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Developmental origins of the human hypothalamic-pituitary-adrenal axis

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Abstract

Introduction: The developmental origins of disease or fetal programming model predicts that intrauterine exposures have life-long consequences for physical and psychological health. Prenatal programming of the fetal hypothalamic-pituitary-adrenal (HPA) axis is proposed as a primary mechanism by which early experiences are linked to later disease risk.

Areas covered: This review describes the development of the fetal HPA axis, which is determined by an intricately timed cascade of endocrine events during gestation and is regulated by an integrated maternal-placental-fetal steroidogenic unit. Mechanisms by which stress-induced elevations in hormones of maternal, fetal, or placental origin influence the structure and function of the emerging fetal HPA axis are discussed. Recent prospective studies documenting persisting associations between prenatal stress exposures and altered postnatal HPA axis function are summarized, with effects observed beginning in infancy into adulthood.

Expert commentary: The results of these studies are synthesized, and potential moderating factors are discussed. Promising areas of further research highlighted include epigenetic mechanisms and interactions between pre and postnatal influences.

Keywords

placenta; cortisol; CRH; fetal programming; prenatal stress; HPA axis; pregnancy; development

1. Introduction

The fetal period is a critical window of development, during which the architecture of the brain and other organ systems are fundamentally shaped. Within the first month of gestation, regions of the central nervous system are already formed and differentiated. Prolific neurogenesis occurs, with the majority of the brain's billions of neurons produced by mid-gestation [1]. An intricately timed sequence of organizational processes ensues, including neuronal migration, differentiation, synaptogenesis, apoptosis, and myelination [2]. Because

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Declaration of Interest

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the developing fetal brain is plastic, it is highly susceptible to *in utero* exposures and experiences.

The developmental origins of disease or fetal programming model predicts that early exposures to a variety of adverse events and signals have life-long consequences for physical and psychological health [3, 4]. Programming refers to the effects of an environmental signal acting during a sensitive developmental period to influence the construction of specific organ systems [3–5]. The developing fetus is sensitive and responsive to maternal nutritional, vascular, immune, and endocrine signals that convey information about the quality of the external environment. In response to these signals, the fetus adjusts its developmental trajectory to prepare for its anticipated life after birth. If signals convey conditions of deprivation or stress, the fetus may accelerate or reduce its growth, or shift resources to benefit certain systems at a cost to other systems [6, 7]. These developmental alterations may be adaptive. For instance, if the postnatal environment matches that predicted by the prenatal environment, the infant may be well-equipped for his or her environment and may thrive. If there is a mismatch, the risk for disease may increase [4, 5, 8].

During fetal life, the hypothalamic-pituitary-adrenal (HPA) axis is under construction and therefore susceptible to prenatal programming influences. The fully mature HPA axis mobilizes the body's physical and psychological resources in response to stress and regulates many homeostatic systems in the body, including the metabolic, cardiovascular, immune, reproductive, and central nervous systems. Given the central role of the HPA axis in many survival functions and links between HPA axis dysregulation and disease [9–15], programming of this system during fetal life is proposed as a primary mechanism by which early experiences are linked to later health outcomes [3, 16–22].

In this review, we examine evidence supporting the hypothesis that prenatal stress exposures shape the developing fetal HPA axis and represent a primary fetal programming mechanism. First, we describe the prenatal endocrine milieu in which the fetal HPA axis develops. We then delineate mechanisms by which fetal exposure to prenatal stress may influence the structure and function of the emerging HPA axis. Finally, we summarize existing literature concerning the effects of prenatal stress on postnatal HPA axis functioning, spanning infancy to adulthood. There is a well-established non-human animal literature documenting the programming influences of prenatal stress on offspring outcomes, including HPA axis functioning [23–26]. Human gestational physiology and fetal HPA axis development differ even from that of closely related nonhuman primates, thereby limiting the generalizability of animal models [27, 28]. Thus, this review will focus solely on studies of prenatal stress and fetal HPA axis development in humans.

2. Biological stress system

The human biological "fight or flight" stress response is triggered under conditions of threat to homeostasis and involves activation of the HPA axis, in coordination with the locus ceruleus-norepinephrine (LC-NE)/sympathetic and immune systems. The primary regulator of the HPA axis is the 41-amino acid neuropeptide corticotropin-releasing hormone (CRH).

CRH-producing neurons in paraventricular nucleus of the hypothalamus are innervated by afferent projections from multiple brain regions, including the brain stem, lamina terminalis, extra-PVN hypothalamic nuclei, and limbic structures, which respond to different physical and emotional stressors [29–31; see Figure 1]. CRH is secreted, along with arginine-vasopressin (AVP), into the hypophyseal portal blood, via axons projecting to the median eminence. CRH binds to its receptors on corticotropes of the anterior pituitary, stimulating production of the 31K dalton prohormone proopiomelanocortin (POMC). POMC is cleaved by enzymes into adrenocorticotrophic hormone (ACTH) and other bioactive peptides. ACTH enters the bloodstream and induces secretion of the glucocorticoid steroid hormone cortisol from the zona fasciculata of the adrenal cortex (see Figure 1). This cascade of hormone events mobilizes the body's physiological and psychological resources to cope with the stressor and maintain homeostasis.

Circulating cortisol exerts its effects by binding to two types of receptors, the type I, high-affinity mineralocorticoid receptor (MR), and the type II, low-affinity glucocorticoid receptor (GR). Cortisol has a 10-fold higher affinity for MRs than for GRs, so at basal concentrations of cortisol, MRs are occupied and GRs remain largely unoccupied [32]. MRs are proposed to regulate the tonic actions of cortisol, including its normative diurnal rhythm and the sensitivity of the stress response, whereas GRs are increasingly occupied during periods of elevated cortisol in response to stress [10, 32–34]. The effects of stress-induced elevations in cortisol include activation and regulation of cardiovascular and immune systems, utilization of energy stores and gluconeogenesis, inhibition of feeding, reproductive, and growth functions, and enhancement of memory and attentional processes [9, 10, 18, 29, 35–37]. High levels of circulating cortisol inhibit further HPA activity by binding to GRs and MRs at the level of the hypothalamus, pituitary, and hippocampus [10, 30]. Under normal conditions, this negative feedback loop terminates the stress response, because its adaptive function is to respond to and prepare for immediate challenges. Prolonged or chronic stress exposures may have adverse effects and result in dysregulation of the HPA axis [9, 36, 38, 39].

HPA axis dysregulation is associated with a variety of pathological conditions, including metabolic and cardiovascular disease, hypertension, obesity, osteoporosis, altered gastrointestinal and immune function, sleep disturbances, and affective disorders [9, 11–15, 35, 37, 40–45]. Links between HPA axis functioning and disease states are likely complex and bidirectional, with HPA axis functioning serving as a risk factor for and/or a consequence of disease. Prospective, longitudinal studies provide evidence that HPA axis dysregulation precedes certain physical and psychological conditions. Higher diurnal cortisol output is predictive of increasing mental health symptoms across childhood [46], and higher cortisol awakening responses have been shown to predict onsets of anxiety and depressive disorders during adolescence and adulthood [47–52]. Blunted patterns of diurnal cortisol output have been associated with higher body mass index both concurrently and longitudinally during adolescence [53]. Higher diurnal cortisol output also prospectively predicts reduced hippocampal volume and memory deficits [54] as well as increased risk of cardiovascular-related mortality in older adults [55].

3. Maternal-placental-fetal stress system

Examining the link between prenatal stress and fetal HPA axis development requires an understanding of the dramatic changes that occur in both the maternal and developing fetal stress systems during the prenatal period. The growth of a new organ, the placenta, is primarily responsible for these changes. The placenta is the interface and area of exchange of signals or information between the maternal and fetal compartments. The placenta additionally produces its own hormones, most of which are identical to those produced in endocrine tissue of the non-pregnant adult [56, 57]. These placental hormones bind to maternal hormone receptors and act as allocrine factors, adjusting maternal physiology to benefit both mother and fetus [58]. Among the many hormones produced by the placenta is CRH, the primary regulator of the stress response system. CRH mRNA is expressed in the placenta by the seventh week of gestation [59], is identical to hypothalamic CRH in structure, immunoreactivity, and bioreactivity, and is released into both maternal and fetal compartments [59–63]. Placental CRH is a primary regulator of stress hormone production during pregnancy and both influences and is influenced by maternal and fetal stress signals. As such, the prenatal stress response system may be best conceptualized as an integrated maternal-placental-fetal steroidogenic unit [58; see Figure 2].

3.1 Changes in the maternal stress system

Over course of gestation, maternal production of stress peptides and hormones increases several-fold, largely as a result of placental CRH production. Concentrations of circulating CRH in the maternal plasma are almost exclusively of placental origin. The minute quantities of maternal hypothalamic CRH released into circulation are rapidly degraded and largely undetectable [58, 64]. Placental CRH production rises exponentially over gestation and increases in maternal plasma up to 1,000 times its non-pregnant level [65, 66]. By the end of gestation, maternal placental CRH levels are equivalent to those observed in the hypothalamic system only during acute psychological stress [67].

