Chapter

1

The Neuroendocrinology of Pregnancy

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1.1 Introduction

The neuroendocrine mechanisms involved in pregnancy are highly complex and include maternal, placental, and fetal systems, which are critical for implantation, maintenance of pregnancy, and timing of parturition (1), and for regulation of fetal-placental blood flow and fetal growth (2).

The brain and placenta are both central organs in the responses to stress (3), and maternal, fetal, and placental hypothalamus-pituitary-adrenal (HPA) axes play a significant role in controlling some of the adaptive mechanisms during pregnancy (4). The human placenta plays a primary role, as it may synthesize and release several neuroactive factors, including hypothalamus-like and pituitary-like hormones. The neurohormones produced by placental tissue act locally in modulating the release of the pituitary-like hormones, resembling the organization of the hypothalamus-pituitary-target gland axes. Furthermore, they are chemically identical and have the same biologic activities as their neuronal counterparts. Thus, the old concept considering the placenta as a passive organ, responsible only for exchange of gas and nutrients to the fetus, has been replaced by a new perspective where the placenta is a fully competent endocrine organ: Trophoblast, membranes, and maternal decidua produce a large variety of molecules including steroid hormones, hypothalamic-pituitary hormones, neuropeptides, growth factors, and cytokines (Table 1.1) (5). These hormones can exert their biologic effects acting as autocrine, paracrine, and endocrine factors (6, 7). However, the placenta also produces a number of hormones, such as human chorionic gonadotropin (hCG) and placental lactogen (hPL), that are not otherwise synthesized in the organism. Placental hormones enter the maternal and fetal circulation, where they are often present at concentrations far in excess of those found for similar hormones in the nonpregnant state, playing a pivotal role in the maternal-fetal

hormonal dialog. Thus, pregnancy represents a highly complex condition where three neuroendocrine systems (maternal, placental, fetal) are integrating their functions for an optimal pregnancy outcome (Figure 1.1).

1.2 Hypothalamus-Pituitary-Adrenal (HPA) Axis

The HPA axis plays a key role in the neuroendocrine response to stress via cortisol secretion, acting to restore homeostasis following stressful events for survival (8). Corticotropin-releasing hormone (CRH) represents the main regulator of the axis: Released from the hypothalamus, this neurohormone stimulates adrenocorticotropic hormone (ACTH) release from the anterior pituitary, and consequently glucocorticoid secretion from the adrenal cortex. Along with the maternal and fetal brain, the human placenta, decidua, chorion, and amnion produce CRH and urocortins (Ucns) peptides (9). In mammals, the CRH/Ucn family consists of at least four ligands: CRH, Ucn (10), Ucn2, and Ucn3, which are implicated as important neuroendocrine mediators in the physiology of early and late pregnancy and in the mechanisms of parturition (11).

1.2.1 Corticotropin-Releasing Hormone (CRH)

The secretion of maternal HPA axis hormones increases throughout pregnancy and is related to placental function, as circulating maternal CRH originates almost entirely from the placenta (6) (Figure 1.1). However, the responsiveness of the HPA axis to stressors is reduced during pregnancy, as shown by reduced ACTH and corticosteroids, in order to neutralize the impact of stress by minimizing stress-induced fetal exposure to maternal glucocorticoid (12). Unlike CRH, it is uncertain whether maternal plasma ACTH

