Chapter

The Interaction between Maternal and Fetal Hypothalamic – Pituitary – Adrenal Axes

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Abstract

The Hypothalamic – Pituitary – Adrenal (HPA) Axis is a unique system that mediates an immediate reactivity to a wide range of stimuli. It has a crucial role in synchronizing the behavioral and hormonal responses to internal and external threats, therefore, increases the chance of survival. It also enables the body systems to adapt to challenges put up by the pregnancy. Since the early stages of pregnancy and throughout delivery, HPA axis of the mother continuously navigates that of the fetus, and both have a specific cross talk even beyond the point of delivery and during postnatal period. Any disturbance in the interaction between the maternal and fetal HPA axes can adversely affect both. The HPA axis is argued to be the mechanism through which maternal stress and other suboptimal conditions during prenatal period can program the fetus for chronic disease in later life. In this chapter, the physiological and non-physiological communications between maternal and fetal HPA axes will be addressed while highlighting specific and unique aspects of this pathway.

Keywords: Hypothalamic–Pituitary–Adrenal Axis, glucocorticoids, maternal stress, fetal programming, intrauterine environment

1. Introduction

It is fundamental to know that HPA axis is considered among the few body systems that start functioning as early as 8–12 weeks of gestation [1]. This indicates that HPA axis is a vital system for fetal development, where Corticotrophin releasing hormone (CRH) and Adrenocorticotropic hormone (ACTH) are crucial for pituitary growth, adrenal cortical differentiation and maturation, as well as steroidogenesis in the fetus, which is driven mainly via Vascular Endothelial Growth Factor (VEGF) and epidermal growth factor (EGF) [2, 3]. Moreover, fetal HPA axis promotes other fetal organ structural and functional maturation such as lung, liver, gastrointestinal tract, central nervous system (CNS) and other organs important for postnatal thrive [4]. However, it has been found that early fetal environment can have detrimental effects on the proper physiological response of HPA axis, and subsequently can increase fetal risk of diseases later in life. In this chapter, possible intrauterine influences on this crucial pathway will be explored.

2. Development and Anatomy of the pituitary gland

The hypophysis is a blend of two tissues. Around week 3 of gestation, a finger of ectoderm grows upward from the roof of the mouth forming a protrusion which known as Rathke's pouch [5]. Later, this will develop into the anterior pituitary or adenohypophysis (**Figure 1A**). Simultaneously, another projection of ectodermal tissue evaginates ventrally from the diencephalon of the developing brain and form the posterior pituitary or neurohypophysis. As the fetus grows and develops, the two tissues grow into one another and become tightly apposed, but their structure remains distinctly different, reflecting their differing embryological origins (**Figure 1B**).

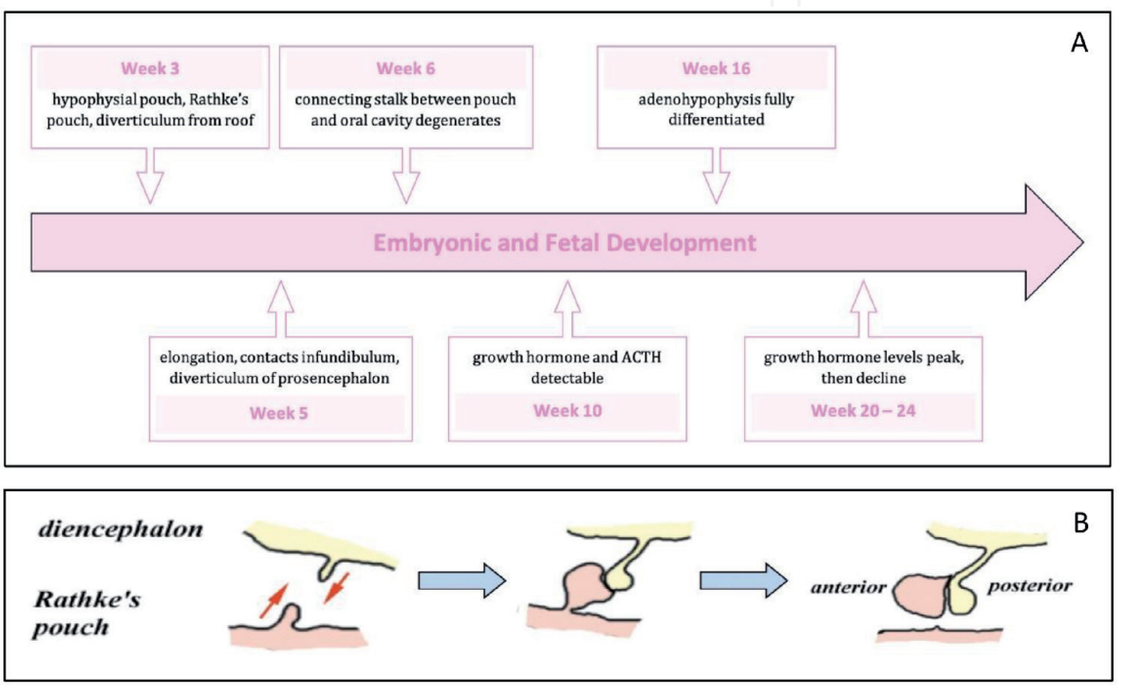

Figure 1.
(A) Timeline of fetal pituitary gland development. (B) Pituitary gland embryogenesis.

