Endocrine Aspects of Pregnancy

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The hormonal changes during human gestation contribute to the physiological adaptation of mother as well as the regulation of fetal growth and homeostasis. Understanding the endocrine mechanisms that maintain and drive the processes of pregnancy will result in a better outcome for the fetus which may have long-term health benefits into adulthood.

Placental hormones affect both mother and fetus

The placenta's primary role is to provide physiological exchange between the fetal and maternal system. Placenta is also an endocrine organ that produces a wide variety of hormones signalling between the mother and fetus to insure optimal control of the gestation. Placental hormones influence maternal pregnancy state, e.g., maternal metabolism and behavior, nutrient intake, and uterine artery blood flow. Maternal pregnancy state promotes placenta growth which in turn promotes fetal growth whereas maternal constraint limits fetal growth. Placental hormones can be found in fetal plasma, amniotic fluid and in maternal plasma. The major placental hormones will be mentioned below.

Human chorionic gonadotropin (HCG) HCG is detectable in maternal blood and urine within 9 days of implantation. It serves as a reliable pregnancy test. HCG replaces luteinizing hormone (LH) as the hormone sustaining corpus luteum function which would otherwise degenerate in the absence of pregnancy. It stimulates the corpus luteum to secrete progesterone and estradiol, and also stimulates DHEA-S production by the fetal adrenal gland. In a male fetus, HCG stimulates testosterone secretion by Leydig cells, an action that is critical to masculine genital tract differentiation. The very high HCG levels also have enough homology with thyroid stimulating hormone (TSH) to increase maternal thyroid activity early in pregnancy.

Human chorionic somatomammotropin (HCS) or Human placental lactogen (HPL) The major function of HCS is to direct maternal metabolism to shunt nutrients to the fetus. It is synthesized within 4 weeks of gestation. Although HCS has growth promoting activity in only a small fraction of GH, the high maternal concentration of HCS makes it capable of contributing to anabolism in the mother. HCS stimulates lipolysis and antagonizes insulin actions, thus, it raises maternal free fatty acid and glucose levels. HCS may also stimulate IGF-2 synthesis in the placenta that contributes to fetal growth.

Placental steroids Before weeks 8-10 of gestation, progesterone and estrogens are synthesized in the maternal corpus luteum. Removal of the corpus luteum before 6 weeks of gestation increases the risk of abortion. By the end of the first trimester, the placenta produces enough of steroids to maintain the pregnancy and the corpus luteum is no longer needed. Placenta steroid hormones which increase throughout pregnancy play a decisive role in maternal-fetal physiological interactions.

Progesterone This placental hormone is essential for successful implantation, initial sustenance, and long-term maintenance of the fetus. Progesterone stimulates the endometrium glands to secrete nutrients on which the early zygote depends. Progesterone maintains the decidual lining of the uterus, where it induces prolactin synthesis. Prolactin helps inhibit maternal immune which responses to fetal antigens of male parent origin, and thus it helps prevent rejection of the fetus. Progesterone which is unable to synthesize by the fetus, is transferred from placenta to be the substrate for the synthesis of cortisol and aldosterone by the fetal adrenal cortex. Progesterone quiets uterine muscle activity by inhibiting prostaglandin production and responsivity to oxytocin. This prevents premature expulsion of the fetus. Progesterone increases maternal ventilation to remove CO_2 load created by increased metabolism. It also promotes lobular development in the mammary glands and greatly enhances the eventual capacity to secrete milk.

Estrogens Progressive increases in estradiol, estrone, and estriol occur throughout pregnancy. Estrogens prepare maternal tissues for labor, lactation, and nursing. The placenta cannot produce necessary androgen precursors of estrogen synthesis. Estradiol and estrone are synthesized from the DHEA-S precursor that derives from the maternal and fetal compartments. The 16-OH-DHEA-S which derives from fetal liver is the precursor for placental estriol synthesis. Estrogens stimulate continuous growth of the uterine muscles necessary for labor. They foster relaxation and soften the pelvic ligaments and junction of the pelvic bones; this allows better accommodation of the expanding uterus. Estrogens augment growth of the ductal system of the breast to prepare it for lactation. They also stimulate large amount of prolactin secretion from the maternal pituitary gland. Within the placenta, estradiol augments progesterone synthesis.

