ENDOCRINOLOGY OF PREGNANCY

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ABSTRACT

A coordinated sequence of events must occur in order to establish and successfully maintain a healthy pregnancy. Synchrony between the development of the early embryo and establishment of a receptive endometrium is necessary to allow implantation and subsequent progression of pregnancy. The endocrinology of human pregnancy involves endocrine and metabolic changes that result from physiological alterations at the boundary between mother and fetus. Known as the feto-placental unit (FPU), this interface is a major site of protein and steroid hormone production and secretion. Many of the endocrine and metabolic changes that occur during pregnancy can be directly attributed to hormonal signals originating from the FPU. The initiation and maintenance of pregnancy depends primarily on the interactions of neuronal and hormonal factors. Proper timing of these neuro-endocrine events within and between the placental, fetal, and maternal compartments is critical in directing fetal growth and development and in coordinating the timing of parturition. Maternal adaptations to hormonal changes that occur during pregnancy directly affect the development of the fetus and placenta. Gestational adaptations that take place in pregnancy include establishment of 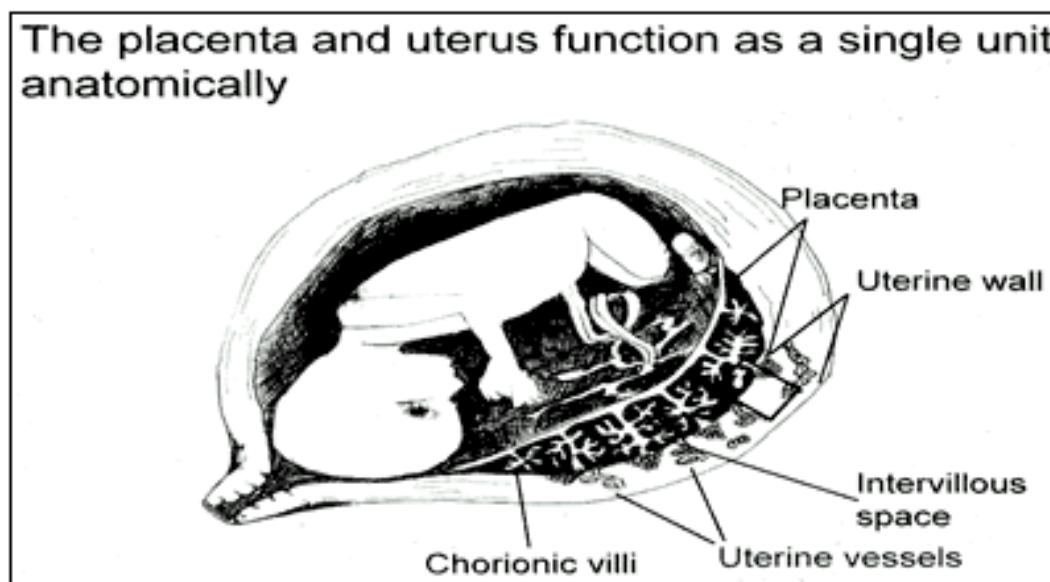a receptive endometrium; implantation and the maintenance of early pregnancy; modification of the maternal system in order to provide adequate nutritional support for the developing fetus; and preparation for parturition and subsequent lactation.

INTRODUCTION

A coordinated sequence of events must occur in order to establish and successfully maintain a healthy pregnancy. The endocrinology of human pregnancy involves endocrine and metabolic changes that result from physiological alterations at the boundary between mother and fetus. Known as the feto-placental unit (FPU), this interface is a major site of protein and steroid hormone production and secretion (Figure 1). Additionally, it serves as an endocrine, respiratory, alimentary, and excretory organ, facilitating the exchange of nutrients and metabolic products between the mother and fetus. The fetus is dependent on this effective exchange with the mother for its proper intrauterine growth and development. Thus, it is not surprising that the fetus initiates and influences maternal adaptations to optimize this exchange via complex hormonal mechanisms. Many of the endocrine and metabolic changes that occur during pregnancy can be directly attributed to hormonal signals originating from the FPU. The initiation and maintenance of pregnancy depends primarily on the interactions of neuronal and

hormonal factors. Proper timing of these neuro-endocrine events within and between the placental, fetal, and maternal compartments is critical in directing fetal growth and development and in coordinating the timing of parturition. Maternal adaptations to hormonal changes that occur during pregnancy directly affect the development of the fetus and placenta. Gestational adaptations that take place in pregnancy include establishment of a receptive endometrium; implantation and the maintenance of early pregnancy; modification of the maternal system in order to provide adequate nutritional support for the developing fetus; and preparation for parturition and subsequent lactation.

Figure 1. The interface between mother and fetus, known as the feto-placental unit (FPU), is a major site of protein and steroid hormone production and secretion.

ENDOMETRIAL RECEPTIVITY

The menstrual cycle, involves a synchronous production of ovarian steroid hormones, estrogen and progesterone, which induces structural and functional changes within the endometrium in anticipation for embryo implantation and the establishment of a pregnancy. During the luteal phase, under the primary influence of progesterone, the proliferative endometrium changes into secretory endometrium, which is well vascularized and composed of spiral arteries. A favorable environment for implantation is established via chemokines, growth factors, and cell adhesion molecules (CAMs) produced by the glandular secretory endometrium (1). The chemokines and CAMs serve to attract the blastocyst to the specific sites of implantation where the endometrium is strategically prepared for invasion and placentation (1). When implantation does not occur, a timely regression and destruction of the fully developed endometrium leads to menstruation. However, if implantation occurs, the endometrium continues to grow and undergoes further morphological and molecular changes to provide supportive environment for the growing embryo (2).

Endometrial "receptivity" refers to this physiological state when the endometrium allows a blastocyst to attach, firmly adhere, penetrate, and induce localized changes in the endometrial stroma resulting in decidualization (2). The specific period, known as the

"implantation window" opens 4-5 days after endogenous or exogenous progesterone stimulation and closes approximately 9-10 days later (3, 4). Implantation has three stages: apposition, adhesion and penetration. Apposition is an initial unstable adhesion of the blastocyst to the endometrial surface. This stage is characterized histologically by the appearance of microprotrusions from the apical surface of the epithelium, termed pinopodes, occurring six days after ovulation and retained for 24 hours during the implantation window. The pinopods express chemokines and CAMs, which attract the blastocyst floating within the endometrial cavity to appose. Additionally, the smooth surface of the pinopodes facilitates the apposition of the blastocyst to the endometrium. Further encouraging the blastocyst to appose to the pinopods is the removal of adhesion inhibiting mucin, while the areas between pinopods have been shown to express MUC-1, which prevents embryo adhesion (5). Once the blastocyst is apposed, a stronger attachment is achieved through local paracrine signaling between the embryo and the endometrium. At this stage, the blastocyst is sufficiently adherent to the endometrium as to resist dislocation of the blastocyst by flushing the uterine lumen. The first sign of the attachment reaction coincides with a localized increase in stromal vascular permeability which is manifested as stromal edema at the site of blastocyst attachment (6). Thus, vascular changes also appear to be an important factor in establishing endometrial receptivity. Following adhesion, the embryo invades through the luminal epithelium into the stroma to establish a relationship with the maternal vasculature. In response to this invasion and the presence of progesterone stimulation, the endometrial stromal cells undergo a process termed decidualization by which they differentiate and become specialized decidual stromal cells. Decidualization is essential for the survival and continued development of the pregnancy. In humans, decidual changes occur throughout the entire endometrium during the luteal phase even in the absence of an embryo, but become widespread in early gestation. These decidual stromal cells are very metabolically active and support the implanting embryo by secreting a wide array of hormones and growth factors including prolactin, relaxin, insulin-like growth factors (IGFs) and insulin growth factor binding proteins (IGFBPs). The endometrial stromal cells are the precursors of decidual stromal cells and appear to originate from both resident uterine mesenchymal stem cells as well as adult bone marrow-derived stem cells (7, 8). Interestingly, bone marrow-derived progenitors have been shown to give rise to functional prolactin-producing decidual stromal cells in decidua of pregnant mice, and appear to play an important role in implantation and pregnancy maintenance (9). The bone marrow is also the source of many leukocytes that infiltrate the endometrium during the secretory phase. In humans, a large influx of leukocytes to the uterus occurs in response to ovulation and rising ovarian P4 production, elevating them to 40% of all endometrial cells in the mid-late secretory phase of the menstrual cycle (10). This gain in leukocyte numbers is primarily due to the accumulation of uterine natural killer (uNK) cells. Studies in mice additionally show that the selected entry of uNK cells into early decidua optimizes angiogenesis and promotes decidual spiral artery vascular remodeling. This influences the timing of uterine lumen closure and thereby the appropriate rate of early fetal development including initiation of trophoblast invasion (11). Macrophages are the second most abundant leukocyte population in the luteal phase endometrium. In addition to uterine NK cells and macrophages, the endometrium contains T cells with no apparent cyclic changes, and rare populations of dendritic cells in luteal phase endometrium, both of which become more abundant in the pregnant decidua. The composition and function of these immune cells at the implantation site and the maternal-fetal interface are highly specialized to foster embryo and placental development and to minimize the chance of immune rejection (12).

Progesterone is essential in mediating the changes that the endometrium undergoes in the luteal phase in preparation for embryo implantation (13). The effects of progesterone on the uterus have been elucidated through elegant experiments in knockout mice as well as studies using progesterone receptor (PR) antagonists. Mice with global PR knockout are infertile due to defects in ovulation and implantation (14). Their endometrium displays hypertrophy and inflammation of the glandular epithelium associated with failure to undergo decidualization. Mice with a specific knockout in PR-B isoform, however, have normal ovarian function, implantation and reproductive capacity (15, 16). In contrast, mice with a specific knockout in PR-A exhibit lack of decidualization in the endometrial stroma along with endometrial epithelial hyperplasia and inflammation (15, 16), indicating that PR-A is critical for embryo implantation and the normal function of the endometrial epithelium and stroma, while PR-B promotes epithelial hyperplasia of the endometrium. Moreover, administration of the progesterone antagonist mifepristone (RU486) in humans during pregnancy induces abortion, fetal loss or parturition, depending on the gestational age (17, 18). If administered at low doses at the mid- or late follicular phase, it prevents pregnancy by delaying endometrial maturation, while at high doses it delays the LH surge and inhibits ovulation (19, 20).

The key to endometrial receptivity is the dynamic and precisely controlled molecular and cellular events that involve coordinated effects of autocrine, paracrine, and endocrine factors. Analysis of the transcriptosome of the endometrium during the implantation window using microarray technology has revealed numerous genes that are up- and down-regulated during the "window of implantation" when compared with late proliferative phase endometrium (4, 21). In particular, transcription factors such as the homeobox (HOX) genes are essential for endometrial receptivity by mediating some functions of the sex steroids. HOXA10- and HOXA11-deficient mice have uterine factor infertility due to an implantation defect (22, 23). Both HOXA10 and HOXA11 mRNAs are expressed in human endometrial epithelial and stromal cells; their expression is upregulated by estrogen and progesterone, and is significantly higher in the mid- and late-secretory phases, coinciding with time of embryo implantation (24, 25). As transcription factors, *HOX* genes regulate other downstream target genes specific to the implantation window, including pinopodes, β3 integrin and insulin-like growth factor-binding protein-1 (IGFBP-1), leading to the proper development of the endometrium and receptivity to implantation (26). Other growth factors, cytokines, and transcription factors produced by the endometrium also assist in the establishment of endometrial receptivity (26, 27). Impaired endometrial receptivity is considered to be a major limiting factor for the establishment of a pregnancy. Implantation during this time of uterine receptivity is associated with high (85%) success rate for continuing a pregnancy, whereas implantation after cycle day 25 has a much lower success rate (11%) (28).

IMPLANTATION

Pregnancy-related proteins can be found in maternal circulation shortly after fertilization. For example, platelet activating factor (PAF)-like substance, which is produced by the fertilized ovum, is present almost immediately (29-32). After ovulation and fertilization, the embryo remains in the ampullary portion of the fallopian tube for up to 3 days. The embryo undergoes a sequence of cell divisions and differentiation that is not dependent on the hormonal milieu of the fallopian tube or the uterus, as fertilization and early embryonic development occur successfully in vitro. The developing conceptus travels toward the uterus, through the isthmic portion of the tube, for approximately 10 hours, and then enters the uterus as an embryo at the 2- to 8-cell stage (33, 34). With further development, between 3-

6 days after fertilization, the embryo becomes a blastocyst floating unattached in the endometrial cavity (34). A schematic representation of the pre-implantation phase of pregnancy is shown in Figure 2. Before implantation, the blastocyst also secretes specific substances that enhance endometrial receptivity. Successful implantation requires precise synchronization between blastocyst development and endometrial maturation. Indeed, there appears to be a cross-talk between the embryo and the endometrium with the endometrium acting as a biosensor that is able to respond favorably to competent embryos but less favorably to incompetent poorly viable embryos destined to fail (35). Ultimately, implantation failure is the result of impaired embryo developmental competence or impaired endometrial receptivity, both having negative effects on the embryo-endometrium cross-talk. It is estimated that embryos account for one third of implantation failures, while suboptimal endometrial receptivity and aberrant embryo-endometrial cross-talk are responsible for the remaining two-thirds (36).
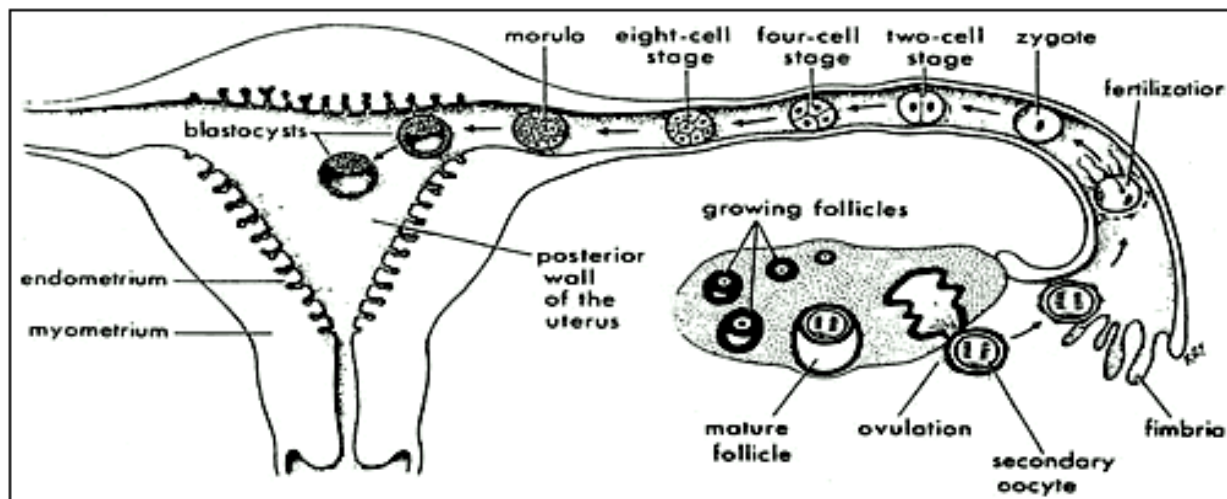
Figure 2. A diagrammatic summary of the ovarian cycle leading to embryo development as it occurs during the first week after fertilization. (Adapted from (37), with permission)

To date, little information exists regarding regulation of steroid production in the embryo. The early embryo and its surrounding cumulus cells secrete detectable estradiol and progesterone well before the time of implantation (38, 39). Mechanical removal of these cells results in the cessation of steroid secretion, while return of the removed cells through co-culture results in restoration of steroid secretion (38). Given this finding, steroid production by the conceptus is thought to be negligible by the time it has reached the endometrial cavity, since it is gradually denuded of cumulus cells as it travels through the fallopian tube.