Based on the histological features, the adenohypophysis and neurohypophysis are subdivided as follow: (**Figure 2**)

- Adenohypophysis (Anterior pituitary):

  Pars distalis: It is the distal thick round part of the adenohypophysis.
  Pars tuberalis: It is the longitudinal part that surrounds the infundibular stalk.
  Pars intermedia: It is a thin layer of tissue that is separated from the pars distalis by a hypophyseal cleft.

- Neurohypophysis (Posterior pituitary):

  Pars nervosa: It is the thick, round distal part of the posterior pituitary.
  Median eminence: It is the upper section of the neurohypophysis above the pars tuberalis.

  Infundibular stalk: It is the "stem" that connects the pars nervosa to the base of the brain [6].

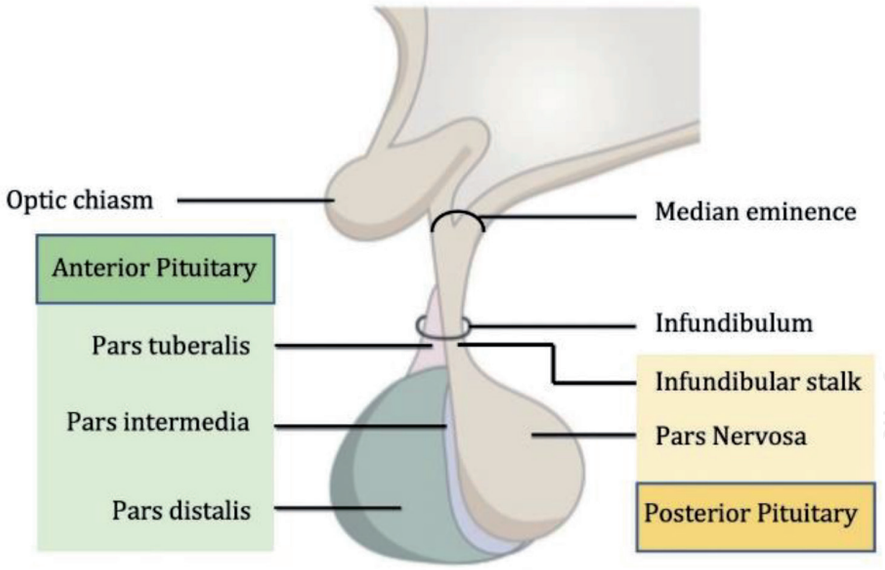

Figure 2.
Anatomy of human pituitary gland.

3. Basic regulation of HPA Axis

The HPA axis is regulated precisely and continuously. The main CNS regulation of HPA axis is through activation of corticotrophin releasing hormone (CRH) from the paraventricular nuclei (PVN) whose cell bodies are located in the hypothalamus