Other placental hormones The inner cytotrophoblast layer of placenta produces hypothalamic-like peptides: GnRH, TRH, CRH, GHRH, and somatostatin. These hormones may regulate in paracrine manner the secretion of pituitary-like peptides: TSH, ACTH, and GH, which

are produced by the outer syncytiotrophoblasts layer. Placental CRH stimulates the fetal and maternal pituitary to secrete ACTH, which in turn increases cortisol and DHEA production. Placental GH variant becomes the dominant GH in maternal blood and acts on maternal tissues. Placental IGF-I and IGF-II may act as the local growth regulators. Placental IGF-II is greater than that of IGF-I at all gestational ages. The 1, 25-dihydroxyvitamin D, synthesized by placenta and mother's renal tissue, helps regulate Ca^{2+} homeostasis and skeletal formation in the fetus. Inhibin A originated from fetus and placenta may suppress the mother's FSH secretion and unneeded ovarian follicle formation. Actvin A is derived from the placenta, decidua, and fetal membranes. It is involved in the control of trophoblast cell differentiation and stimulates HCG and progesterone synthesis by the placenta.

Changes of maternal hormones during pregnancy

Understanding of normal pregnancy-induced alterations in endocrine function is important to avoid unnecessary diagnostic tests and therapy that may be seriously detrimental to the mother and the fetus. These hormonal changes during gestation are discussed as follows.

Prolactin Prolactin rises progressively during pregnancy and peaks at the time of delivery, with the contributions from both the maternal pituitary and the decidua. Prolactin has similar action to HPL, in that it stimulates the growth and development of the breasts and regulates fat metabolism. Lactation itself is largely suppressed by the great excess of estrogens and progesterone during pregnancy. After parturition, elevated prolactin together with the withdrawal of estrogens and progesterone result in the onset of milk secretion. Milk synthesis is maintained in a nursing mother by prolactin and is facilitated by insulin and cortisol. Basal prolactin concentrations gradually decline 8 weeks after the delivery. They are transiently elevated during each period of suckling. An inhibitory effect of high prolactin level on GnRH secretion in the nursing mother is able to suppress LH and ovulation. Following the cessation of nursing, a decrease in circulating prolactin triggers the release of LH and initiates a resumption of menstrual cycle.

Relaxin It is produced by the *corpus luteum*, decidua, and placenta under HCG stimulation. Relaxin decreases uterine muscle contractility by reducing the activity of uterine myosin kinase. Relaxin relaxes the mother's pelvic outlet and softens the cervix by increasing collagenase enzyme activity. Thus, relaxin acts initially to maintain the uterine quiescence in order to prevent early abortion, but later it facilitates easier childbirth. Recently, it has been proposed that relaxin up regulates vascular gelatinase activity, thereby contributing to renal vasodilation, hyperfiltration, and reduced myogenic activity of small renal arteries during pregnancy.

Insulin Early motherhood is in an anabolic state with normal or even increased maternal sensitivity to insulin during the first half of pregnancy. During the second half of pregnancy, the mother shifts into a catabolic state and insulin resistance takes place. Insulin resistance causes excessive maternal lipolysis and elevation of postprandial plasma levels of glucose and amino acids as the uptake of nutrients by maternal tissues is reduced. This accelerates the nutrient transport across the placenta into the fetus. HCS is a key hormone responsible for maternal insulin resistance. Elevated levels of estrogens, progesterone, placental GH, and cortisol also antagonize insulin action in the mother. Insulin resistance of pregnancy, when it is added to an underlying vulnerability to diabetes, produces gestational diabetes in 4% of pregnancies.

Renin-Angiotensin System (RAS) Normal pregnancy is characterized by an estrogen-induced increase in circulating levels of renin and angiotensinogen. The higher levels of angiotensin II stimulate the adrenal zona glomeru losa to increase aldosterone secretion. This induces Na^{+} retention which is needed to support a high maternal plasma volume and to build the extracellular fluid of the fetus. The RAS has been implicated in the pathogenesis of preeclampsia.

Thyroid hormones, cortisol and parathyroid hormone Total plasma thyroxine and cortisol levels are elevated because of estrogen-induced increases in their respective binding globulins. Free thyroxine and triiodothyronine may increase in the first trimester, and these necessary hormones may be transferred to the fetus and serve it before the fetal thyroid gland begins to function. Placental TSH may augment maternal thyroid gland activity. Free cortisol also rises modestly. This may contribute to maternal adipose tissue gain and to mammary gland development. High placental CRH stimulates ACTH secretion from maternal pituitary, thus produces maternal hypercortisolism. Parathyroid hormone secretion increases in the mother and augments the plasma levels of 1,25-hydroxyvitamin D to sustain maternal plasma levels of Ca^{2+}.