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Table 1.1. Neuroactive placental factors
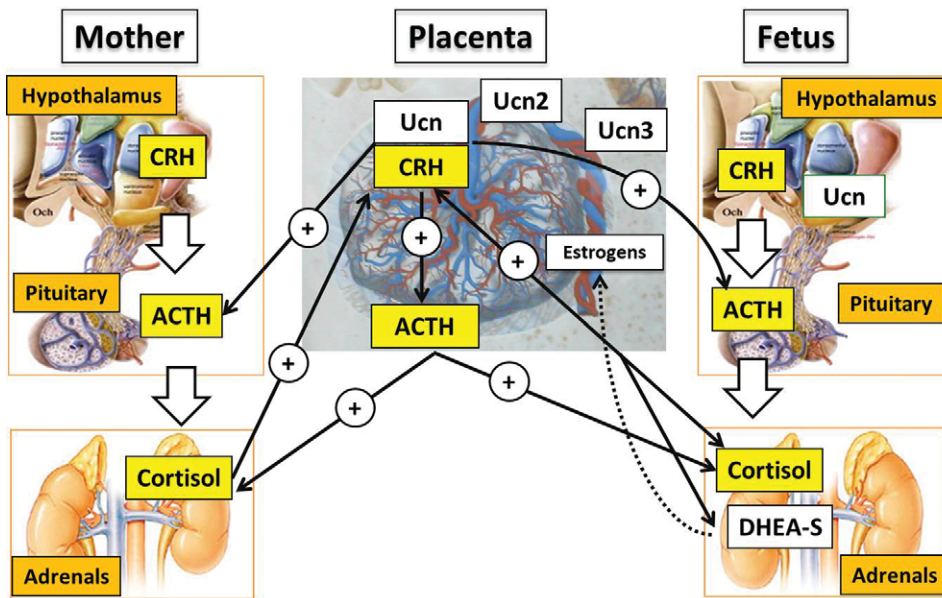
Hypothalamus-like hormones	• Corticotropin-releasing hormone (CRH) • Urocortins (Ucn1, Ucn2, Ucn3) • Gonadotropin-releasing hormone (GnRH) • Growth hormone-releasing hormone (GHRH) • Somatostatin (SST) • Thyrotropin-releasing hormone (TRH) • Oxytocin (OT)
Pituitary-like hormones	• Human chorionic gonadotropin (hCG) • Adrenocorticotropic hormone (ACTH) • Opioids (b-endorphin) • Placental growth hormone (PGH) • Human placental lactogen (hPL)
Neuropeptides	• Neuropeptide Y (NPY) • Chromogranin A (CgA) • Neurokinin B (NKB) • Monoamines
Neurosteroids	• Allopregnanolone
Neurotransmitters	• Dopamine • Epinephrine • Norepinephrine • Serotonin
Growth hormones	• Transforming growth factor-β (TGF-β) • Activin A • Follistatin • Follistatin-related gene (FLRG) • Inhibin A and B • Insulin-like growth factors (IGFs) • IGF-binding proteins (IGF-BPs) • Fibroblast growth factor (FGF) • Epidermal growth factor (EGF) • Vascular endothelial growth factor (VEGF)
Steroid hormones	• Progesterone • Estrogens
Vasoactive peptides	• Adrenomedullin (ADM) • Endothelins (ETs) • Calcitonin gene-related peptide (CGRP) • Parathyroid hormone-related peptide (PTH-rp)
Metabolic hormones	• Leptin • Ghrelin

originates from the maternal pituitary and/or from the placenta. Maternal ACTH and cortisol, but not CRH, undergo a typical circadian rhythmicity in the maternal circulation, suggesting that CRH is mostly of placental origin (13).

In the plasma of nonpregnant women, CRH concentrations are very low (around 15 pg/ml) or undetectable. The human placenta expresses large amounts of CRH (1000 times higher than in myometrium and choriodecidua) resulting in high CRH levels in maternal serum during pregnancy. Plasma CRH levels increase during the first trimester of pregnancy, then rise steadily until term (14). CRH levels are approximately 800 pg/ml during late third trimester and peak (2000–3000 pg/ml) during labor, becoming undetectable within 24 hours after delivery. In the fetal circulation, a linear correlation exists between maternal and fetal plasma CRH levels: CRH concentrations in umbilical venous plasma are higher than in the umbilical artery, supporting the notion that placenta is a major source of fetal plasma CRH (Figure 1.1).