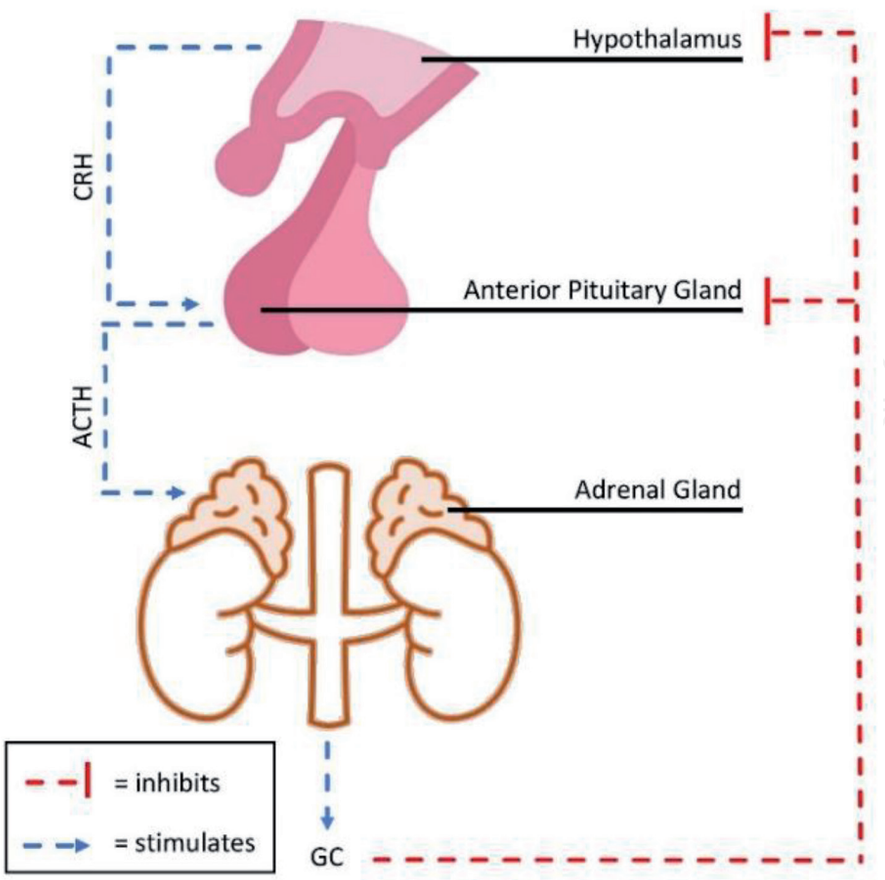

Figure 3.
Basic physiology of HPA axis regulation. CRH, corticotrophin releasing hormone; ACTH, adrenocorticotropic hormone; GC, glucocorticoids.

and also produce arginine vasopressin (AVP). Through pituitary-portal circulation in median eminence of the hypothalamus, CRH will be secreted and carried to the anterior loop of the pituitary gland. Subsequently, this will stimulate the secretion of Adrenocorticotropic hormone (ACTH) into the peripheral circulation. As a result, the adrenal cortex will be stimulated for synthesis and secretion of glucocorticoids into the blood stream (**Figure 3**) [7].

4. Circadian rhythm of cortisone secretion

The cortisone secretion in our circulation exhibits a specific regular rhythm known as the circadian rhythm (**Figure 4**). This is because plasma cortisone level will be high in early morning and gradually decreases in the circulation as we approach the night, and reaches its lowest level, the nadir, during early hours of our sleep. Then, the plasma level of cortisone gradually increases to return to its high level. This pattern can be disrupted by many factors such as stress, disease, exercise, and during physiological adaptation to pregnancy.

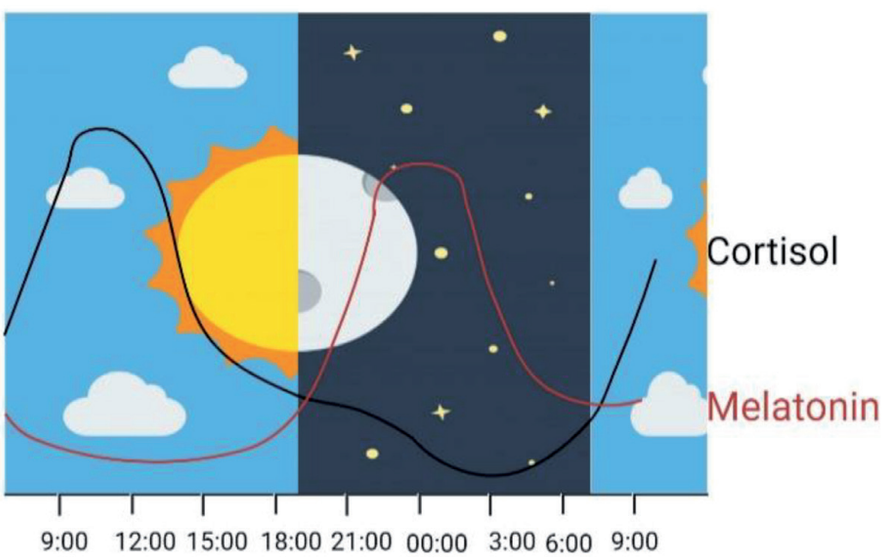

Figure 4.
Circadian rhythm of cortisol secretion.

5. Molecular mechanism of glucocorticoid action

The glucocorticoid receptor (GR), a member of the nuclear steroid receptor superfamily that acts as a ligand-dependent transcription factor to regulate the expression of glucocorticoid-responsive genes [8].

The GR can activate or suppress gene expression depending on the glucocorticoid response element sequence in the promoter region of GR responsive genes or binding DNA indirectly via other transcription factors (**Figure 5**). The association of GR with various cell types, such as ovary, suggests that it has a direct impact on gonadal reproduction [9, 10].

Glucocorticoid receptors are usually found in the cytoplasm as a complex with heat shock proteins (HSP) 90, 70, and 23. When the glucocorticoids are secreted from the adrenal cortex, they enter the target cell cytoplasm and mobilize the HSP to bind the GR. This complex will then be translocated to the nucleus,