Increased unbound placental CRH in maternal plasma stimulates the synthesis and release of maternal ACTH from the anterior pituitary and downstream production of cortisol from the adrenal glands [68–71]. Maternal plasma cortisol levels increase 3–5-fold over the course of gestation, reaching levels comparable to those observed in Cushing’s disease and certain psychopathological conditions [64, 66]. Unlike the negative feedback function of cortisol on CRH expression in the hypothalamus, maternal cortisol stimulates expression of CRH in the placenta [70]. A positive feedback loop is established, allowing for the simultaneous increase of placental CRH, ACTH, and cortisol in the maternal compartment over the course gestation [59, 66, 68, 70, 71; see Figures 2 and 3]. The maternal HPA axis is still subject to negative feedback inhibition, and as pregnancy advances towards term, increased levels of these hormones further blunt maternal HPA axis responsiveness to physiological and psychological stressors [72–78]. This dampening in stress responsivity likely serves an adaptive purpose, protecting the mother and her fetus from the deleterious effects of environmental stressors [72, 79, 80].

3.2 Developing fetal stress system

Because the fetal stress system is immature, it relies heavily upon maternal and placental inputs, functioning more so as an endocrine network than a linear axis [81]. The structures of the emerging fetal HPA axis undergo tremendous growth and organization during the prenatal period, and as gestation advances, fetal stress hormone production is increasingly evident.

The fetal hypothalamus forms from the ventral diencephalon and is differentiated by 9–10 weeks' gestation (see refs. 82, 83). The primordium of the anterior pituitary, Rathke's pouch, is formed from an invagination of oral ectoderm and is first evident at approximately 5 weeks' gestation (see refs. 58, 84–87). The hypothalamic-hypophyseal portal system is intact as early as 11 weeks' gestation [88]. CRH immunoactivity and bioactivity are detectable in fetal hypothalamic tissue extracts as early as 12–13 weeks' gestation, with bioactivity increasing as a function of gestational age [89]. CRH-immunoreactive fibers are present in the median eminence by 14–16 weeks' gestation [90], and CRH immunoactivity is present in the fetal pituitary from 12 weeks' gestation onwards [89]. The fetal hypothalamus therefore has the capacity to stimulate pituitary ACTH production from early in the second trimester. *In vitro,* fetal pituitary corticotrophs secrete significant amounts of ACTH as early as 8 weeks' gestation [91, 92], and administration of synthetic CRH stimulates ACTH secretion by the pituitary as early as 14 weeks' gestation [93, 94]. The extent to which endogenous fetal hypothalamic CRH is involved in regulating ACTH release *in vivo* remains uncertain [58]. Examination of endocrine profiles in preterm infants suggests that sequential release of hypothalamic CRH, ACTH and cortisol may not be established until late in gestation [95, 96].

The fetal adrenal cortex arises from the intermediate mesoderm. The adrenal primordium forms posteromedial to the urogenital ridge and is distinguishable at 33 days' post-conception [97–99]. By 8 weeks' gestation, the distinct zones of the cortex are apparent, and by 9 weeks' gestation, the cortex is completely encapsulated [27, 92, 97, 99]. The fetal adrenal cortex is active beginning early in gestation and is one of the most highly vascularized fetal organs [27]. Adrenal steroid hormones are involved in the regulation of intrauterine homeostasis and the maturation of organ systems [22, 27, 100]. *De novo* synthesis of cortisol from its precursor cholesterol requires the presence of specific steroidogenic enzymes, including 3β-hydroxysteroid dehydrogenase/Δ^{4-5} isomerase (3β-HSD). A recent examination of first trimester fetal adrenals documented by immunohistochemistry a transient expression of 3β-HSD from approximately 7–10 weeks' gestation [92]. *Ex vivo* tissue culture revealed cortisol synthesis regulated by ACTH and negative feedback apparent at the anterior pituitary. Therefore, early in gestation, *de novo* production of cortisol from cholesterol likely occurs briefly, which may function to regulate female sexual differentiation via inhibition of adrenal androgen production [92]. During most of the second trimester, fetal adrenal expression of 3β-HSD is suppressed [101–103]. From approximately 23–24 weeks onward, 3β-HSD and other requisite enzymes are again apparent, and cortisol production increases as gestation advances [101–103].

In addition to the patterning of steroidogenic enzymes, placental factors regulating fetal exposure to maternal cortisol are hypothesized to influence the timing of fetal pituitary-

adrenal activity. From early to mid-gestation, transfer of maternal cortisol to the fetus may function to suppress fetal ACTH production [104]. As gestation advances, increasing levels of the placental enzyme 11β-hydroxysteroid dehydrogenase 2 (11β-HSD-2) oxidize maternal cortisol into its metabolite cortisone, which does not act on glucocorticoid receptors [105–110]. Reduced maternal cortisol in the fetal circulation may then disinhibit the fetal pituitary, resulting in increased ACTH production [104, 107]. ACTH secreted from the fetal pituitary is the primary regulator of fetal adrenocortical development, stimulating the proliferation of adrenocortical cells in vivo [27].

However, rising levels of fetal cortisol over the second half of gestation [111–113] are *not* paralleled by large increases in fetal ACTH [111, 114]. Evidence suggests that placental hormones, particularly placental CRH, play a central role in regulating fetal adrenal development. Both the fetal pituitary and adrenal glands express CRH receptors [115, 116]. *In vitro,* CRH up-regulates ACTH receptor expression in isolated fetal adrenal cells [117]. Increasing levels of placental CRH could therefore enhance adrenal responsiveness to ACTH, promoting adrenal cortisol synthesis despite the limited availability of circulating fetal ACTH [117]. Placental CRH also may directly regulate adrenal cortisol production, as CRH stimulates cortisol synthesis and expression of requisite steroidogenic enzymes in isolated fetal adrenal cells [118, 119]. Increased fetal cortisol would in turn increase placental CRH levels, forming a positive feedback loop parallel to that of maternal cortisol and placental CRH [27, 70]. Higher levels of CRH in the umbilical vein as compared to the umbilical artery suggest that CRH in the fetal circulation is largely of placental origin [61].

Although the likely multiple mechanisms by which fetal cortisol production is regulated are not fully understood, escalation of fetal cortisol production from the end of the second trimester through the third trimester is evident [111–113]. By 30 weeks, the fetal adrenal cortex resembles a rudimentary form of the adult adrenal cortex [120]. Late in pregnancy, at approximately 34–35 weeks' gestation, levels of 11β-HSD-2 decrease [107, 108, 121], allowing for greater transfer of maternal cortisol into the fetal compartment. Increased maternal cortisol in the fetal circulation would suppress fetal ACTH production. The increased transfer of maternal cortisol to the fetus is thought to constitute a back-up mechanism to ensure fetal organ maturation and may explain why fetuses with glucocorticoid deficiencies are born without signs of organ immaturity [27, 58]. By term, approximately 75% of the cortisol in fetal circulation is of fetal origin, with the remaining 25% of maternal origin [105]. In addition to ensuring adequate maturation of fetal organ systems, elevated maternal and fetal cortisol late in gestation may act to influence the timing of parturition [27, 70, 100, 121, 122].

4. Fetal exposure to prenatal stress hormones

Fetal exposure to maternal and placental stress hormones is considered a primary biological pathway by which various forms of prenatal psychological and biological stress influence the development of the fetal HPA axis. Maternal cortisol and placental CRH are key prenatal stress hormones which may program the emerging fetal HPA axis. The maternal-placental-fetal steroidogenic unit produces massive amounts of these stress hormones during pregnancy. While exponential increases in these hormones are normative and necessary for

successful gestation and parturition, the fetus is vulnerable to further stress-induced increases in these hormones. In cases of extreme stress to the system and rapidly accelerating levels of stress hormones, especially placental CRH, preterm birth may result [66, 123, 124]. Increasing evidence suggests that stress-induced increases in hormones also exert programming influences on fetal HPA axis development independent of birth phenotype.

4.1 Exposure to maternal cortisol

The effects of elevated maternal cortisol appear to be dependent upon the timing of exposure. As previously stated, the fetus is less protected from maternal cortisol during early and late gestation, when placental 11β-HSD-2 levels are lower [105–109, 121]. Excess maternal cortisol during early to mid-gestation appears to exert negative effects on the fetus, whereas elevated maternal cortisol near term is beneficial, promoting fetal organ maturation and enhanced neurodevelopment [125–129]. Although 11β-HSD-2 limits fetal exposure to maternal cortisol as gestation advances, it is only partial barrier [130, 131], with approximately 15% of maternal cortisol crossing through the placenta unmetabolized [106, 131, 132]. Mid to late-gestational maternal and fetal cortisol levels are correlated, with approximately 40% of their variance shared [130, 131]. Additional associations have been documented between maternal cortisol and amniotic fluid cortisol [133] and between maternal and neonatal ACTH and cortisol levels at birth [134].