Mechanisms regulating placental CRH release are not the same as those regulating hypothalamic release: prostaglandins (PGs), neurotransmitters (norepinephrine, acetylcholine), neuropeptides, and cytokines (IL-1) all stimulate CRH, whereas progesterone (P4), nitric oxide, and estrogens decrease placental CRH production. In the mother, cortisol inhibits hypothalamic CRH and ACTH release, with a negative feedback. In striking contrast, cortisol stimulates CRH release by the decidua, trophoblast, and fetal membranes, and it drives maternal and fetal HPA activation with a positive feedback loop (15). This positive feedforward system is a unique feature of placental CRH, suggesting that it might not require such "safety switch-off" mechanisms, and the demand for the actions of CRH increases as pregnancy progresses toward term (4). In fact, at term and in labor, circulating levels of CRH, ACTH, and cortisol are increased (16), although they are not necessarily indicative of maternal HPA axis activation.

Placental CRH has complex effects including a role in the onset of labor (17, 18), resembling the timer of a biological clock counting from the early stages of gestation and signaling the timing of parturition (19). Interestingly, maternal CRH levels have been reported to be lower in women delivering post-term and higher in those who will deliver preterm compared to those in women

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Figure 1.1 Maternal, placental, fetal neuroendocrine systems with three hypothalamus-pituitary-adrenal (HPA) axes integrating their functions. CRH, corticotropin-releasing hormone. ACTH, adrenocorticotropic hormone. Ucn, urocortin. DHEA-S, dehydroepiandrosterone sulfate.

delivering at term. These findings corroborate the important role of this neurohormone in regulating the placental "clock" of human pregnancy and in influencing its length (20).

Regarding endocrine functions, CRH regulates implantation, trophoblast cell growth and invasion, tissue remodeling through modulation of secretion of matrix metalloproteinases, and vascular tone through activation of the nitric oxide pathway, as well as inflammation through PGs release (2).

CRH also plays a pivotal role in regulating estrogen and progesterone production in the third trimester (21), corroborating the hypothesis that placental CRH levels are linked to the length of gestation in humans. The rapid rise of CRH in late pregnancy is associated with estriol (E3) surge and critically altered progesterone (P)/E3 and estriol/estradiol (E3/E2) ratios that create an estrogenic environment predisposing to the onset of labor (22). CRH also regulates myometrial contractility, exerting diverse roles at different stages of gestation. In fact, it mediates both relaxation and contraction of myometrium, depending on different patterns of expression and biologic effects of CRH receptors.

CRH and Ucn exert their actions by activating CRH receptors, named CRHR1 and CRHR2 (23). CRH has high affinity only for CRHR1, Ucn shows approximately the same affinity for both receptors, whereas Ucn2 and Ucn3 bind with high affinity only to the CRHR2. Nonpregnant human myometrium expresses three CRHR subtypes: 1α, 1β, and 2β. As pregnancy progresses, the myometrium starts to express CRHR2α.

CRH-R1 and CRH-R2 stimulate divergent signaling pathways. CRH-R1 contributes to the maintenance of myometrial relaxation during pregnancy through activation of the adenylyl cyclase/cAMP pathway. In chorion trophoblast cells, CRH exerts a tonic stimulatory effect on 15-hydroxyprostaglandin dehydrogenase (PGDH) activity, an effect that may help to maintain a metabolic barrier that prevents bioactive PGs passing from the chorioamnion to the myometrium preventing myometrial activation during pregnancy (24). In contrast, at term, CRH induces phosphorylation of CRH-R2 variants, with subsequent stimulation of the phospholipase C/inositol triphosphate pathway and increase of myosin light chain phosphorylation, promoting myometrial contractility (25, 26). Furthermore, CRH induces stimulation of placental and membrane PGs output, and the inhibition of progesterone production (27).

CRH binding protein (CRH-BP) binds circulating CRH with high affinity, inhibiting its

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functions (28); in fact their interaction results in the dimerization of the protein and clearance of CRH from the circulation. Maternal serum CRHBP levels do not change significantly during most of gestation, but they fall during the final weeks of normal pregnancy and still further with the onset of labor (29). Significantly lower CRH and higher CRHBP levels are present in post-term pregnancies, suggesting that the lack of the reciprocal changes in CRH and CRHBP levels may delay the onset of labor.