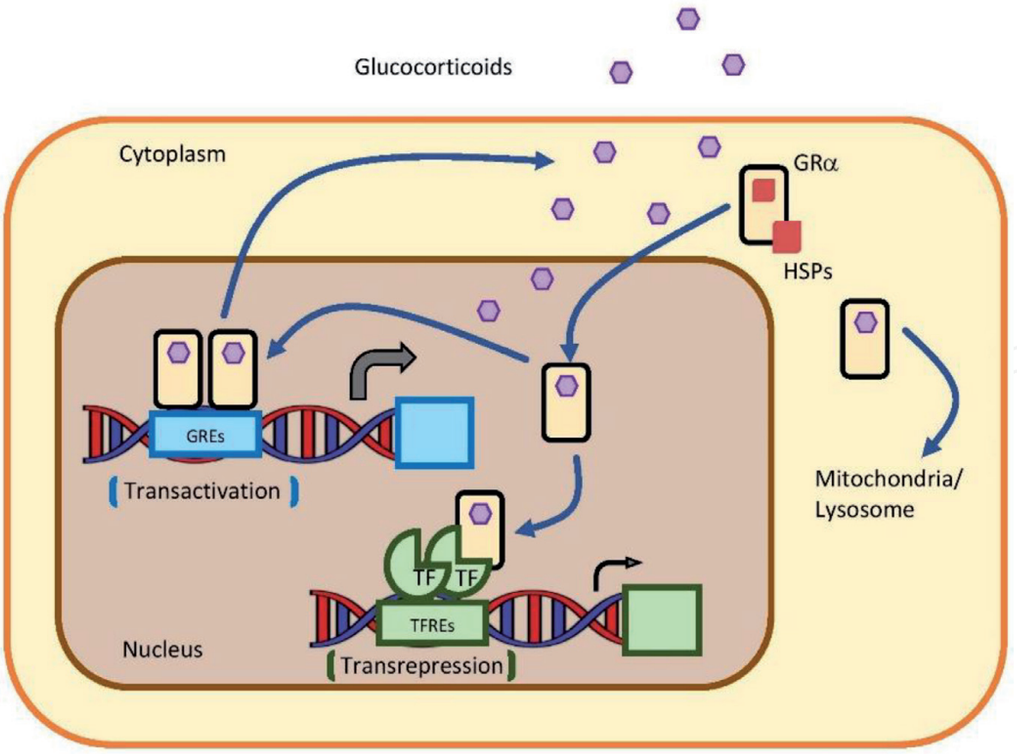

Figure 5.
Molecular mechanism of glucocorticoid action. GRα, glucocorticoid receptor alpha; HSPs, heat shock proteins; GREs, glucocorticoid responsive elements; TF, transcription factor; TFREs, transcription factor responsive elements.

where it binds to a specific DNA sequence in the promotor region of the GR responsive genes, resulting in activation of gene expression via attracting other transcription factors, which will bind to the promotor region as well as RNA polymerase II. GR can also modulate target gene expression through protein–protein interaction rather than direct DNA binding [11–13].

6. Hypothalamic pituitary adrenal Axis interaction with different body systems

The HPA axis is a very complex system that plays a crucial role in many physiological and pathological processes in the human body. One of earliest evidence that has led to the discovery of adrenal hormones and its fundamental functions was dated back to 1855 [14]. Thomas Addison found that adrenal insufficiency was associated with a group of manifestations that indicate dysfunction of other systems. Among these manifestations is excess of circulating lymphocytes. This has been confirmed in other studies that show adrenal gland removal will eventually result in thymus gland hypertrophy [15]. Hence, the wide pharmacological use of glucocorticoids to suppress the immune response in severe inflammation and anaphylactic reaction is mainly based on this interaction between the immune system and the HPA axis. Moreover, Addison noted that other systems involved include the gastrointestinal system (nausea, vomiting, loss of appetite and abdominal pain), cardiovascular system (hypotension), musculoskeletal system (muscle and joint pain and extreme fatigue), integumentary system (hyperpigmentation and hair loss), nervous system (irritability, depression and behavioral abnormality) and endocrine system (hypoglycemia).

7. Interaction between HPA Axis and reproductive hormones

It has been found that the HPA axis exhibits inhibitory effects on the female reproductive system through the inhibitory effects of CRH and CRH-induced proopiomelanocortin peptides on the hypothalamic gonadotropin-releasing hormone secretion. Moreover, glucocorticoids will suppress pituitary secretion of luteinizing hormone (LH) as well as ovarian production of estradiol and progesterone, with increased peripheral tissue estrogen resistance. Therefore, it was evident that stress, eating disorders, chronic excessive exercise, melancholic depression, chronic alcoholism, and Cushing disease result in patients suffering from amenorrhea, known as hypothalamic amenorrhea. This is characterized by low follicular stimulating hormone (FSH), LH, Estradiol (E2) and progesterone, associated with anovulation at the same time, and hence the name hypo-gonadotrophic hypogonadism.

On the other hand, estrogen is a profound stimulator of CRH gene promotor region and will, therefore, cause an increase in CRH production and its end-product, cortisone, rendering the female body in a hypercortisolism state, especially around the ovulation time of the menstrual cycle and during the early stages of pregnancy.

