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Chapter

Neuroendocrinology of Pregnancy: Participation of Sex Hormones

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Abstract

Pregnancy is characterized by hormonal changes, critical for the mother's physiological adaptation, exercising a role in the fetus's development, maintenance, protection, and nutrition. Since born, the neuroendocrine system's involvement is necessary to prevent the embryo from being rejected by the mother's immune system. These changes are regulated by fluctuations in hormones such as Progesterone, Testosterone, Androstenedione, Dehydroepiandrosterone, Estradiol, Prolactin, human Placental Lactogen, human Chorionic Gonadotropin, and Thyroid hormones, which promote the mother's development and the fetus (maternal-fetal development). Therefore, given the great importance of these hormones during pregnancy, this chapter will explain the preclinical and clinical participation of sex hormones in maternal-fetal development.

Keywords: pregnancy, hormonal changes, maternal-fetal development

1. Introduction

During pregnancy, the neuroendocrine system undergoes significant hormonal fluctuations determined by stimulatory and inhibitory inputs from the mother and fetus to maintain the internal environment (milieu). This process is regulated mainly by both the maternal brain and the placenta, acting through the maternal-placental-fetal unit (MPFU). It also serves as a protection system against stress and immune responses [1, 2].

Interestingly, the neuroendocrine responses generate a feedback circuit regulated by the placenta. This organ begins its development in days six-seven after conception. It has been considered a passive organ for many years, acting as a barrier between the mother and the fetus, provide nourishing and eliminate metabolism products such as urea, uric acid, and creatinine. However, the placenta is a neuroendocrine organ that can synthesize and release hormones, neuroactive factors, and other mediators, allowing the proper development of the fetus's maternal tissues to ensure an optimal pregnancy, allowing the fetus to adapt and survive under conditions of stress, infections, hypoxia, and malnutrition [3, 4]. This neuroendocrine mechanism involves at least three different endocrine axes; the hypothalamus-pituitary-gonads axis (HPG), the hypothalamus-pituitary–adrenal gland axis (HPA), and the hypothalamus-pituitary-thyroid axis (HPT), to ensure optimal maternal-fetal development [1].

Specifically, the HPG axis, which is the central axis involved in regulating the reproductive function in vertebrates by a releasing pulsing of GnRH at the

hypothalamus and placenta, has a decisive role in the different stages of pregnancy. In this sense, it plays a central role in regulating MPFU development through positive and negative regulation of sex hormones [1].

2. Gonadotropin-releasing hormone (GnRH), FSH, and LH, primary mediators of sex hormones releasing

The GnRH is a hormone synthesized by the hypothalamic neurons. It travels through the portal-pituitary-system to bind to its receptors (GnRHR-I) in pituitary cells (gonadotrophs), activating the synthesis of FSH (Follicle-stimulating hormone) and LH (Luteinizing hormone). These hormones are released into the systemic circulation to act on sex organs regulating both oogenesis and spermatogenesis. Interestingly, GnRH isoforms (GnRH-I and GnRH-II) have also been identified in other tissues, including the testicles, prostate, mammary gland, endometrium, and placenta. In these organs, it has been shown that GnRH-II acts by binding to GnRHR-II receptors [5].

The functions associated with these isoforms are the production of the β-human chorionic gonadotropin (β-hCG) by the syncytiotrophoblast in the early stages of pregnancy. Here, β-hCG intervenes in at least two vital functions, avoiding luteolysis and ensuring Progesterone's production (P4) until the placenta is implanted. Thus, specific conditions that interfere with this endocrine axis before weeks seven to nine of gestation would culminate in pregnancy loss [5].

Moreover, recent evidence indicates that GnRH is involved in the maternal-fetal environment's remodeling (milieu) that allows the fetus's correct implantation. This process is accompanied by increased proliferation of trophoblasts, which invade the decidua and form the outer and inner layers of syncytiotrophoblast, directly contacting maternal tissue. In this condition, the expression of specific metalloproteinases (MMP) is affected. Preclinical studies have shown that both isoforms (GnRH-I and GnRH-II) modify cellular matrix metalloproteinases' expression. Two of them, MMP-2 and MMP-9, are the most directly involved in the migration and invasion of trophoblasts [5].

In addition to the above, it has been shown that both isoforms can produce proangiogenic cytokines, playing a central role in the rerouting of immune system cells involved in the restructuring of the arteries in the maternal-fetal interface [5]. Therefore, GnRH's direct participation is vital for all physiological, hormonal, and structural changes that will culminate in the fetus's correct implantation.

On the other hand, GnRH causes the stimulation of the pituitary hormone's LH and FSH to regulate the sexual function. However, preclinical studies showed that both hormones are inhibited because of Progesterone and Estrogen increased production during pregnancy. Moreover, FSH and LH level rises on day ten after birth, which correlates to the decrease in sex hormones. In this sense, it has been established that the reduction of sex hormones after delivery performs negative feedback, which can achieve the complete reestablishment of reproductive function two months later after birth [6].

Interestingly, these data provide information valuable in understanding the positive and negative feedback mechanisms that play the sexual hormones during the pregnancy to maintain the MPFU.

3. Progesterone, the "pregnancy hormone"

Progesterone (P4) is considered the "pregnancy hormone" because it is critical for gestational maintenance [3]. During this stage, P4 is produced mainly by the ovary's

luteal body until the twelfth week of pregnancy. After that, its release is principally maintained by the placenta, reaching levels of up to 3 μg/g, while blood concentrations range from 100 to 500 nM, being four to six times its basal levels [7, 8]. These values rise significantly as gestational age progresses. It is involved in both the maintenance and development of the endometrium and inhibiting the uterus' smooth muscle from preventing premature contractions (spontaneous abortion) [8].

Interestingly, the increase in this hormone's levels seems to be regulated by an independent mechanism that generally restricts the synthesis of this hormone, being produced by the placental trophoblast cells in response to the stimuli produced in the uterine-fetal microenvironment [9]. At this level, its synthesis is carried out by converting the maternal cholesterol to the pro-hormone pregnenolone into the mitochondrial cytochrome P450. After that, by the action of 3-β-hydroxysteroid dehydrogenases (HSD), it is metabolized to Progesterone. Of the total synthesized Progesterone, 90% go into the maternal circulation, and the remaining 10% goes into fetal circulation [10].