Conceptus-secreted progesterone may itself affect tubal motility as the conceptus is carried to the uterus (40). Progesterone, by action mediated through catecholamines and prostaglandins (PG), is believed to relax utero-tubal musculature. Moreover, progesterone is thought to be important in tubal-uterine transport of the embryo to the uterine cavity, since receptors for progesterone are found in highest concentrations in the mucosa of the distal one third of the fallopian tube. Estradiol, also secreted by these structures, may balance the progesterone effect so as to maintain the desired level of tubal motility and tone (40). Progesterone antagonizes estrogen-augmented uterine blood flow through depletion of

estrogen receptors in the cytoplasm (41). Likewise, estrogen and progesterone also appear to balance one another in the maintenance of blood flow at the implantation site. Both estrogen and progesterone are known to upregulate the expression of multiple angiogenic factors in the uterus, including VEGF, bFGF, PDGF, and TGF-β (42). It is well known that estrogen stimulates an increase in uterine angiogenesis, blood flow and vasodilation by acting both directly on endothelial cells, and/or indirectly on other endometrial cell types via numerous potential promoters (43). In pregnant baboons and sheep, estrogen stimulated uterine and placental blood flow (44). Estrogen treatment significantly increased the paracellular cleft width between endometrial endothelial cells within 6 h considered to result in the increased vascular permeability associated with estrogen administration (45). Unlike estrogen, the angiogenic effects of progesterone in the uterus are believed to occur without concurrent vasodilation (46), as there was no change in endometrial endothelial paracellular cleft width 6 h after progesterone treatment in baboons (45). However, much is still unknown regarding uterine blood flow regulation in pregnancy and how the implanting embryo may influence this process. Human chorionic gonadotropin (hCG) messenger ribonucleic acid (mRNA) is detectable in the blastomeres of 6- to 8-cell embryos; however, it is not detectable in blastocyst culture media until the 6th day (47-49). After implantation is initiated, the embryo is actively secreting hCG, which can be detected in maternal serum as early as the 8th day after ovulation. However, due to the absence of direct vascular communication, secretion of hCG into the maternal circulation is initially limited (50). The primary role of hCG is to prolong the biosynthetic activity of the corpus luteum, which allows continued progesterone production and maintenance of the gestational endometrium. As implantation progresses, the conceptus continues to secrete hCG and other pregnancy-related proteins, and resumes detectable steroid production (38, 39, 51).

Termed trophectoderm (aka outer cell mass), blastomeres lining the periphery of the blastocyst are destined to form the placenta and can be identified at 5 days post-fertilization. The main structural and functional units of the placenta are the chorionic villi, which increase significantly in number during the first trimester of pregnancy. The structure of the chorionic villi is pictured in Figure 3. The villous structure provides a tremendous absorptive surface area to facilitate exchange between the maternal and fetal circulation. The maternal blood arrives from the spiral arteries and circulates through the intervillous space. Fetal blood moves in the core of the chorionic villi within the villous vessels; thus, fetal and maternal blood is never mixed in this system. The key cells inside the chorionic villi are the cytotrophoblasts. They have the ability to proliferate, invade and migrate or to differentiate, through aggregation and fusion, to form a syncytial layer of multi-nucleate cells lining the placental villi, known as the syncytiotrophoblasts.

By 10 days post-fertilization, 2 distinct layers of invading trophoblasts have formed. The inner layer, the cytotrophoblasts, is composed of individual, well-defined and rapidly dividing cells. The outer layer, the syncytiotrophoblasts, is a thicker layer comprised of a continuous cell mass lacking distinct cell borders. Syncytiotrophoblasts line the fetal side of the intervillous space opposite the decidualized endometrium of the maternal side. Immunohistochemically, cytotrophoblasts stain for hypothalamic-like protein hormones: gonadotropin releasing hormone (GnRH), corticotrophin releasing hormone (CRH), and thyrotropin releasing hormone (TRH) (52-64). Juxtaposed syncytotrophoblasts stain immunohistochemically for the corresponding pituitary-like peptide hormones: human chorionic gonadotropin (hCG; analogous to pituitary luteinizing hormone, LH), adrenocorticotropic hormone (ACTH) and human chorionic thyrotropin (hCT). Anatomically, this arrangement suggests that these 2 layers mirror

the paracrine relationship of the hypothalamic-pituitary axis (52-64).

Syncytiotrophoblasts, the principal site of placental steroid and protein hormone biosynthesis, have a large surface area and line the intervillous space which exposes them directly to maternal bloodstream without the vascular endothelium and basement membrane which separates them from the fetal circulation (Figure 3-5). This anatomic arrangement explains why placental proteins are secreted almost exclusively into the maternal circulation in concentrations much higher than those in the fetus (65). The syncytiotrophoblast layer contains the abundant subcellular machinery characteristic of cells primarily responsible for hormone synthesis. Amino acids of maternal origin are assembled into pro-hormones. Pro-hormones are then packaged into early secretory granules and transferred across the trophoblastic cell membranes as mature granules. Mature granules become soluble as circulating hormones in maternal blood as they pass through the intervillous space (65).
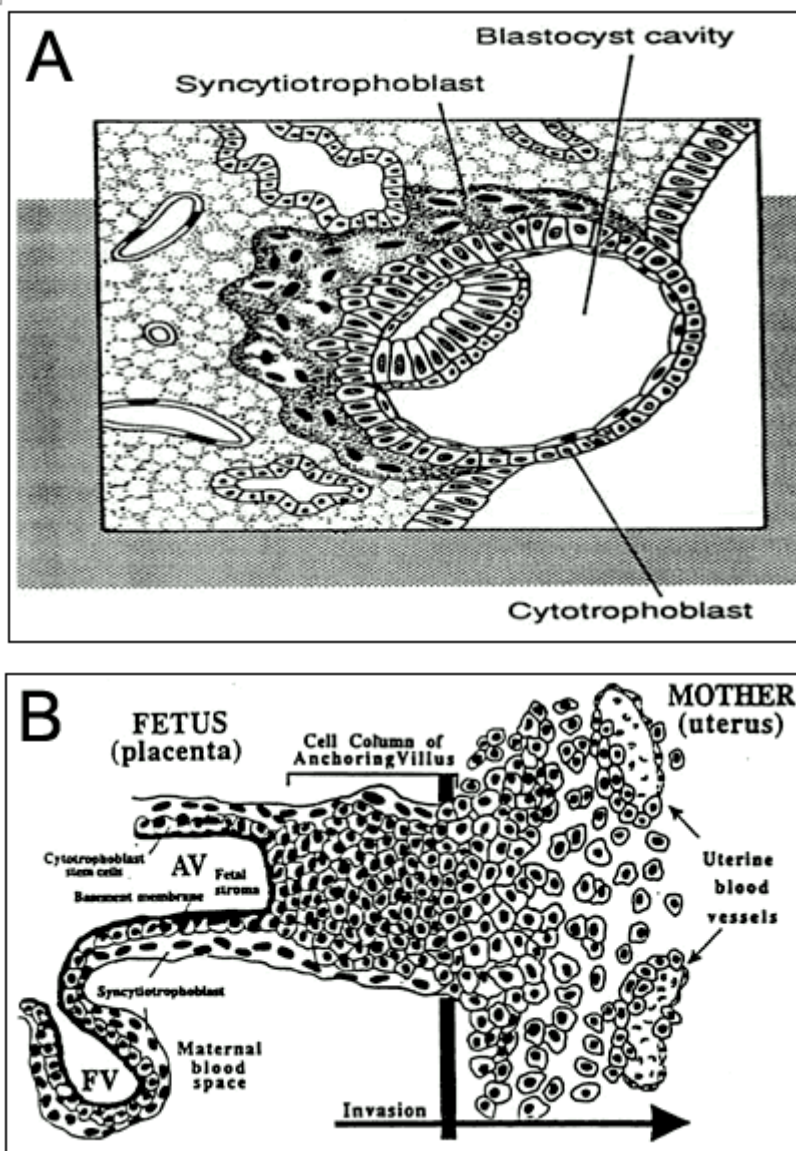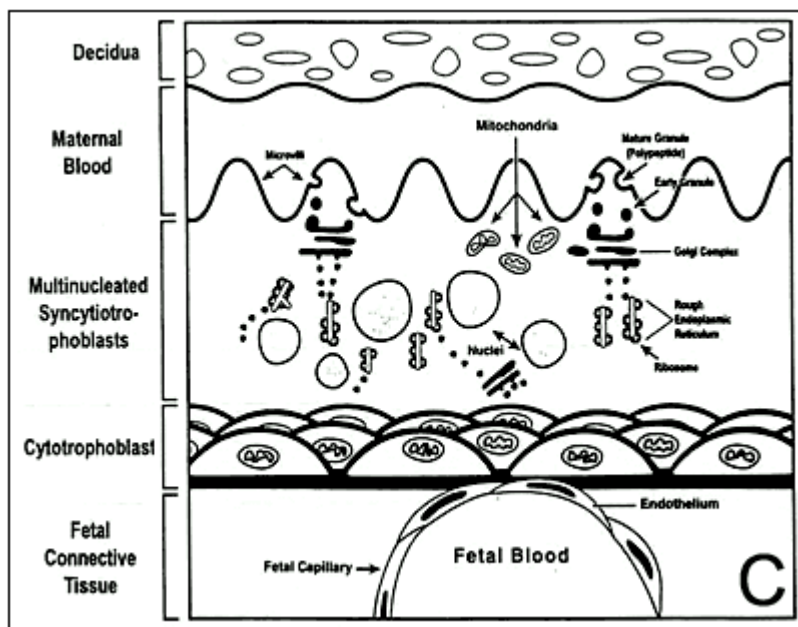
Figure 3. A. A depiction of a blastocyst implanting in the uterus. B. A longitudinal section of a chorionic villus at the feto-maternal interface at about 10 weeks' gestation. The villous serves as a bridge between maternal and fetal compartments. C. Human placental ultra-structure seen in cross section. Syncytiotrophoblasts line the fetal surface of the intervillous space and interact with the maternal blood supply to secrete placental hormones directly into the circulation. Decidua lines the maternal surface of the intervillous space and secretes protein hormones. (From (66), with permission)

DECIDUA AND DECIDUAL HORMONES

The decidua is the endometrium of pregnancy. Decidualized endometrium is a site of maternal steroid and protein biosynthesis that relates directly to the maintenance and protection of the pregnancy from immunologic rejection. For instance, decidual tissue secretes cortisol, and in combination with hCG and progesterone secreted by the conceptus, cortisol produced by the decidua acts to suppress the maternal immune response conferring the immunologic privilege required by the implanting conceptus (67, 68).

Decidual Prolactin

Decidual prolactin is a peptide hormone having chemical and biological properties identical to pituitary prolactin (69). Prolactin, derived from decidualized endometrium, is first detectable in the endometrium at a time corresponding to implantation-cycle day 23. Progesterone is known to induce decidual prolactin secretion (70). Scant decidual prolactin enters the fetal or maternal circulation after it is transported across the fetal membranes from the adherent decidua and is released into the amniotic fluid (71). Unaffected by bromocriptine administration, decidual production of prolactin takes place independent of dopaminergic control (69).

Decidual prolactin secretion rises in parallel with the gradual rise in maternal serum prolactin seen until 10 weeks' gestation, then it rises rapidly until 20 weeks, and falls as term approaches (72). Decidua-derived prolactin serves to regulate fluid and electrolyte flux through fetal membranes by reducing permeability of the amnion in the fetal-to-maternal direction (69-71, 73-77). Circulating prolactin in the fetus is secreted by the fetal pituitary gland, while prolactin found in the maternal circulation is secreted by the maternal

pituitary gland under the influence of estrogens. Unlike decidual prolactin, these circulating levels are both suppressed by maternal ingestion of bromocriptine.

Decidual Insulin-like Growth Factor Binding Protein-1 (IGFBP-1)

IGF binding protein-1 (IGFBP-1) is a peptide hormone that originates from decidual stromal cells. In non-pregnant women, circulating IGFBP-1 does not change during cycling of the endometrium, while IGFBP-3 is the main circulating IGFBP. During pregnancy, however, there is a several-fold increase in serum IGFBP-1 levels that begins during the first trimester, peaks during the second trimester, and falls briefly only to peak a second time before term (78). IGFBP-1 inhibits the binding of insulin-like growth factor (IGF) to receptors in the decidua and inhibits fetal growth. Newborn birth weight correlates directly with maternal IGF-1 levels, and inversely with circulating IGFBP-1 levels (79).

Progesterone-Associated Endometrial Protein (PAEP)

Previously known as pregnancy protein-14, PAEP is a glycoprotein hormone synthesized by secretory and decidualized endometrium that is detectable around cycle day 24 (80). In serum, it rises sharply around cycle day 22 to 24, reaching its peak value at the onset of menstruation; if pregnancy occurs, levels remain high (81). In pregnancy, PAEP rises in parallel with hCG (78). Like hCG, PAEP is thought to have immunosuppressant properties in pregnancy (80). PAEP levels are often low in those patients with conditions, such as ectopic pregnancy, in which there is little decidual tissue produced (82).

PROLONGATION OF CORPUS LUTEUM FUNCTION

Primary steroid products of the corpus luteum are progesterone, 17β-progesterone, estradiol and androstenedione. Low-density lipoprotein (LDL) cholesterol is the main precursor responsible for corpus luteum progesterone production (83). Between 6- and 7-weeks' gestation, corpus luteum function naturally begins to decline. During this luteal-placental transition period, production of progesterone shifts to the developing placenta (Figure 4).

Pulsatile pituitary LH secretion in the early luteal phase followed by hCG secreted from the implanting conceptus act to stimulate progesterone production from the corpus luteum. Removal of the corpus luteum before 6 weeks of gestation increases the risk of abortion (67a). Thus, regarding early pregnancy, progesterone is considered the most important steroid product in this group because progesterone alone can maintain a pregnancy that would otherwise abort in a lutectomized woman (84). For example, exogenous progesterone, given to an agonadal woman pregnant through egg-donor in vitro fertilization (IVF), maintains the pregnancy through the first trimester until placental progesterone secretion is established (85). For this reason, in patients with corpus luteum dysfunction or in whom the corpus luteum has been removed surgically, supplementation with exogenous progesterone is frequently initiated and extended beyond approximately 10 weeks of gestation, the critical period of the luteal-placental shift.
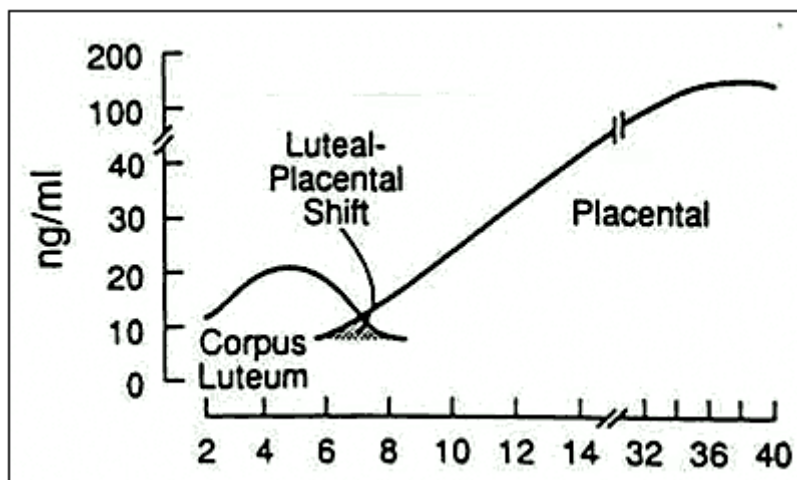
Figure 4. A shift in progesterone production from the corpus luteum to the placenta occurs at approximately the 7th to 9th week of gestation. The small, shaded area represents the estimated duration of this functional transition. (From (86), with permission)

In women with first-trimester threatened abortion, progesterone concentrations at the time of initial evaluation are often predictive of ultimate outcome (87). Abortion will occur in approximately 80% of those with progesterone concentrations under 10 ng/mL; viable pregnancies are virtually never observed at concentrations of <5.0 ng/mL (88).