Fetal stress responses are independent from those of the mother (30): The fetal hypothalamus releases CRH, together with placental CRH, inducing fetal pituitary ACTH secretion and the synthesis of cortisol by the fetal adrenal gland and maturation of the fetal lungs. In turn, the rising cortisol concentrations in the fetus stimulate placental CRH production through a positive feedback mechanism (Figure 1.1). ACTH in turn controls adrenocortical functional development, including angiogenesis and expression of steroidogenic enzymes.

The maturation of the fetal lungs as a result of increasing cortisol concentrations represents a fundamental aspect of fetal adaptive mechanisms to extra-uterine life activated in part by the stress of delivery. Moreover, fetal lung maturation is associated with increased production of surfactant protein A and phospholipids, both pro-inflammatory factors, that may stimulate myometrial contractility through increased production of PGs by fetal membranes and the myometrium itself. Thus, the fetus herself contributes to the onset of labor (15, 31).

Given its multiple effects on a number of placental functions, the role for CRH as a marker of pregnancy pathology has been proposed. CRH is abnormally secreted when obstetric complications occur, such as in pre-term birth (PTB), pre-eclampsia (PE), pregnancy-induced hypertension (PIH), and fetal growth restriction (FGR). In the case of miscarriage, CRH peptide has been found to be more expressed in the placenta in spontaneous abortion than in elective abortion of the same gestational age. In early pregnancy, high glucocorticoid secretion is associated with miscarriage compared with women with ongoing gestation, suggesting that maternal stress in the first trimester is associated with a higher risk for spontaneous abortion (32). Furthermore, CRH expression is significantly higher in preterm than in

term placentas (20) and maternal CRH levels at mid-gestation are higher in women who subsequently would have spontaneous PTB (33). Interestingly, chorioamnionitis associated with PTB activates the placental CRH pathway in vivo (34). In hypertensive disorders of pregnancy, maternal plasma and cord blood CRH levels are higher in women affected by PIH and PE compared to healthy women (35). Additional data confirm that pregnancies complicated by PE and FGR are associated with abnormal placental vascular resistance and abnormally high umbilical vein CRH levels.

1.2.2 Urocortins (Ucns)

Urocortin (Ucn) is synthesized and secreted by placental and fetal membranes, similar to CRH. However, urocortin is undetectable in maternal plasma during pregnancy, with no rise with increasing gestational age (36). Plasma levels are higher at labor, but they do not change significantly at the different stages of labor. Ucn has similar effects as CRH, augmenting matrix metalloproteinase, ACTH, and PGs secretion from cultured human placental cells, enhancing myometrial contractility. Ucn stimulates placental ACTH secretion, via a CRHR1-dependent mechanism, without any significant difference from CRH-induced ACTH release (37). Ucn has high affinity for CRHR1 and CRHR2 families and the CRH binding protein; particularly, Ucn exhibited greater affinity for CRHR2, acting as its natural ligand. Human myometrium expresses Ucn (38), which activates a number of intracellular signaling pathways that contribute to the activation of myometrial contractility.

Ucn2 and Ucn3 are localized in syncytiotrophoblast and extravillous trophoblast cells, while Ucn2 is also localized to blood vessel endothelial cells, leading to the suggestion of a role of Ucn2 in regulating the placental vascular endothelial behavior. In the fetal membranes, Ucn2 is distributed only in amnion, while Ucn3 is found in both amnion and chorionic cells (39). Ucn2 and Ucn3 modulate HPA axis activity at the hypothalamic level in a paracrine or autocrine fashion, but unlike CRH and Ucn, peripheral Ucn2 or Ucn3 administration does not increase either pituitary or placental ACTH secretion (39). Hypothalamic Ucn2 expression is increased by glucocorticoids and modulates basal HPA-axis circadian amplitude (40). Ucn2 plays a

major role in the control of myometrial contractility during human pregnancy, involving the binding with CRHR2 (41).