Placental P4 plays an essential role in establishing a pregnancy, as it is responsible for inhibiting uterine contractions that occur at the myometrium's smooth muscle. In this context, the deficiency of this hormone during the luteal phase has been widely related to infertility and loss of the pregnancy, presenting abortion, a situation that can occur at any stage of pregnancy [8, 9]. Besides, it is involved in the formation of decidua (a layer that coats the endometrium). In this sense, P4 is involved in the structural changes that the uterus undergoes during this period by increasing blood vessels' permeability and endometrial density. Moreover, it has been suggested that the increase in decidual density is related to a lower likelihood of miscarriage. Also, P4 ensures the integrity of the fetus-maternal interface during the process of trophoblastic invasion and placenta formation [8, 11, 12]. What is more, P4 blocks the early production of T-cell lymphopoiesis protective role intrauterine environment's immune system (milieu). For that reason, it has been suggested that Progesterone acts as an immunosteroid since a satisfactory pregnancy depends on maternal tolerance to the fetal 'semi-allograft' [8].

Similarly, it has been suggested that the increase in P4 levels induces changes in gene expression in the uterine endometrium, indirectly favoring embryo growth [12]. Furthermore, it is a crucial factor between the endocrine and immune system since it has been shown that this hormone is involved in the implantation of tissue, preventing it from being rejected by the mother, a mechanism that appears to be mediated by Th cells (helper T cells), as well as by the interleukins (IL) IL-3, IL-4, IL-5, and IL-10, in such a way, it has been suggested that through inhibition of Th 1 cells and increased production of interleukins, Progesterone is involved in the implantation of the fetus and its maintenance [7, 8].

On the other hand, P4 is involved in regulating the expression of uterine dendritic cells. These are known as antigen-presenting cells (APCs) involved in innate immune response and tolerance maintenance. However, in immature stages, these cells have a tolerogenic phenotype characterized by the low expression of co-stimulating molecules and pro-inflammatory cytokines. Thereby, it has been shown that in the early stages of pregnancy, Progesterone prevents dendritic cells' maturation. All these previous actions contributed to the maintenance of pregnancy [8].

More interesting, it has been shown that P4 is also involved in reducing gestational stress. In this sense, it has been shown that it can over-express the mPRα gene, which encodes for a membrane receptor present in Cytolytic T lymphocytes CD8 + T cells, and whose increase has been linked to a protective effect against stress-induced abortion [7].

Finally, it is known that P4 levels decrease at the end of pregnancy, a phenomenon that is related to the onset of labor. Hence, an excellent regulatory mechanism

of P4 (both at the endocrine and immunological level) from the beginning to the culmination of pregnancy, it is necessary to the implantation, maintenance, and completion of this [12, 13].

4. The modulatory hormones in pregnancy; testosterone (T), androstenedione (A4), and dehydroepiandrosterone (DHEA)

The androgenic hormones T, A4, and DHEA, plays a central role in regulating reproductive processes in many mammalian species. Besides, the presence of androgen receptors has also been demonstrated in different tissues such as the ovary, the myometrium, and placenta, where they are known to participate in implanting the fetus and placentation. In this sense, it has been shown that, once pregnancy occurs, androgen synthesis takes place in the small luteal cells (SLC) of the corpus luteum by stimulation of the human chorionic gonadotrophin (hCG) [3, 14]. In addition to the above, once the placenta has been established, it becomes an independent androgen production source [14]. In this aspect, placental syncytiotrophoblast uses the circulating DHEA, provided by the maternal and fetal adrenal glands, turning it into A4 and T. Which, in turn, as will be discussed later, can be converted to estrogens by different routes to regulate embryonic development [3, 15]. Interestingly, it has been suggested that myometrium could be another important source of androgens during pregnancy; a recent *in vitro* study showed that this tissue could also produce T and A4 [15].

Suppressively, these hormones are coordinated synthesized during pregnancy. Specifically, it has been shown that T levels increase in the first trimester of pregnancy, reaching a plateau in the second trimester, to later decrease slightly, rising considerably in the last month of pregnancy [14, 15]. Concerning A4, the study carried out by Satué et al. (2018) in mares shows that this hormone rises during gestation, from the second month of pregnancy, reaching a peak maximum in the first stage of pregnancy, and, in the second state, it reduces significantly, reaching its lowest levels in the last month of gestation. However, a clinical study conducted by Makieva et al. (2014) showed that A4 remains stable throughout pregnancy without significant fluctuations. About DHEA, it increases progressively from the first to the fifth month of pregnancy, reaches its highest levels, then begins to decrease between months 6 and 7, reaching its lowest levels in the last month of pregnancy in mares, which is agree with the observed in pregnant women, with levels up to 50% lower than those observed in non-pregnant women, an effect associated with negative E2 feedback to the maternal adrenal glands [14, 15].

The fluctuations in these hormones have specific functions during pregnancy. The significant increase observed in the first months of gestation is associated with the function of the corpus luteum, which uses T for estrogens' production (analyzed in the next topic), regulating the implantation and decidualization. Later, the decrease observed in the middle of the gestation is related significantly to the development of the fetal gonads, providing the necessary substrates for the synthesis of placental estrogens. So, the primary site of estrogen synthesis at this stage could be the fetus. Finally, T's elevation in the last stage of pregnancy, but not of A4 and DHEA, could be associated with the restructuring that the cervix must undergo to be prepared for the moment of delivery. At this stage, it has been shown that the cervix can convert T into another metabolite, Dihydrotestosterone (DHT), through the action of 5-alpha-reductase. This androgen is involved in restructuring the cervix's extracellular matrix tissue, including the structural changes that allow the myometrium's contractility [14, 15].

Therefore, these interesting data confirm the surprising interrelation and interdependence between estrogens and androgens produced by MPFU to protect and ensure pregnancy's proper development.

5. Estrogens in pregnancy, an orchestral regulatory mechanism

Estrogens are a group of four different steroid hormones: Oestrone (E1), 17β-Oestradiol (E2), Oestriol (E3), and Oesterol (E4), cyclically synthesized in response to changes during the ovarian cycle, specifically during the pre-ovulation phase, favoring folliculogenesis. However, estrogens also play a central role in the growth of the uterus and mammary gland. It increases the blood flow indispensable for transporting nutrients between the uterus and the fetus [16]. During pregnancy and up to the time of delivery, significant amounts of estrogens are released by the maternal-fetus-placental unit, formed by the luteal body, placenta, and the fetal adrenal cortex [3], suffering significant adjustments between the weeks seven to nine of pregnancy, reaching its highest levels at the time of delivery [17, 18].