Corpus Luteum Relaxin

Relaxin is a peptide hormone produced by the corpus luteum, and not detected in non-pregnant women or men. Although it is argued that the corpus luteum is the sole source of relaxin in pregnancy, it has also been identified in the placenta, decidua and chorion (89-91). The maternal serum concentrations of relaxin rise during the first trimester, when the corpus luteum is dominant, and decline in the second trimester. Interestingly, when women with a normal pregnancy were compared with pregnant women using egg donor (therefore, no corpus luteum), relaxin was only identified in the women with a pregnancy derived from her own eggs. However, the duration of pregnancy and labor outcomes were not different between the two groups (92). The presence

of relaxin suggests that it may play a role in early pregnancy, but its function is still unclear.

In animals, relaxin softens (ripens) the cervix, inhibits uterine contractions, and relaxes the pubic symphysis (93). These changes are similar to those seen during human labor. Additionally, in vitro studies of human cervical stromal cells have shown that relaxin induces changes consistent with cervical ripening (94, 95). Human relaxin primarily binds to relaxin receptors in the decidua and chorionic cytotrophoblasts (96). Relaxin, originating in the decidua and binding to its receptors in the fetal membranes, increases cytokine levels that can activate matrix metalloproteinases and lead to rupture of fetal membranes and labor (97). Thus, relaxin may play a facilitatory role in labor, however its role is still not clearly defined.

PLACENTAL COMPARTMENT

Unique to mammals, the placenta plays a major role in balancing fetal growth and development with maternal homeostasis. The fetus develops in an environment where respiration, alimentation and

excretory functions are provided by the placenta. The human placenta is hemochorial, which means the chorion is in direct contact with maternal blood. Cyto- and syncytiotrophoblast cells of the placenta have direct access to the maternal circulation. In contrast, the trophoblast layer prevents most maternal hormones from entering the fetal compartment, and consequently the fetal/placental endocrine system generally develops and functions independently of that of the mother. Over time, the placenta has evolved as a system through which viviparity or livebirth could take place with dependable success.

The placenta functions, to some extent, as a hypothalamic-pituitary-end organ-like entity owing to the inherent ability of this type of system, with its stimulatory and inhibitory feedback mechanisms, to dynamically regulate factors that affect fetal growth and development under a variety of conditions. In the fully developed hypothalamic-pituitary-end organ schema of humans, neural inputs to the hypothalamus serve to regulate the secretion of hypothalamic releasing hormone peptides. However, in the placenta there are no such direct neural inputs, and the exact mechanism(s) responsible for regulation of the secretion of hypothalamic-like placental peptides is unknown.

Changes in maternal hormone concentrations play a critical role in modulating the metabolic and immunologic changes required for successful outcome in pregnancy. The fetus and placenta produce and secrete steroids and peptides into the maternal circulation as well as stimulate maternal hormone production. The origins and amounts of the fetal and placental hormones secreted during pregnancy changes dramatically over the course of the gestational period. Some of the pregnancy-related protein hormones previously discussed are, in part, responsible for the altered steroid concentrations typical of pregnancy.

Placental Steroid Hormones

The placenta is a site of active steroidogenesis which depends on highly integrated and active interactions with both mother and fetus. This is consequent to an elegant complementary of enzymatic deficiencies between placental and fetal compartments (Table 1). The placenta is characterized by significant aromatase, sulfatase, and 11β-hydroxysteroid dehydrogenase type 2 activities juxtaposed with a lack of P450C17 (17α-hydroxylase and 17/20 lyase) activity.

| Table 1. Enzymatic Limitations by Compartment	
Fetal	**Placental**
3β-hydroxysteroid dehydrogenase 17α-hydroxylase	StAR protein 17/20 lyase 16α-hydroxylase

PLACENTAL PROGESTERONE

The placenta is the main source of progesterone during pregnancy. From the luteal phase to term, maternal progesterone levels rise six- to eight-fold. (Figures 5 and 8) Although, progesterone originates almost entirely from the corpus luteum before 6 weeks' gestational age, its production shifts more to

the placenta after the 7th week. Beyond 10 weeks, the placenta is the major definitive source of progesterone (51, 98).

While the placenta produces large amounts of progesterone, it has a limited capacity to synthesize cholesterol de novo (Figure 7). Maternal cholesterol enters the trophoblasts in the form of low-density

lipoprotein (LDL) cholesterol which serves as the principal precursor for the biosynthesis of progesterone by the placenta (51, 83, 99). The fetal contribution of progesterone is negligible. This is evident as progesterone levels remain high even after fetal demise. In the non-human primate estrogen regulates placental progesterone production (100). Progesterone concentrations are less than 1 ng/mL during the follicular phase of the normal menstrual cycle (101, 102). However, in the luteal phase of cycles in which fertilization occurs, progesterone concentrations rise from about 1-2 ng/mL on the day of the LH surge to a plateau of approximately 10-35 ng/mL over the subsequent 7 days. Concentrations remain within this luteal-phase range from the 10th week from the last menstrual flow, and then show a sustained rise that continues until term (Figure 5). At term, progesterone concentrations can range from 100-300 ng/mL (51). Most of the progesterone produced in the placenta enters the maternal circulation.
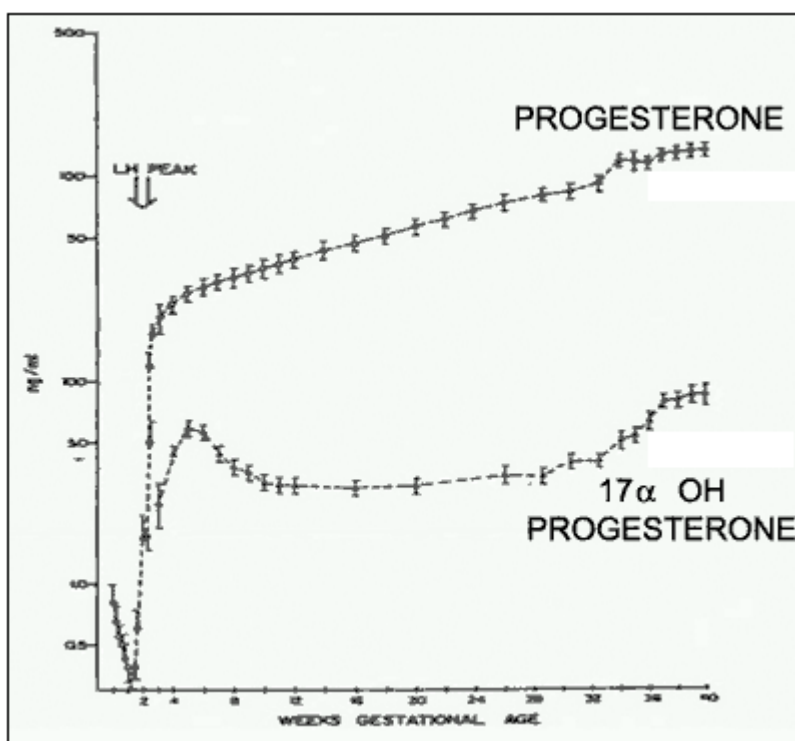
Figure 5. Relative values of circulating concentrations (mean ±SEM) of progesterone and 17α-progesterone during the course of human pregnancy from fertilization to term. The data displayed demonstrates values before and after the luteinizing hormone (LH) surge. Gestational ages are calculated from last menstrual flow. (Adapted from (103), with permission)

The human deciduas and fetal membranes also synthesize and metabolize progesterone (104). In this case, neither cholesterol nor LDL-cholesterol are significant substrates; pregnenolone sulfate may be the most important precursor. Progesterone has been shown to exert important functions in implantation and parturition to include promotion of endometrial decidualization; inhibition of smooth muscle contractility; decrease in prostaglandin (PG) formation, which helps maintain myometrial quiescence and prevent the onset of uterine contractions; and inhibition of immune responses like

those involved in graft rejection. It is believed to work in concert with hCG and decidual cortisol to inhibit T-lymphocyte-mediated tissue rejection and confer immunologic privilege to the implanted conceptus and developing placenta (105, 106). In animal models, progesterone extends the survival of transplanted human trophoblasts, and high intervillous concentrations of progesterone are of major importance in blocking the cellular immune rejection of the foreign antigens originating from the pregnancy (106).

In addition to its roles in endometrial and myometrial function, progesterone also serves as a substrate for fetal adrenal gland production of glucocorticoids (cortisol) and mineralocorticoids (aldosterone) (107). This important function is consequent to the deficiency of 3β-hydroxysteroid dehydrogenase (3β-HSD) activity in the active fetal zone of the fetal adrenal gland.

PLACENTAL 17α-HYDROXYPROGESTERONE

Like progesterone, during the first several weeks of gestation and through the time of the luteal-placental shift, 17α-hydroxyprogesterone concentrations primarily reflect the steroidogenic status of the corpus luteum (108). However, by the tenth week of gestation, 17 α-hydroxyprogesterone has returned to baseline levels, indicating that the placenta has little 17 α-hydroxylase activity. During the third trimester the placenta uses fetal D5-sulfoconjugated precursors to secrete increasing amounts of 17α-hydroxyprogesterone, and at this point the placenta becomes the major source of this hormone at term (108).

Concentrations of 17α-hydroxyprogesterone are less than 0.5 ng/mL during the follicular phase of normal menstrual cycles. In cycles leading to pregnancy, 17α-hydroxyprogesterone concentrations rise to about 1 ng/ml on the day of the LH surge, decline slightly for about 1 day, and rise again over the subsequent 4-5 days reaching a level of 1-2 ng/ml. Concentrations then increase slightly to a mean of approximately 2 ng/ml (luteal phase levels) by the end of the 12th week. This level remains stable until a gestational age of about 32 weeks at which time it begins an abrupt, sustained rise at about 37 weeks to approximately 7 ng/ml, a level that persists until term (108) (Figures 5 and 8). The rise in 17α-hydroxyprogesterone that begins at 32 weeks strongly correlates with the fetal maturational processes known to begin at this time. Hence, 17α-hydroxyprogesterone concentration exhibits a bimodal pattern in normal pregnancy.

PLACENTAL 17β-ESTRADIOL

The corpus luteum is the exclusive source of 17β-estradiol during the first 5-6 weeks of gestation. After the first trimester, the placenta is the major source of circulating 17β-estradiol (51). The rate of estrogen production and the level of circulating estrogens increase markedly during pregnancy. Concentrations of 17β-estradiol are less than 0.1 ng/mL during the follicular phase of the cycle and reach about 0.4 ng/mL during the luteal phase of normal menstrual cycles (101). Following fertilization, 17β-estradiol increases gradually to a range of 6-30 ng/mL at term (102) (Figures 6 and 8). Because it is deficient in 17-hydroxylase enzyme activity and 17-20 desmolase (lyase) activity, the placenta is unable to convert progestogens to estrogens. Thus, the placenta relies on 19-carbon androgen precursors produced by the fetal and maternal adrenal glands. Sources of estrogen biosynthesis by the maternal-fetal-placental unit are depicted in Figure 8. The major source of fetal adrenal dihydroepiandrostenediene sulfate (DHEAS) is LDL-cholesterol circulating in the fetal blood. A minor source of fetal adrenal DHEAS is derived from pregnenolone secreted by the placenta. Twenty percent of fetal cholesterol is derived from the maternal compartment. Since amniotic fluid

cholesterol levels are negligible, the main source of cholesterol is the fetal liver. As gestation advances, increasing quantities of 17β-estradiol are synthesized from the conversion of circulating maternal and fetal DHEAS by the placenta. At term, approximately equal amounts of estrogens are produced from circulating maternal DHEAS and fetal DHEAS (51, 109). The fetal endocrine system is notable for extensive conjugation of steroids with sulfate. Consequently, the placenta relies on sulfatase activity to cleave sulfate conjugates in the fetal compartment. Naturally occurring placental sulfatase deficiency results in a low estrogen state in pregnancy (110).

The cytochrome P450 aromatase enzyme is responsible for converting 19-carbon precursors to estrogen (111). The efficiency of this enzyme affords the fetus protection from virilization even in the presence of large amounts of aromatizable androgens.
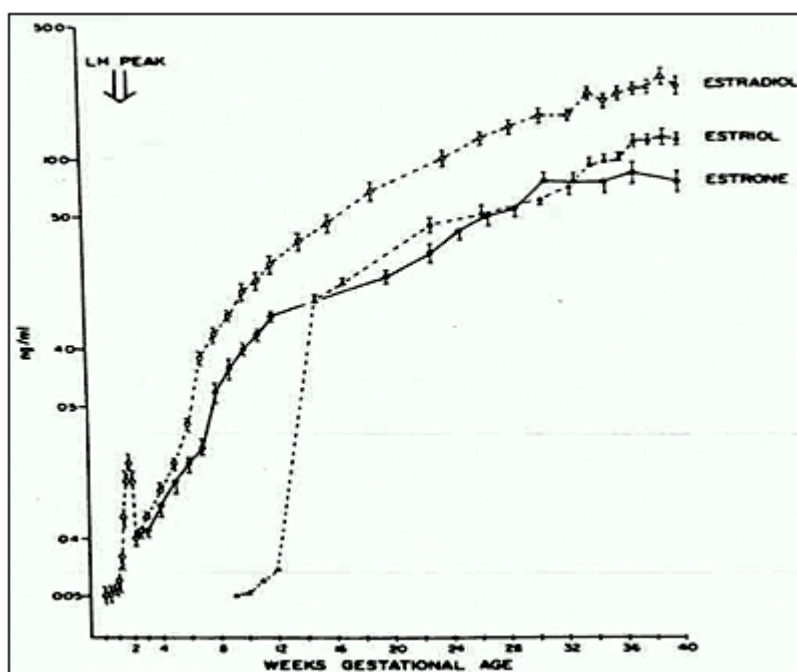
Figure 6. Relative values of circulating concentrations (mean ±SEM) of 17β-estradiol, estriol and estrone during the course of human pregnancy from fertilization to term. Data displayed demonstrate values before and after the luteinizing hormone (LH) surge. Gestational ages are calculated from last menstrual flow. (Adapted from (112), with permission)

The vasodilatory function of estrogens in pregnancy are well described. In animal models, direct estrogen injection into the uterine arteries produces striking increases in blood flow. Without question, 17β-estradiol is the most potent estrogen in this role. Estriol and estrone, though less active, also produce this effect (113). Because the exposure of the utero-placental bed to direct estriol secretion is enormous, estriol may be the principal up-regulator of uterine blood flow. This may be the dominant role of estriol in human pregnancy (113). Estrogen regulated mechanisms may also allow the fetus to govern production and secretion of progesterone during the third trimester. In primates, estrogen regulates the biosynthesis of placental progesterone by regulating the availability of LDL-cholesterol for conversion to

pregnenolone and its downstream steroid products (114). Estrogens are also thought to contribute to mammary gland development and fetal adrenal gland function.

PLACENTAL ESTRADIOL

Estriol is first detectable in maternal serum at 9 weeks of gestation (51, 109, 115, 116). This temporal relationship closely corresponds to the early stages of steroidogenic maturation in the fetal adrenal cortex

(51). Hence, the continued production of estriol is dependent upon the presence of a living fetus. Concentrations of estriol are less than 0.01 ng/ml in non-pregnant women. First detectable at approximately 0.05 ng/ml by 9 weeks, estriol increases gradually to a range of approximately 10-30 ng/ml at term (51, 98, 115, 117). Between 35- and 40-weeks gestational age, estriol concentrations increase sharply in a pattern that reflects a final surge of intrauterine steroidogenesis just prior to term (Figures 6 and 8).