Maternal plasma and cord blood Ucn levels have been found to be higher in women delivering pre-term compared to those delivering at term. Furthermore, Ucn levels in arterial cord blood are higher than in venous cord blood and in maternal plasma, suggesting a fetal rather than an exclusively placental source of the peptide at preterm parturition (42). Similarly, maternal plasma and cord blood Ucn levels are higher in women affected by hypertensive disorders of pregnancy associated with FGR compared with healthy women (43). Interestingly, early PE placental samples show stronger immunoreactivity for Ucn2 than for Ucn3, while Ucn3 immunostaining was stronger in late PE samples (44). Ucn has been found to contribute to the pathogenesis of FGR possibly through negative regulation of placental system A activity, which represents a placental amino acid transporter whose normal activity is fundamental for maintaining fetal growth (45).

1.3 Hypothalamus-Pituitary-Gonadal Axis: Gonadotropin-Releasing Hormone (GnRH)

The gonadotropin-releasing hormone (GnRH) is the main regulator of the hypothalamus-pituitary-gonadal axis. It acts on the anterior pituitary to induce the synthesis and secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), in turn exerting their actions on the ovaries.

From early pregnancy, the hypothalamus-pituitary-gonadal axis decreases its function, because of the rise of maternal serum inhibin levels during the first weeks of gestation and the secretion of maternal progesterone, limiting ovarian functioning in pregnancy.

However, GnRH is produced also by the human placental tissue and it is immunologically and chemically identical to hypothalamic GnRH (46). The total placental concentration of GnRH progressively increases during the first 24 weeks of gestation but declines later in pregnancy. Interestingly, placental and circulating GnRH levels increase during the first trimester, probably modulating human chorionic gonadotropin (hCG) production by trophoblast cells (47). Furthermore, it has been shown in animal models that GnRH causes a

significant decrease in the maximal contraction intensity of myometrium, inhibiting the release of placental prostaglandins. It has been observed that maternal circulating GnRH levels at 25–35 weeks of gestation were significantly higher in women who later had post-term pregnancies, and conversely, it was found to be significantly lower in those undergoing PTB.

1.4 Hypothalamus-Growth Hormone Axis: GH-Releasing Hormone (GHRH) and Somatostatin (SST)

Synthesis and secretion of pituitary growth hormone (GH) is regulated by two hypothalamic-releasing factors: GH-releasing hormone (GHRH) and somatostatin (SST), which has inhibitory properties (48). In women, circulating concentrations of GH-like immunoreactivity increase during pregnancy, although this is not associated with pituitary production. In fact, it rather reflects placental production of a bioactive GH variant (49).

During early pregnancy, pituitary GH is only measurable in maternal serum and it is secreted in a highly pulsatile pattern; conversely, in late pregnancy, 85 percent of circulating levels of bioactive GH derive from placenta, with relatively constant maternal serum concentrations. Placental GH, unlike pituitary GH, is unresponsive to hypothalamic GHRH, whereas glucose is the primary modulator of placental GH secretion. In fact, hypoglycemia induces placental GH synthesis with subsequent increase of maternal blood glucose level, protecting the fetus from nutrient deficiency (50). Placental GH stimulates insulin-like growth factor 1 (IGF-1) and its binding protein (IGFBP-3), reducing plasma clearance of IGF-1 and resulting in negative feedback suppression of maternal GH secretion.

SST levels in maternal circulation in pregnancy do not differ from nonpregnant state, suggesting a scarce placental contribution, while levels in fetoplacental circulation originate from the fetus.

1.5 Hypothalamus-Pituitary-Thyroid Axis

The hypothalamic thyrotropin-releasing hormone (TRH) regulates the release of thyroid-stimulating

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hormone (TSH) by the anterior pituitary, representing the major effector on thyroid function. Human placenta shows immunoreactivity for TRH, although its bioactivity is still controversial. It seems that placental human chorionic gonadotropin (hCG) plays a major role is in regulating thyroid function in pregnancy. It is structurally similar to TSH and is able to bind TSH receptors with subsequent thyrotropic activity.

hCG belongs to the glycoprotein hormones family that also comprises LH, FSH and TSH. All members are heterodimers consisting of an α and a β subunit. The α subunit is common to all four glycoprotein hormones, while the β chains determine the biological activity and display extensive homology; that between hCG and LH about 80 percent. hCG is produced in large amounts by syncytiotrophoblasts. It is elaborated by all types of trophoblastic tissue, including that from hydatiform mole and choriocarcinoma.

