The Hormones of the Placenta
By: Shaya Oratz
Shaya graduated in June 2014 with a B.S. in biology.

Abstract
The human pregnancy begins with fertilization and implantation. As the embryo evolves and develops within the uterus of the mother, the placenta is formed. The placenta is a transient organ that develops to meet and accommodate specific needs during pregnancy. Its two major functions are the exchange of nutrients and gases between the mother and fetus and its role as an endocrine unit. Through the production and release of many hormones the placenta works to regulate the many necessary physiological changes in the mother in order to maintain the pregnancy, meet the needs of the developing fetus and prepare the mother’s body for birth. The placenta releases both steroid and peptide hormones. Each hormone has specific target tissues and is used to signal a specific response. These responses work to facilitate a healthy pregnancy and a healthy outcome for the newborn.

Introduction
Pregnancy, specifically human gestation, begins even before the release of a mature oocyte and ends with parturition, approximately 9 months later. Pregnancy is an amazing phenomenon that integrates many complex physiological processes and ultimately results in reproduction of the human species. During this vital time the placenta is formed as a transient organ, and it continues to play a critical role in maintaining the health of both the embryo/fetus and the mother up until the time of delivery. It continuously evolves to meet the changing needs of the developing fetus within its maternal physiological environment (Linzer and Fisher, 1999).

The placenta has two major functions. The first function is the exchange of metabolic and gaseous products between maternal and fetal bloodstreams. In this way the placenta is able to provide oxygen and nutrients, as well as remove waste products for the developing fetus. The second function is hormone production (Linzer and Fisher, 1999). The hormones produced and released by the placenta assist in triggering the maternal physiological changes necessary to meet the needs of the fetus, as well as the changes needed to prepare the mother for the specific needs of the baby after birth. These changes are widespread amongst the various systems of the mother and are coordinated largely by circulating hormones. Some of these hormones are hormones that are commonly found circulating within the adult (non-pregnant) female in various concentrations. Others are hormones unique to the pregnant female only and are not otherwise found in the body. This role makes the placenta an important endocrine organ necessary for the successful continuation of a pregnancy (Sadler, 2012) (Linzer and Fisher, 1999).

Background
In order to understand how the placenta functions, it is important to first understand how it is formed, beginning with fertilization. During ovulation, one mature oocyte is usually released by the ovaries and is transported into the uterine tube by the sweeping action of tubal fimbriae. When all biological conditions are suitable, and if a sperm meets the released egg, then fertilization of the embryo generally takes place in the fallopian tubes. The fertilized egg then goes through a series of cell divisions eventually creating a tightly grouped ball of sixteen cells called a morula. On approximately the third or fourth day after fertilization the morula begins to travel down the fallopian tube, eventually reaching the uterus. A fluid filled cavity begins to appear within the morula, and it develops into a blastocyst. The inner cell mass of the blastocyst will form the embryoblast, which gives rise to tissues of the embryo proper, and the rest of the cell mass, which surrounds the inner cells and blastocyst cavity, will form the trophoblast, which later contributes to the placenta (Sadler, 2012).

By this time, the zona pellucida, which is the glycoprotein membrane that surrounded the ovum, has disappeared and implantation into the uterus begins as the blastocyst continues to evolve. This occurs on the sixth day after fertilization, as trophoblastic cells begin to penetrate between the epithelial cells of the uterine mucosa (Sadler, 2012). At this time, the mucosa of the uterus is in the secretory phase of the menstrual cycle, in response to progesterone that is released by the corpus luteum that remains following ovulation. The corpus luteum is maintained for the first few weeks of pregnancy by the release of hCG from the trophoblast and it continues to release specific hormones that affect the uterus and allow implantation to occur. Eventually, however, the corpus luteum degenerates and is replaced by the placenta, which then becomes responsible for continued hormone production (Cole, 2012).

In preparation for implantation, the glands and arteries of the uterine endometrium become coiled and three distinct layers form in the endometrium. The formation of the placenta then results from mutual interaction of the trophoblast and the endometrium. Under normal circumstances, the blastocyst implants along the anterior or posterior wall of uterine endometrium, where it becomes embedded between the openings of the glands and continues to root itself more deeply into the endometrium until it becomes completely embedded and almost entirely covers the uterine wall, on approximately the eleventh or twelfth day. (Sadler, 2012).