Figure 7. Synthesis of estrogen and progesterone within and between the maternal, placental and fetal compartments. (Adapted from (118), with permission)

The placenta lacks 16α-hydroxylase activity and consequently, estriol with its 16α-hydroxyl group, must be synthesized from an immediate fetal precursor. The fetal liver provides 16α-hydroxylation

of DHEAS for placental estriol synthesis. Interestingly, hepatic 16α-hydroxylation activity disappears postnatally.
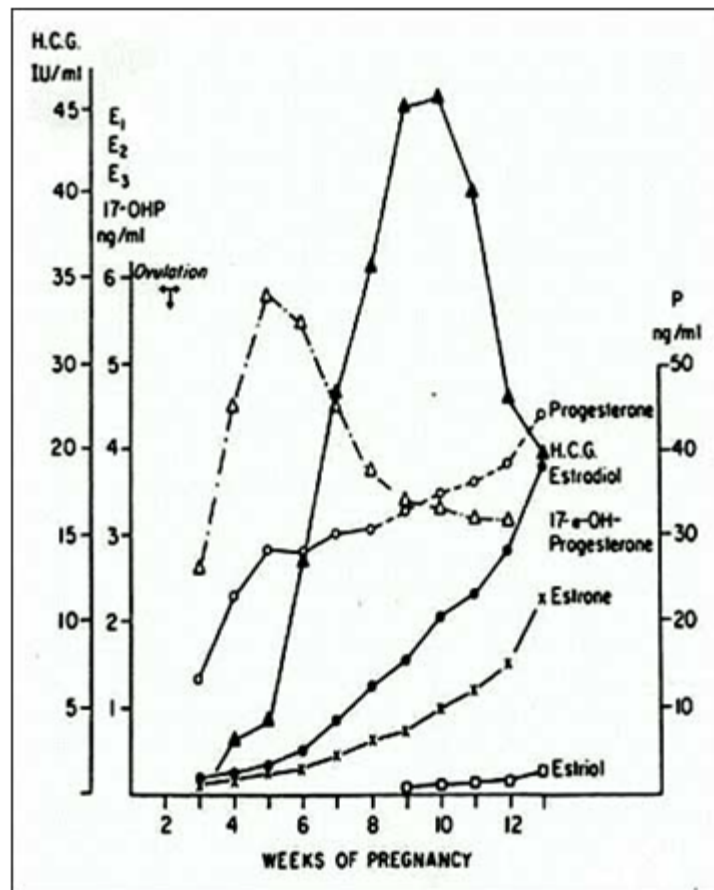
Figure 8. Circulating maternal steroid hormone levels throughout early pregnancy. The first-trimester relationship of these steroid hormones to human chorionic gonadotropin (hCG) is shown.
Progestogens
Progesterone o--o--o-
17-a-hydroxyprogesterone -Δ-Δ-Δ-
Estrogens
17-β-estradiol - - -
Estriol -o-o-o-
Estrone -x-x-x-
Human chorionic gonadotropin (hCG)
-Δ-Δ-Δ-
(From ref. 89, with permission)

PLACENTAL ESTRONE

For the first 4-6 weeks of pregnancy, estrone originates primarily from maternal sources such as the ovaries, adrenals, or peripheral conversion (102).

Later, the placenta secretes increasing quantities of estrone from the conversion of circulating maternal and fetal DHEAS. The placenta continues to be the major source of circulating estrone for the remainder of the pregnancy (51). Estrone concentrations are less than 0.1 ng/mL during the follicular phase and may reach a maximum of 0.3 ng/mL during the luteal phase of a normal menstrual cycle. Following fertilization, estrone concentrations remain within the luteal phase range through weeks 6-10 of gestation (98). Subsequently there is a gradual increase to a wide range of 2-30 ng/ml at term (51, 98, 102) (Figures 6 and 8). In the absence of fetal adrenal gland function, as in the case of anencephaly, maternal estrogen levels are extremely low, suggesting that the maternal contribution of DHEAS to total estrogen synthesis is negligible.

Placental Protein Hormones

As detailed previously, the placental cytotrophoblast-syncytiotrophoblast relationship mirrors the hypothalamic-pituitary system. The surface of the syncytiotrophoblast is in direct contact with maternal blood within the intervillous space, and consequently, placental proteins are preferentially secreted into the maternal compartment. Table 2 outlines the various peptides associated with the endocrinology of human pregnancy.

Table 2. Pregnancy Specific Protein Hormones by Compartment		
Fetal	**Placental**	**Maternal**
Alpha-fetoprotein	**Hypothalamic-like (cytotrophoblast)**	**Decidual derived**
	- GnRH	-Prolactin
	- CRH	-IGFBP-1
	- TRH	-PP14
	- GHRH	**Corpus luteum derived**
	- Somatostatin	-Relaxin
	Pituitary-like (syncytiotrophoblast)	
	- hCG	
	- hGH	
	- ACTH	
	- hPL	
	- hCT	
	- Oxytocin	
	Growth factors	
	- Inhibin	
	- Activin	
	- IGF-I/IGF-II	
	Other proteins	
	- Pregnancy specific β1-glycoprotein	
	- PAPP-A	

PLACENTAL PROTEINS: HYPOTHALAMIC-LIKE PROTEINS

Placental Gonadotropin Releasing Hormone (GnRH)

Gonadotropin releasing hormone derived from the placenta is biologically and immunologically similar to the hypothalamic decapeptide GnRH (54). Gonadotropin releasing hormone activity has been localized to the cytotrophoblast cells along the outer surface of the syncytiocytotrophoblast layer. Human chorionic gonadotropin (hCG) has been localized to the adjacent syncytiocytotrophoblast layer. GnRH production peaks at about 8 weeks' gestation and then decreases as the pregnancy advances in gestational age (54-57). Furthermore, GnRH levels parallel those of hCG in both the placenta and maternal circulation (57).

Placental GnRH stimulates hCG release through a dose-dependent, paracrine mechanism (119). There is little augmentation of hCG secretion by GnRH in first trimester placental culture, because hCG production is already close to maximum (57). In contrast, at mid-trimester there is a marked dose-dependent GnRH augmentation of hCG release in vitro, with this effect diminishing in the term placenta. Likely due to the low affinity of placental GnRH receptors and dilution effect of the maternal circulation, intravenous administration of GnRH during pregnancy does not increase serum hCG. Thus, it seems most likely that locally produced placental GnRH is responsible for stimulation of placental hCG production via paracrine mechanisms (119). GnRH release is increased by estrogen, activin-A, insulin and prostaglandins, and inhibited by progesterone, inhibin, follistatin and endogenous opiates (120).

Placental Corticotrophin Releasing Hormone (CRH)

Placental CRH is structurally similar to the hypothalamic peptide, CRH (121, 122). Due to this similarity, it is easily measured in amniotic fluid as well as fetal and maternal plasma. Pro-CRH mRNA is present in cytotrophoblasts (123). CRH is also intensely immunoreactive in the decidua (53). CRH is

found in maternal serum at low levels during the first and second trimesters of uncomplicated pregnancies, but rises dramatically in the third trimester of normal gestations or earlier if there are pregnancy complications resulting from such factors as prematurity, diabetes, or hypertension.(124). The highest levels of CRH are found at labor and delivery. Although concentrations of CRH in fetal plasma are lower than those found in maternal plasma, there exists a significant correlation between maternal and fetal plasma CRH (124). There is a 3-fold rise, in amniotic fluid CRH between the second and third trimester (124, 125). Placenta-derived CRH stimulates placental ACTH release in a dose-dependent manner in vitro (126, 127). Corticotrophin releasing hormone and ACTH are both released into fetal and maternal circulation; their activity is moderated by maternal CRH binding proteins (124). Placental CRH participates in the surge of fetal glucocorticoids associated with late third trimester fetal maturation (124, 126, 128). When uterine blood flow is restricted, secretion of both CRH and ACTH is increased. Corticotrophin releasing hormone is a potent utero-placental vasodilator (129, 130). Corticotrophin releasing hormone is released into the fetal circulation in response to fetal stress and in conditions leading to fetal growth restriction (131-133). High circulating maternal CRH is believed to be responsible for the elevated plasma ACTH and cortisol found in pregnancy, which renders them unresponsive to feedback suppression of plasma cortisol (124-126, 128, 134). Corticotrophin releasing hormone stimulates prostaglandin synthesis in fetal membranes and placenta. In pre-eclampsia, fetal asphyxia, premature labor, and other conditions leading to fetal growth restriction CRH is frequently elevated (131-133).

Placental Thyrotropin Releasing Hormone

Thyrotropin releasing hormone is found in the cytotrophoblast layer; however, this molecule is

different from the tripeptide produced by the hypothalamus (135). It is localized primarily in the syncytiotrophoblast but also in the fetal and maternal blood vessels as well as in the extravillous trophoblast. The concentration of TRH is higher in the fetal circulation, which is likely due rapid protease degradation on the maternal side (136). Since hCG is regarded as the principal placenta-derived thyroid stimulator, a significant role for TRH is uncertain, although it may be involved in thyroid function regulation during fetal life (137).

Placental Growth Hormone Releasing Hormone (GHRH)

GHRH has also been identified in the human placenta, but its cellular localization and function are unknown (126). Its structure is identical to that of the hypothalamic GHRH peptide. The levels of placental GHRH do not contribute to maternal circulating levels of the extra villous the presence of GHRH receptor in the placenta GHRH does not regulate placental growth hormone production.

Somatostatin (SRIF)

Somatostatin (SRIF) is a peptide that exerts a variety of regulatory actions interacting with G protein-coupled receptors. Placental somatostatin has been found in early pregnancy villi, cytotrophoblast and in the decidua; while its binding sites have been identified in term placental membranes and cytotrophoblast (64, 138, 139). The amount of placental somatostatin decreases with increasing gestation and it does not contribute to maternal circulating levels of the peptide. The role of placental somatostatin remains unclear.

PLACENTAL PROTEINS: PITUITARY-LIKE HORMONES

Placental Human Chrorionic Gonadotropin (hCG)

Human chorionic gonadotropin is a glycoprotein structurally similar to follicle stimulating hormone (FSH), luteinizing hormone (LH), and thyroid stimulating hormone (TSH). It is similar to luteinizing hormone (LH) in action. As is true of the other glycoprotein hormones, hCG is composed of 2 non-identical subunits that associate non-covalently (52, 140). The α subunit consists of an amino acid sequence essentially identical to and shared with the other pituitary glycoprotein hormones. On the other hand, the β subunit is structurally similar to the α subunit yet it differs enough to confer specific biologic activity on the intact dimeric hormone. The subunits differ primarily at the carboxyl terminus where the β subunit of hCG has a 30-amino-acid tailpiece that is not present in the human LH β subunit. Glycosylation in this region of HCG accounts for the longer half-life (32-37 hours) of hCG relative to LH (24h vs. 2h, respectively). The molecular weight of the hCG dimer is estimated at 36.7 kDa with the α subunit contributing 14.5 kDa and the β subunit 22.2 kDa (140). The hCG α subunit is found in the cytotrophoblast layer only (57, 60).

As mentioned previously, hCG mRNA is detectable in embryos as early as the 6- to 8-cell stage (47). After implantation of the conceptus, hCG is detectable in the syncytiotrophoblast layer (outer trophectoderm layer) (57, 60-62). Human chorionic gonadotropin is secreted by the syncytiotrophoblasts of the placenta into both the fetal and maternal circulation. Plasma levels increase, doubling in concentration every 2-3 days between 60 and 90 days of gestation. At 3-4 weeks' gestation, the mean doubling time of dimeric hCG is 2.0 ±1.0 days and increases to about 3.5 ±1.5 days at 9-10 weeks (57). The average peak hCG level is approximately 110,000 mIU/mL and occurs at 10 weeks' gestation (57). Between 12 and 16 weeks, average hCG decreases rapidly with the concentration halving every 2.5 ±1.0 days before

reaching 25% of first trimester peak values. Levels continue to fall from 16 to 22 weeks at a slower rate (mean halving rate of 4.0 ±2.0 days) to become approximately 10% of peak first trimester values (57). During the third trimester mean hCG levels rise in gradual, yet significant, manner from 22 weeks until term (57). Interestingly, hCG levels are comparatively higher in women bearing female fetuses.

Human chorionic gonadotropin secretion is related directly to the mass of hCG-secreting trophoblastic tissues. In vivo, the release of hCG has been correlated with the widths of trophoblast tissue from 4 to 20 weeks and with placental weight from 20 to 38 weeks, respectively (57). The rapidly rising hCG seen between 3-4 and 9-10 weeks' gestation coincides with the proliferation of immature trophoblastic villi and the extent of the syncytial layer (57). As expected, declining hCG levels are associated with a relative reduction in the mass of the syncytiotrophoblast and cytotrophoblast tissue. From 20-22 weeks until term a gradual increase in dimeric hCG corresponds with a similar increase in placental weight and villus volume (57).

Thus, in early gestation rising hCG levels reflect the histological finding of a rapidly proliferating and increasingly invasive placenta. Later in pregnancy, declining hCG levels are associated with a relative reduction in the number and mass of trophoblasts; therefore, hCG levels mirror the placenta's morphologic transformation from an organ of invasion to an organ of transfer (57).

Levels of the β subunit of hCG mirror those of dimeric hCG. The α subunit, undetectable until around 6 weeks' gestation, rises in a sigmoid fashion to reach peak levels at 36 weeks. Levels of the individual subunits are very low relative to dimeric hCG; they are approximately 2,000-fold to 150-fold less than dimeric forms at 6 and 35 weeks, respectively) (57).

With respect to the regulation of hCG production and secretion, hCG secretion appears to be related to placental GnRH release (119). In vitro, hCG is released in pulses at a frequency and amplitude that correlate with the release of placental GnRH (119). In addition, hCG production is stimulated by glucocorticoids and suppressed by DHEAS (126). In vitro, cyclic AMP (cAMP) analogues augment hCG secretion. In humans, similar to pituitary secretion of gonadotropins, decidual inhibin and prolactin inhibit hCG production by term trophoblasts whereas decidua-derived activin augments it (140, 141), with stimulation by estrogen and a negative feedback by progesterone.