17β-Oestradiol (E2) is the most abundant hormone synthesized during pregnancy. In connection with this, until the third month of pregnancy, significant levels of E2 are released by the luteal body, a period from which the primary site of estrogen production is the placenta [3]. It should be noted that the placenta has no autonomic innervation, so these increases occur in response to close communication between the mother and the fetus, where the hormone acts in an autocrine-paracrine form in the development of the mammary gland and uterus, as well as in the development of sexual characteristics in the fetus. This connection allows the placenta and fetus to exchange and share steroid precursors, thus achieving their hormonal self-regulation [18].

Several studies have shown that the increase in estrogen levels is the result of a mutual exchange between the mother and placenta, in which the placenta uses the circulating androgen DHEA produced by the adrenal glands of the MPFU, where it is converted to Testosterone and Androstenedione and then metabolized to E1 and E2 with the help of the cytochrome cyp450 aromatase enzyme [3, 7]. In such a way, both the mother and the fetus contribute to the increase in estrogen synthesis, regulating their production. In addition to this, and due to the high maintenance of this hormone throughout pregnancy, there is sufficient evidence to suggest that regulation in levels of this hormone could also be at the neural level, where E2 could act as a trigger factor of the HPA gland axis. So, the adaptive changes that occur in the mother-fetus are regulated by a positive feedback mechanism, in which the binding of E2 to their receptors at the brain could be sending signals to the adrenal glands for producing a more significant amount of DHEA, thus maintaining their constant levels [19]. Therefore, it seems clear that estrogen levels regulation during pregnancy occurs both locally, by an interaction of the placental-fetal unit and in an autonomic way, with the direct participation of the Central Nervous System.

Concerning its functions, estrogen has been shown to act through binding to nuclear receptors, participating in multiple processes to ensure the maintenance of pregnancy having different roles: in human endometrial explant cultures, they are involved in uterine vascular restructuring by binding to their nuclear receptors present in epithelial and stromal cells of the cervix and endometrium, acting regulating the expression of different genes that control intrauterine growth, maturation of vital organs such as mammary glands for breastfeeding and childbirth [16–18, 20]. Besides, it promotes the processes of angiogenesis and vasodilation that allow the transfer and exchange of nutrients and oxygen between the placenta and

the fetus through uterine and fetal circulation, a process associated with an increase in endothelial production of nitric oxide [3, 21].

On the other hand, in the primary culture of endometrial-epithelial cells (ESC), it has been found that E2 plays an essential role at the beginning of pregnancy by acting in processes such as differentiation and cell proliferation through the secretion of insulin growth factor type 1 (IGF-1) [22]. Also, it increases the rate at which the fertilized egg travels through the fallopian tube, so low estrogen levels promote ectopic pregnancies because the egg stays longer in the fallopian tube [23].

In addition to the above, estrogens E1, E3, and E4, also, play a central role in pregnancy. E1 is the most abundant conjugated estrogen (estrone sulfate) during pregnancy; it increases from the first trimester of pregnancy, reaching its maximum peak in the 35th week of gestation; among its functions, the decrease of estrogenicity has been indicated in the time of delivery [24]. E3 (Oestriol) is also considered a derivative of estradiol, whose primary role during pregnancy is increased uteroplacental blood flow during pregnancy. However, a specific function has also been suggested in the induction of myometrial cells' contractions through the increase of connexin-4, allowing the restructuring of the myometrium that will trigger the initiation of labor [3]. On the other hand, Oesterol (E4) has an uncertain function during pregnancy since it is produced exclusively by the fetal liver starting up from the ninth week of pregnancy, reaching its significantly elevated levels after week 30, with a peak at week 40. Although its function is unclear, preclinical studies have shown that it can bind to estrogen and progesterone receptors at the uterus, producing histological structural changes and biochemical fluctuations, essential during the differentiation of endometrial cells in pregnancy and delivery [25].

Therefore, during pregnancy, the hyperestrogenic state plays a significant role in maternal-fetal development, being a key piece in fetal growth. Hence, all these actions make the estrogen pleiotropic essential hormones in pregnancy.

6. Prolactin in pregnancy, more than a lactation hormone

Prolactin (PRL) is a protein hormone synthesized by the lactotroph cells of the anterior pituitary gland. Unlike other pituitary hormones, its release is inhibited by Dopamine (DA), a hypothalamic factor produced by dopaminergic neurons located in the arcuate nucleus, which has not only been shown to be able to regulate the release of PRL but can act at the lactotrophic cells, regulating their proliferation [1]. In addition, PRL can control its release, directly stimulating dopaminergic neurons and through direct and indirect mechanisms regulated by E2 [23].

In this sense, a preclinical rat model study showed that in the different reproductive stages, PRL intervenes in a coordinated manner with E2 and Dopamine in regulating the proliferative activity of lactotrophic cells. In this collaborative process, these cells' activity is elevated in the estrus and delivery stages. But it is decreased during the early stages of pregnancy and lactation, even though PRL levels are increased in all these reproductive stages. In this context, it has been suggested that E2 participates in stimulating the release of PRL during the early stages of pregnancy and lactation by acting at the hypothalamic level regulating both the increase in prolactin levels and the activity of the lactotroph cells when DA is not present, play a dual role in the release of this hormone [23, 26].

Evermore, during pregnancy, essential adaptations occur to allow the release of significant amounts of this hormone by the stimulation caused by the mammary gland and the luteal body [27], with substantial elevations from the twentieth week of pregnancy, until after childbirth [26]. Specifically, PRL has been shown to play a vital role in regulating IL-10 and IL-12 interleukins (essential regulators of immune

responses during inflammatory processes). On the one hand, IL-12 interleukin has a pro-inflammatory function, activating itself in response to situations such as stress. On the other hand, IL-10 is an anti-inflammatory cytokine, which intervenes in the regulation of the expression of IL-12. In this sense, it has been shown that, during pregnancy, PRL increases the concentration of IL-10, an effect suggested is associated with the proper maintenance of this [28].