At the time of implantation the development of the placenta begins, as the trophoblast continues to develop by differentiating in
The villi on the embryonic pole continue to grow and develop, giving rise to the chorion frondosum, which is a bushy chorion area, while the villi on abembryonic pole eventually degenerate. The portion of the endometrium that lies over the embryonic pole becomes abundant with lipids and glycogen and becomes firmly attached to the chorion. This is the decidua basalis. The remaining portion of the endometrium that lies over the abembryonic pole also degenerates. Together, the chorion and the decidua basalis make up the placenta, which becomes the only portion of the chorion where the exchange of maternal and fetal materials takes place. Maternal blood from the lacunae of the syncytiotrophoblast begins to fill the intervillous spaces of the chorion. Septa continue to form from the decidua, protruding into intervillous space, but never actually reaching the chorion. This, in turn, forms compartment-like structures, called cotyledons, that are not fully separated by the septa. It is in these compartments that high pressure arteries bring oxygen-rich blood towards the villous trees that have developed in the chorion and then back towards endometrial veins. The intervillous spaces of a mature placenta contain approximately 150 mL of blood, which is replenished about 3-4 times per minute. At all times there is a layer of syncytium that separates maternal blood from fetal tissue, as part of the placental membrane. The villi serve to increase surface area and are the primary site of placental exchange (Sadler, 2012).

As the pregnancy progresses, the placenta continues to grow, covering approximately fifteen to thirty percent of the internal surface of the uterus (Carlson, 2004). This growth serves to accommodate the ever growing needs and demands of the developing fetus and ensures sufficient transfer of nutrients. Continuous proliferation, differentiation, and fusion of cytotrophoblast is what maintains and expands this syncytial interface throughout pregnancy as syncytiotrophoblast cells are shed into maternal circulation when they reach the end of their life cycle (Forbes and Westwood, 2010). A clear relationship has been established, with a direct relationship between placental weight and fetal weight throughout pregnancy. This points to the ever important role that the placenta unit plays in fetal growth, through its various functions (Alsat et. al. 1997).

One major function of the placenta at this point, as mentioned, is the exchange of nutrients and wastes. Through the process of diffusion, gases, such as oxygen, carbon dioxide, and carbon monoxide are exchanged between mother and fetus. Additionally, the exchange of nutrients and electrolytes, such as amino acids, fatty acids, carbohydrates, and vitamins are also diffused through the placental barrier. Although immunity is beginning to develop, maternal antibodies are also transported from the mother to the fetus via the placenta (DeChemey et. al. 2013).

The seconds major function of the placenta is the production of hormones which serve to maintain the pregnancy, to uphold an optimal environment within the physiology of the mother, and to prepare the mother for birth. The release of hormones by the placenta is an endocrine communication system that stimulates
specific reactions on target tissue, facilitating changes necessary for the state of the pregnancy. The myometrium, which lies just beneath the endometrium is a vital tissue during the pregnancy period, and it is a critical target for fetal placental communication. The major hormone changes that occur through these placental communications are noted specifically in the increased levels of estrogen, progesterone, and choric gonadotropin. However, there are other hormones as well, that participate in this complex system of fetal-maternal interaction, although on a smaller scale, (DeChemey et. al. 2013).

Steroid Hormones
Over the years much research has been done in order to determine the actual role of the placenta in hormone production. One group of hormones produced by the placenta are the steroid hormones estrogen and progesterone. Various studies have been done to verify that it is actually the placenta that produces the elevated levels of these hormones during pregnancy. Studies in which pregnant women underwent surgery to remove the corpus luteum at various stages of pregnancy resulted in a substantial amount of lost pregnancies when the corpus luteum was removed before the eighth week. Removal of the corpus luteum after the eighth week did not result in abortions. These results suggest that after the eighth week there are a significant amount of placental secretions (Csapo et. al. 1972). Furthermore, women with ovarian failure who participated in an ovarian assisted reproduction program demonstrated increased peripheral blood progesterone and estradiol levels by the fifth week of pregnancy. These levels were above the background levels achieved by the constant replacement regimen. With the absence of ovarian function, this study also suggests the role of the placenta in maintaining proper hormone levels and sustaining pregnancy (Scott et. al. 1991).

Estrogen
Estrogen is a steroid hormone that is produced in the syncytiotrophoblast of the placenta (Alsat et. al. 1997), with the placenta becoming the primary source of this hormone approximately during the ninth week of pregnancy. Estrogen levels remain low during the first trimester of pregnancy and then progressively increases, remaining elevated, until labor.