Because some maternal cortisol does reach the fetus, elevations in maternal cortisol in response to physical or psychological stress may subsequently elevate cortisol levels in the fetal circulation [106, 111, 130, 131, 135]. Increased maternal stress also may increase fetal exposure to cortisol by downregulating placental 11β-HSD-2 activity, thus allowing a greater proportion of maternal cortisol to cross into the placenta and then enter fetal circulation. Several key biological stress signals act to downregulate placental 11β-HSD-2, including catecholamines [136], proinflammatory cytokines [137, 138], and hypoxic factors [139]. Prenatal maternal anxiety and depressive symptoms are respectively associated with reduced placental 11β-HSD-2 gene expression and activity [140]. Decreased 11β-HSD-2 activity may account for the greater concordance observed between maternal and amniotic fluid cortisol as a function increased maternal anxiety [141].

Exposure to excessive concentrations of cortisol could alter glucocorticoid receptor density and function at each level of the fetal HPA axis, thereby calibrating the sensitivity of the system to feedback mechanisms [23, 142]. Glucocorticoid receptors are highly expressed throughout the developing brain, particularly so in regions providing excitatory (e.g., amygdala) and inhibitory (e.g., hippocampus) inputs to the HPA axis [22, 24, 30, 143–147]. GRs and MRs are abundant in the hippocampus [10, 32], with both receptor types expressed in this region as early as 24 weeks' gestation [147]. Prenatal glucocorticoid exposure is associated with decreased hippocampal GR and MR density in non-human animals, resulting in decreased negative feedback regulation of the HPA axis [10, 142, 147–150]. Additional findings from animal models indicate that excess glucocorticoids alter the density of MRs and GRs and increase production of CRH in the amygdala, with increased forward drive to the axis [25, 142, 148]. In humans, exposure to elevated maternal cortisol early in

gestation is associated with increased volume of the right amygdala in female children [127]. The balance of GRs and MRs in the hippocampus and other brain regions is critical to HPA axis sensitivity, drive, and inhibition, with a GR/MR imbalance resulting in dysregulation of the axis and is implicated in depression and other psychopathological conditions [10, 151].

4.2 Exposure to placental CRH

Like the hypothalamus, the placenta produces CRH in response to stress. Unlike the negative feedback influence of cortisol on hypothalamic CRH expression, maternal and fetal cortisol stimulate placental CRH expression, constituting parallel positive feedback loops [27, 59, 64, 68, 70]. Elevations in maternal cortisol may therefore act on fetal development indirectly through increased placental CRH production. *In vivo,* elevated levels of maternal cortisol early in gestation are associated with accelerated trajectories of placental CRH [66, 152]. CRH is also released from cultured human placental cells in a dose-response manner to a number of other major biological stress signals, including catecholamines, proinflammatory cytokines, and angiotensin-II [153, 154]. Consistent with these *in vitro* studies, stress-related intrauterine conditions such as reduced uterine blood flow, nutrient restriction, and infection are associated with increases in placental CRH [155–157]. Elevated placental CRH levels also are observed in women with higher maternal pregnancy-specific anxiety [158], perceived stress [159] and depressive symptoms [160–162], and in women with lower social support from family [163]. Thus, placental CRH may represent an integrative pathway by which various prenatal stressors of both maternal and fetal origin shape the developing fetal HPA axis.

As previously discussed, placental CRH likely acts to increase fetal cortisol production, both directly, by stimulation of the fetal adrenals, and indirectly, by increasing fetal adrenal responsiveness to ACTH [115–119]. Upregulated placental CRH via any of the biological stress signals promoting its production could therefore induce exaggerated fetal adrenal cortisol production or program the sensitivity of the adrenal glands to ACTH [70, 111, 118]. Elevated placental CRH in the fetal circulation presumably permeates the immature fetal blood-brain barrier [164], where CRH receptors are widely expressed from 13 weeks' gestation [165]. CRH mRNA-expressing neurons are particularly abundant in the amygdala and hippocampus, which provide excitatory and inhibitory input to the hypothalamus, respectively [30, 144]. Animal models indicate that excess circulating CRH upregulates CRH and CRH receptor mRNA expression in these regions, with consequences for neuronal function and integrity [24, 142, 144]. For example, administration of CRH to the brains of immature rodents results in progressive loss of hippocampal neurons, which may impair hippocampal negative feedback regulation of the HPA axis [144]. Several human studies provide additional support for programming effects of placental CRH on the fetal brain, linking placental CRH exposures with fetal neurodevelopment [166–168] and with stress-related outcomes in infancy and childhood [169, 170].

5. Prenatal stress exposures and postnatal HPA axis function

Programming of the developing fetal HPA axis is proposed as a plausible mechanism by which prenatal stress influences offspring physiological and psychological outcomes,

including risk for cardiovascular and metabolic disease, compromised immune function, and mental disorders [18–21, 171]. We review here studies in which postnatal HPA axis functioning is the direct outcome of interest and in which maternal prenatal stress is indexed directly rather than inferred from birth phenotype (for reviews of studies linking shortened gestation and small size at birth with altered HPA axis functioning, see refs. 21, 172, 173). One challenge that limits the ability to draw firm conclusions about persisting influences of prenatal stress exposures on HPA axis functioning is the broad range of measures of both prenatal stress and HPA axis functioning utilized. For this review, we conceptualize prenatal stress as encompassing both stress exposures, such as life events, and different physiological or psychological responses to stress, such as cortisol levels or symptoms of anxiety or depression [174]. In characterizing HPA axis functioning, some studies have considered basal cortisol levels at a single time point. Other investigations have measured cortisol response to laboratory or naturalistic stressors. Saliva samples are collected prior to the stressor (baseline) and at several intervals post-stressor to examine the peak and recovery of the cortisol response. Finally, several studies have evaluated profiles of diurnal cortisol output. In the mature HPA axis, cortisol levels follow a normative diurnal rhythm, with a 50–100% increase in levels observed upon awakening (termed the cortisol awakening response, or CAR), peak levels approximately 30–45 minutes after awakening, and a decline in levels across the remainder of the day [175–177]. Table 1 summarizes these existing studies, with findings observed in the neonate, infant, child, adolescent, and adult. While variable in their methodologies and results, these studies provide strong support for the notion that prenatal stress programs the developing fetal HPA axis, with persisting consequences for its function.

5.1 Neonate

Several studies have assessed levels of neonatal cortisol upon or shortly after delivery. Neonates exposed to elevated levels of maternal depressive symptoms over the latter half of gestation exhibited higher levels of ACTH as compared to infants exposed to low levels of maternal depressive symptoms [178]. Two other investigations found that neonates of mothers with elevated prenatal depressive symptoms had higher levels of urinary cortisol [179, 180]. Only one known study to date has examined cortisol responses to a stressor in a neonatal sample [128]. Elevated maternal cortisol from 21 to 35 weeks' gestation was associated with an exaggerated neonatal salivary cortisol response to the painful stress of the heel-stick blood draw, with the strongest effects observed at 25 weeks' gestation. Cumulatively, these studies suggest that prenatal stress predicts heightened HPA axis activity during the neonatal period.

5.2 Infant

Studies that have assessed cortisol responses to routine stressors in the first several months of infancy and have documented elevated cortisol responses in stress-exposed infants. Stroud et al. [181] measured 1-month-old infants' cortisol responses to a neurobehavioral examination in which the infant is observed and handled during periods of sleep, wakefulness, crying, and non-crying. Infants of mothers with prenatal depressive disorders demonstrated higher baseline cortisol levels and greater responses to the stressor, as compared to infants of mothers who were not depressed during their pregnancy. This effect was observed primarily in female infants. Furthermore, placental 11β-HSD-2 methylation

appeared to moderate these effects. Among those infants exposed to prenatal maternal depression, decreases in 11β-HSD-2 methylation were associated with increases in baseline cortisol. Tollenaar et al. [182] similarly found that higher maternal pregnancy-related anxiety predicted higher infant cortisol responses to a bathing session at 5 weeks of age.

There is some evidence that after the first several months of life, a developmental shift in HPA axis functioning occurs, and a period of hyporesponsiveness to stress is observed [183]. Several studies have measured cortisol responses to vaccinations or laboratory stressors in infants ranging from 2 to 17 months of age. These investigations, while diverse in their findings, on average suggest that infants exposed to higher levels of prenatal stress may present with greater HPA axis hypoactivity at this stage of development. A few of these studies have assessed infant cortisol responses to vaccination. Higher maternal pregnancy-related anxiety was associated with decreased infant cortisol reactivity to vaccination in 2-month-old infants [182]. Alternatively, Braithwaite et al. [184] found no effect of maternal prenatal depressive symptoms on cortisol response to vaccination in 2–4-month-old infants. Other studies have examined infant cortisol responses to standardized laboratory stressors. Rash [185] measured the effects of maternal prenatal diurnal cortisol output on cortisol response to a frustration task in 6-month-old infants. Infants who exhibited decreases in cortisol in response to the task (as opposed to an increase) were exposed to a flatter maternal diurnal profile (less of a decline in cortisol over the course of the day) at 15 weeks' gestation. Another investigation examined cortisol response to the stressful still-face procedure in 7-month-old infants of mothers with and without prenatal anxiety disorders [186]. Differences in infant cortisol profiles only emerged 25–40 minutes post-stressor; infants of mothers without prenatal anxiety exhibited decreases in cortisol, and infants of mothers with prenatal anxiety displayed non-significant increases in cortisol. Finally, two studies have examined infant cortisol responses to a maternal separation paradigm [140, 182]. Higher maternal pregnancy-related anxiety was associated with a lower cortisol response in 12-month-old infants [182], and higher amniotic fluid cortisol was associated with higher baseline cortisol and a blunted cortisol response in 17-month-old infants [140].