The primitive trophoblast produces hCG very early in human pregnancy, since hCG is detectable 9 days after the midcycle LH peak. Maternal serum hCG peaks at 8–10 week and then declines to reach a plateau at 18–20 week of gestation (51). The elevation in circulating hCG seems to cause a transient fall in maternal serum TSH near the end of the first trimester in normal pregnancy. Thus, the lowering of TSH corresponds to a transient and partial blunting of the pituitary-thyroid axis associated with an increased hormonal output from the thyroid (52).

1.6 Oxytocin

Oxytocin (OT) is synthesized by neurons of the supraoptic and paraventricular nucleus in the hypothalamus and secreted by the posterior pituitary; its major target organs are the pregnant uterus and mammary glands, as it regulates myometrial contractility and milk ejection (53). Although placental expression and secretion of OT has been shown, their contribution to the mechanisms of parturition remains not fully elucidated. Placental OT secretion is increased by several paracrine factors such as CRH, activin A, and PGs operating within human intrauterine tissues.

Circulating OT levels gradually rise in pregnancy and become even higher during labor, when pulses of oxytocin become progressively bigger and more frequent. Basal levels of OT

increased three- to four-fold during pregnancy and pulses increase in frequency, duration, and amplitude from late pregnancy through labor. A large oxytocin pulse occurs with the birth, and pulses continue afterwards, contributing to placenta expulsion and preventing postpartum bleeding (54). At the onset of labor, the uterine sensitivity to OT markedly increases in association with both an upregulation of OT receptor mRNA levels and a strong increase in the density of myometrial OT receptors, reaching a peak during early labor (53).

Given that the placental content of OT is approximately five times greater than in the posterior pituitary lobe, it is possible that the placenta might be the main source of OT during pregnancy. Estrogens are the major regulators of OT expression, inducing an increased expression of OT mRNA in decidua, chorion, and amnion in a concentration-dependent manner and with a bimodal response pattern. Indeed, nocturnal elevation of maternal plasma OT and estradiol concentrations correlate with circadian uterine activity (55).

Fetal membranes (amnion and chorion) and maternal decidua transmit hormonal signals to the myometrium and contribute to local changes in the estrogen-to-P4 ratio, suggesting that OT may act primarily as a local mediator and not as a circulating hormone during parturition (56).

During labor, OT is released into both the blood and brain, with high oxytocin levels in the cerebrospinal fluid, acting as a neuromodulator, with widespread central effects. OT enhances mood and wellbeing, promotes friendly social interactions, reduces anxiety and pain, lowering physiological and psychological stress. In addition, it reduces sympathetic nervous system activity ("fight or flight") and increases parasympathetic nervous system activity, playing a major role in influencing maternal behavior (54, 57).

1.7 Prolactin and Placental Lactogen (hPL)

Prolactin (PRL) is produced by lactotroph cells in the anterior pituitary gland under the inhibitory control of dopamine (DA). High circulating PRL levels are essential for maintaining pregnancy by providing luteotropic support to the corpus luteum, thereby stimulating progesterone secretion in early pregnancy (58).

The increasing PRL levels throughout gestation are linked to increasing estrogen levels, which also rise from early pregnancy. In humans, the placenta produces an increasing amount of placental lactogen (hPL) throughout pregnancy (59). hPL is structurally similar to PRL and binds to PRL receptors. Differently from PRL, hPL is not subjected to hypothalamic regulation by DA, hence providing a source of lactogenic hormones that is not subject to the normal negative feedback regulation (60).

The levels of hPL in maternal circulation are very low in early pregnancy and increase progressively, showing some correlation with placental weight. hPL accounts for 7–10 percent of proteins synthesized by the placenta at term, and the production rate of hPL increases as pregnancy progresses, approximately in proportion to placental mass with peak levels being reached during the last weeks of gestation. Thus, hPL represents one of the major metabolic and biosynthetic activities of the syncytiotrophoblast in humans (about 1g/day production near term) (61).