An important role of estrogen during pregnancy is the synthesis of contractile proteins in the myometrium, as well as local concentration of contraction associated proteins, such as oxytocin and connexin-43 (Cx-43). It also increases prostaglandin production and regulates the expression of nitrate oxide synthase isoforms. Estrogen, therefore, plays a significant role in preparing the uterus for labor contractions and delivering the baby. Although estrogen assists in the priming of the myometrium for labor, it is important to note that the estrogen alone is not clinically effective in the induction of labor. Furthermore, a pregnancy can continue to exist and labor is still possible, even amongst women with low levels of circulating estrogen (Ticconi et. al. 2006). However, in cases of low placental estrogen synthesis, changes that generally occur in the reproductive tract before parturition, such the ripening of the cervix, generally do not occur (Strauss et. al. 1996). The actions of estrogen are therefore efficient in conjunction with other factors (Ticconi et. al. 2006).

Other significant functions of estrogen are the stimulation of uterine growth, as well as development of the mammary glands, in preparation for birth. The development of the mammary gland begins initially at puberty with estrogen exposure and is completed in the third trimester of pregnancy (Sadler, 2012).

Progesterone
Progesterone is another major steroid hormone that is produced by the placenta. Until approximately ten weeks gestation, progesterone is produced by the corpus luteum that remains after ovulation. In a normal menstrual cycle where pregnancy does not occur, the corpus luteum degenerates soon after ovulation. However, when pregnancy does occur, hCG that is released from the trophoblast stimulates the maintenance of the corpus luteum, which, in turn, releases progesterone. This prevents the shedding of the endometrium lining (Cole, 2012) and allows for proper implantation (Kumar and Magon, 2012). Progesterone continues to be released by the corpus luteum until approximately week eight to ten gestation. It then continues to be produced by the placenta, specifically by the syncytiotrophoblasts of the chorion, in response to the uptake of maternal lipoproteins. The expression of low density lipoproteins appears to be directly related to the presence of progesterone (Ticconi et. al. 2006).

Progesterone acts in multiple ways to decrease the contractility of the myometrium lining of the uterus. By decreasing Cx-43 expression, stimulating nitrate oxide expression, and down-regulating calcium channels and oxytocin receptors, progesterone serves to maintain a state of dormancy during most of the pregnancy. Three progesterone receptor subtypes, PR-A, PR-B, and PR-C have been identified. Only PR-B mediates the expression of progesterone responsive genes, whereas PR-A represses this activity. During most of pregnancy, PR-A levels are low. At the time of labor, however, PR-A levels increase drastically, as do PR-A receptors, thereby suppressing the effects of placental progesterone during this crucial time and allowing uterine contractions to progress, despite maternal circulating progesterone (Ticconi et. al. 2006).

Although progesterone has a quiescent effect on the uterus, another primary function of this hormone is its effect on the cervix. Progesterone has been found to have a direct effect on the length of cervix, and in this way serves to prevent preterm labor. Studies have shown that a shortened cervix in the second trimester is often an early indicator that preterm labor will occur. Both natural and synthetic progesterone have been found to have a
strengthening and lengthening effect on the cervix, and are thereby often effective in postponing preterm labor. Local withdrawal of progesterone at the cervical level appears to have the opposite effect of softening and effacing the cervix in preparation for delivery. Although exact mechanisms are unknown at this time, progesterone has been shown to have an effect on mucus plug formation and possibly contributes to improved antimicrobial activity in this area (Campbell, 2011).

Another important function of progesterone is its contribution to mammary gland development. Although the mammary glands begin to develop at puberty, continued development and preparation for lactation is still necessary. Progesterone had been found to be associated with ductal proliferation and lobuloalveolar differentiation. This enables the mammary glands to produce and secrete milk after delivery (Lydon et al. 2000).

**Peptide Hormones**

**Human Chorionic Gonadotrophin**

Human Chorionic Gonadotrophin (hCG) is a pregnancy hormone that is critical to both the establishment and maintenance of the pregnancy, playing a role in multiple facets of the pregnancy process. hCG is a glycoprotein hormone that is similar in structure to luteinizing hormone (LH). It is synthesized and secreted primarily by the syncytiotrophoblasts, and it binds to specific hCG receptors in target tissues (Ticconi et al. 2007). It is detectable early in pregnancy, as soon as eight to nine days after ovulation and levels continue to rise until the final weeks of pregnancy. Emerging evidence continues to demonstrate a wider range of biological effects that hCG has on various tissues types than was previously recognized.