Human chorionic gonadotropin, the primary luteotropic factor involved in supporting and maintaining the corpus luteum, ensures the continuous secretion of progesterone until the placenta can perform this function (142). It has immunosuppressive properties, likely involving maternal T-lymphocyte function and it possesses thyrotropic activity (143). Human chorionic gonadotropin may stimulate steroidogenesis in the early fetal testes resulting in virilization and sexual differentiation in males (144, 145). The functions of hCG are summarized in Figure 9.
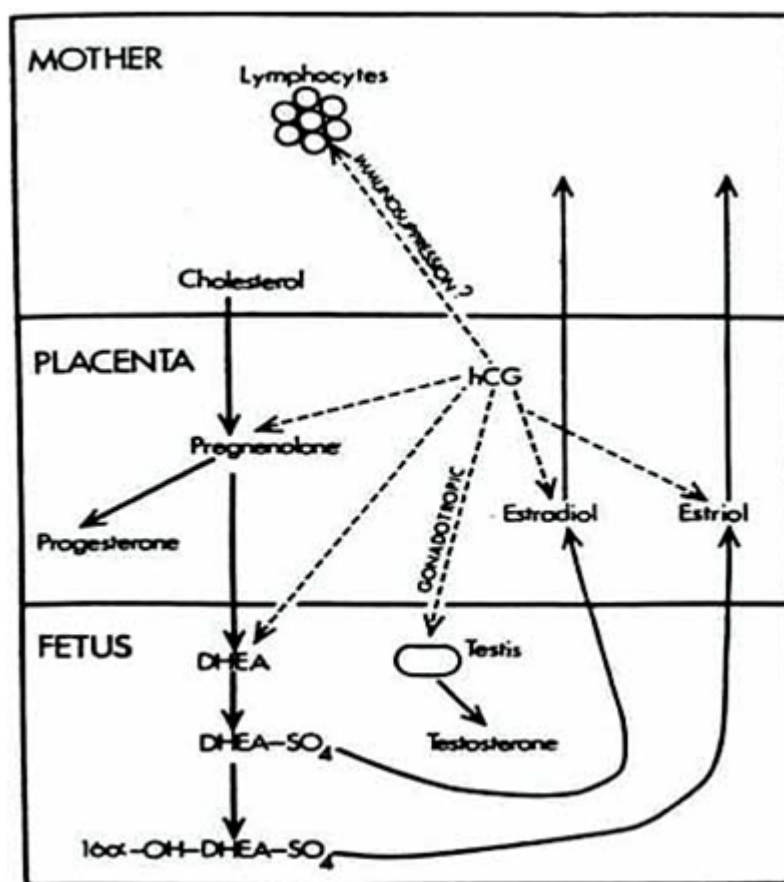
Figure 9. The physiological roles of human chorionic gonadotropin (hCG) during the course of human pregnancy from fertilization to term. (Adapted from (146), with permission)

Placental Growth Hormone (GH)

Growth hormone is a single-chain peptide hormone structurally related to prolactin and human chorionic somatomammotropin (hCS). Up to the first 15-20 weeks of pregnancy, pituitary growth hormone (GH) is the main form present in the maternal circulation. From 15-20 weeks to term, placental GH gradually replaces pituitary GH, which eventually becomes undetectable (147-151). In contrast to the pulsatile output of pituitary GH, the daily profile of placental GH release is non-pulsatile (150). Syncytiotrophoblasts directly bathing in maternal blood are the site of placental GH synthesis. This cell layer is the placental site of the major glucose transporter, Glut1, and responds to rapid variations in maternal blood glucose levels by modifying placental GH secretion (152, 153).

The rate of secretion of pituitary GH is known to change rapidly, depending on the net result of multiple stimulatory and inhibitory input. The regulation of placental GH is quite different. The rate of synthesis of placental GH, and thus the maternal circulating levels, increases with the growth of the placenta (154). Growth hormone releasing hormone (GHRH) does not modulate placental GH expression in vitro, in vivo, or in the presence of glucose (155, 156). Figure 10 shows both the stimulatory and inhibitory mediators of maternal pituitary GH output, including the influence of placental growth hormone.

Production of maternal insulin-like growth factor-1 (IGF-I) is regulated by placental growth hormone. IGF-1 concentrations in the maternal plasma, studied in a large number of pregnancies, correlate with the corresponding placental GH. The IGF-1 levels do not vary significantly during the first weeks of gestation, but then increase gradually from 165 ±44.5 mg/L at about 24-25 weeks' gestation, and reach levels of 330.5 ±63.5 mg/L in a manner similar to the increases seen in placental GH. It should be noted that circulating maternal IGF-I levels also reflect placental IGF-I secretion. This growth factor, however, does not appear to be strongly expressed in human placenta; in particular; it is not expressed in the syncytiotrophoblast cell layer (157).

The biologic activities of GH and related peptide hormones can be classified into two general categories: somatogenic and lactogenic. Somatogenic activities are related to linear bone growth and alterations in carbohydrate metabolism (158, 159). The primary function of GH is to protect nutrient availability for the fetus. Via local and hepatic IGF-1, placental GH stimulates gluconeogenesis and lipolysis in the maternal compartment.
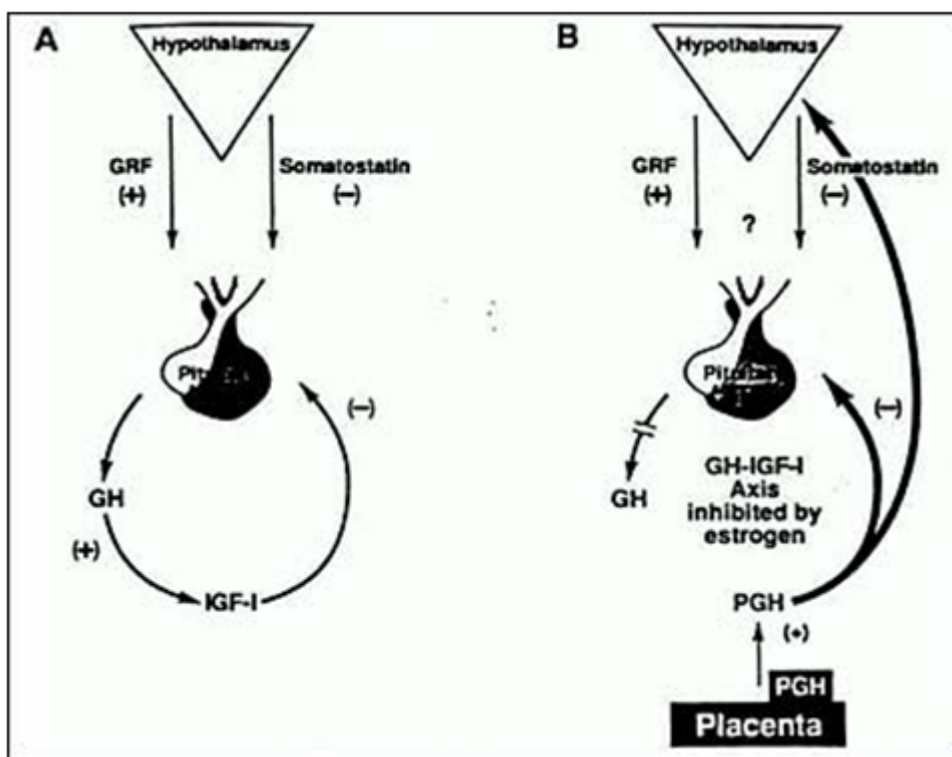
Figure 10. Shown is a representation of the hypothalamic-growth hormone-IGF-I axis, with details of its modification during pregnancy. A. In the non-pregnant state, pituitary GH secretion is regulated through hypothalamic control. Pituitary GH regulates the secretion of IGF-I, which, in turn, exerts negative feedback action on GH at the hypothalamic-pituitary level. B. During the latter half of pregnancy, the GH-IGF axis is inhibited by large amounts of estrogen. The large increase in placental GH exerts an inhibitory effect on GH secretion mediated by placental GH on the hypothalamus and pituitary. (From (160), with permission)

Placental Human Placental Lactogen (hPL), [Human Chorionic Somatomammotropin (hCS)]

Human placental lactogen is a single-chain polypeptide with two intramolecular disulfide bridges. The structures of hPL, prolactin, and growth hormone are very similar. Eighty-five percent of its amino acids are identical to human pituitary growth hormone and human pituitary prolactin (69, 161). Furthermore, hPL shares biologic properties with both growth hormone and prolactin (69, 161). Thus, it has primarily lactogenic activity but also exhibits some growth hormone-like activity; therefore, it is also referred to as chorionic growth hormone (hCGH) or human chorionic somatomammotropin (hCS). Human placental lactogen is secreted from the syncytiotrophoblast cell layer. Unlike hCG concentrations, levels of hPL rise with advancing gestational age and plateau at term. Human placental lactogen is first detectable during the fifth week of gestation, and rises throughout pregnancy maintaining a constant hormone weight to placenta weight relationship (162). Concentrations reach their highest levels during the third trimester, rising from approximately 3.5 µg/mL to 25 µg/mL at term (162). Although the level of hPL in serum at term is the highest of all placenta-derived protein hormones, its clearance from the circulation is so rapid that it cannot be detected after the first post-partum day.

Since hPL is secreted primarily into the maternal circulation, most of its functions occur at sites of action in maternal tissues. Human placental lactogen is thought to be responsible for the marked rise in maternal plasma IGF-1 concentrations as the pregnancy approaches term (162-164). Human placental lactogen exerts metabolic effects during pregnancy via IGF-I. It is associated with insulin resistance, enhances insulin secretion which stimulates lipolysis, increases circulating free fatty acids, and inhibits gluconeogenesis; in effect, it antagonizes insulin action, induces glucose intolerance, as well as lipolysis and proteolysis in the maternal system (69). In response to fasting and glucose loading, hPL levels rise and fall (162). These metabolic effects favor the transport of ketones and glucose to the fetus in the fasting and fed states, respectively.

Circulating levels of glucose and amino acids are reduced, while levels of free fatty acids, ketones, and triglycerides are increased. The secretion of insulin is augmented in response to a glucose load. The fuel requirements of the developing fetus are met primarily by glucose. It provides the energy needed for protein synthesis and serves as a precursor for the fat synthesis and glycogen formation. Fetal blood glucose levels are generally 10-20 mg/100 ml below those of the maternal circulation; thus, diffusion and facilitated transport favor the net movement of glucose from mother to fetus.

Pregnancy is associated with profound alterations in maternal metabolism. The fetal-maternal relationship favors glucose use by the fetus and forces the maternal tissues to increase their use of alternative energy sources. The endocrine hallmark of this hormonal environment is insulin resistance. Several hormones prevalent during pregnancy are believed to responsible for this altered milieu: estrogens, progesterone, glucocorticoids, human placental lactogen (hPL) and placental GH. Additionally, placental cytokines such as tumor necrosis factor-alpha (TNF-α) contribute to this metabolic state (165).

Placental Adrenocorticotropic Hormone (ACTH)

Placental ACTH is structurally similar to pituitary ACTH (166-178). Under the paracrine influence of

placental CRH released from proximal cytotrophoblasts, placental ACTH is secreted by syncytiotrophoblasts into the maternal circulation (179-181). Circulating maternal ACTH is increased above non-pregnancy levels, but still remains within the normal range (182, 183).

Placental ACTH stimulates an increase in circulating maternal free cortisol that is resistant to dexamethasone suppression (179, 182). Thus, relative hypercortisolism in pregnancy occurs despite high-normal ACTH concentrations. This situation is possible due to two main differences in endocrine relationships during pregnancy. First, the maternal response to exogenous CRH is blunted (182). Second, a paradoxical relationship exists between placental CRH, ACTH, and their end-organ product, cortisol; glucocorticoids augment placental CRH and ACTH secretion, not suppress it (127, 180). This positive feedback mechanism allows an increase in glucocorticoid secretion in times of stress in excess of the amount necessary if the mother were not pregnant (127).

Placental Human Chorionic Thyrotropin (hCT)

Human chorionic thyrotropin is structurally similar to pituitary TSH, but it does not possess the common α subunit (135). The placental content of hCT is very small (58). Human chorionic gonadotropin possesses $1/4000^{th}$ of the thyrotropic activity of TSH, and is thought to exert a more significant effect on the maternal thyroid than does hCT (137), particularly in conditions with high hCG levels such as trophoblastic disease.

PLACENTAL PROTEINS: GROWTH FACTORS

Placental Inhibin/Activin/Follistatin

Inhibin and activin are heterodimeric glycoproteins with the former comprised of an α and β subunit and the latter composed of two β subunits. Inhibin is secreted by the corpus luteum and is present in decidualized endometrium (184, 185). Inhibin and activin dimers have been localized to the syncytiotrophoblast layer, but their individual subunits have been localized to both cytotrophoblasts and syncytiotrophoblasts (186).

Inhibin begins to increase in the maternal circulation above non-pregnant levels by 12 days post-fertilization, dramatically increasing at about 5 weeks' gestation to peak at 8-10 weeks. Subsequently, levels decrease at 12-13 weeks and stabilize until around 30 weeks before they rise again as term approaches (185). The early fluctuations in inhibin levels reflect release from the corpus luteum, whereas the increase seen in the third trimester originates from the placenta and decidua. After delivery, inhibin is undetectable. The inhibin A dimer is the principal bioactive inhibin secreted during pregnancy. Quantification of inhibin A is part of the prenatal quad screen that can be administered during pregnancy at a gestational age of 16–18 weeks. An elevated inhibin A (along with an increased beta-hCG, decreased AFP, and a decreased estriol) is suggestive of the presence of a fetus with Down syndrome.

Activin-A is the major trophoblastic activin product, which similarly increases in maternal circulation throughout pregnancy and peaks at term (187). Interestingly, higher levels of activin-A are found in mid-gestation in women with preeclampsia (188, 189). Similar to their action in the ovarian follicle, inhibin and activin are regulators within the placenta for the production of GnRH, HCG, and steroids; as expected, activin is stimulatory and inhibin is inhibitory.

Follistatin is the activin-binding protein expressed in placenta, membranes, and decidua (190). Since follistatin binds activin, it antagonizes the stimulatory effects of activin on placental steroid and peptide production.

Placental Insulin-Like Growth Factors-I and II (IGF I and II)

Without question, the most important site of IGF-I and IGF-II production is the placenta (191). IGF-I and IGF-II are involved in prenatal growth and development. These growth factors do not cross the placenta into the fetal circulation; however, they may be involved in placental growth (192, 193). An increase in maternal IGF-I levels during pregnancy with a rapid decrease after delivery indicates a significant placental influence. There is however, no change in IGF-II levels throughout pregnancy. In animal studies, the IGF-I produced in the placenta regulates the transfer of nutrients across the placenta to the fetus and thus enhances growth. Interestingly, neonates with intrauterine growth restriction have reduced levels of IGF-I. IGF-II secreted by the placenta is also important in influencing β cell sensitivity to glucose and modulation of maternal insulin and glucose concentrations during pregnancy (194).

Placental Soluble FMS-Like Tyrosine Kinase (SFLT-1) and Souble Endoglin (sENG)

Soluble Flt-1 is a circulating splice variant of Flt-1, the receptor for VEGF and placental growth factor (PLGF), while sENG is the circulating receptor for transforming growth factor-β (TGF-β). VEGF, PLGF, TGF-β as well as other pro-angiogenic proteins are known to be essential for normal placental and fetal vascular development. Soluble Flt-1 and sENG are almost undetectable in the circulation of non-pregnant individuals, and are produced in large quantities by the placenta leading to marked elevation in their circulating levels during pregnancy which steadily rise until term (195, 196). These two soluble receptors are increased in serum and placentas of preeclamptic women compared to normal pregnancies and their abnormal elevation presages the development of preeclampsia. Experimental evidence indicates that sENG cooperates with sFlt-1 to induce endothelial dysfunction *in vitro* and preeclampsia *in vivo (197)*. It is thought that sFlt-1 and sENG neutralize their ligands, reducing the concentration of VEGF, PLGF, and TGF-b in maternal circulation, which results in a shift in the angiogenic balance towards anti-angiogenesis, which in turn leads to endothelial damage and the clinical onset of the syndrome. However, large prospective studies have failed to show sufficient accuracy of these biomarkers for clinical utility in preeclampsia prediction (198, 199).

PLACENTAL PEPTIDE HORMONES: OTHER PLACENTAL PEPTIDES

In addition to the pregnancy-related proteins produced analogous to hypothalamic and pituitary glycoproteins, the placenta also produces several other proteins that have no known analogues in the non-pregnant state. These proteins have been isolated and identified from serum drawn during pregnancy or purified from placental tissue. Figure 11 shows the changes in concentration of each of these pregnancy-related proteins throughout gestation.

Placental Pregnancy-Specific b1-Glycoprotein (SP1)

Pregnancy-specific b1-glycoprotein is a glycoprotein hormone that can be detected about 18-23 days after ovulation. It is secreted from trophoblast cells (200, 201). Initially, it exhibits a 2- to 3-day doubling time, reaching peak concentrations between 100-200 ng/mL at term. Pregnancy-specific b1-glycoprotein has immunosuppressive effects on T-lymphocyte proliferation, and is thought to be involved in preventing rejection of the implanting conceptus (202).