Gonadotropins and GH FSH and LH secretion from maternal pituitary is suppressed by high concentrations of estrogen, progesterone, prolactin and inhibin A. Similarly, maternal pituitary GH secretion is decreased through the negative feedback resulting from the actions of HCS and placental variant GH actions.

Hormonal regulation of fetal growth and fetal programming

Hormones affect both tissue accretion and differentiation *in utero*. Hormones act on fetal growth both directly, via genes, and indirectly, through changes in placental growth, fetal metabolism, and/or the production of growth factors and other hormones by the fetoplacental tissues. Three main sources of hormones present in fetal circulation include endocrine glands of the fetus, uteroplacental tissues, and maternal circulation. The key hormones involved in regulatory processes of fetal growth are anabolic hormones, i.e., insulin, IGFs, and thyroid hormones and catabolic hormone, i.e., glucocorticoids.

Insulin Insulin acts as a signal of nutrient availability and promotes growth of the fetus. The increase in fetal insulin in response to maternal hyperglycemia, is responsible for the increase growth and macrosomia observed in diabetic pregnancies.

IGFs IGF-I and IGF-II in fetal plasma derive from feto-placental tissues throughout gestation. Fetal IGF-I appears to be the signal of nutrient sufficiency, which regulates tissue accretion in utero, whereas, fetal IGF-II provides a more general stimulus to cell growth, and regulate tissue specific changes in cell differentiation during late gestation. A positive correlation has been demonstrated between cord blood IGF-II and placental weight.

Thyroid hormones Thyroid hormones derive from fetal thyroid glands and maternal circulation that augment the development of the fetal nervous system, bone, skin, lungs, and skeletal muscle. They also act as signals of energy availability. Thyroid hormones stimulate tissue

accretion and differentiation via modulation of IGF production and by metabolic actions, which increase fetal O_2 consumption.

Glucocorticoids Glucocorticoids are essential for the development and maturation of fetal organs required for extrauterine survival. However, glucocorticoids inhibit tissue accretion when their concentrations are elevated. An increase in maternal glucocorticoids crossing to the fetus, may have a deleterious effect on fetal growth and postnatal development. Placental and fetal 11β-HSD2 enzyme, which converts cortisol and corticosterone to their inactive metabolites, is a key factor in limiting fetal and placental exposure to maternal glucocorticoids.

Events *in utero* may determine long-term health outcomes into adulthood. This is known as ***fetal programmimg.*** Prenatal glucocorticoid exposure can permanently reset endocrine system, such as the somatotrophic and hypothalamic-pituitary-adrenal axes, which in turn, may contribute to the pathogenesis of adult disease. Low birth weight is associated with elevated cortisol levels at birth and has been linked to hypertension, glucose intolerance, cardiovascular disease, respiratory disease, stroke, etc. in later life.

Leptin In pregnant women, leptin is produced by both the maternal and fetal adipose tissues as well as by placental trophoblast. Estrogen is linked to the regulation of leptin and its receptor. Glucocorticoids also enhance leptin synthesis and secretion in adipose tissue. Leptin has direct effects on implantation, placental endocrine function, and conceptus development. In addition, leptin is linked to mechanisms affecting pregnancy-associated pathologies that include preeclampsia, gestational diabetes, and intrauterine growth restriction. Moreover, it has been suggested that alterations in leptin levels in utero prompt substantive hypothalamic changes in the fetus that eventually result in altered nutritional intake, energy metabolism, and adiposity in children and adults.

Termination of pregnancy depends on specific hormonal changes

The exact mechanism of parturition in humans remains unclear. Increased fetal cortisol in association with increase in CRH, prostaglandins, and oxytocin within the utero-placental system appears to initiate the process of giving birth.

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Abbreviations :

HCG	= human chorionic gonadotropin
TSH	= thyroid stimulating hormone
DHEA	= dehydroepiandrosterone
DHEA-S	= dehydroepiandrosterone sulfate
16-OH-DHEA-S	= 16α- hydroxydehydroepiandrosterone sulfate
11β-HSD2	= 11β - hydroxysteroid dehydrogenase