, milk production decreases without emptying and from local pressure on the alveoli. The fluid is resorbed and the engorged breasts decrease in size. Dopamine production increases and further inhibits prolactin secretion. Use of dopamine agonists for lactation suppression is not recommended because of reports of severe hypertension, seizures, and myocardial infarctions postpartum. Prolactin concentrations fall to normal, gonadotropins increase and estradiol production resumes. Ovulation can occur within 14-30 days of weaning.

Practice Questions:

1. The primary source of estrogen and progesterone in the first six weeks of pregnancy is:
    a. The granulosa cells
    b. The placenta
    c. The adrenal gland
    d. The corpus luteum
2. What hormone maintains pregnancy?
    a. Estriol
    b. Human placental lactogen
    c. Progesterone
    d. Human chorionic gonadotropin
3. What is the role of estradiol in the breast during pregnancy?
    a. Proliferation of adipose tissue
    b. Growth of the ductal system
    c. Growth of the epithelial cells
    d. Differentiation of myoepithelial cells

Answers
D
C
B