Placental Pregnancy-Associated Plasma Protein-A (PAPP-A)

Pregnancy-associated plasma protein-A is the largest of the pregnancy-related glycoproteins. It originates, mainly, from placental syncytiotrophoblasts (203, 204). Pregnancy-associated plasma protein-A can first be detected at approximately 32-33 days after ovulation. With a 3-day doubling time, its levels initially rise rapidly, and then continue to rise more slowly until term (203). Like SP-1 and hCG, PAPP-A is believed to play an immunosuppressive role in pregnancy (204). It has recently gained favor as a clinically useful, first-trimester screening marker for Down syndrome (trisomy 21). Authors have confirmed decreased PAPP-A levels in association with early pregnancy failure (205). However, when compared with serum hCG and progesterone measurements to evaluate the clinical usefulness of PAPP-A values in predicting the outcome of early pregnancy, hCG and progesterone remained the best clinical tools (206).

Placental Protein-5 (PP5)

This glycoprotein is produced by the syncytiotrophoblasts. It is detected beginning at 42 days after ovulation, and steadily rises until term (207). Placental protein-5 has anti-thrombin and anti-plasmin activities, and is believed to be a naturally occurring blood coagulation inhibitor active at the implantation site (208).
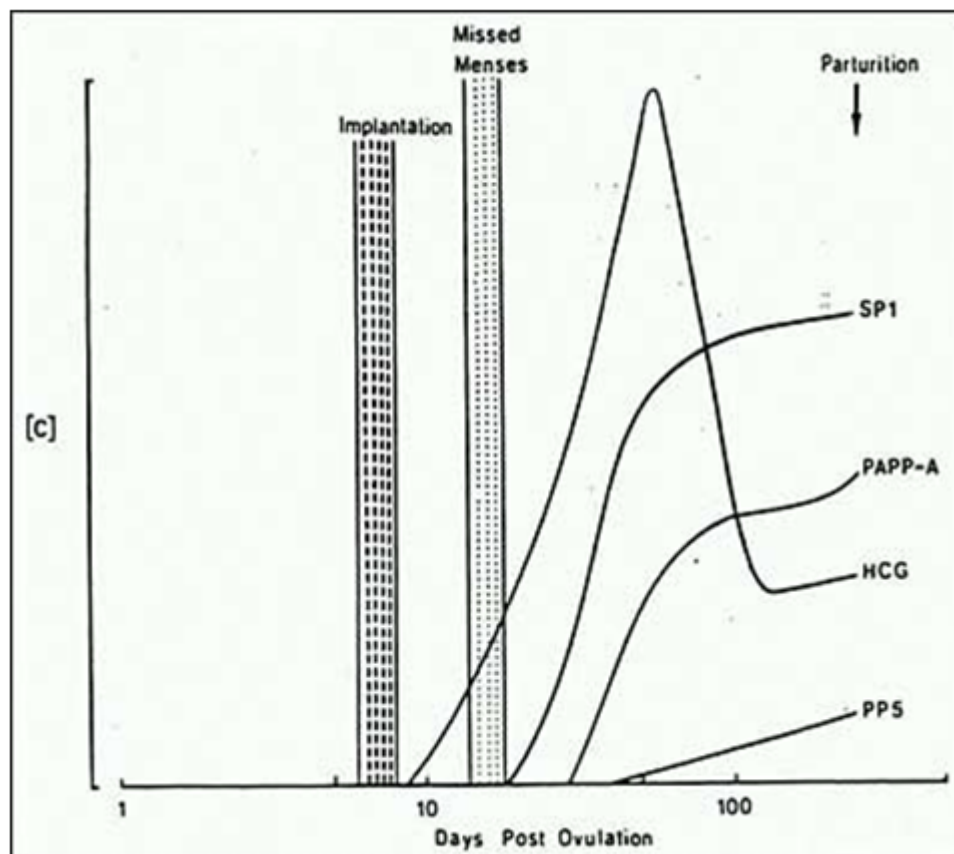
Figure 11. Maternal serum concentrations of human chorionic gonadotropin (hCG) and some other pregnancy-associated protein hormones (SP-1, PAPP-A, PP-5) throughout pregnancy. The timing of

implantation, missed menses and parturition is shown to demonstrate the temporal relationships. (Modified from (209), with permission)

PLACENTAL METABOLIC PROTEINS

Placental Leptin

Leptin is a key regulator of satiety and body mass index (BMI), and its levels are thought to reflect the amount of energy stores and nutritional state (210). The placenta is the principal source of leptin during pregnancy (211). Most of the leptin produced by the placenta is secreted into the maternal circulation, and as a consequence leptin levels are elevated during pregnancy. In the first trimester, maternal plasma leptin levels are double nonpregnant values and continue to increase during the second and third trimesters (212-214). In the second and third trimesters leptin is also expressed in the chorion and amnion (215). The amount of leptin directed to the fetus is uncertain, and its role in fetal development is also unclear. Leptin levels decline to normal nonpregnant levels within 24 hours after delivery (216). Interestingly, leptin levels during pregnancy do not correlate with BMI as they do in the nonpregnant state (217). Although not clear, it is thought that leptin may be utilized by the placenta to modulate maternal metabolism and partition energy supplies to the fetus (218). There is evidence that placental leptin is anti-apoptotic and promotes proliferation, protein synthesis and the expression of tolerogenic maternal response molecules such as HLA-G (219). Placental leptin expression is regulated by hCG, insulin, steroids, hypoxia and many other growth hormones, suggesting that it may have an important endocrine function in trophoblast cells (219). Additionally, the human placenta also expresses leptin receptors, and therefore can act in a paracrine manner to modulate placental function (220, 221).

Placental Ghrelin

Ghrelin, is a gastric peptide isolated primarily from the stomach which is thought to stimulate GH release and participates in the regulation of energy homeostasis, increasing food intake, decreasing energy output, as well as exert a lipogenetic effect (222). Ghrelin and its receptors have been isolated in the placenta, clearly indicating a role for ghrelin in reproduction. Circulating ghrelin levels peak at mid-gestation, then with advancing gestational age declining ghrelin levels are observed. After delivery, near prepregnancy levels of ghrelin are seen (223). It is thought that ghrelin may well be involved in regulation of energy intake during pregnancy (224), however its exact role is still unknown.

PLACENTAL MATURATION

As pregnancy advances, the relative numbers of trophoblasts increase as feto-maternal exchange begins to dominate the placenta's secretory functions. Later, throughout the second and third trimester, the placenta adapts its structure to reflect its function such that near term, the villi consist mainly of fetal capillaries with sparse supporting stroma beyond that which is required to maintain its anatomic integrity. In contrast to the early placental villus where trophoblasts are abundant as part of a continuous layer of basal cytotrophoblasts, the term placenta's membranous interface between the fetal and maternal circulation is extremely thin (65). Thus, as the gestation progresses toward term, the number of cytotrophoblasts declines and the remaining syncytial layer becomes thin and barely visible. This structural arrangement facilitates transport of compounds across the feto-maternal interface. Consistent with the cytologic changes that occur in the maternal fetal interface from mid-gestation to term, striking changes in the global gene expression

profile of this tissue has been demonstrated over this interval (225).

FETAL COMPARTMENT

The endocrine system, a system that is functional from the time of intrauterine existence through old age, is one of the first systems to develop during fetal life. As in the placenta, the regulation of the fetal endocrine system relies, to some extent, on precursors secreted by the other compartments. As the fetus develops, its endocrine system matures and eventually becomes more independent, preparing the fetus for extrauterine life.

Fetal Hypothalamus and Pituitary

By the end of the fifth week of gestation, the primitive hypothalamus can be identified as a swelling on the inner surface of the diencephalic neural canal (226). By the 9th to 10th week, the median eminence of the hypothalamus is evident. By week 14 to 16 the hypophysiotropic hormones GnRH, TRH, CRH, GHRH and somatostatin appear in the fetal hypothalamus (227). The portal-vessel system that delivers the releasing hormones to the anterior pituitary is fully developed by 18 weeks of gestation (227).

The anterior pituitary cells that develop from those cells lining Rathke's pouch are capable of secreting growth hormone (GH), follicle-stimulating hormone (FSH), luteinizing hormone (LH) and adrenocorticotropic hormone (ACTH), in vitro, as early as 7 weeks of fetal life (Figure 12).
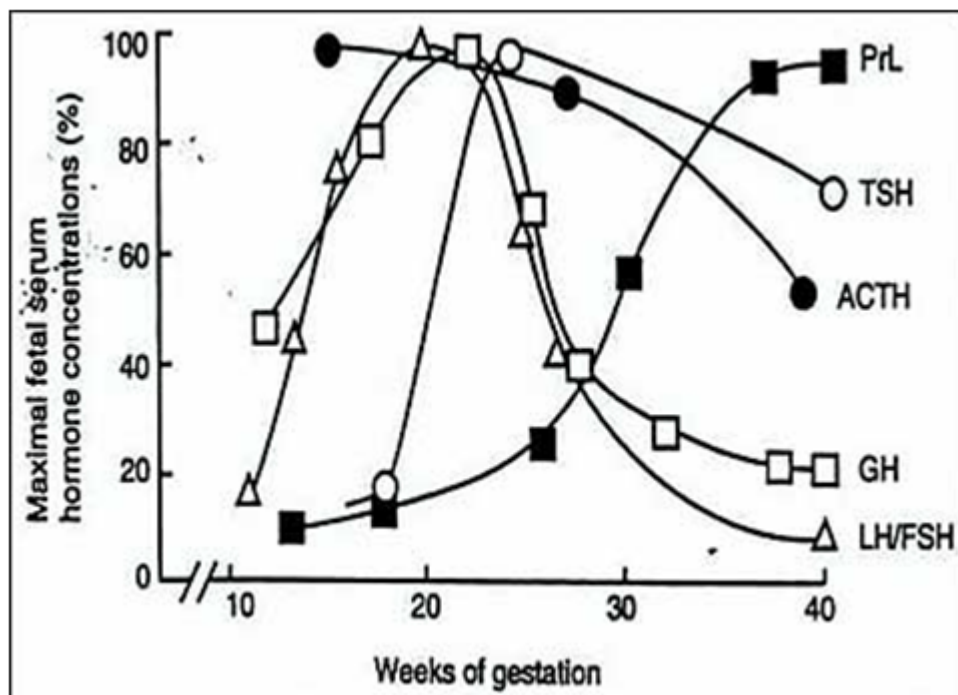
Figure 12. Fetal serum pituitary hormone levels. PrL indicates prolactin; TSH, thyroid-stimulating hormone; ACTH, corticotropin; GH, growth hormone; LH/FSH, luteinizing hormone/follicle stimulating hormone. (Modified from (228), with permission)

Fetal Thyroid Gland

The fetal thyroid gland develops initially in the absence of detectable TSH. By 12 weeks' gestation, the thyroid is capable of iodine-concentrating activity and thyroid hormone synthesis (226) . Prior to that time, the maternal thyroid appears to be the primary source for T_4. The levels of TSH and T_4 are relatively low in fetal blood until mid-gestation. At 24-28 weeks' gestation, serum T_4 and reverse tri-iodothyronine (rT_3) concentrations begin to rise progressively until term while the TSH concentration peaks. At birth, there is an abrupt release of TSH, T_4, and T_3. The relative hyperthyroid state of the newborn is believed to facilitate thermoregulatory adjustments for extrauterine life. The function of the fetal thyroid hormones is crucial for somatic growth and neonatal adaptation.

Fetal Gonads

The internal genitalia in the embryo have the inherent tendency to feminize. The Wolffian (mesonephric) and Mullerian (paramesonephric) ducts are discrete primordia that temporarily coexist in all embryos during the ambisexual undifferentiated development period (up to 8 weeks). The critical factors in determining which of the duct structures stabilize or regress are the hormones secreted by the testes: Anti-Mullerian hormone (AMH) and testosterone. The testis is histologically identifiable at 6 weeks' gestation. Primary testis differentiation begins with development of the Sertoli cells at 8 weeks' gestation. SRY, the sex-determining region on the Y chromosome, determines male gonadal sex and directs the differentiation of the Sertoli cell (229). Sertoli cells secrete AMH which triggers the resorption of the Mullerian ducts in males and prevents development of female internal structures (230). At approximately 8 weeks' gestation Leydig

cells differentiate and testosterone secretion commences. Maximum levels of fetal testosterone are observed at about 15 – 18 weeks and decrease thereafter.

Differentiation of the ovaries occurs several weeks later than that of the testis. If the primordial germ cells lack the SRY region on the Y chromosome, ovaries develop from the indifferent gonads. Fetal ovarian function becomes apparent by 7 to 8 weeks gestation; the time when the ovary becomes morphologically recognizable. During this time ovarian differentiation is occurring with mitotic multiplication of germ cells, reaching 6-7 million oogonia, their maximal number, by 16-20 weeks' gestation (231, 232).

The pattern of luteinizing hormone (LH) levels in fetal plasma parallels that of follicle-stimulating hormone (FSH). The decline in pituitary gonadotropin content, and plasma concentration of gonadotropins after mid-gestation is believed to result from the maturation of the hypothalamic-pituitary-gonadal axis. The hypothalamus becomes progressively more sensitive to sex steroids originating from the placenta and circulating in fetal blood. Early secretion of fetal testosterone is important in initiating sexual differentiation in males. In the absence of testosterone, the Wolffian system regresses. Human chorionic gonadotropin (hCG), supplemented by fetal LH, is believed to be the primary stimulus effecting the early development and growth of Leydig cells as well as stimulating the subsequent peak of testosterone production. In females, the fetal ovary is involved primarily in the formation of follicles and germ cells and less involved in hormone secretion.

Fetal Adrenal Glands

The human fetal adrenal gland is a remarkable organ due to its incredible capacity for steroid biosynthesis in utero, and because of its unique morphologic features. The human fetal adrenals are disproportionately large, and at mid-pregnancy their size exceeds that of the fetal kidneys. At term, the adrenals are as large as those of adults, weighing 10 grams or more. The region that ultimately develops into the adult adrenal cortex, the outer or definitive zone, accounts for only about 15% of the fetal gland (Figure 13). The unique inner or fetal zone comprises 80-85% of the volume of the adrenal in utero, and is largely responsible for the tremendous secretory capacity of this organ. The fetal zone rapidly undergoes involution at parturition and by one year it has completely disappeared (233). Changes in the fetal adrenal volume throughout fetal life and into young adulthood are graphically depicted in Figure 14.

The adrenal function of 10 preterm infants of gestational age 27-34 weeks was assessed for up to 80 days after delivery. The changes in steroid excretion with time in preterm infants of gestation over 28 weeks reflect involution of the fetal adrenal zone at a similar rate to term infants. These findings are consistent with the removal at birth of the inhibitory effects of estrogen on the 3 beta-hydroxysteroid dehydrogenase enzyme. The continued function of the adrenal fetal zone beyond the first month in preterm infants of less than 28 weeks' gestation may however be due to persistence of some other fetal regulatory adrenal mechanism. This suggests that it is gestation that determines fetal zone activity rather than birth (234).

The fetal adrenal gland secretes large quantities of steroid hormones (up to 200-mg daily) near term. The rate of steroidogenesis is 5-times that observed in the adrenal glands of adults at rest. The principal steroids secreted are C-19 steroids (mainly DHEAS), which serve as substrates for estrogen biosynthesis by the placenta (Figure 13).