Reproductive tissue is found to be under the influence of the local HPA axis hormones. The ovaries and the endometrium both contain CRH and its receptors as autocoid regulators. These HPA axis components are crucial in the ovulatory process, corpus luteum lysis, endometrial shedding in menstruation, and blastocyst endometrial implantation, if pregnancy occurs. Placental CRH plays an important role in the adaptation of other systems to pregnancy and acts as a parturition clock, involved in the initiation of labor [16].

The Gonadal function is under the influence of the hypothalamic–pituitary-gonadal (HPG) axis, which is run just parallel to HPA axis. In the HPG axis, the Gonadotrophin-releasing hormone (GnRH) released from the hypothalamus will be transported by the portal circulation to the anterior pituitary to enhance and cause the release of gonadotrophic hormone, FSH, and LH. FSH will bind its receptors and promote granulosa cell growth and release of estradiol and other hormones like inhibin, activin and follistatin. Whereas LH will promote the oocyte maturation, ovulation, and corpus luteum luteinization. High levels of circulating estrogen and progesterone can cause negative feedback inhibition on hypothalamic release of GnRH and pituitary production of FSH and LH. In situations of high glucocorticoid release, as in stress or in Cushing disease, the individual will suffer from hypogonadotropic hypogonadism. Glucocorticoids cause gonadal dysfunction through binding to glucocorticoid receptors in the hippocampus region of the brain and will, subsequently, affect the individual behavior and cause inhibition of GnRH release. This will lead to a significant reduction in FSH and LH production with subsequent decrease in circulating estrogen and progesterone hormones. Glucocorticoids impact the ovaries directly by inhibiting steroid hormone synthesis or causing glucocorticoid-induced apoptosis [17, 18].

8. HPA Axis during pregnancy and labor

It is clear now that HPA axis interacts with the reproductive hormones and plays an essential role in the normal menstrual cycle, ovulation, and embryo endometrial implantation. However, this interplay is very precise, necessitating a balance between the levels of the glucocorticoids and reproductive hormones to maintain normal fertility and reproductivity of the human being.

During early pregnancy, in human, the cortisol level is lower than that in late pregnancy. As the pregnancy continues, the cortisol level increases, resulting in a greater difference between nadir and peak. The lower levels of glucocorticoids in early pregnancy are suggested to facilitate the blastocyst implantation in the endometrium, as evidenced by higher salivary cortisol levels 1–3 weeks post-conception found in women with miscarriage when compared to those with continuous pregnancy.

Women with chronic stress in early pregnancy have been noted to have blunting of cortisol levels in the morning, with no change in the nadir point of the circadian rhythm. As pregnancy progresses to mid and late gestation, HPA control will be altered and hypo-responsiveness to stress will also be evident. Unfortunately, the placental production of HPA peptides will challenge precise maternal HPA axis function assessment [19, 20].

However, in animal studies, in early pregnancy, the basal and stress-exposed HPA axis activities were found to be similar to non-pregnant animals. Nonetheless, in late pregnancy, pregnant rats show reduced basal activity of HPA axis in addition to less reactivity to stress exposure. The hypo-responsiveness in late pregnancy has been investigated in animal models. In rats, the decreased HPA axis activity and hypo-responsiveness to stress in late pregnancy could be due to attenuated vasopressin secretion from the hypothalamus with maintained CRH. The lack of augmenting vasopressin effect will result in a weak response of the anterior pituitary to CRH and subsequently, less ACTH release in basal conditions and upon stress exposure. Moreover, there will be reduced excitatory input signals from the stress processing network in the limbic forebrain, brainstem and other brain centers delivered to PVN in the hypothalamus. On the other hand, some other experimental studies on rats found that progesterone neuropeptide metabolite, allopregnanolone, exhibits an inhibitory effect on HPA axis. Allopregnanolone level is higher in late pregnancy than in early pregnancy due to higher levels of circulating progesterone hormone [21]. Other research groups have postulated that an increased level of circulating cortisol in maternal circulation towards the end of the pregnancy downregulates the hypothalamic CRH release and mediates hypo-responsiveness to stress [22–24]. This HPA axis hypo-responsiveness to stress during late pregnancy could be a biological defense mechanism to maintain the fetus in a safe environment, clear of any detrimental effect of stress-induced high glucocorticoid secretion [21, 25].

The fetus, also, protected from the unwanted effects of high maternal glucocorticoids by placental 11 β Hydroxysteroid dehydrogenase B2 enzyme (11β HSDB2) (**Figure 6**). This enzyme is responsible for inactivating 80–90% of maternal cortisol to inactive cortisone before delivering it to the fetal circulation. Despite all these natural mechanisms to minimize fetal overexposure to maternal glucocorticoids, these mechanisms fail to offer such protection during maternal stress, infection, and inflammation. Maternal and amniotic fluid (fetal) cortisol levels were both found to have a positive correlation, indicating that any increase in maternal serum cortisol level will be associated with some degree of fetal cortisol levels as well (as measured by amniotic fluid) [26].