5.3 Child

Multiple studies have examined either cortisol response or diurnal cortisol output in childhood. All of these studies document hyperactivity of the HPA axis in children exposed to higher levels of prenatal stress. Elevated levels of maternal prenatal depression and anxiety predicted higher cortisol levels across a series of tasks in 2–5-year-old female children, with no differences observed in profiles of response to the tasks [187]. Higher prenatal maternal early morning salivary cortisol and pregnancy related-anxiety were associated with higher overall cortisol levels in 4–6-year-old children on the day of a vaccination [188] and higher overall cortisol levels in 5-year-old children on school days [189]. Another study measured 10-year-old children's cortisol responses to a laboratory stressor and identified three cortisol profiles over the stressor: low levels with no response, moderate levels with no response, and high levels with response [190]. Prenatal maternal intimate partner violence increased the likelihood of membership in the high response group, as compared to the low and moderate flat groups. One additional study measured diurnal

cortisol output in 10-year-old children and found that higher maternal prenatal anxiety was associated with higher awakening cortisol levels [191].

5.4 Adolescent

A few investigations have extended examination of offspring HPA axis functioning into the adolescent period. Two studies assessed adolescents' diurnal cortisol output and documented hypoactivity in adolescents exposed to prenatal stress. Higher maternal prenatal anxiety and depression predicted an altered pattern of diurnal salivary cortisol in 15-year-old children, reflected in a reduced cortisol awakening response and a flatter cortisol decline (smaller decrease from awakening to evening) over the day [192]. Similarly, elevated prenatal maternal anxiety was associated with a flatter diurnal cortisol decline in 14–15-year-old children [193]. One additional study defined prenatal stress as exposure to a disaster during pregnancy [194]. A birth cohort of 14-year-old Finnish twins whose mothers were pregnant during the Chernobyl disaster was compared with a reference group of twins whose mothers were pregnant one year after the disaster. Cortisol levels measured once upon arrival to a laboratory visit were higher in adolescents whose mothers were in their second or third trimester during the Chernobyl disaster, as compared to non-exposed adolescents.

5.5 Adult

Finally, one known study has examined the effects of prenatal stress, measured by maternal experience of a major negative life event during pregnancy, on multiple measures of HPA axis activity in adulthood [195]. Young adult children who reported that their mothers had experienced a negative life event during their pregnancy were compared with an age-matched control group. As compared to the control group, the prenatal stress-exposed group exhibited hypoactivity in several domains, reflected in lower pre-stressor cortisol levels and lower cortisol levels during pharmacological stimulation of the pituitary via an $ACTH_{1–24}$ stimulation test. However, the prenatal stress-exposed group also exhibited increased reactivity to the stressor, with greater increases in cortisol in response to the stressor. No differences in diurnal cortisol output were exhibited between the two groups. A limitation of this investigation was that prenatal maternal negative life events were obtained retrospectively by adult children in communication with their mothers at the time of assessment.

5.6 Synthetic glucocorticoid exposure

Administration of synthetic glucocorticoids (GCs) is the standard of care for pregnant women at risk for premature delivery between 24 and 34 weeks' gestation, because this treatment effectively reduces mortality and promotes lung maturation among infants born preterm [196, 197]. Synthetic GCs are not metabolized by placental 11β-HSD-2 and therefore readily cross into the placenta, where they act on developing fetal organ systems [198, 199]. Evidence indicates that prenatal synthetic GC exposures are associated with dysregulated postnatal HPA axis function. For example, compared to non-exposed preterm neonates, exposed preterm neonates exhibit no increases or decreases in cortisol in response to a heel-stick blood draw [200–203]. Because determining if preterm delivery will actually occur is difficult and imprecise, many women who receive synthetic GCs often go on to deliver beyond 37 weeks' gestation [204]. One study demonstrated that full-term neonates

exposed to synthetic GCs prenatally exhibited a larger cortisol response to the heel-stick procedure, as compared to non-exposed neonates [205]. These effects appear to persist into childhood, with prenatal synthetic GC exposure predicting greater increases in cortisol in response to a laboratory stressor in term-born children [206] and in preterm-born adolescents [207]. Several studies have also documented that children and adolescents exposed to prenatal synthetic GCs display alterations in diurnal cortisol output, evident in an absence of a CAR [207, 208] and a flatter decline in cortisol over the day [208]. This literature provides additional support for the programming effects of excess glucocorticoids on long-term HPA axis function.

6. Expert commentary

A growing body of research has linked prenatal stress exposures with HPA axis functioning from infancy into adulthood. HPA axis dysregulation in prenatal stress-exposed individuals has been documented at multiple levels of functioning, including diurnal rhythms and responses to stress. It remains unclear as to how these different aspects of HPA axis function may interact or reflect similar or different markers of risk [209], particularly since studies have primarily focused on either diurnal rhythms or responses to stress and not their synergistic effects. Additionally, there is no clear consensus within the literature as to whether prenatal stress is associated with hyperactivity or hypoactivity of the axis. The wide variation in methodologies employed across these studies may in part account for the apparent inconsistency in findings (see ref. 209 for a relevant discussion).

It is also plausible that these discrepancies reflect meaningful developmental patterns. First, there is evidence that both diurnal cortisol output and cortisol response to stress vary over the course of development. Several studies indicate that after the first few months of infancy, during which stress reactivity is observed, a period of hyporesponsiveness of the stress system occurs, coinciding with the emergence of the diurnal rhythm of the HPA axis [183, 210–213]. Factors like sleep patterns and quality of caregiving are proposed to underlie this normative developmental shift, which may persist from 2 months until midway through the second year of life [183, 211–213]. Interestingly, the effects of prenatal stress on infant cortisol response observed in the study by Tollenaar et al. [182] appear to follow this shift, with higher prenatal stress predicting hyperactivity at 5 weeks, and hypoactivity at 2 and 12 months. Additional developmental changes in HPA axis functioning may occur as a result of puberty [214, 215]. Second, activity of the HPA axis may differ depending upon whether stressors are acute or chronic. Exposure to prenatal stress may result in a more reactive HPA axis initially, but prolonged hyperactivity may eventually result in downregulation of the system, with a dampening of diurnal cortisol output and hyporeactivity to stress later in life [183, 216, 217]. Support for this phenomenon is evident in the patterns of hypocortisolism observed in children and adults exposed to severe or chronic stress [183, 217]. Two of the studies discussed above examined diurnal cortisol output in 10-year-old [191] and 15-year-old [192] children drawn from the same longitudinal cohort study. While there were too few children participating in both the 10 and 15-year follow-ups to directly test the possibility of a shift from hyperactivity to hypoactivity of the axis, the pattern of findings is consistent with such a shift.

In terms of their characterizations of prenatal stress, investigations have focused on maternal psychological functioning or maternal cortisol output. A primary assumption of this research is that elevations in maternal and placental stress hormones mediate the effects of prenatal psychological stress on fetal HPA axis development. However, results of studies examining links between maternal prenatal psychological stress and stress hormones, primarily maternal cortisol, are equivocal at best (see ref. 218 for a systematic review). The paradoxical increase in maternal stress hormones and decrease in psychological and physiological responsiveness to stress as gestation advances may partly explain why psychological and biological markers of maternal stress are not reliably coupled. Most investigations have focused on individual differences between average levels of maternal prenatal psychological stress and stress hormones, examining whether mothers with higher psychological stress also exhibit higher stress hormone levels. A more precise measure of the concordance between psychological and physiological stress may be intra-individual associations between these parameters of stress. One research group has reported positive covariation between prenatal maternal negative mood and salivary cortisol over the course of the day [219, 220]. There is also some evidence that prenatal maternal psychological stress alters overall trajectories of cortisol output over gestation [221] and is reflected in integrated measures of cortisol activity, such as cortisol measured in hair [222]. It is additionally plausible that prenatal maternal psychological stress influences fetal HPA axis development through mechanisms other than prenatal maternal cortisol, such as placental CRH exposures or vascular or immune channels [223–227]. Research must continue to evolve and utilize a more comprehensive approach in understanding the variety of stress exposures that may influence fetal HPA axis development.