The fetal adrenal gland contains a zone, unique to in-utero fetal life that accounts for the rapid growth of the adrenal gland; this zone regresses during the first few weeks after birth. In addition to the fetal zone, an outer layer of cells forms the adrenal cortex (definitive zone). The fetal zone differs not only histologically, but also biochemically from the cortex (i.e., the fetal zone is deficient in 3b-hydroxysteroid dehydrogenase enzyme activity and, therefore, secretes C-19 steroids (mainly DHEAS); the cortex secretes primarily cortisol).
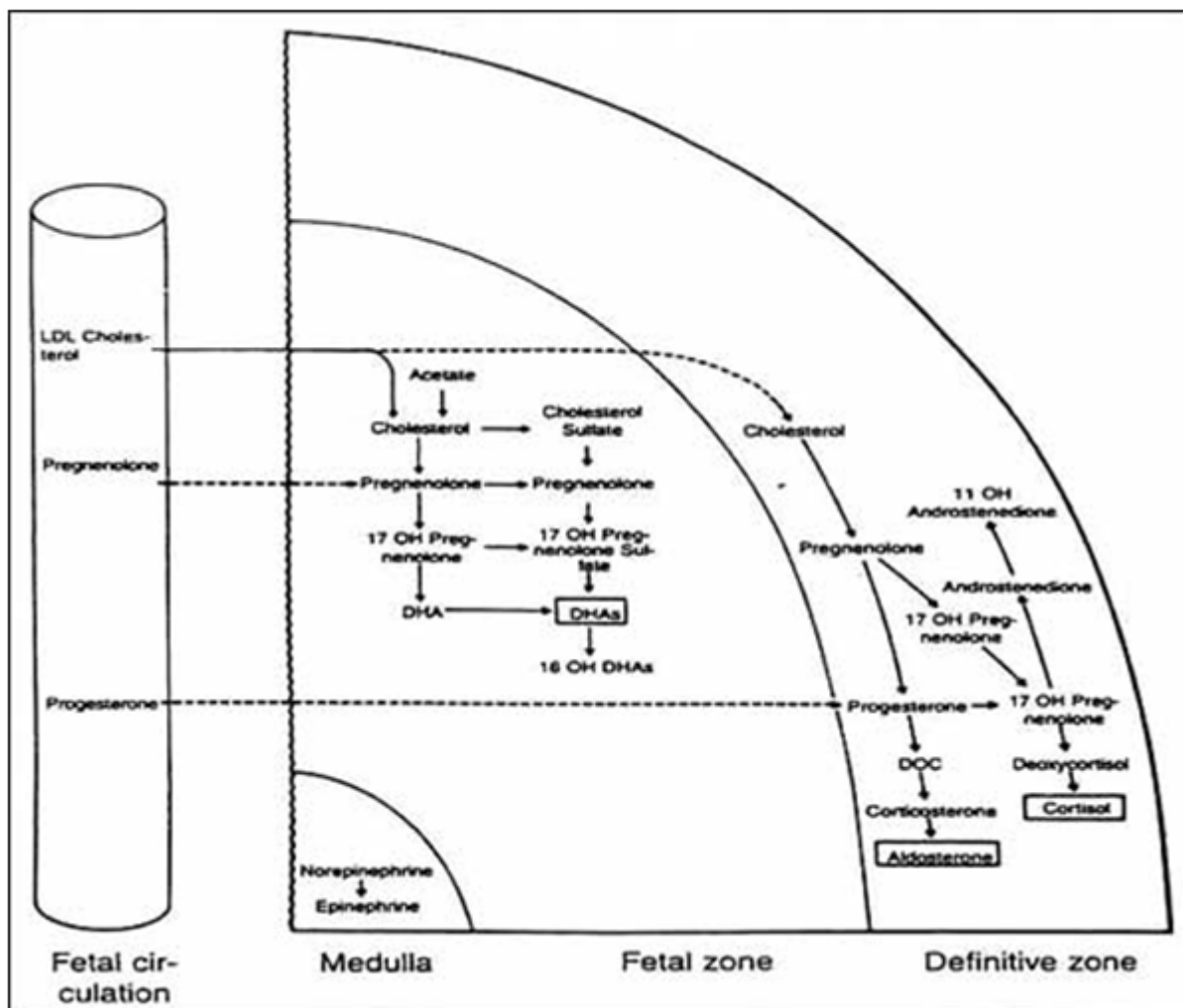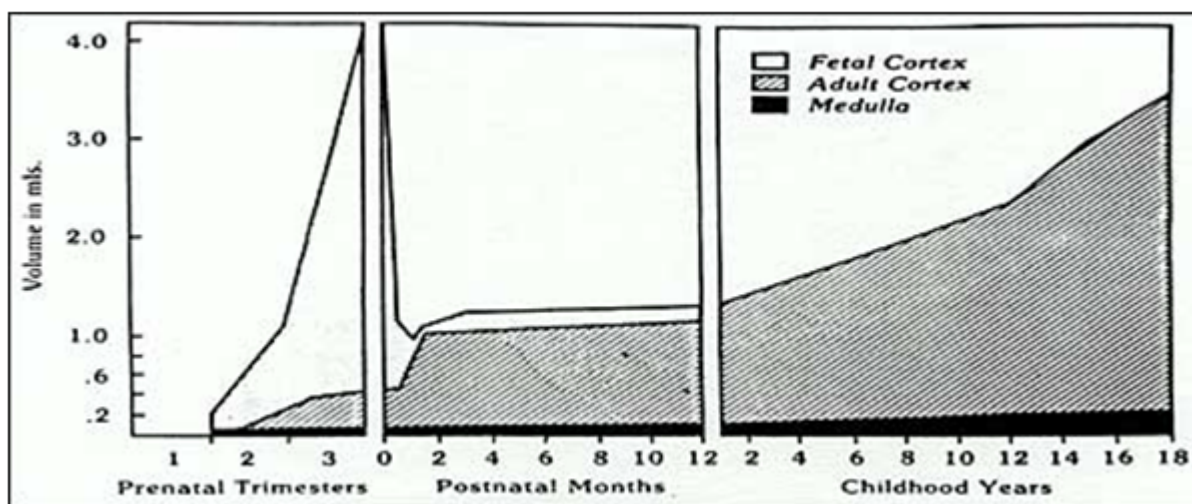
Figure 14. An illustration demonstrating generalized pathways for steroid hormone formation in the fetal adrenal gland. DHA: dehydroepiandrosterone. DHAS: dehydroepiandrosterone sulfate. LDL: low-density lipoprotein cholesterol. (Modified from (235), with permission)

Figure 15. Changes in the fetal adrenal volume throughout fetal life and into young adulthood. (Modified from (236), with permission)

Research involving the fetal adrenal gland has attempted to determine the factors that stimulate and regulate fetal adrenal growth and steroidogenesis. Other work has focused on the mechanisms responsible for fetal zone atrophy after delivery. All investigations have shown that, in vitro, adrenocorticotropic (ACTH) stimulates steroidogenesis. Furthermore, there is clinical evidence that, in vivo, ACTH is the major trophic hormone of the fetal adrenal gland. For example, in anencephalic fetuses, the plasma levels of ACTH are very low and the fetal zone is markedly atrophic. Maternal glucocorticoid therapy suppresses fetal adrenal steroidogenesis by suppressing fetal ACTH secretion. Despite these observations, ACTH -related peptides, growth factors and other hormones have been proposed as possible trophic hormones for the fetal zone. After birth, the adrenal gland shrinks in size by more than 50% because of the regression of fetal zone cells.

Fetal Parathyroid Glands and Calcium Homeostasis

In the fetus, calcium concentrations are regulated by the movement of calcium across the placenta from the maternal compartment. In order to maintain fetal bone growth, the maternal compartment undergoes adjustments that provide a net transfer of sufficient calcium to the fetus. Maternal compartment changes that permit calcium accumulation include increases in maternal dietary intake, increases in maternal 1, 25-dihydroxyvitamin D3 levels, and increases in parathyroid hormone (PTH) levels. The levels of total calcium and phosphorus decline in maternal serum, but ionized calcium levels remain unchanged. During pregnancy, the placenta forms a calcium pump in which a gradient of calcium and phosphorus is established which favors the fetus. Thus, circulating fetal calcium and phosphorus levels increase steadily throughout gestation. Furthermore, fetal levels of total and ionized calcium, as well as phosphorus, exceed maternal levels at term.

By 10-12 weeks' gestation, the fetal parathyroid glands secrete PTH. Fetal plasma levels of PTH are low during gestation, but increase after delivery. In contrast to the unchanged maternal calcitonin levels, the fetal thyroid gland produces increasing levels of calcitonin. Since there is no transfer of parathyroid hormone across the placenta, changes noted in fetal calcium levels are related to fetal changes in these hormones (PTH and calcitonin). These adaptations

are consistent with the need to conserve calcium and stimulate bone growth within the fetus. After birth, neonatal serum calcium and phosphorus levels fall. Parathyroid hormone levels start to rise within 48 hours after birth. Calcium and phosphorus levels steadily increase over the following several days, with some dependence on dietary intake of milk.

Fetal Endocrine Pancreas

The pancreas' exocrine function begins after birth, while the endocrine function (hormone release) can be measured from 10 to 15 weeks onward. The α-cells which contain glucagon, and the β-cells which contain somatostatin, can be recognized by 8 weeks' gestation (234). Alpha cells are more numerous than β-cells in the early fetal pancreas and reach a peak at midgestaion; β-cells increase through the second half of gestation so that by term the ratio of α-cells to beta cells is approximately 1:1 (237, 238). Human pancreatic insulin and glucagon concentrations increase with advancing fetal age, and are higher than concentrations found in the adult pancreas. In vivo studies of umbilical cord blood obtained at delivery and fetal scalp blood samples obtained at term show that fetal insulin secretion is low and tends to be relatively unresponsive to acute changes in glucose. In contrast, fetal insulin secretion in vitro is responsive to amino acids and glucagon as early as 14 weeks' gestation. In maternal diabetes mellitus, fetal islet cells undergo hypertrophy such that the rate of insulin secretion increases.

Fetal Alpha-Fetoprotein (AFP)

Alpha-fetoprotein is a glycoprotein synthesized first by the yolk sac, then the gastrointestinal tract, and lastly by the fetal liver (239, 240). After entering the fetal urine, it is readily detected in amniotic fluid. Amniotic fluid AFP (afAFP) peaks between 10-13 weeks' gestation, and then declines from 14-32 weeks. In the fetus, AFP peaks at 12-14 weeks and

steadily decreases until term (241). The fall in fetal plasma AFP (fpAFP) is most likely due to the combination of increasing fetal blood volume and a decline in fetal production. The concentration gradient between fpAFP and maternal serum AFP (msAFP) is approximately 150- to 200-fold. Detectable as early as 7 weeks' gestation, msAFP reaches peak concentrations between 28-32 weeks (241). The seemingly paradoxical rise in msAFP in association with decreasing afAFP and fetal serum levels can be accounted for by the increasing placental permeability to fetal plasma proteins that occurs with advancing gestational age (241). Alpha-fetoprotein acts as an osmoregulator to help adjust fetal intravascular volume (241). It may also be involved in certain immunoregulatory functions (242). Amniotic fluid AFP and maternal serum AFP are clinically important because they are elevated in association conditions such as neural tube defects (243). Additionally, msAFP is decreased in pregnancies in which the fetus has Down syndrome (trisomy 21) (244).

MATERNAL COMPARTMENT

Maternal Hypothalamus and Pituitary

Little information is definitively known about the endocrine alterations of the maternal hypothalamus during pregnancy. Thought to result from estrogen stimulation, the anterior pituitary undergoes a 2- to 3-fold enlargement during pregnancy, primarily because of hyperplasia and hypertrophy of lactotroph cells. Thus, plasma prolactin levels parallel the increase in pituitary size throughout gestation. In contrast to the lactotrophs, the size of the other pituitary cells decreases or remains unaltered during pregnancy. In line with these findings, maternal levels of somatotrophs and gonadotrophs are lower and the level of thyrotrophs and corticotrophs remains unchanged. In contrast, adrenocorticotrophic hormone (ACTH) levels do increase with advancing

gestation. Corticotrophin-releasing hormone (CRH) in the maternal plasma increases during pregnancy due to increased placental secretion, but alterations in binding-protein concentrations prevent increased biologic activity of this releasing hormone.

The size of the posterior pituitary gland diminishes during pregnancy (245). Additionally, maternal plasma arginine vasopressin (AVP) levels remain low throughout gestation and are not believed to play a pivotal role in human pregnancy. In contrast, maternal oxytocin levels progressively increase in the maternal blood and parallel the increase in maternal serum levels of estradiol and progesterone (246). Uterine oxytocin receptors also increase throughout pregnancy, resulting in a 100 fold increase in oxytocin binding at term in the myometrium (247).

Maternal Thyroid Gland

As a result of increased vascularity and glandular hyperplasia, the thyroid gland increases in size by 18% during pregnancy; however, true goiter is not usually present (248). Enlargement is associated with an increase in the size of the follicles with increased amounts of colloid and enhanced blood volume. This enlargement may be a response to the thyrotropic effect of hCG, which may account for some of the increase in serum thyroglobulin concentrations observed during pregnancy. During gestation the mother remains in a euthyroid state. Total thyroxine (T_4) and tri-iodothyronine (T_3) levels increase but do not result in hyperthyroidism because there is a parallel increase in T_4-binding globulin that results from estrogen exposure (Figure 15). The increase seen in binding-protein concentrations is similar to that observed in women who use oral contraceptives (OC). A modest increase in the basal metabolic rate (BMR) rate occurs during pregnancy secondary to increasing fetal requirements. Some T_4 and T_3, but no TSH, are transferred across the placenta.
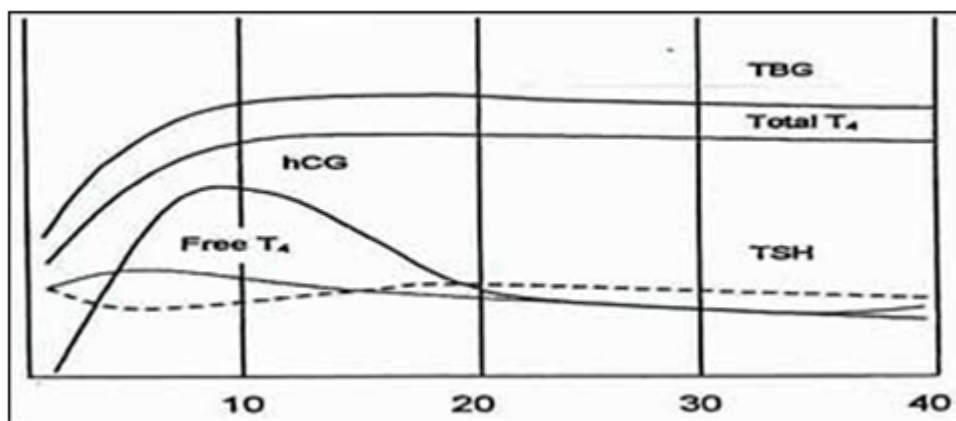
Figure 15. Relative changes in maternal thyroid function during the course of human pregnancy from fertilization to term. (Modified from (249), with permission)

Maternal Adrenal Glands

The maternal adrenal gland does not change morphologically during pregnancy. However, plasma adrenal steroid levels increase with advancing gestation. Total plasma cortisol concentrations increase to three times nonpregnant levels by the third trimester. The hypoestrogenic state of pregnancy results in increased hepatic production of cortisol-binding globulin. This increase in cortisol-

binding globulin results in decreased metabolic clearance of cortisol, resulting in an increase in plasma free cortisol and total free cortisol. Additionally, cortisol production increases due to an increase in maternal plasma ACTH concentration and the hyperresponsiveness of the adrenal cortex to the ACTH stimulation (250). Despite the elevated free cortisol levels, pregnant women do not exhibit any overt signs of hypercortisolism, likely due to the anti-glucocorticoid activities of the elevated levels of progesterone.

Plasma renin substrate levels are increased as a consequence of the effects of estrogen on the liver. The higher levels of renin and angiotensin during pregnancy, lead to elevated angiotensin II levels and markedly elevated levels of aldosterone. Similar to cortisol, the elevated aldosterone levels do not have a detrimental effect on maternal health. The high level of progesterone is thought to displace aldosterone from its renal receptors.