Maternal serum hPL levels reflect placental biosynthesis and are positively correlated with the size of the fetus (62), suggesting the possibility of using this hormonal marker for the screening of FGR. The rate of change of serial hPL measurements correlated well with intrauterine fetal growth velocity in the third trimester as estimated by ultrasound and to the deviation in birth weight (63). Elevated lactogen hormones contribute to regulating several functions: establishment of maternal behavior; food intake, suppression of stress responses during late pregnancy and lactation, to minimize the risk of adverse fetal programming from glucocorticoids; prevention of stress-induced hyperthermia; regulation of oxytocin neurons during parturition and lactation, hence contributing to myometrial contractility and milk ejection; and maternal recognition of the offspring, possibly by PRL-induced neurogenesis (64, 65).

1.8 Other Neuroendocrine Factors

1.8.1 Neuropeptide Y (NPY)

Neuropeptide Y (NPY) is a sympathetic neurotransmitter discovered in 1982 and has been shown to be involved in increased blood pressure, angiogenesis, and vasoconstriction. Sympathetic nerves and chromaffin cells of the adrenal glands have been hypothesized to be the major source of circulating NPY outside of pregnancy. In pregnant women, acidic extracts of human placental tissues collected at term contain high immunoreactive NPY (66).

NPY is present in cervical tissue from both early pregnant women and women at term, but no difference in intensity or distribution of NPY-containing nerves was demonstrated between early and term pregnant women or between women in labor and women before onset of labor. In pregnant women, maternal plasma NPY levels are higher than in nonpregnant women, without significant changes throughout gestation (67). Plasma NPY levels fall within a few hours after delivery, supporting the placental origin of the circulating NPY in pregnancy.

A role of NPY during labor at term and preterm is yet to be defined, but a functional association between the increase of NPY during labor and vaginal delivery is in accordance with the spontaneous labor-induced increase of other stress-related hormones such as catecholamines, cortisol and ACTH. It has been suggested that NPY is implicated in PE and PIH, as elevated maternal plasma NPY levels have also been reported in women affected by hypertensive disorders (68), whereas a reduced placental expression of NPY was observed, suggesting the involvement of the receptors in the abnormalities of placental angiogenesis (66).

1.8.2 Relaxin

Relaxin is a peptide hormone that is a member of the insulin family. In women, circulating relaxin is a product of the corpus luteum of pregnancy, but is also synthesized by other reproductive organs such as the uterus, decidua, and placenta, where relaxin acts locally. Circulating relaxin is secreted in a pattern similar to that of hCG.

Relaxin binds to its receptor RXFP1, which has been localized to a wide variety of reproductive and non-reproductive tissues. Relaxin has many uterotropic effects including stimulating uterine growth and vascularization, remodeling extracellular matrix components, and regulating vascular endothelial growth factor in preparation for implantation. Evidence also supports a role for relaxin in the systemic maternal vascular adaptations required for a healthy pregnancy.

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Diminished relaxin levels in early pregnancy are linked with increased risks of miscarriage and the development of preeclampsia (69). Furthermore, it has been shown that women who are more likely to deliver preterm have increased circulating relaxin levels (70).

1.8.3 Parathyroid Hormone-Related Protein (PTHrP)

Parathyroid hormone-related protein (PTHrP) is an oncofetal protein that is expressed in many mammalian tissues. There is substantial evidence to support its role in pregnancy and labor as a placental calcium transport activator, potent vasorelaxant, and inhibitor of uterine contractions (71).

Human amnion is a major source of PTHrP and PTHrP mRNA abundance in amnion decreases during labor at term. Similarly, there is a dramatic decrease in amniotic fluid PTHrP concentrations associated with term labor, which is not evident in amniotic fluid obtained from preterm labor. These results suggest that at term, the dramatic decrease in PTHrP activity in tissue and amniotic fluid might be part of the physiological mechanism involved in the onset and/or progression of labor (72).