Careful consideration should also be given to factors that may moderate fetal exposure to prenatal stress. Particularly important may be the timing of prenatal stress. It is known that prenatal exposures during different gestational intervals exert differential effects, depending on the fetal developmental processes occurring at the time [24, 171, 228]. Furthermore, since maternal stress responsiveness is downregulated as gestation advances, stressful events experienced early in pregnancy trigger greater maternal stress responses and therefore have the potential to exert greater influence on the fetus than stressors experienced later in gestation [72–78, 229, 230].

Fetal sex also may moderate the programming effects of prenatal stress on the fetal HPA axis. Substantial evidence indicates that there are sex-specific trajectories of fetal development, related to the response of the placenta to stress [231, 232]. Female and male fetuses appear to exhibit contrasting growth strategies, whereby in response to stress exposures, female fetuses adjust their growth and male fetuses do not [232, 233]. This may be because the female placenta is more sensitive and responsive to changes in cortisol concentrations during gestation as compared to the male placenta. For example, in the presence of maternal inflammatory disease, female placental 11β-HSD-2 expression and activity are significantly decreased, with corresponding elevations in circulating cortisol levels and reductions in birthweight [234]. Conversely, male placental GR mRNA expression is increased, with no changes observed in 11β-HSD-2 activity, cortisol level, or growth [234]. Similarly, Osei-Kumah et al. [235] measured alterations in placental gene expression as a function of maternal inflammatory disease and observed many more gene

alterations in female placentae as compared to male placentae. Thus far, the potential moderating effect of fetal sex on the relationship between prenatal stress and HPA axis outcomes has been largely unexamined. Several studies document stronger effects of maternal prenatal stress on cortisol output in female children [181, 187, 191]. Additionally, van den Bergh et al. [193] reported an effect of maternal prenatal anxiety on diurnal salivary cortisol profiles in both sexes, but the altered cortisol profile was associated with depressive symptoms only in female adolescents. It is clear that additional research is needed to understand the precise mechanisms by which various prenatal stressors influence patterns of HPA axis development and factors that may moderate these effects.

7. Five-year view

During the fetal period, experiences and exposures shape developing organ systems to promote optimal functioning in life after birth. A growing number of prospective, longitudinal studies have assessed links between prenatal stress and later developmental outcomes, including HPA axis functioning. The primary focus of these existing investigations has been exposure to elevations in maternal psychological distress and maternal cortisol. Additional stress signals likely shape the developing fetal HPA axis. Among these is placental CRH, a direct and integrative index of fetal exposure to a variety of stressors. Placental CRH is upregulated by maternal and fetal cortisol, catecholomines, proinflammatory cytokines, and vascular changes [70, 137, 138, 153, 154, 156] and appears to directly influence fetal pituitary-adrenal growth and steroidogenesis [115–119]. Future research should focus on placental CRH as an indicator of prenatal stress-induced alterations in HPA axis functioning.

An emerging and promising area of research suggests that gene-environment interactions may also mediate the effects of prenatal stress on HPA axis development and function. Epigenetic mechanisms involve changes in gene expression, which can arise during critical periods of development in response to environmental exposures and may remain stable into adulthood [18, 236, 237]. Increasing evidence suggests that prenatal stress is associated with epigenetic change in HPA axis genes, particularly methylation in the promoter region of NR3C1, the gene encoding the glucocorticoid receptor [238]. As previously mentioned, GRs play a critical role in negative feedback inhibition of the HPA axis response. For example, increased methylation of NR3C1 results in decreased expression of hippocampal GR, dampening of HPA axis negative feedback, and a prolonged increase in circulating glucocorticoid levels in rodents [146]. In adult humans, childhood abuse is associated with increased promoter methylation and decreased expression at the NR3C1 gene in hippocampal brain tissue [239].

Several studies have examined links between prenatal stress and peripheral measures of NR3C1 methylation. Higher levels of prenatal maternal depression and anxiety [240, 241] and diurnal cortisol output [241] were associated with increased methylation of NR3C1 in cord blood, which predicted increased infant cortisol response to stress at 3 months [240]. Elevations in prenatal maternal depression and anxiety also predicted increased placental NR3C1 and 11β-HSD-2 methylation [242]. One study considered the impact of prenatal exposure to chronic stress and war-related trauma in a sample of mothers and infants in the

Democratic Republic of Congo, documenting methylation of multiple genes regulating HPA axis function (CRH, CRHBP, NR3C1, and FKBP5) in maternal blood, cord blood, and placental tissue [243]. There is some evidence that the effects of prenatal-induced epigenetic modifications may extend into adolescence and adulthood [244] and may be further transmitted across multiple generations [245]. While the relationship between epigenetic variation in the periphery and in brain is currently unknown, these findings encourage further examination of the interactive influence of genes and environmental stressors on HPA axis development.

Finally, future research could examine how the pre and postnatal environments act independently or synergistically to shape development of the HPA axis. A few investigations have considered the additive or moderating effects of the postnatal environment on stress responsiveness [186, 246–249]. Kaplan et al. [249] reported that postnatal maternal sensitivity moderated the effects of prenatal maternal mood disorder on baseline cortisol in 4-month-old infants. Specifically, infants of mothers with a prenatal maternal mood disorder exhibited elevated cortisol only in context of low maternal sensitivity, and infants of mothers without a prenatal maternal mood disorder had low cortisol regardless of maternal sensitivity. In this sense, the effects of prenatal stress may be amplified in context of an impoverished postnatal environment or may be attenuated in a high-quality environment. The predictive adaptive response hypothesis alternatively posits that developmental adjustments made in response to prenatal stress signals are adaptive when the actual postnatal environment matches that predicted by the prenatal environment [4, 5, 8]. Consistent with this argument, one study indicated that infants exhibited more extreme salivary cortisol responses to a maternal separation stressor, reflected in an extended response and lack of recovery, if maternal prenatal and postnatal depressive symptom levels were discordant [247]. Infants exposed to consistently low levels of depressive symptoms exhibited the most normative profiles of response and recovery from the stressor. Collectively, these studies provide additional evidence that the developing fetal HPA axis is sensitive to and shaped by the conditions of the intrauterine environment, but additionally suggest that the effects of prenatal stress exposures should be considered in the context of the postnatal environment.

While the multiple complex mechanisms regulating the development of the fetal HPA axis are not fully understood, studies reviewed here provide strong evidence that prenatal stress exposures shape the developing axis and exert persisting influence on its function into adulthood. Given the fundamental role of the HPA axis in regulating many of the body’s homeostatic systems and associations between HPA axis dysregulation and disease [9–15], programming of the axis is a plausible mechanism underlying links between early exposures and later health outcomes, including risk for cardiovascular, metabolic, immune, and mental disorders [3, 16–22]. The HPA axis is an ancient physiological system that has been maintained by natural selection and conserved across species, promoting adaptation and survival in response to environmental threats [250]. The sensitivity and plasticity of the developing fetal HPA axis stress to exposures signaling the state of the external environment also appears to be deeply rooted in human evolutionary history [251] and would have been of value to our ancestors, ensuring offspring would be well-suited to survive in a presumably limiting and hostile environment [4, 5]. However, activation of this same stress reponse

system may no longer be adaptive in modern environments characterized by urbanization, nutritional abundance, and a sedantary lifestyle, in which stressors are frequent and chronic but seldom require fight or flight [252, 253]. Stress related-alterations in physiology may instead prove detrimental to health and confer risk for disease. Interventions focused on improving the quality of maternal and fetal health *in utero* may assist in closing the gap between the stress responses conferred on us by our evolutionary past and those better suited for modern day circumstances.

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Reference annotations

* Of interest

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Findings highlight the importance of considering the interactive effects of the prenatal and postnatal environments on HPA axis function

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8. Key issues

- The developmental origins of disease or fetal programming model predicts that prenatal experiences have life-long consequences for physical and psychological health.
- The hypothalamic-pituitary-adrenal (HPA) axis mobilizes the body's physical and psychological resources in response to stress and regulates many homeostatic systems. Programming of the developing fetal HPA axis is proposed as a primary mechanism by which early experiences are linked to later disease risk.
- The placenta is largely responsible for the massive changes that occur in both the maternal and developing fetal stress systems during the prenatal period. An integrated maternal-placental-fetal steroidogenic unit regulates the prenatal endocrine milieu.
- The precise mechanisms by which prenatal stressors may shape the nascent fetal HPA axis are not fully understood. In addition to cortisol, placental CRH is a promising candidate, because it is a signal that integrates a variety of stressors and appears to directly influence fetal pituitary-adrenal activity.
- Prospective, longitudinal investigations have provided evidence that elevations in maternal prenatal psychological stress and cortisol are associated with alterations in HPA axis functioning, reflected in diurnal rhythms and responses to stress. Findings are observed in the neonate, infant, child, adolescent, and adult.
- Prenatal stress is associated with both hyperactivity or hypoactivity in HPA axis functioning. It is also plausible that these differential effects reflect meaningful developmental patterns.
- Several factors may moderate the effects of prenatal stress on HPA axis function, including the time of gestation at which the stressor occurs and the sex of the fetus.
- An emerging literature suggests that epigenetic changes in HPA axis genes may mediate the effects of prenatal stress on fetal HPA axis development and function.
- The effects of prenatal stress may be amplified or attenuated as a function of the postnatal environment. Alternatively, the predictive adaptive response hypothesis posits that developmental adjustments made in response to prenatal stress are adaptive if there is a match between the prenatal and postnatal environments.