Interestingly, it has been found across different species, including human, that ACTH and cortisol are increased on the day of parturition [27–35]. During the first and second stages of labor (cervical dilation and fetal expulsion, respectively), there will be high maternal HPA axis hormones [28, 36–39]. This could be contributed to by increased endometrial and placental CRH and ACTH, which subsequently induces fetal HPA axis hormones secretion, including ACTH and cortisol, during the third trimester of pregnancy and up to the time of delivery. The unique biological role of placental CRH is to act as a stopwatch for pregnancy and determine the labor initiation

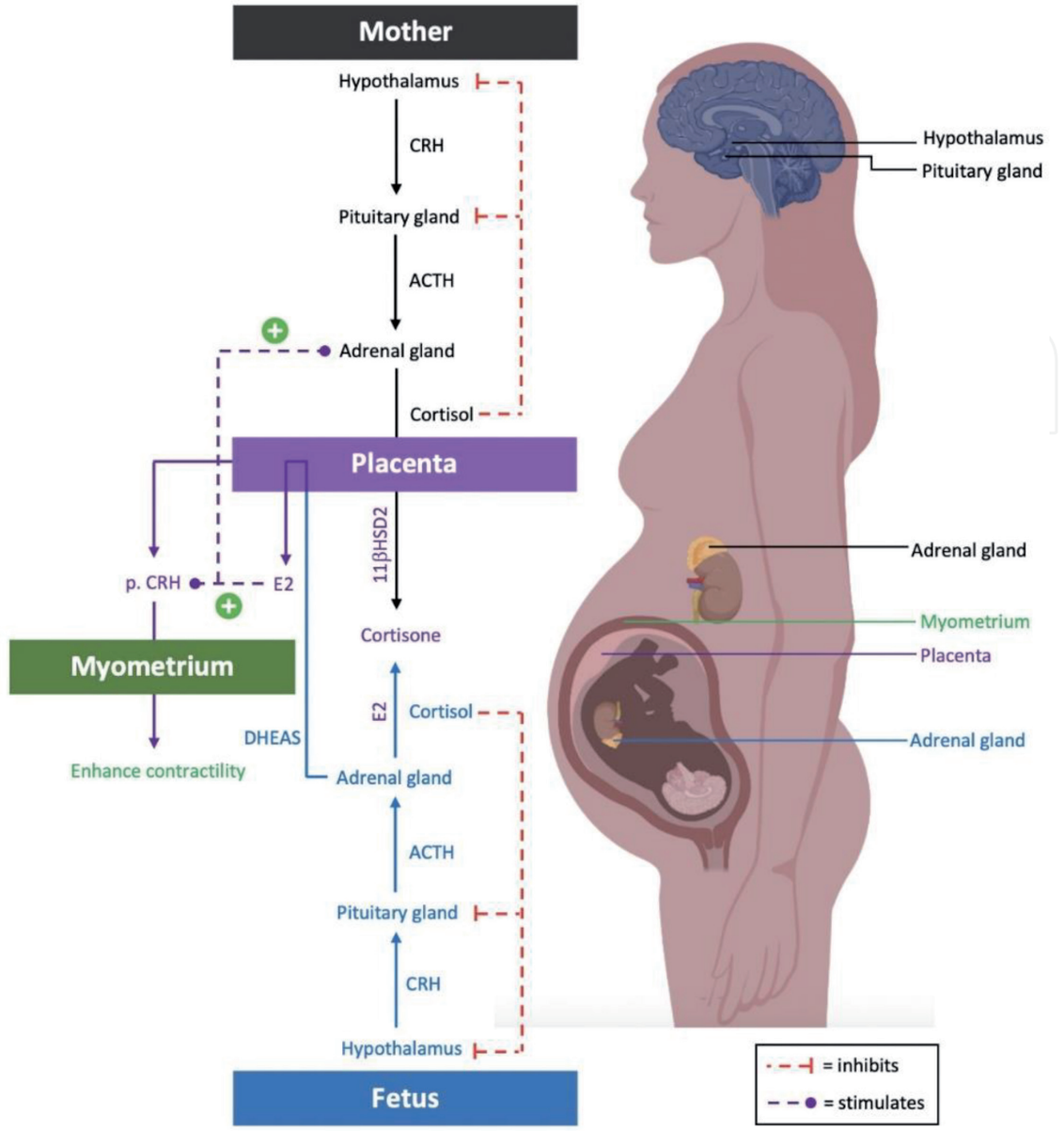

Figure 6.
Interaction of maternal and fetal HPA axes during pregnancy.

timing [40–42]. This was suggested by many studies which found an exponential increase of placental CRH in maternal and fetal circulation as pregnancy progresses (**Figure 7**). Moreover, higher levels of placental CRH in maternal circulation are associated with preterm delivery, whereas pregnant women with lower levels have longer pregnancy.