1.8.4 Opioids

Three families of opioid peptides are recognized: endorphin (END), enkephalin (ENK), and dynorphin (DYN). They derive from three prehormones: pro-opiomelanocortin (POMC) for β-END, proenkephalin (P-ENK) for ENK and prodynorphin (P-DYN) for DYN. Mu (μ), kappa (κ), and delta (δ) are the main opioid receptor types, but κ receptors are the more important type present in the placenta. Placental content of κ receptors increases with gestational age, and term placental content of κ receptors correlates with type of delivery.

CRH stimulates pro-opiomelanocortin hormone (POMC) release from human cultured placental cells, suggesting placental regulation of POMC secretion, somewhat similar to that occurring in pituitary cells. However, in contrast to the negative feedback activity of glucocorticoids, dexamethasone is not effective either in suppressing ACTH or b-END release from placental cells or in reducing the CRH-induced release of placental ACTH/b-END release. Indeed, there is abundant evidence to show that corticosteroids increase rather than decrease expression and synthesis of CRH from trophoblasts.

Many studies agree on a large increase of plasma b-END during labor and at parturition, although they do not indicate whether the peptide has pituitary or placental origin. Maternal plasma levels of ENK are not significantly different from those of nonpregnant women and do not change throughout pregnancy, supporting a local role of the peptide. On the contrary, maternal plasma DYN levels in the third trimester and at delivery are higher than in nonpregnant women and high levels are also detectable in amniotic fluid and in umbilical vein plasma (73).

1.8.5 Neurosteroids

The placenta is a source of several neurosteroids comprising progesterone itself, its derivatives 5a-pregnane-3a-ol-20- one (allopregnanolone) and 5a-dihydroprogesterone, and its precursor pregnenolone sulfate (74). Apart from progesterone, the role of placental neurosteroids in the physiology of pregnancy is largely unknown. These hormones may contribute to the neurochemical and behavioral changes of pregnancy and puerperium because they interfere with GABAergic circuits and have anxiolytic effects (75).

The levels of allopregnanolone in maternal serum increase progressively during gestation and, in contrast to progesterone, are augmented in hypertensive complications of pregnancy (76). In PE, there is an increased activity of tyrosine hydroxylase in placental tissue, and this is likely to contribute the higher levels of catecholamines in the maternal circulation (77). It is also a neuroactive hormone and may contribute to the psychological adaptation associated with pregnancy and puerperium. In fact, serum allopregnanolone levels were detectable postpartum and were significantly decreased in women with maternity "blues" (78).

A recent study showed that in healthy pregnant women, maternal serum allopregnanolone and progesterone levels significantly increased throughout gestation. No major changes were found at delivery, with the exception of a significant decrease of maternal and cord serum allopregnanolone levels during emergency cesarean section (76). This suggests the critical role of these

steroids in maternal brain adaptation during pregnancy and perhaps in the development of the fetal brain. It has been suggested that allopregnanolone is brain protective during PTB or FGR, reducing the impact of hypoxia (79).

1.9 Conclusions

The neuroendocrine system in pregnancy involves highly complex maternal, fetal, and placental mechanisms, which are critical for the maintenance of pregnancy, the timing of parturition, fetal growth, and protection from adverse fetal programming. The brain and placenta are both central organs in the responses to stress, and the maternal, fetal, and placental hypothalamus–pituitary–adrenal (HPA) axes play a significant role in controlling some of the adaptive mechanisms during pregnancy. Indeed, the placenta, may be considered as a neuroendocrine organ rich in neurohormones, neuropeptides, and neurosteroids. Stress-related hormones, such as CRH, urocortins, oxytocin, and prolactin, are key placental neuroendocrine factors mediating both endocrine (metabolism, immune function, cardiovascular changes) and paracrine (uterine contractility, local hormone production) mechanisms involved in term and pre-term birth. Aberrations in neurohormones secretion, as an adaptive response of the feto-placental unit to adverse environmental conditions, may contribute to the development of gestational disorders, such as hypertensive disorders of pregnancy, intrauterine growth restriction, and gestational diabetes.

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