Androgen levels are elevated during pregnancy, but the free androgen levels remain normal to low secondary to the estrogen-induced increase in hepatic synthesis of sex hormone-binding globulin. Dehydroepiandrosterone (DHEA) and DHEAS production is increased twofold during pregnancy. However, serum concentrations of DHEAS are reduced to less than nonpregnant levels secondary to enhanced 16 –hydroxylation and placental use of DHEAS in estrogen production (251).

Maternal Endocrine Pancreas

A dual-hormone secretion mechanism is partially responsible for the metabolic adaptation of pregnancy in which glucose is spared for the fetus by the maternal endocrine pancreas. Compared to the non-pregnant state, in response to a glucose load, there is a greater release of insulin from the β-cells and a greater suppression of glucagon release from the α-cells. Associated with the increased release of insulin, the maternal pancreas undergoes β-cell hyperplasia and islet-cell hypertrophy, with an accompanying increase in blood flow to the endocrine pancreas. During pregnancy, when fasting blood glucose levels fall, they rise to a greater extent in response to a glucose load than do levels in non-pregnant women. The increased release of insulin is related to insulin resistance due to hPL, which spares transfer of glucose to the fetus. Glucagon levels are also suppressed in response to a glucose load, with the greatest suppression occurring near term.

REGULATION OF FETO-MATERNAL STEROIDOGENESIS

Using in vitro investigations utilizing placental tissue explants as well as in vivo, catheterized primate models to study steroidogenic regulation in pregnancy, researchers have determined LDL-cholesterol, fetal pituitary hormones, intra-placental regulators, and intra-adrenal regulators act as the primary modulators of feto-placental steroid production (252-254).

Regulation by Low Density Lipoprotein Cholesterol (LDL)

A limiting factor in adrenal steroid output is the availability of LDL-cholesterol, the primary lipoprotein used in fetal adrenal steroid synthesis (Figure 16). Circulating LDL-cholesterol accounts for 50-70% of the cholesterol utilized for fetal adrenal steroidogenesis (255-257). The fetal adrenal is known to contain high affinity, low-capacity LDL binding sites. The presence of ACTH increases this binding capacity (256, 258, 259). Within the adrenal gland, hydrolysis of LDL makes cholesterol available for conversion to steroids. The majority of fetal LDL-cholesterol is made, de novo, in the fetal liver (260). In addition, cortisol from the fetal adrenal cortex and estradiol (aromatized from fetal DHEAS) augment

this de novo synthesis within the fetal liver. These systems interact in a manner that is linked, self-perpetuating, and serves to increase steroid production to meet the needs of the maturing fetus (260).
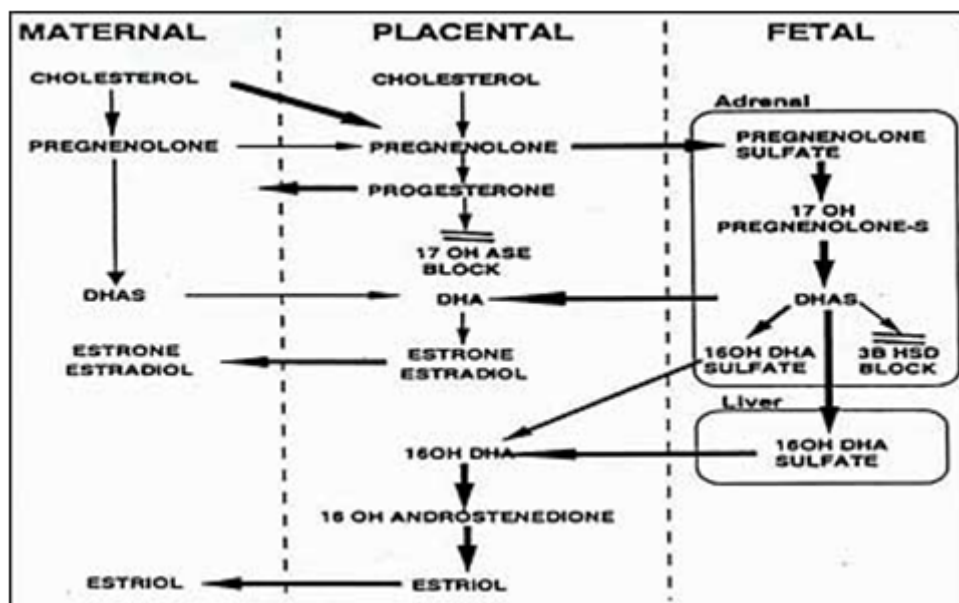
Figure 16. Shown are the maternal, placental and fetal compartments for estrogen and progesterone synthesis in human pregnancy. The fetal adrenal gland lacks 3β-hydroxysteroid dehydrogenase, but has sulfation and 16α-hydroxylase capabilities. Likewise, the placenta lacks 17α-hydroxylase activity but contains sulfatase in order to cleave the sulfated fetal products. Modified from (261), with permission)

Regulation by Fetal Pituitary Hormones

Fetal ACTH regulates steroidogenesis in both adrenal zones. Adrenocorticotropic hormone receptor activity is diminished in the fetal zone of the cortex during the early second trimester when other factors, such as hCG, are more important in the maintenance of this zone (260). In vitro studies in human fetal adrenal tissue, demonstrate that ACTH stimulates the release of D5 pregnenolone sulfate and DHEAS, whereas in adult adrenal cortex secretes only cortisol when stimulated by ACTH (260). Moreover, ACTH can act on its own adrenal-cell membrane receptor to express a direct stimulatory effect on steroidogenic enzymes (260).

Adrenocorticotropic hormone extracted from the human fetal pituitary gland has been shown, in vitro, to stimulate the production of DHEAS and cortisol (262, 263). Interestingly, concentrations of ACTH throughout gestation do not correlate with the increasing mass of the fetal adrenal cortex or the increasing steroidogenic function that are hallmarks of the third trimester (259). Fetal pituitary ACTH is detectable by 9 weeks' gestation (263, 264). Thereafter, levels of ACTH increase steadily until 20 weeks' gestation. The levels remain stable until approximately 34 weeks, when a significant decline is initiated and persists until term (259).

Prolactin may act as a co-regulator, along with ACTH, hCG and certain growth factors, in fetal

adrenal steroid production (265, 266). Both in vitro and in vivo, prolactin augments ACTH-stimulated adrenal androgen production (253). Fetal pituitary prolactin is detectable at 10 weeks' gestation (264). Umbilical cord prolactin levels increase with advancing gestational age and rise in parallel with increased fetal adrenal mass (267).

Regulation by Intra-Placental Mechanisms

The placenta is an important co-regulator of the fetal adrenal zone due its ability to secrete hCG, placental CRH, progesterone and estradiol (233). In vitro and in vivo, hCG receptor activity is present in the fetal zone, and hCG stimulates fetal adrenal production of DHEAS (233, 268). However, after the 20th week of gestation ACTH primarily influences the fetal zone of the adrenal, and at this time hCG plays only a minor role. Placental CRH, acts in a paracrine relationship with placental ACTH, to complement the actions of the fetal hypothalamus and pituitary in producing the surge in fetal glucocorticoids notable in the late third trimester as fetal growth and maturity become increasingly important (125, 269).

Placental progesterone inhibits D5 to D4 steroid transformations in the fetal zone of the adrenal (101, 270). This effect is another explanation for fetal adrenal 3β-HSD deficiency. Placental estradiol modifies the production and metabolism of corticosteroids and progesterone. In vivo, the placenta regulates the inter-conversion of maternal cortisol to cortisone, and the fetal pituitary production of ACTH (264, 269). Modulation of the transfer of maternal cortisol across the placenta, into the fetus, is the primary mechanism through which this effect occurs.

Regulation by Intra-Adrenal Mechanisms

With advancing gestational age, the fetal adrenal becomes more sensitive to circulating ACTH (253).

Between 32 and 36 weeks' gestation, the fetal adrenal mass increases (271-273). Blood flow to the fetal adrenal is affected by many factors that, in turn, affect the exposure of the fetal adrenal receptors of the different trophic stimuli. Growth factors modulate adrenal steroid pathways just as they do in the adult adrenal cortex. The fetal adrenal produces IGF-I and IGF-II; ACTH originating from either the fetal pituitary or the placenta can stimulate production of their respective mRNAs (274, 275).

PARTURITION

Parturition is a coordinated process of transition from a quiescent myometrium to an active rhythmically contractile state requiring elegant interplay between placental, fetal and maternal compartments. Though fetal maturity does not always predate the onset of labor, the two processes are related in primates. The timing of birth is a crucial determinant of perinatal outcome. Both preterm birth (<37wk) and post-term pregnancy (>42 wk) are associated with greater risk of adverse perinatal outcomes. The traditional dogma, supported by robust evidence from animal studies, has the fetoplacental unit as being in charge of the timing of parturition (276). While this is certainly true in some species, the presence of such a "placental clock" is not established in humans. Rather, it has become clear that the maternal endometrium/decidua also plays an important role in triggering the cascade of event leading to parturition (277).

The precise mechanisms involved in human parturition are thought to involve CRH, functional progesterone withdrawal, increased estrogen bioavailability, and finally, increased responsiveness of the myometrium to prostaglandins and oxytocin. There is no simple chain of events as there are in other species.

Numerous lines of evidence support a role for CRH in human parturition. Studies have demonstrated increased CRH and decreased CRH-binding protein levels prior to the onset of both term and preterm labor (278, 279). CRH directly stimulates release of prostaglandins in decidua and myometrium (280). Interestingly, a paradoxical augmentation of placental CRH release by serum cortisol is maximal in the last ten weeks of pregnancy. This may be a function of cortisol competition with progesterone for placental glucocorticoid receptors, thereby blocking the inhibitory action of progesterone on CRH synthesis (281).

The ratios of estradiol and progesterone in various animal models are closely related to the stimulation of myometrial gap-junction formation (282). With decreasing progesterone relative to estradiol, gap junctions permit cell-cell communication for the synchronized myometrial smooth muscle contractions required for labor. Progesterone and the estrogens are antagonistic in the parturition process. Progesterone produces uterine relaxation, stabilizing lysosomal membranes and inhibiting prostaglandin synthesis and release. By contrast, estrogens destabilize lysosomal membranes and augment the synthesis of prostaglandin and their release (283). Although gradual increase in umbilical cord DHEAS and maternal estriol occurs toward term, there is no corresponding drop in either fetal or maternal progesterone concentrations (284).

Though a reduction in maternal or fetal progesterone levels during spontaneous labor has not been documented, functional progesterone withdrawal at the receptor level is believed to be involved in the process of parturition. This may occur via altered progesterone receptor isoform PR-A/PR-B levels in myometrium (285). Undoubtedly, progesterone is important in uterine quiescence because in the first trimester removal of the corpus luteum leads rapidly to myometrial contractions (84). Likewise, labor

ensues following the administration of progesterone receptor antagonists in the third trimester (286). The anti-progesterone agents occupy progesterone receptors and inhibit the action of progesterone, which is clearly essential for maintenance of uterine quiescence. Consistent with these findings, pharmacologic treatment of women at risk for preterm labor with progesterone or synthetic progestational agents has demonstrated efficacy in the prevention of preterm labor (287-289).

A role for estrogen in the process of parturition is supported by the finding that pregnancies are often prolonged when estrogen levels in maternal blood and urine are low, as in placental sulfatase deficiency or when associated with anencephaly (290). In human studies, there is a correlation in uterine activity with circulating maternal estrogens and progesterone as labor approaches (291-293). Feto-placental estrogens are closely linked to myometrial irritability, contractility, and labor. In primates, estrogens ripen the cervix, initiate uterine activity, and established labor (294). Estrogens also increase the sensitivity of the myometrium to oxytocin by augmenting prostaglandin biosynthesis (283, 295). Because placental release of estrogens is linked to the fetal hypothalamus, pituitary, adrenals, and placenta the fetal pituitary adrenal axis appears to fine-tune parturition timing in part through its effect on estrogen production.

Prostaglandins (PG) are thought to play a central role in human parturition. For years, it has been known that rupture, stripping, or infection of the fetal membranes, as well as instillation of hypertonic solutions into the amniotic fluid results in the onset of labor. These facts have led to the hypothesis that a fetal-amniotic fluid-fetal membrane complex is a metabolically active unit that triggers the onset of labor. Evidence supporting a causative role of prostaglandins in the labor process is present since PGs induce myometrial contractions in all stages of

gestation. While there is still no direct evidence relating endogenous PGs to labor, there are several lines of evidence implicating PGs in this process; PG levels increase in maternal circulation and amniotic fluid in association with labor; indomethacin prevents the onset of labor in nonhuman primates and stops preterm labor in humans; stimuli that are known to induce labor (e.g. cervical ripening, rupture of membranes) are associated with PG release; the process of cervical ripening is mediated by PGs. Important to this hypothesis is the understanding that at least one mechanism in the onset of parturition is the release of stored precursors of PGs from the fetal membranes.

The major precursor for PGs is arachidonic acid, which is stored in glycerophospholipids. The fetal membranes are enriched with two major glycerophospholipids, phosphatidylinositol and phosphatidylethanolamine. As gestation advances, the progressively increasing levels of estrogen stimulate the storage, in fetal membranes, of these glycerophospholipids containing arachidonic acid.

A series of fetal membrane lipases, including phospholipase A2 and Phospholipase C control the release of arachidonic acid from storage in fetal membrane phospholipids. Once in a free state, arachidonic acid is available for conversion to PG. Additional factors that augment and accentuate the normal process of labor include the liberation of corticosteroid by the mother and fetus, resulting in a decrease in the production of myometrial prostacyclin, a smooth muscle relaxant.

Active labor is characterized by a dramatic increase in the number of oxytocin receptors in the myometrium. Once begun, the process appears to be self-perpetuating. The level of maternal catecholamines increases, resulting in the liberation of free fatty acids, including arachidonic acid; there is also an increase in the level of maternal or fetal

cortisol, which decreases the production of uterine smooth muscle prostacyclin. It is unlikely that oxytocin is the initiator of labor despite the fact that oxytocin receptors are present in the myometrium and increase before labor, and it stimulates decidual prostaglandin E2 and prostaglandin F2a production. There is firm evidence of increasing, rhythmical fetal adrenal and placental steroid output over the 5 weeks just before term that is important in preparing human pregnancy for the final cascade of oxytocin and prostaglandins that stimulate labor (283, 291-293, 295, 296).

KEY POINTS

- Synchrony between the development of the early embryo and establishment of a receptive endometrium is necessary to allow implantation and subsequent progression of pregnancy.
- The placenta is a unique, dynamic organ with the inherent ability to produce, regulate, and inhibit factors that directly affect fetal growth and development.
- During the luteal-placental transition period, between 6-10 weeks of gestation, corpus luteal function and progesterone production naturally declines and shifts to the developing placenta.
- Steroidogenesis in pregnancy is characterized by enzymatic deficiencies within the placental and fetal compartments which foster interdependent transfer of precursors among compartments for the synthesis of steroid hormones. This process is modulated by LDL-cholesterol, fetal pituitary hormones, intra-placental regulators, and intra-adrenal regulators.
- Redundancy in protein hormone – receptor interactions such as hPL and hPGH serve to ensure that adequate nutrition is supplied to the developing fetus.
- A relatively insulin resistant state is generated within the maternal compartment to supply glucose and free fatty acids for fetal nutrition.

- Human parturition exemplifies the interplay between placental, fetal, and maternal compartments, characterized by increased estrogen bioavailability, functional progesterone withdrawal, increased CRH synthesis and release, culminating in increased responsiveness of the myometrium to prostaglandins and oxytocin.

ACKNOWLEDGMENT

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