At the clinical level, this hormone has been shown to provide luteotropic support to the luteal body by intervening in the biosynthesis of P4 for its maintenance in the first three months of pregnancy, having an indirect function in the implantation of fetus in the uterus, as well as in the induction of vascular factors necessary for the increase in the volume of the luteal body [1, 29]. On the other hand, it acts directly on the mammary gland, determining the growth and development of alveoli, promoting the expression of genes related to milk synthesis and lactopoiesis. It also helps maintain the luteal body's integrity and decidual cell survival [30]. Moreover, it is involved in the synthesis of relaxin, a hormone responsible for dilating the cervix during labor, thus facilitating the fetus's expulsion [27].

PRL, it has been shown to play an essential role in regulating leptins expression in the gestational stage [31]. Leptins are hormones produced mostly by adipocytes, whose central role is related to the regulation of body weight, appetite, and energy homeostasis. The increase in their plasma levels is associated with the rise in the amount of body fat. However, during the gestational stage, vast quantities of leptins are released by the ovary and placenta, remaining constant throughout pregnancy, intervening in the regulation of fetal weight and growth, and with the development of gestational diabetes [32]. In this sense, the increase in PRL levels has been suggested to inhibit the receptor to leptins (LepR), thus blocking the signaling pathways that regulate the development of gestational diabetes [31].

Finally, it has a central role in mother–child recognition by increasing the generation of neurons at the olfactory bulb level, which is essential for such recognition [29]. For that reason, PRL recognizes like a multifaceted hormone, with dual actions during and after delivery.

7. Human placental lactogen, an exclusive metabolic hormone in pregnancy

The human placental lactogen hormone (hPL), known as human Chorionic somatomammotropin, is a polypeptide hormone elevated during pregnancy and is produced exclusively by the placenta [3]. hPL levels are detected between the first and second weeks of placenta gestation. However, it is released into the maternal circulation between the third to sixth week of pregnancy, being possible its detection, which increases until reaching its constant levels with a significant increase at the end of pregnancy with substantial effects after delivery [3].

Although there is controversy regarding its participation during pregnancy, it has been suggested that its primary function is the regulation of maternal metabolism of lipids and carbohydrates, being crucial to maintaining energy homeostasis between mother and fetus. In this sense, at the preclinical level, it has been shown that it stimulates the production of the IGF-1 factor in maternal hepatocytes. It modulates intermediate metabolism by increasing food intake (orexigenic drive), which favors the increase in glucose available for transfer to the fetus and prevents the development of gestational diabetes caused by peripheral resistance, typical at this stage [1, 3].

Moreover, it has been suggested that it has a central role in intrauterine growth because more than 50% of neonates with stunted growth have shown a deficiency

in hPL levels. It is also believed that, by stimulating the uptake of glucose, glycerol, and free fatty acids, it could significantly participate in fat deposits, serving as an energy-saving mechanism for the fetus [1, 3].

Furthermore, it is well documented that in a normal state of pregnancy, insulin sensitivity decreases with the advance of the gestational state, which allows the fetus to maintain energy, an effect caused by a joint inhibitory action of peptide hormones (C-reactive protein, leptins, and hPL) on insulin levels causing dysfunction of pancreatic β-cells, named "diabetogenic condition." However, a clinical study conducted by Ngala et al. (2017) showed that, throughout pregnancy, important maternal factors could predict the development of gestational diabetes mellitus (GDM) in addition to the already known factors of obesity and family history. In this sense, the levels of glucose, insulin, glycosylated hemoglobin (GHb), and hPL, among others, are increased in pregestational pregnant women, an effect not observed in non-diabetic pregnant women. Interestingly, under this condition, E2 and P4 levels decreased in pre-diabetic women, while in healthy women, the levels of both hormones are increased. On the other hand, between weeks 24–28 of gestation, an increase in Progesterone, Estradiol, Leptins, GHb, and Fasting blood glucose (FBG) was observed in developing GMD, an effect associated with the increased insulin resistance. Controversially, although there is little information linking hPL with the development of GDM, it is believed that the decrease in the levels of this hormone after delivery is associated with the reduction in glucose resistance and with the increased risk of diabetes-prediabetes in nursing mothers [33, 34].

Interestingly, hPL participates in lactation by stimulating the breast epithelium, facilitating breast development during the gestational stage. In this process, both hormones (hPL and PRL) act in maternal behavior, suppressing stress responses in the last stage of pregnancy and lactation [1]. In this sense, it has been shown that dopaminergic neurons' activity can be maintained by hPL [23].

All these results confirm the metabolic action of hPL in pregnancy and lactation, alone or together to other placental and maternal hormones.

8. Human chorionic gonadotropic (hCG), the placental essential hormone

HCG is considered one of the essential hormones during gestational development, having similarities with other members of the same family of glycoproteic proteins such as LH and pituitary FSH. Its synthesis is regulated by the luteal body and placenta, exercising a pleiotropic role during gestation by autocrine and paracrine mechanisms [3]. It is possible to detect significant levels from day eight after fertilization, reaching its maximum levels around the tenth week of development. After which, it maintains at constant levels when the placenta is fully developed. At this point, the luteal body's secretions are no longer necessary [3].

It participates in the process of steroidogenesis and in the restoration-maintenance of the luteal body, where it acts as a relay system, whose purpose is to prevent menstruation by increasing the synthesis of P4, allowing that the embryo can be implanted in the uterine endometrium, ensuring pregnancy until placental production of Progesterone is well established [3].

The hCG has also been shown to have a structure like Thyroid stimulating hormone (TSH) to bind to the same receptors, having implications for regulating thyrotropic activity. Preclinical studies have shown that maternal TSH decreases at the end of the third trimester of pregnancy. This decrease correlates with increased

placental hCG and fetal thyroxine-binding globulin (TGB) [1]. *In vitro* studies have shown that it can have angiogenic effects; it increases vascular-endothelial growth factor (VEGF) and placental microvascular endothelial cells [3].

Moreover, clinical studies have shown that it is also involved in the differentiation of cytotrophoblast in syncytiotrophoblast, constituting an essential factor in the secretion of relaxing decidual production of PRL. On the other hand, it has androgenic properties. It can promote the synthesis of DHEA by the fetal adrenal cortex, regulating both testicular function and fetal male differentiation during the first weeks of gestation [35]. In addition, it has been suggested that it has participated in other functions; in the immune system, stimulates the production of the anti-inflammatory interleukins IL-8 and IL-10, and inhibits lymphocyte response, preventing rejection of the fetus, suggesting an immunosuppressive role of hCG during pregnancy; it stimulates testicular Leydig cells for testosterone production and provides nutrients and hormones for optimal maintenance of intrauterine microenvironment [3, 35]. So, the metabolic implications of this hormone suggested it like a metabolic hormone in pregnancy.