One of the major functions of hCG during the first trimester is the prevention of luteolysis and stimulation of progesterone production in the corpus luteum (Cole, 2012). As mentioned, this ensures that the uterus, which is generally in the secretory stage of the menstrual cycle at the point of fertilization, maintains an optimal state for implantation to occur (Ticconi et al. 2007). By sustaining the production of progesterone, hCG indirectly works to maintain the decidual cells of the endometrium, thereby preventing apoptosis. At this point, hCG also functions to promote angiogenesis in the uterine vasculature, allowing for improved circulation and maximum blood supply to the area as the placenta forms. hCG has also been shown to control growth and development of the umbilical cord in this way (Cole, 2012). hCG, which is considered to be similar to thyroid stimulating hormone (TSH), mildly stimulates the thyroid gland to produce more thyroid hormone throughout pregnancy. This is especially important, as the thyroid hormone passes through the placenta and is critical for brain and nervous system development in the fetus. At approximately twelve weeks, the fetus begins to produce its own thyroid hormone (Kilby et al. 2005).

After the first trimester, hCG continues to play a pivotal role in maintaining the pregnancy through various mechanisms. Studies have shown that hCG strongly induces the proliferation of myometrial smooth muscle cells. This contributes to the continuous growth of the uterus throughout pregnancy, providing an optimal environment for the simultaneous continuous growth and development of the fetus. HCG also assists in inhibition of uterine contractility. Just like progesterone, HCG has been found to directly decrease expression of connexin 43. It has also been found to reduce the expression of PR-A, further reducing uterine contractility in this way. HCG also decreases intracellular concentration of free calcium in the smooth muscle cells, thereby inhibiting the amplitude of response to oxytocin-stimulated contractions. Additionally, hCG is the only pregnancy hormone that has been found to inhibit the expression of phosphodiesterase (PDE) 5 enzyme, which is involved in the hydrolysis of cAMP and cGMP that regulate myometrial relaxation. This further assists in modulating uterine contractility and in inhibition of preterm labor (Ticonni et al. 2007). During the final weeks of pregnancy, levels of hCG tend to drop, in preparation for delivery. This drop allows for increased responsivity to prostaglandin and oxytocin, enabling contractions to occur (Ticconi et al. 2006).

Another important function of hCG is its effect on the fetal membranes. A study conducted by Ticconi et al (2007) demonstrated increased expression of the isoform of nitric oxide synthase in response to hCG. This, in turn, may contribute to the relaxed state of the uterus as well as to immune system activity in the fetal membranes, although this has not yet been proven (Ticconi et al. 2007). Additionally, hCG promotes anti-macrophage inhibitory factor, thereby preventing rejection of the foreign fetal tissue by the mother throughout pregnancy (Cole, 2012). Additionally, new studies have found hCG receptors in many fetal organs and tissues. This may indicate that hCG also plays a role in fetal growth during pregnancy. These receptors are then removed upon parturition. It is also interesting to note the hCG receptors are also found in the hippocampus, hypothalamus, and brain stem of the mother. This may explain the presence of nausea and vomiting that often occurs in pregnancy, as receptors detect this hormone in maternal circulation (Cole, 2012).

Another form of hCG is the sub-type hyperglycosylated hCG. Although it is an autocrine, and not a hormone, hyperglycosylated hCG promotes cytotrophoblast cell growth during the early stages of pregnancy. HCG then promotes the fusion and differentiation of these cells to syncytiotrophoblast cells, leading to the formation of the villous system. This, combined with angiogenesis and umbilical cord formation, becomes the fetal maternal interface of the placenta (Cole, 2012).


**Chorionic Somatomammotrophin**

Chorionic somatomammotrophin (hCS), also known as placental lactogen hormone (LH) is a lactogenic protein that is also produced by the syncytiotrophoblasts of the placenta (Ayala et. al. 1989). It is considered to be similar, immunologically, to pituitary growth hormone, and it effects fetal growth in an indirect manner, according to present studies. It is secreted almost exclusively into maternal circulation, with only small amounts crossing into fetal circulation. It can first be detected in the maternal blood stream at approximately six weeks gestation, and it plays a significant role in maternal metabolism, as maternal hCS concentrations tend to rise throughout pregnancy with irregular fluctuations (Handwerger and Freemar, 1987). During approximately the last month of pregnancy, hCS levels usually level off. It has been found that depressed levels of maternal hCS correlate with intrauterine growth retardation and are associated with high risk pregnancies. It should also be noted that levels of hCS have been noted to increase in direct proportion to increased placental volume (Macmillan et. al. 1976).