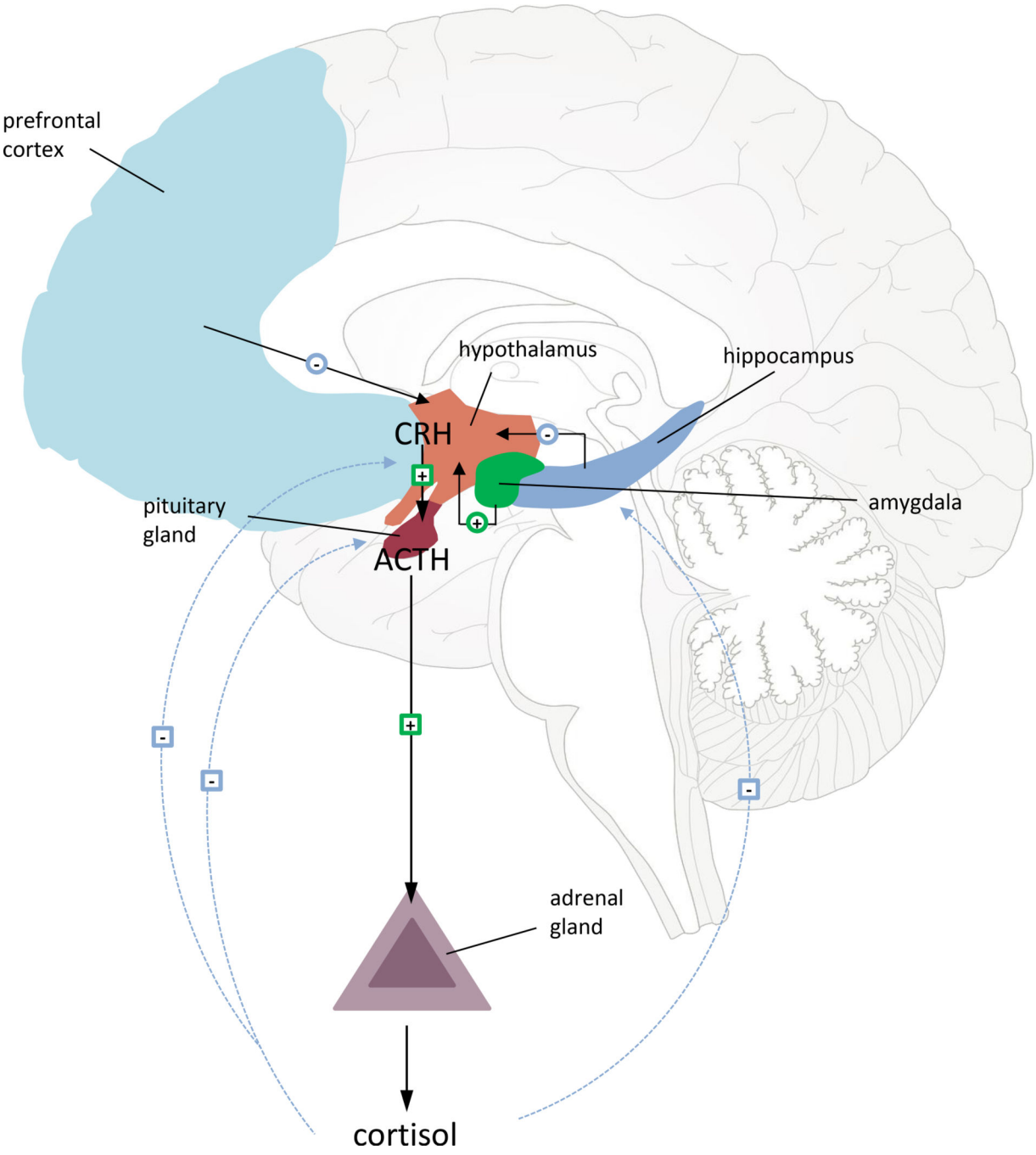

Figure 1.

Schematic representation of the hypothalamic-pituitary-adrenal (HPA) axis. In response to stress, corticotropin-releasing hormone (CRH) is synthesized in the paraventricular nucleus (PVN) of the hypothalamus and released into the hypophyseal portal blood. CRH binds to its receptors on pituitary corticotropes, stimulating the release of adrenocorticotrophic hormone (ACTH). Circulating ACTH binds to its receptors in the adrenal cortex and stimulates the release of cortisol, which mobilizes body systems to respond to the stressor. Elevated circulating cortisol inhibits further HPA axis activity (blue squares) by binding to its two

receptor types, glucocorticoid receptors (GRs) and mineralocorticoid receptors (GRs), at the level of the hypothalamus, pituitary, and hippocampus. CRH-producing neurons in the PVN of the hypothalamus are innervated by afferent projections from multiple brain regions (blue and green circles), including the amygdala, which provides excitatory input, and the prefrontal cortex and hippocampus, which provide inhibitory input.

ACTH: Adrenocorticotropic hormone; CRH: Corticotropin-releasing hormone; GR: glucocorticoid receptor; MR: mineralocorticoid receptor; PVN: paraventricular nucleus

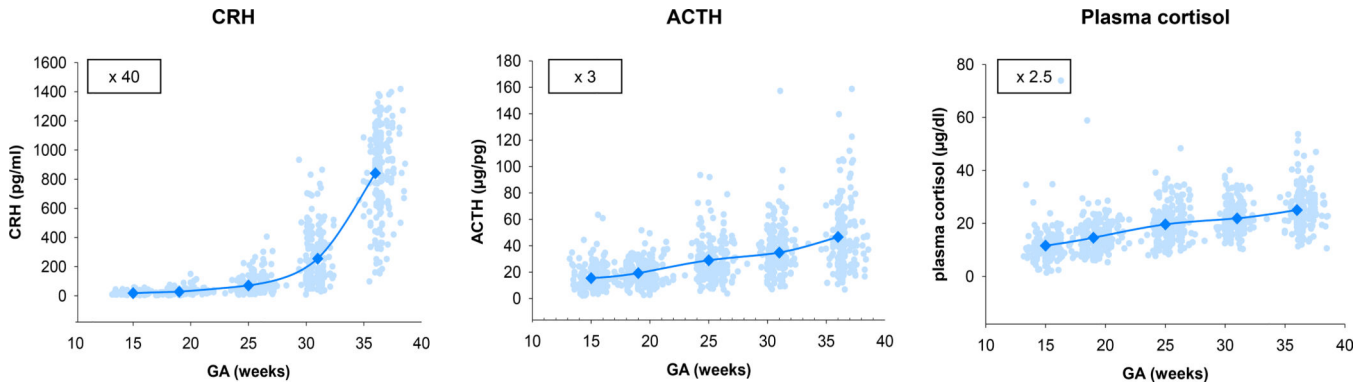

Figure 2.

Increases in hypothalamic-pituitary-adrenal and placental hormones in maternal circulation over gestation. Points represent mean levels of these hormones at each gestational interval. ACTH: Adrenocorticotropic hormone; CRH: Corticotropin-releasing hormone; GA: Gestational age