9. Cortisol and glucocorticoids; is it just stress in pregnancy?

The secretion of cortisol levels during pregnancy is regulated by the placenta, which, by secreting the corticotropin-releasing hormone (CRH), produces an exponential increase in cortisol from the eighth week of gestation up to three times above systemic values [5, 36]. It is present in both the maternal and fetal phases but at different levels; under normal conditions, cortisol levels reach 200 ng/ml at the end of pregnancy, while fetal levels range from around 20 ng/ml [37]. These differences are due to the presence of a natural barrier that prevents maternal cortisol, whose molecular composition can cross the placenta, quickly reaches fetal space [38, 39].

This barrier corresponds to the uterus/fetus interface and is mainly composed of maternal decidua and fetal placenta chorion. Here the regulation of cortisol is carried out through placental glycoprotein P, as well as the enzyme 11-β-hydroxysteroid-dehydrogenase (11-β-HSD) type 2 of trophoblastic and fetal cells, which inactivates cortisol by converting it into cortisone to avoid exposure of the fetus to high levels of cortisol [37, 40]. However, because of its role in organ maturation and labor, fetal cortisol increases towards the end of pregnancy by several mechanisms: a) decrease of 11-β-HSD type 2 in fetal tissues, b) increased synthesis of cortisol by the fetal adrenal gland, and c) increased 11-β-HSD type 1 in fetal tissues, which converts cortisone, into active cortisol [41].

As for the functions of cortisol during pregnancy, glucocorticoids (GC) have been described as participating in the processes of implantation and formation of decidua, as well as in fetal development and maturation, and initiation of childbirth [17, 36, 42]. Elevated levels of GC present during pregnancy are involved in the suppression of inflammation of the uterus, placenta, and fetal membranes, which contributes to maintaining the homeostasis necessary for the maintenance of pregnancy [42]. Moreover, recent evidence suggests that significant increases in cortisol levels play a critical role in the baby's growth in the postnatal stage [43]. In this sense, studies have shown that high concentrations of cortisol during the fetal phase positively correlated with weight gain within the first five years of postnatal growth, indicating that the higher increase in placental cortisol levels, the more significant weight gain can be observed in children during this stage, suggesting that hormonal changes within the maternal-fetal environment have repercussions in post-birth stages, a highly relevant endocrinological aspect [43].

Conversely, cortisol is also involved in developing pregnancy complications, being responsible for the so-called "Hypothalamic Stress Amenorrhea," whose consequence is the generation of miscarriages [8, 44]. On the one hand, it has been shown that low maternal cortisol levels compromise the placenta's structure. In contrast, elevated levels can lead to miscarriages, uterine contractions from placental CRH deregulation, the elevation of fetal cortisol levels, and obstetric alterations by activation of the HPA gland axis [14, 36, 38, 45]. In this sense, two main axes, the HPA, and the sympathetic nervous system-adrenal medulla exerts a negative effect on the reproductive system when activated in stressful situations. In this feedback mechanism, the CRH that is produced at the pituitary can act, in a short negative feedback mechanism, directly inhibiting GnRH at the hypothalamus.

Even more, cortisol act at the pituitary to inhibit the release of LH and FSH, and, consequently, inhibits steroidal ovarian hormones, Estrogen, and P4, resulting in abortion. It has been confirmed in preclinical and clinical studies, where exposure to stressors, such as noise, has been verified to induce miscarriages, with a significant decrease in P4 levels [8, 44]. More interesting, stress increases the excitability of the sympathetic nervous system, resulting in a decrease in blood flow supply to the placenta caused placental hypoxia and increased generation of reactive oxygen species, causing damage to trophoblasts; the outer layer of the blastocyst, responsible for providing nourishing to the embryo [44].

Finally, it has also been suggested that high cortisol levels could mediate a disbalance in T helper cells Th 1 and Th 2, with a specific impact in the decrease of adaptative immune system responses that allow the fetus's maintenance. However, more studies are needed to confirm this [44]. So, it is evident that cortisol is not just a "stress hormone"; it has several functions supporting the MPFU.

10. Thyroid hormones in pregnancy; regulation by sex hormones?

During pregnancy, high estrogens and corticosteroids induce an increase in TGB levels in the liver, which is significant from week twenty of gestation, reaching its maximum level from week twenty to twenty-four. The rise in TGB during the first half of pregnancy is related to further deiodination of the inner ring of the hormones T4 (Thyroxine) and T3 (Triiodothyronine) at the placenta, which is responsible for the physiological effect attributed to them [46, 47].

As far as the fetus is concerned, it has been shown that there are at least two mechanisms for it to contribute to thyroid hormones: the development of the fetal thyroid gland and the maternal thyroid gland. More interesting, the increase in concentrations of T4 in the first half of pregnancy and the expression of receptors to thyroid hormones in the brain, suggesting its participation in the development of brain structures of the fetus. Moreover, from weeks twelve-fourteen, in which the fetal thyroid begins to synthesize T4, its levels increase progressively, until reaching its maximum levels between week thirty-four to thirty-six, remaining elevated until the delivery time [46].

About iodine levels begin to be detected from ten to eleven weeks of gestation, a stage in which the fetal thyroid can concentrate. Around the twelfth week, the pituitary starts to produce and synthesize TSH and TRH (Thyrotropin-releasing hormone) by the hypothalamic neurons [46].

Before the fetal thyroid develops, the placenta has a particular involvement in maternal-fetal thyroid regulation. It is responsible for exchanging thyroid hormones to the fetus, suggesting an essential role in early fetal growth. Among the functions

attributed to thyroid hormones are the brain's development and the acceleration of fetal pulmonary maturation. The effect has been demonstrated in preclinical and clinical models in which fetal pulmonary growth has been shown to increase after intraamniotic injection of T3 or T4. On the other hand, the effect at the brain level has been demonstrated in intrauterine hypothyroidism conditions. It is related to irreversible damage to the brain and mental disability in children born under these conditions [46, 47].