The placental CRH is a weak stimulator of maternal pituitary ACTH, therefore, the exponential increase in placental CRH levels is not associated with an equivalent increase in maternal cortisol levels. However, the main effect of placental CRH would be exerted on the myometrial responsiveness to the uterotonic effect of oxytocin and prostaglandin F2α (PGF2α). This effect of CRH is suggested to be through the reduction in C-AMP in the myometrium. It also acts as a potent vasodilator of feto-placental vessels, adding more efficacy in delivering oxytocin and prostaglandin to the myometrium and enhancing the contractility [1]. Whereas in fetal circulation, it acts directly on the fetal pituitary gland, stimulating ACTH release with subsequent increase in cortisol and dehydroepiandrosterone sulphate (DHEAS) release from fetal adrenal glands. This increase in fetal cortisol level is

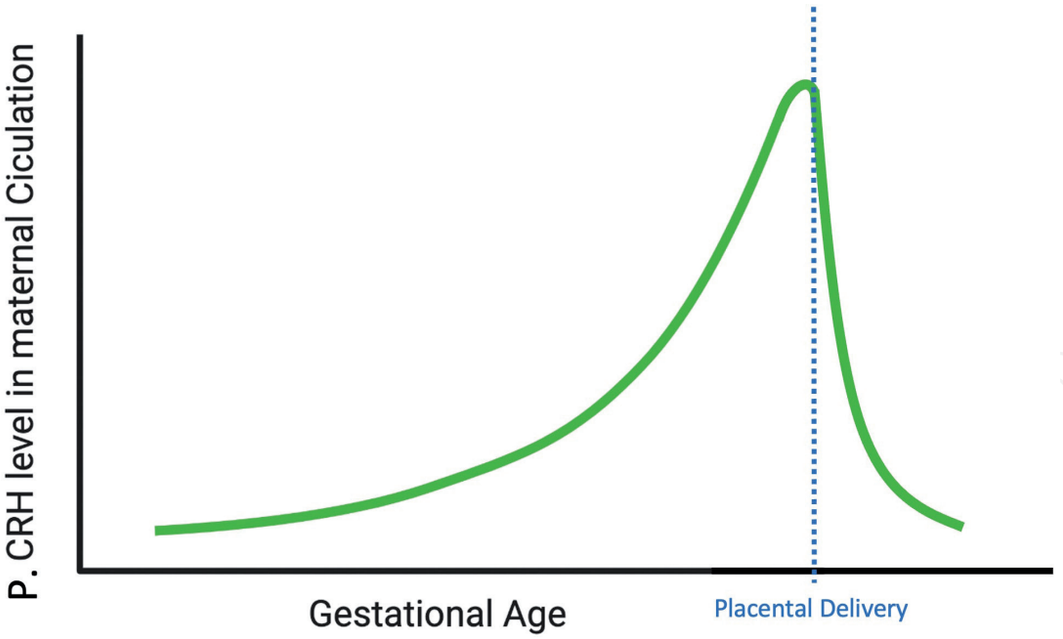

Figure 7.
Placental CRH exponential increase in maternal circulation as pregnancy progress.

essential for fetal lung maturity and alveolar surfactant production. It also induces more placental CRH production that initiate parturition onset [3, 43].

9. HPA Axis during lactation

After placental delivery, the placental-CRH levels fall sharply in the maternal circulation leading to a reduction in maternal cortisol levels (**Figure 7**). However, because there will be no change in glucocorticoid binding protein (GBP), the biologically active glucocorticoid level in maternal circulation will be maintained. Despite that, HPA axis will continue to be hyporesponsive to stress up to 1–3 months postpartum then gradually returns to normal function [44, 45]. In contrast, the salivary cortisol level in lactating mothers was found to be still high at 2 months after delivery [23].

Despite higher basal levels of HPA axis hormones during lactation, those women also exhibit less HPA axis responsiveness to stress. Interestingly, this blunted response to stress during lactation is more evident in multiparous rather than primiparous breast-feeding mothers [46].

The effect of lactation on modulating the HPA axis in basal status and in response to stress are postulated to be mediated through multiple neurohormonal mechanisms, one of which is low estradiol and other sex steroids. This results in loss of the induction effects of estradiol on the maternal adrenal cortex. Hence, this can be translated into lower cortisol levels in response to stress during lactation as compared to that during pregnancy [47, 48].

Moreover, suckling also can modulate HPA axis function depending on the environmental factors of the mother. Suckling can stimulate HPA axis only in the presence of the offspring and during early, but not late, lactation. This could be due to high circulating levels of oxytocin [49–51] and prolactin hormones [52, 53] during lactation. Because these hormones are known suppressors of HPA axis, they can cause a reduction in ACTH release.

Interestingly, maternal caring of the offspring during early postpartum period was associated with enhanced negative feedback inhibition of fetal hypothalamic CRH and reduced stress response behaviors [54, 55].