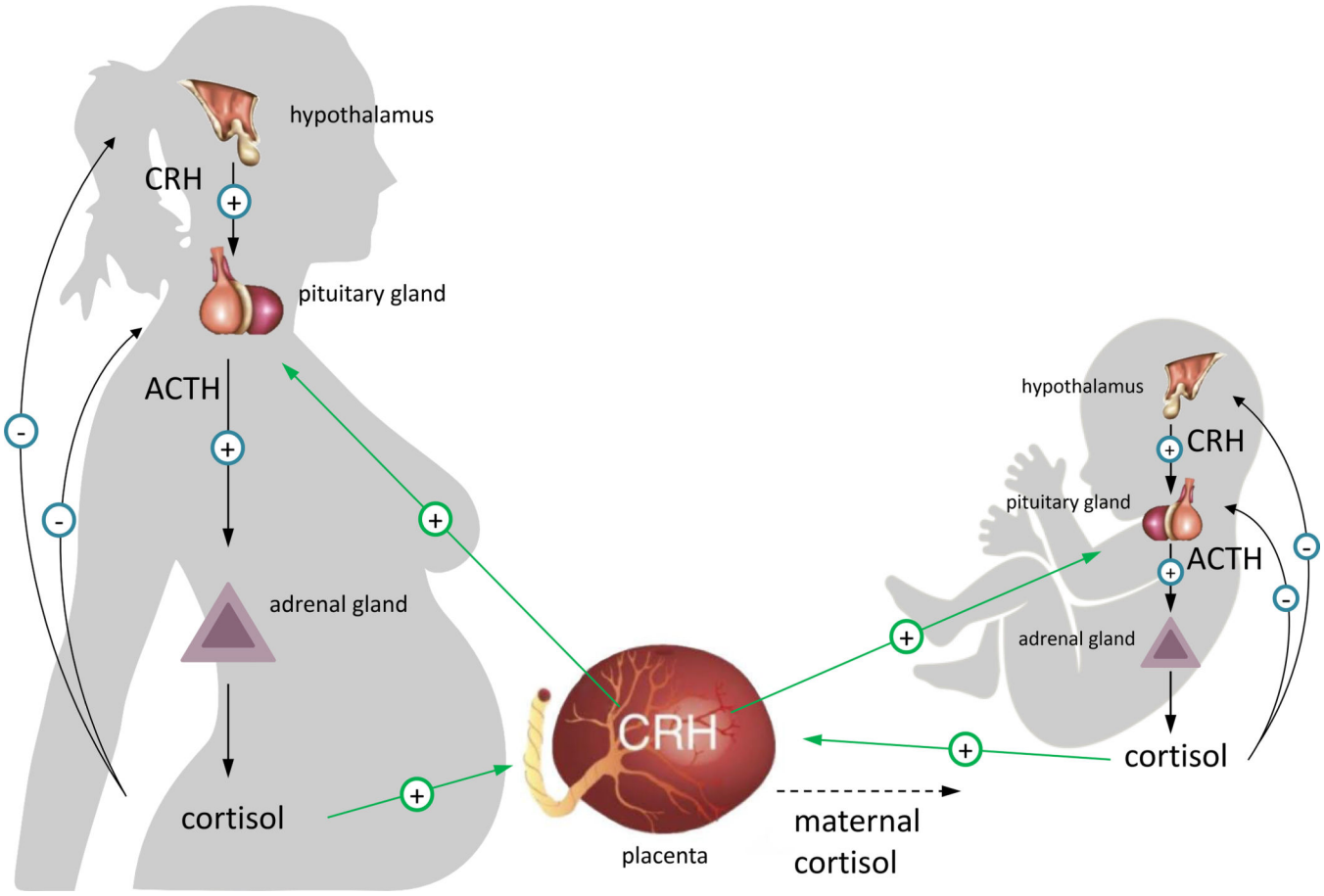

Figure 3.

Schematic representation of the maternal-placental-fetal steroidogenic unit. Placental corticotropin-releasing hormone (CRH) influences both maternal and fetal stress hormone production. In the maternal compartment, increases in placental CRH promote increased synthesis and release of ACTH and cortisol. Maternal cortisol in turn stimulates placental CRH production, generating a positive feedback loop (green lines). The placental enzyme 11β-hydroxysteroid dehydrogenase 2 (11β-HSD-2) oxidizes maternal cortisol into cortisone, but it is only a partial barrier, with some maternal cortisol entering fetal circulation. The developing fetal hypothalamic-pituitary-adrenal axis is regulated in part by maternal cortisol and placental CRH. Maternal cortisol may inhibit fetal pituitary ACTH release. Placental CRH likely stimulates production of fetal cortisol, both by increasing fetal adrenal responsiveness to ACTH and by direct stimulation of the adrenal. Increased fetal cortisol would in turn stimulate placental CRH production, constituting a second positive feedback loop (green lines). The massive amounts of hormones produced by the maternal-placental-fetal unit benefit both mother and fetus and influence the timing of parturition.

ACTH: Adrenocorticotropic hormone; CRH: Corticotropin-releasing hormone; 11β-HSD-2: 11β-hydroxysteroid dehydrogenase 2

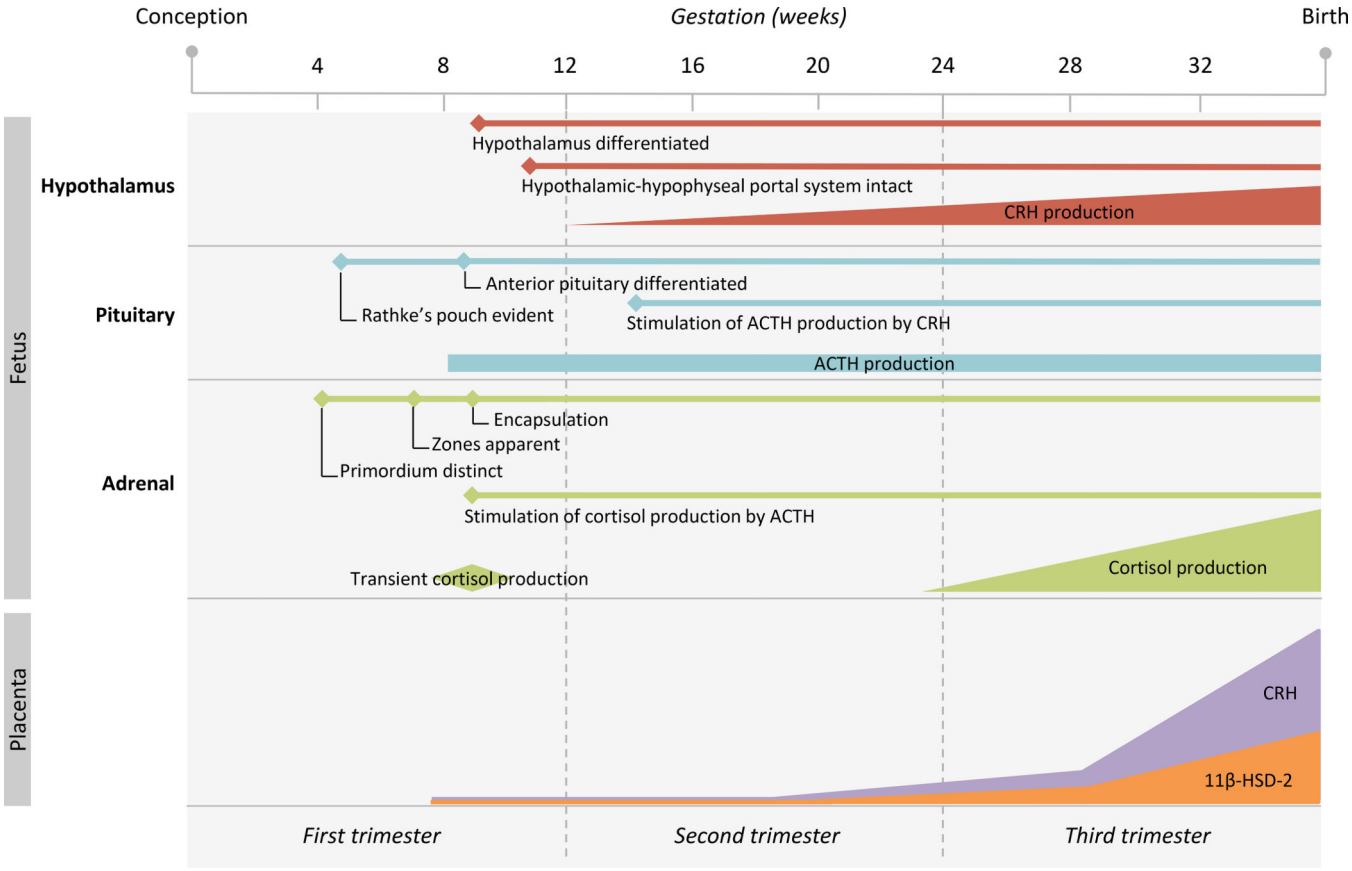

Figure 4.

Time table summarizing fetal hypothalamic-pituitary adrenal (HPA) axis development.

ACTH: Adrenocorticotropic hormone; CRH: Corticotropin-releasing hormone; 11β-HSD-2: 11β-hydroxysteroid dehydrogenase 2

Table 1.