Interestingly, clinical studies conducted in children whose mothers suffered from hypothyroidism, a condition that occurs in 0.05–0.02% during pregnancy, have shown that these irreversible changes specifically affect neurodevelopment. In this sense, it has been demonstrated that any situation that leads to the development of clinical hypothyroidism (generally associated with Graves' disease) and hypothyroxinemia (associated with overtreatment of antithyroid drugs) that can occur during the first trimester of pregnancy can lead to a cognitive delay in children, learning disorders, maturational delay, encephalopathy, and seizures among other conditions [48].

Significantly, the increase in TSH, T3, and T4 during pregnancy could have protective effects against fetal anemia because it has been suggested that they may have cardiotonic effects by direct activation of the sympathetic-adrenal nervous system, in addition to being shown to stimulate the production of erythropoietin, which is involved in the production of red blood cells and therefore in the release of oxygen to tissues [47].

In this sense, it is fascinating to understand that sex hormones regulate the release of thyroid hormones and the vital functions involved, like brain development, being crucial during pregnancy and childhood.

11. Conclusions

Pregnancy is a physiological state characterized by critical hormonal changes. Collective participation of the endocrine system is necessary to carry out adequate development and maintenance of both the mother and the fetus. This system is responsible for generating an optimal environment that provides an adequate microenvironment of communication between the maternal-placental-fetal unit, facilitating the exchange of nutrients, hormones, and oxygen, essential throughout the gestational period. These neuroendocrine processes are produced thanks to the synchronous and fluctuating production of sex hormones regulated by endocrine, paracrine, and autocrine mechanisms. Their function is essential before, during, and after the gestational period to ensure the fetus's correct development and growth.

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Conflict of interest

The author declares no conflicts of interest.

Nomenclature

MPFU	Maternal-placental-fetal unit
HPG	Hypothalamus-pituitary-gonads axis
HPA	Hypothalamus-pituitary–adrenal gland axis
HPT	Hypothalamus-pituitary-thyroid axis
GnRH	Gonadotropin-releasing hormone
GnRHR-I and GnRHR-II	Gonadotropin-releasing hormone receptors I and II
FSH	Follicle-stimulating hormone
LH	Luteinizing hormone
β-hCG	β-Human chorionic gonadotropin
P4	Progesterone
MMP	Metalloproteinases
3β-HSD	3-β-hydroxysteroid-dehydrogenases
11β-HSD	11-β-hydroxysteroid-dehydrogenase
Th cells	Helper T cells
IL	Interleukins
APCs	Antigen-presenting cells
T	Testosterone
A4	Androstenedione
DHEA	Dehydroepiandrosterone
E1	Oestrone
E2	17β-Oestradiol
E3	Oestriol
E4	Oesterol
ESC	Endometrial-epithelial cells
IGF-1	Insulin growth factor type 1
PRL	Prolactin
DA	Dopamine
LepR	Leptin receptors
hPL	Human placental lactogen hormone
TSH	Thyroid Stimulating Hormone
TGB	Thyroxine-binding globulin
VEGF	Vascular-endothelial growth factor
CRH	Corticotropin-releasing hormone
GC	Glucocorticoids
T4	Thyroxine
T3	Triiodothyronine
TRH	Thyrotropin-releasing hormone
SLC	Small luteal cells
GDM	Gestational diabetes mellitus
GHb	Glycosylated Hemoglobin
FBG	Fasting blood glucose

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References

[1] Voltolini C, Petraglia F. Neuroendocrinology of pregnancy and parturition. Handb Clin Neurol. 2014;124:17-36. doi: 10.1016/B978-0-444-59602-4.00002-2. PMID: 25248577.

[2] Lahita RG. The effects of sex hormones on the immune system in pregnancy. Am J Reprod Immunol. 1992 Oct-Dec;28(3-4):136-7. doi: 10.1111/j.1600-0897.1992.tb00775.x. PMID: 1285863.

[3] Costa MA. The endocrine function of human placenta: an overview. Reprod Biomed Online. 2016 Jan;32(1):14-43. doi: 10.1016/j.rbmo.2015.10.005. Epub 2015 Oct 27. PMID: 26615903.

[4] Behura SK, Dhakal P, Kelleher AM, Balboula A, Patterson A, Spencer TE. The brain-placental axis: Therapeutic and pharmacological relevancy to pregnancy. Pharmacol Res. 2019 Nov;149:104468. doi: 10.1016/j.phrs.2019.104468. Epub 2019 Oct 7. PMID: 31600597; PMCID: PMC6944055.

[5] Sasaki K, Norwitz ER. Gonadotropin-releasing hormone/gonadotropin-releasing hormone receptor signaling in the placenta. Curr Opin Endocrinol Diabetes Obes. 2011 Dec;18(6):401-8. doi: 10.1097/MED.0b013e32834cd3b0. PMID: 22024993.

[6] Hirano M, Igarashi A, Suzuki M. Dynamic changes of serum LH and FSH during pregnancy and puerperium. Tohoku J Exp Med. 1976 Mar;118(3):275-82. doi: 10.1620/tjem.118.275. PMID: 772883.

[7] Zen M, Ghirardello A, Iaccarino L, Tonon M, Campana C, Arienti S, Rampudda M, Canova M, Doria A. Hormones, immune response, and pregnancy in healthy women and SLE patients. Swiss Med Wkly. 2010 Apr 3;140(13-14):187-201. PMID: 20175004.

[8] Arck P, Hansen PJ, Mulac Jericevic B, Piccinni MP, Szekeres-Bartho J. Progesterone during pregnancy: endocrine-immune cross talk in mammalian species and the role of stress. Am J Reprod Immunol. 2007 Sep;58(3):268-79. doi: 10.1111/j.1600-0897.2007.00512.x. PMID: 17681043.

[9] Yang R, You X, Tang X, Gao L, Ni X. Corticotropin-releasing hormone inhibits progesterone production in cultured human placental trophoblasts. J Mol Endocrinol. 2006 Dec;37(3):533-40. doi: 10.1677/jme.1.02119. PMID: 17170093.

[10] Tuckey RC. Progesterone synthesis by the human placenta. Placenta. 2005 Apr;26(4):273-81. doi: 10.1016/j.placenta.2004.06.012. PMID: 15823613.