HCS works in a manner that is similar to human growth hormone (hGH). It works to effect both carbohydrate and protein metabolism in the mother. Like hGH, hCS enhances insulin secretion and impairs glucose tolerance in the mother, thereby facilitating and increasing the supply of glucose and energy that is available to be delivered to the fetus. HCS also facilitates an increase in lipolysis in adipose tissue of the mother. This helps to ensure that more free fatty acids are available for energy use by the mother instead of glucose. In this way even more glucose is available for use by the fetus. Furthermore, ketones that are formed from the free fatty acids can cross the placenta and can be used by the fetus. Large amounts of hCS released from the second month of pregnancy onward appear to be related to breast, nipple, and alveolar growth, although exact mechanisms are uncertain (Handwerger and Freemar, 1987).

**Placental Growth Hormone**

During the early stages of pregnancy, until approximately 20 weeks, pituitary growth hormone (GH), which originates in the pituitary gland of the mother, is the primary growth hormone found in maternal circulation. Then, from approximately twelve to twenty weeks, until term, placental growth hormone gradually replaces pituitary growth hormone, which eventually becomes undetectable in maternal circulation. Placenta growth hormone is similar in structure to pituitary growth hormone, but is produced in the syncytiotrophoblasts of the placenta. Additionally, it binds to cell receptors with similar affinity to pituitary GH. PGH has a relatively short half-life and there is a rapid fall in serum concentrations within one hour after removal of the placenta following delivery (Lacroix et. al. 2002).

Placental GH is secreted in a continuous, non-pulsatile fashion into maternal circulation only and is not detected in fetal blood at all. This continuous secretion of placental GH into maternal circulation has critical implications for maternal physiological adaptation to gestation, as it impacts metabolism. Although it does not have a direct impact on fetal growth, this hormone works to stimulate gluconeogenesis, lipolysis, and anabolism in the liver and other organs of the mother. In this way it serves to increase nutrient availability for the fetal-placental unit, indirectly affecting fetal growth. This is especially important during the last few months of pregnancy when fetal growth is most prominent. Furthermore, intrauterine growth restriction has been found to be associated with decreased levels of placental GH, indicating the crucial role this hormone plays for the developing fetus. Both the rate of synthesis, as well as maternal blood levels of this hormone, have been found to be directly related to growth of the placenta (Lacroix et. al. 2002.) (Alsat et. al. 1997).

Placental GH demonstrates high somatogenic activity, and just like pituitary GH, it has been found to induce weight gain. It has also been found to be one of the key regulators of maternal Insulin Like Growth Factor 1 (IGF1). Additionally, placental GH concentration has been found to decrease in response to high levels of glucose. As the syncytiotrophoblast, which regulates the expression of Glut1, a major glucose transporter, enters into direct contact with maternal blood circulation, elevated glucose levels may be detected by these cells. The syncytiotrophoblast then respond to variations in maternal blood glucose by modifying placental GH secretion. Recent data on the expression of placenta GH and its receptors in the vill of the trophoblast open new questions as to other roles that this hormone may play (Lacroix et. al. 2002).

**Insulin-Like Growth Factor**

The presence of various growth factors (GF) in maternal circulation is generally increased throughout gestation and specific growth factors, such as insulin-like growth factor (IGF), have been found to be linked to fetal growth. Two specific IGF types, IGF 1 and IGF 2 have been identified, and both have been found to be positively correlated to fetal birth weight (Forbes and Westwood, 2010). These peptide hormones work by binding to specific receptors on target tissues in order to mediate a variety of metabolic and mitogenic processes. Although IGF 1 and IGF 2 each have individual receptors, both typically bind to IGF 1 receptor (IGF1R) through the aid of binding proteins. This receptor is found in all cell types of the placenta, including trophoblast, villous endothelium, and mesenchymal cells and is thought to regulate the mitogenic effects of IGF 1 and IGF 2. IGF binding proteins that are generally found in abundance in the area of the placenta are also correlated to fetal growth (Hiden et. al. 2009).
Although exact mechanisms remain unclear, it appears that one way in which IGFs affects fetal growth is through its effect on the placenta. Placentally derived IGF2 have been found to have a role in promoting trophoblast invasion, thereby promoting placental growth and function. Studies have also shown that exposure of the syncytiotrophoblast surface to IGFs enhanced cytotrophoblast proliferation and differentiation. Because placenta growth has been closely associated with fetal growth, continuous proliferation of cytotrophoblast cells in order to maintain the placenta is crucial. By stimulating placental growth, IGF works to enhance nutrient transport and delivery to the fetus, thereby promoting fetal growth (Forbes and Westwood, 2010).