Studies documenting associations between prenatal stress and postnatal HPA axis functioning

Study	Sample	Prenatal Exposure	HPA Axis Outcome	Findings
Neonate				
Davis et al. (2011)	116 women and their neonates	Maternal cortisol and psychosocial stress at 15, 19, 25, 31, and 37 weeks' gestation	Salivary cortisol response to heel-stick blood draw at approximately 24 hours after birth; samples collected pre-stressor and at 20 and 40 min post-stressor	Elevated maternal cortisol from 21–35 weeks' gestation was associated with larger neonatal cortisol response; strongest effects were at 25 weeks' gestation
Field et al. (2004)	119 women and their neonates	Maternal depressive symptoms and first morning urinary cortisol at approximately 20 weeks' gestation	Urinary cortisol within 24 hours of delivery	Neonates of mothers with elevated depressive symptoms had higher cortisol levels
Lundy et al. (1999)	63 women and their neonates	Maternal depressive symptoms and urinary cortisol during third trimester (M = 32 weeks' gestation, range = 27–35 weeks' gestation)	Urinary cortisol within 24 hours of delivery	Neonates of mothers with elevated depressive symptoms had higher cortisol levels
Marcus et al. (2011)	154 women and their neonates	Maternal depressive symptoms at 28, 32, and 37 weeks' gestation	ACTH and cortisol levels from umbilical cord artery blood at delivery	Neonates exposed to elevated levels of maternal depressive symptoms had higher ACTH levels than neonates exposed to low-stable depressive symptoms
Infant				
Braithwaite, Murphy, & Ramchandani (2016)	88 women and their 2–4-month-old infants	Maternal depressive symptoms during second or third trimester (*M* = 28 weeks' gestation; range = 15–41 weeks' gestation)	Salivary cortisol response to inoculation; samples collected anytime in day before stressor, immediately after stressor, and at 20 and 40 min post-stressor	No association between maternal depressive symptoms and infant cortisol response
Grant et al. (2009)	88 women and their 7-month-old infants	Maternal anxiety symptoms assessed via structured clinical interview during last trimester of pregnancy; women classified as meeting (or not meeting) criteria for prenatal anxiety disorder during last six months of pregnancy	Salivary cortisol response to the still-face procedure; samples collected at pre-stressor and at 15, 25, and 40 min post-stressor	Infants of mothers without prenatal anxiety disorders exhibited decrease in cortisol from 25–40 minutes post-stressor, while infants of mothers with prenatal anxiety disorders exhibited non-significant increase in cortisol across this interval
O'Connor et al. (2012)	125 women and their 17-month-old infants	Amniotic fluid cortisol during second or third trimester (*M* = 17 weeks' gestation; range = 15–37 weeks' gestation)	Salivary cortisol response to a maternal separation paradigm; samples collected pre-stressor and at 20 minutes post-stressor	Infants exposed to higher levels of amniotic fluid cortisol exhibited higher pre-stress cortisol levels and blunted stress responses (slight decrease over stressor)
Rash et al. (2016)	254 women at their 6-month-old infants	Maternal diurnal salivary cortisol output (4 samples over 2 consecutive days) and psychosocial stress at 15 weeks' and 32 weeks' gestation	Salivary cortisol response to set of structured laboratory frustration tasks at 6 months; samples collected pre-stressor and at approximately 15 minutes post-stressor	Infants who exhibited a decreased in cortisol in response to the task (as opposed to an increase) were exposed to a flatter maternal diurnal profile (less of a decline in cortisol over the course of the day) at 15 weeks' gestation
Stroud et al. (2016)	153 women and their 1-month-old infants	Maternal depressive symptoms assessed via structured clinical interview at approximately 23, 30, and 36 weeks' gestation; women classified as exhibiting prenatal depressive disorder, preconception-only depressive	Salivary cortisol response to NICU Network Neurobehavioral Scale; samples collected pre-stressor, end of stressor, and at 20 and 40 minutes post-stressor	Infants of mothers with prenatal depressive disorders exhibited higher baseline cortisol levels and higher cortisol response than infants of mothers with pre-conception only or no depressive disorders (effect

Study	Sample	Prenatal Exposure	HPA Axis Outcome	Findings
		disorder, or no depressive disorder		was driven by female infants); among infants of mothers with prenatal depressive disorders, decreased placental 11β-HSD-2 methylation associated with increased baseline cortisol levels
Tollenaar et al. (2011)	173 women and their infants (assessed at 5 weeks, 8 weeks, 5 months, and 12 months)	Maternal anxiety, daily hassles, pregnancy related anxiety, and dirunal salivary cortisol output (5 samples per day over 2 consecutive days) during third trimester (M = 37 weeks)	Salivary cortisol response to a bathing session at 5 weeks, vaccination at 8 weeks, still-face procedure at 6 months, and maternal separation paradigm at 12 months; samples collected pre-stressor and at 25 and 40 minutes post-stressor	Higher pregnancy-related anxiety predicted higher infant cortisol response to stressor at 5 weeks and lower cortisol response to stressors at 8 weeks and 12 months
Child				
de Bruijn et al. (2009)	103 women and their 2–5-year-old children	Maternal anxiety and depressive symptoms at 12, 24, and 36 weeks' gestation; children whose mothers scored above a standardized cutoff or higher than 1 SD above the sample mean on one of the three measurements of anxiety or depression at any of the gestational intervals classified as the prenatally exposed group	Salivary cortisol response to a mother-child play task and a frustration task; samples collected at start of home visit, and at 22 minutes after each task	No differences in response patterns between prenatally exposed and non-exposed children, with both groups showing a decrease in cortisol levels over the tasks; among female children, higher overall cortisol levels in prenatally exposed; no effects among male children
Gutteling, de Weerth, & Buitelaar (2004)	24 women and their 4–6-year-old children	Maternal pregnancy-related anxiety, daily hassles, perceived stress, and early morning cortisol levels at 15–17 weeks' gestation; children placed in low and high prenatal stress groups by median split for each of the four prenatal stress measures	Salivary cortisol response to vaccination; samples collected pre-stressor and at 15, 20, 25, and 30 minutes post-stressor	Higher maternal prenatal daily hassles, pregnancy-related anxiety, and early morning cortisol levels were associated with higher overall child cortisol levels
Gutteling, de Weerth, & Buitelaar (2005)	29 women and their 5-year-old children	Maternal pregnancy-related anxiety, daily hassles, perceived stress, and early morning cortisol levels at 15–17 weeks' gestation; children placed in low and high prenatal stress groups by median split for each of the four prenatal stress measures	Diurnal salivary cortisol output on weekend day (5 samples over the day), on the first day of school (4 samples over the day), and on a school day one week later (4 samples over the day)	Higher maternal pregnancy-related anxiety and early morning cortisol levels were associated with higher overall child cortisol levels on school days
Martinez-Torteya et al. (2016)	N = 119 women and their 10-year-old children	Third trimester (M = 33 weeks' gestation) maternal report of exposure to intimate partner violence (IPV) during pregnancy	Salivary cortisol response to Trier Social Stress Test for Children; samples collected pre-stressor and at 20 and 40 minutes post-stressor	Identified three profiles of child cortisol response: consistently low levels, consistently moderate levels, and consistently high levels with increase from pre-stressor to 20 min post-stressor; exposure to maternal prenatal IPV increased likelihood of membership in high response group, as compared to consistently low and moderate response groups
Child				
O'Connor et al. (2005)	74 women and their 10-year-old children	Maternal anxiety and depressive symptoms at 18 and 32 weeks' gestation	Diurnal salivary cortisol output (4 samples per day over 3 consecutive days	Higher maternal prenatal anxiety at 32 weeks' gestation predicted higher child awakening cortisol levels
Adolescent				

Study	Sample	Prenatal Exposure	HPA Axis Outcome	Findings
Huizink et al. (2008)	121 14-year-old twin pairs of Finnish women pregnant during the Chernobyl disaster and 157 14-year-old twin pairs of women who were pregnant one year after the disaster	Exposed or not exposed to Chernobyl disaster during pregnancy	Salivary cortisol levels measured once upon arrival to a laboratory visit	Adolescents whose mothers were in their second or third trimesters during the Chernobyl disaster had higher cortisol levels as compared to the reference group
O'Donnell et al. (2013)	899 women and their 15-year-old adolescents	Maternal anxiety and depressive symptoms at 18 and 32 weeks' gestation	Diurnal salivary cortisol output (4 samples per day over 3 consecutive days)	Higher maternal prenatal anxiety and depressive symptoms were associated with a lower cortisol awakening response and a flatter diurnal decline (smaller decrease) in cortisol levels in adolescents; effects similar at 18 & 32 weeks' gestation
Van den Bergh et al. (2008)	58 women and their 14–15-year old adolescents	Maternal anxiety symptoms at 12–22, 23–32, and 32–40 weeks' gestation	Diurnal salivary cortisol output (3 samples over one day)	Elevated prenatal maternal anxiety at 12–22 weeks' gestation was associated with a flatter diurnal decline (smaller decrease) in cortisol levels in adolescents; in female adolescents this cortisol profile was associated with higher depressive symptoms
Adult				
Entringer et al. (2009)	31 young adults whose mothers reported experiencing a major negative life event during pregnancy and a control group of 30 age-matched young adults	Maternal prenatal life events were obtained retrospectively by young adult children in communication with mothers at time of the assessment	ACTH and serum cortisol responses to Trier Social Stress Test (samples pre-stressor and at 15, 25, 35, and 105 minutes post-stressor), pharmacological stimulation of pituitary ($ACTH_{1–24}$ test), and diurnal salivary cortisol output (20 samples over one weekday)	Prenatal stress-exposed group exhibited lower baseline cortisol levels and greater increases in cortisol (baseline to peak) in response to stressor, as well as trend-level higher ACTH levels during the stressor; prenatal stress-exposed group exhibited lower cortisol levels during $ACTH_{1–24}$ test; no differences in diurnal cortisol output between the two groups