[11] Hızlı D, Köşüş N, Köşüş A, Kasap B, Kafali H, Turhan NÖ. First-trimester reference ranges for decidual thickness and its relation to progesterone levels. J Perinat Med. 2012 Sep;40(5):521-5. doi: 10.1515/jpm-2012-0035. PMID: 23104794.

[12] Leitao B, Jones MC, Fusi L, Higham J, Lee Y, Takano M, Goto T, Christian M, Lam EW, Brosens JJ. Silencing of the JNK pathway maintains progesterone receptor activity in decidualizing human endometrial stromal cells exposed to oxidative stress signals. FASEB J. 2010 May;24(5):1541-51. doi: 10.1096/fj.09-149153. Epub 2009 Dec 21. PMID: 20026682; PMCID: PMC2857868.

[13] Jeschke U, Mylonas I, Richter DU, Höcker I, Briese V, Makrigiannakis A, Friese K. Regulation of progesterone production in human term trophoblasts in vitro by CRH, ACTH and cortisol (prednisolone). Arch Gynecol Obstet. 2005 Jun;272(1):7-12. doi: 10.1007/s00404-005-0728-0. Epub 2005 Apr 16. PMID: 15834733.

[14] Makieva S, Saunders PT, Norman JE. Androgens in pregnancy: roles in parturition. Hum Reprod Update. 2014 Jul-Aug;20(4):542-59. doi: 10.1093/humupd/dmu008. Epub 2014 Mar 18. PMID: 24643344; PMCID: PMC4063701.

[15] Satué K, Marcilla M, Medica P, Ferlazzo A, Fazio E. Testosterone, androstenedione and dehydroepiandrosterone concentrations in pregnant Spanish Purebred mare. Theriogenology. 2019 Jan 1;123:62-67. doi: 10.1016/j.theriogenology.2018.09.025. Epub 2018 Sep 26. PMID: 30292857.

[16] Corcoran JJ, Nicholson C, Sweeney M, Charnock JC, Robson SC, Westwood M, Taggart MJ. Human uterine and placental arteries exhibit tissue-specific acute responses to 17β-estradiol and estrogen-receptor-specific agonists. Mol Hum Reprod. 2014 May;20(5):433-41. doi: 10.1093/molehr/gat095. Epub 2013 Dec 19. PMID: 24356876; PMCID: PMC4004081.

[17] Chang K, Lubo Zhang. Review article: steroid hormones and uterine vascular adaptation to pregnancy. Reprod Sci. 2008 Apr;15(4):336-48. doi: 10.1177/1933719108317975. PMID: 18497342; PMCID: PMC2408771.

[18] Gambino YP, Maymó JL, Pérez-Pérez A, Dueñas JL, Sánchez-Margalet V, Calvo JC, Varone CL. 17Beta-estradiol enhances leptin expression in human placental cells through genomic and nongenomic actions. Biol Reprod. 2010 Jul;83(1):42-51. doi: 10.1095/biolreprod.110.083535. Epub 2010 Mar 17. PMID: 20237333.

[19] Brunton PJ, Russell JA. The expectant brain: adapting for motherhood. Nat Rev Neurosci. 2008 Jan;9(1):11-25. doi: 10.1038/nrn2280. PMID: 18073776.

[20] King AE, Collins F, Klonisch T, Sallenave JM, Critchley HO, Saunders PT. An additive interaction between the NFkappaB and estrogen receptor signalling pathways in human endometrial epithelial cells. Hum Reprod. 2010 Feb;25(2):510-8. doi: 10.1093/humrep/dep421. Epub 2009 Dec 2. PMID: 19955102; PMCID: PMC2806182.

[21] Bai J, Qi QR, Li Y, Day R, Makhoul J, Magness RR, Chen DB. Estrogen Receptors and Estrogen-Induced Uterine Vasodilation in Pregnancy. Int J Mol Sci. 2020 Jun 18;21(12):4349. doi: 10.3390/ijms21124349. PMID: 32570961; PMCID: PMC7352873.

[22] Shao R. Understanding the mechanisms of human tubal ectopic pregnancies: new evidence from knockout mouse models. Hum Reprod. 2010 Mar;25(3):584-7. doi: 10.1093/humrep/dep438. Epub 2009 Dec 19. PMID: 20023297; PMCID: PMC2817566.

[23] Grattan DR. 60 YEARS OF NEUROENDOCRINOLOGY: The hypothalamo-prolactin axis. J Endocrinol. 2015 Aug;226(2):T101-22. doi: 10.1530/JOE-15-0213. Epub 2015 Jun 22. PMID: 26101377; PMCID: PMC4515538.

[24] Honjo H, Kitawaki J, Itoh M, Yasuda J, Yamamoto T, Yamamoto T, Okada H, Ohkubo T, Nambara T. Serum and urinary oestrone sulphate in pregnancy and delivery measured by a direct radioimmunoassay. Acta Endocrinol (Copenh). 1986 Jul;112(3):423-30. doi: 10.1530/acta.0.1120423. PMID: 3751457.

[25] Holinka CF, Diczfalusy E, Coelingh Bennink HJ. Estetrol: a unique steroid in human pregnancy. J Steroid Biochem Mol Biol. 2008 May;110(1-2):138-43. doi: 10.1016/j.jsbmb.2008.03.027. Epub 2008 Mar 29. PMID: 18462934.

[26] Yin P, Arita J. Differential regulation of prolactin release and lactotrope proliferation during

pregnancy, lactation and the estrous cycle. Neuroendocrinology. 2000 Aug;72(2):72-9. doi: 10.1159/000054574. PMID: 10971142.

[27] Soares MJ. The prolactin and growth hormone families: pregnancy-specific hormones/cytokines at the maternal-fetal interface. Reprod Biol Endocrinol. 2004 Jul 5;2:51. doi: 10.1186/1477-7827-2-51. PMID: 15236651; PMCID: PMC471570.

[28] Matalka KZ, Ali DA. Stress-induced versus preovulatory and pregnancy hormonal levels in modulating cytokine production following whole blood stimulation. Neuroimmunomodulation. 2005;12(6):366-74. doi: 10.1159/000091130. PMID: 16557037.

[29] Bachelot A, Binart N. Reproductive role of prolactin. Reproduction. 2007 Feb;133(2):361-9. doi: 10.1530/REP-06-0299. PMID: 17307904.