**Vascular Endothelial Growth Factor**

Vascular endothelial growth factor (VEGF) is an essential hormone for placental growth, and it has a significant impact on coordinating angiogenesis, blood flow, and the breakdown of the extracellular matrix in the placenta. It is found to be present in the blood vessels of both placenta and the umbilical cord, and it is hypothesized that it acts as a paracrine hormone on fetoplacental circulation. In this way it contributes to the growth and maintenance of the placenta as well as delivery of oxygen and nutrients to the fetus. This hormone further assists in vasodilation, as there is no sympathetic innervation in the spiral arteries and in the placenta. These functions are vital for the growth and development of the fetus, as adequate nutrient supply is crucial. Studies have noted a decreased vascular response to VEGF in cases of intrauterine growth retardation. This indicates the importance of the effects of this hormone, and further research is needed to verify the exact mechanisms of the decreased responsivity in these cases, and how this can be prevented (Krukier and Pogorelova, 2006) (Szukiewicz et al. 2005).

**Relaxin**

Relaxin is a peptide hormone that is considered to be similar to insulin. It is produced and secreted during pregnancy, at first by the corpus luteum in the ovary, and then later by the decidua, endometrium, and trophoblast of the placenta. Highest levels of relaxin are detectable in the first trimester of pregnancy. Then, levels tend to drop and stabilize. It mediates its effect both on the reproductive organs, as well as on other organs in the body (Dschietzig and Stangl, 2003).

This peptide hormone originally received its name due to its relaxing and elongating effects on the interpubic ligament. It further assists in softening the cervix and the tissues of the birth canal, thereby facilitating the passage of the fetus during parturition. This was later attributed to the ability of relaxin to reduce cervical collagen concentration and increase collagen solubility during pregnancy. Estrogen was then found to further enhance these effects (Dschietzig and Stangl, 2003).

As years went on, more research has been conducted to try to uncover some other important functions of this hormone. Relaxin has been found to have regulating effects on oxytocin secretion, although data is conflicting in regard to exactly how. Other effects of relaxin include its ability to inhibit uterine contractile activity throughout gestation. However, this effect has been found to be mild in humans. Relaxin also promotes the growth and differentiation of the mammary parenchyma and stroma in preparation for lactation. It is further considered essential for the development of mammary nipples (Dschietzig and Stangl, 2003).

**Conclusion**

The placenta is a transient organ that is formed during pregnancy for the purpose of nourishing the developing embryo/fetus and for maintaining an optimal physiological environment within the mother in order to sustain the pregnancy. During this approximately ninth month period, the placenta undergoes continuous growth and change in order to accommodate the ever changing needs of the mother and fetus. One of the major roles of this organ is its function as an endocrine unit with its release of many hormones which have widespread effects on the maternal tissues and organs. This is what allows the pregnancy to continue and thrive, ultimately resulting in parturition and birth of the fetus.
References


Campbell S. Universal cervical-length screening and vaginal progesterone prevents early preterm births, reduces neonatal morbidity and is cost saving; doing nothing is no longer an option. Ultrasound in Obstetrics and Gynecology, 2011; 38: 1-9


Dschietzig T, Stangl K. Relaxin: a pregnancy hormone as central player of body fluid and circulation homeostasis. Cellular and Molecular Life Sciences, 2003; 60: 688-700


Handwerger S, Freemark F. Role of placental lactogen and prolactin in human pregnancy. Advances in Experimental Medicine and Biology, 1987; 219: 399-420


Kilby MD, Barber K, Hobbs E, Franklin JA. Thyroid hormone action in the placenta. Placenta, 2005; 26: 105-113

Krukier II, Pogorelova TN. Production of vascular endothelial growth factor and endothelin in the placenta and umbilical cord during normal and complicated pregnancy. Bulletin of Experimental Biology and Medicine, 2006; 141(2): 216-218


Macmillan DR, Hawkins R, Collier RN. Chorionic somatomammatropin as index of fetal growth. Archives of Disease in Childhood, 1976; 51: 120-123