10. HPA Axis role in Fetal programming of adult disease

Optimal intrauterine fetal environment is pivotal for healthy fetal organ growth and maturation, hence subsequent proper function throughout the lifespan of the individual. Suboptimal conditions encountered in this environment can produce lifelong detrimental effects on the human body. This is the main concept of the fetal programming hypothesis by Barker [56, 57].

Therefore, any type of intrauterine insult can result in fetal programming of adult disease. This has been revealed by a bulk of epidemiological studies and also by many animal experimental studies. Our data from maternal low protein diet model have shown that maternal low protein diet during a specific period of gestation can program metabolic syndrome phenotype in the offspring in later life [58]. This metabolic phenotype was a result of altered expression of key lipid metabolism related genes and insulin signaling pathway. Preliminary data from our animal model and from other groups [59–61] indicates that the programming effect was through a fetal glucocorticoid overexposure secondary to placental 11 β HSD 2B downregulation [62]. In addition to its main site in the placenta, 11 β HSD 2B is also found to be expressed in a wide range of fetal tissue such as the brain and liver. Placental 11 β HSD 2B is crucial for protecting the fetus from exposure to excess maternal cortisol, however, normal expression of brain 11 β HSD 2B is found to play a fundamental role in preventing depression and other psychological disorders in later life independent from placental isoform, suggesting a tissue specific function for 11 β HSD 2B [63]. While in liver, the overexpression of 11 β HSD 1 enhances hepatic lipid deposition and other metabolic abnormalities [64]. Additionally, it has been shown that the under expression of fetal brain 11 β HSD 2B is associated with downregulation of serotonin (5-hydroxytryptamine) receptor type 1A (5 HT1A) which is, in turn, associated with psychological abnormalities in later life [63]. This can explain the association between the early separation anxiety in human infants and permanent hypercortisonemia as well as high β endorphin later in life with psychopathic manifestations [65].

With regard to metabolism, glucocorticoid excess has been linked to clinical observations associated with metabolic syndrome, such as central obesity, hypertension, hyperlipidemia, and glucose intolerance [66–68]. In liver, glucocorticoids increase the activities of enzymes involved in fatty acid synthesis and promote the secretion of lipoproteins [67, 69]. The hepatic lipogenic effect of glucocorticoids is consistent with clinical findings that glucocorticoid therapy causes triglyceride accumulation within the liver and is responsible for the non-alcoholic fatty liver disease [70, 71]. Therefore, it has been suggested that prenatal exposure to maternal glucocorticoids could be responsible, at least in part, for the development of the offspring phenotype [62].

As these adrenal hormones have powerful programming properties during the perinatal period, it can be speculated that long-term disturbances observed in offspring may be, in part, mediated by maternal glucocorticoid excess. Consistent with this hypothesis is the fact that hypertension in rats induced by maternal dietary protein restriction can be prevented by pharmacological blockade of glucocorticoid biosynthesis in the pregnant dam and her offspring, but reversed by concomitant corticosterone administration [67, 72]. In low protein animal model of adult disease, adrenalectomy resulted in the removal of the hypertensive state in a corticosterone-dependent manner [67, 73]. This animal model has shown low protein-exposed offspring developed disturbances of hypothalamic–pituitary–adrenal axis activity and up-regulation of glucocorticoid-sensitive enzymes in liver and brain [74].

Across a wide range of human epidemiological and experimental studies and other animal models of programming, the HPA axis is the universal target of the different intrauterine insults through which the programming of adult disease will be mediated [75–81].

11. Conclusion

To sum up, the HPA axis is a complex neurohormonal network that controls a vast majority of the body physiological performance. It is not surprising that the HPA axis develops very early in the embryo, at around 3 weeks of gestation and ACTH become detectable at around 10 weeks of gestation. This can be translated to the fact that the HPA axis is a crucial pathway that respond to surrounding threat to ensure survival. HPA axis has a double phase function, i.e., in-utero and ex-utero. During each phase it will interact differently with the environment. While the HPA axis is controlling the other endocrine systems in the body, however, it remains under continuous feedback loop regulation by downstream hormones. This is a precise way to maintain hormonal balance and homeostasis. During intrauterine life, the fetal HPA axis interacts with the maternal axis through the placental barrier, which is equipped with 11 β HSD enzyme, the placental security guard, allowing only 10–20% of active maternal cortisol to access the fetal circulation. Regardless of the insult encountered during intrauterine life, the HPA axis in mother and fetus will be dysregulated and the placenta barrier mechanism impaired. The detrimental effects will continue beyond the intrauterine life and will be conveyed later in adult life as cardiovascular, metabolic, and psychological diseases. Maternal stress, illness, infection, inflammation, malnutrition, and other stressors are all able to induce fetal programming of adult disease through the HPA axis. Finally, healthy lifestyle as an effective strategy in disease prevention should undoubtedly be started long before the birth of the individual. The mother should start a healthy lifestyle to ensure the wellbeing of her offspring in the adult life as soon as the pregnancy is detected.

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Conflict of interest

The authors declare no conflict of interest.

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