[30] Tessier C, Prigent-Tessier A, Ferguson-Gottschall S, Gu Y, Gibori G. PRL antiapoptotic effect in the rat decidua involves the PI3K/protein kinase B-mediated inhibition of caspase-3 activity. Endocrinology. 2001 Sep;142(9):4086-94. doi: 10.1210/endo.142.9.8381. PMID: 11517188.

[31] Nagaishi VS, Cardinali LI, Zampieri TT, Furigo IC, Metzger M, Donato J Jr. Possible crosstalk between leptin and prolactin during pregnancy. Neuroscience. 2014 Feb 14;259:71-83. doi: 10.1016/j.neuroscience.2013.11.050. Epub 2013 Dec 4. PMID: 24316468.

[32] Butte NF, Hopkinson JM, Nicolson MA. Leptin in human reproduction: serum leptin levels in pregnant and lactating women. J Clin Endocrinol Metab. 1997 Feb;82(2):585-9. doi: 10.1210/jcem.82.2.3731. PMID: 9024259.

[33] Ngala RA, Fondjo LA, Gmagna P, Ghartey FN, Awe MA. Placental peptides metabolism and maternal factors as predictors of risk of gestational diabetes in pregnant women. A case-control study. PLoS One. 2017 Jul 21;12(7):e0181613. doi: 10.1371/journal.pone.0181613. PMID: 28732072; PMCID: PMC5521813.

[34] Simpson S, Smith L, Bowe J. Placental peptides regulating islet adaptation to pregnancy: clinical potential in gestational diabetes mellitus. Curr Opin Pharmacol. 2018 Dec;43:59-65. doi: 10.1016/j.coph.2018.08.004. Epub 2018 Sep 7. PMID: 30199758.

[35] Licht P, Russu V, Wildt L. On the role of human chorionic gonadotropin (hCG) in the embryo-endometrial microenvironment: implications for differentiation and implantation. Semin Reprod Med. 2001;19(1):37-47. doi: 10.1055/s-2001-13909. PMID: 11394202.

[36] Field T, Diego M. Cortisol: the culprit prenatal stress variable. Int J Neurosci. 2008 Aug;118(8):1181. doi: 10.1080/00207450701820944. PMID: 18589921.

[37] Shams M, Kilby MD, Somerset DA, Howie AJ, Gupta A, Wood PJ, Afnan M, Stewart PM. 11Beta-hydroxysteroid dehydrogenase type 2 in human pregnancy and reduced expression in intrauterine growth restriction. Hum Reprod. 1998 Apr;13(4):799-804. doi: 10.1093/humrep/13.4.799. PMID: 9619527.

[38] Diego MA, Jones NA, Field T, Hernandez-Reif M, Schanberg S, Kuhn C, Gonzalez-Garcia A. Maternal psychological distress, prenatal cortisol, and fetal weight. Psychosom Med. 2006 Sep-Oct;68(5):747-53. doi: 10.1097/01.psy.0000238212.21598.7b. PMID: 17012528.

[39] Chan J, Rabbitt EH, Innes BA, Bulmer JN, Stewart PM, Kilby MD, Hewison M. Glucocorticoid-induced

apoptosis in human decidua: a novel role for 11beta-hydroxysteroid dehydrogenase in late gestation. J Endocrinol. 2007 Oct;195(1):7-15. doi: 10.1677/JOE-07-0289. PMID: 17911392.

[40] Myatt L. Placental adaptive responses and fetal programming. J Physiol. 2006 Apr 1;572(Pt 1):25-30. doi: 10.1113/jphysiol.2006.104968. Epub 2006 Feb 9. PMID: 16469781; PMCID: PMC1779654.

[41] Myatt L, Sun K. Role of fetal membranes in signaling of fetal maturation and parturition. Int J Dev Biol. 2010;54(2-3):545-53. doi: 10.1387/ijdb.082771lm. PMID: 19924634.

[42] Rosen T, Krikun G, Ma Y, Wang EY, Lockwood CJ, Guller S. Chronic antagonism of nuclear factor-kappaB activity in cytotrophoblasts by dexamethasone: a potential mechanism for antiinflammatory action of glucocorticoids in human placenta. J Clin Endocrinol Metab. 1998 Oct;83(10):3647-52. doi: 10.1210/jcem.83.10.5151. PMID: 9768679.

[43] Street ME, Smerieri A, Petraroli A, Cesari S, Viani I, Garrubba M, Rossi M, Bernasconi S. Placental cortisol and cord serum IGFBP-2 concentrations are important determinants of postnatal weight gain. J Biol Regul Homeost Agents. 2012 Oct-Dec;26(4):721-31. PMID: 23241122.

[44] Tian CF, Kang MH. Common stress and serum cortisol and IL-12 levels in missed abortion. J Obstet Gynaecol. 2014 Jan;34(1):33-5. doi: 10.3109/01443615.2013.830089. PMID: 24359046.

[45] Marsman R, Rosmalen JG, Oldehinkel AJ, Ormel J, Buitelaar JK. Does HPA-axis activity mediate the relationship between obstetric complications and externalizing behavior problems? The TRAILS study. Eur Child Adolesc Psychiatry. 2009 Sep;18(9):565-73. doi: 10.1007/s00787-009-0014-y. Epub 2009 Apr 8. PMID: 19353232; PMCID: PMC2721131.

[46] Springer D, Jiskra J, Limanova Z, Zima T, Potlukova E. Thyroid in pregnancy: From physiology to screening. Crit Rev Clin Lab Sci. 2017 Mar;54(2):102-116. doi: 10.1080/10408363.2016.1269309. Epub 2017 Jan 19. PMID: 28102101.

[47] Thorpe-Beeston JG, Nicolaides KH. Fetal thyroid function. Fetal Diagn Ther. 1993 Jan-Feb;8(1):60-72. doi: 10.1159/000263749. PMID: 8452651.

[48] Temboury Molina MC, Rivero Martín MJ, de Juan Ruiz J, Ares Segura S. Enfermedad tiroidea autoinmunitaria materna: repercusión en el recién nacido [Maternal autoimmune thyroid disease: relevance for the newborn]. Med Clin (Barc). 2015 Apr 8;144(7):297-303. Spanish. doi: 10.1016/j.medcli.2013.10.024. Epub 2014 Jan 30. PMID: 24486115.