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The Link Between Perinatal Glucocorticoids Exposure and Psychiatric Disorders

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ABSTRACT: The perinatal period is particularly sensitive to a variety of insults during which stress-regulating systems can be permanently altered and psychopathologies ensue. The programming of physiological, endocrinological, and behavioral functions by perinatal adversities is mediated by altered levels of glucocorticoids or the hypothalamic-pituitary-adrenal axis activity in either the mother or offspring. In this article, I review the integrated data from human studies and from animal models that suggest the programming effects of perinatal glucocorticoids exposure. Finally, the concept of developmental origins of psychiatric disorders is discussed. **(*Pediatr Res* 69: 19R–25R, 2011)**

Vulnerability to psychopathology may be influenced by perinatal adversities (1–3), the mechanisms of which likely involve changes in neurodevelopment (1) and in the set point of neuroendocrine systems (4). Evidence has shown that perinatal adversities interact with genetic and postnatal environmental factors (5). The programming of physiological, endocrinological, and behavioral functions by perinatal adversities is believed to be critically mediated by altered levels of glucocorticoids or the hypothalamic-pituitary-adrenal (HPA) axis activity in either the mother or offspring (5,6). The effects of glucocorticoids on the developing brain can act as vulnerability factors for the later development of psychopathology (5).

The HPA Axis and Its Development

Activation of the HPA axis after exposure to a stressor is part of an adaptive response that enables an organism to respond appropriately to changes in the environment (7). Stress signals are conveyed to hypothalamus to increase the production of hypothalamic corticotrophin-releasing hormone (CRH). CRH is transported *via* hypophyseal portal system to the pituitary, where it elicits the release of ACTH from the anterior lobe of the pituitary gland, which finally stimulates the secretion of glucocorticoids, principally cortisol in human, corticosterone in rodents, from the adrenal glands. Glucocorticoids then interact with their receptors in multiple target tissues, including the HPA axis and hippocampus, where they exert an inhibitory negative feedback effect over the synthesis of hypothalamic releasing factors for ACTH, notably CRH and vasopressin.

The two glucocorticoid receptors (GR), mineralocorticoid receptor (MR), and GR, differ in ligand affinity and distribution throughout the brain (7). The ontogeny of MR and GR in the brain and the development of HPA axis have been studied primarily in rat. There is a distinct ontogenic profile for GR and MR in the fetal rat brain (8). GR mRNA is present in the anterior hypothalamus, hippocampus, and pituitary by gestational d 13 (8). Later, MR mRNA is present in the hippocampus by gestational d 16 and the hypothalamus by d 17 (8). In the rat, GR and MR in the fetal brain are low throughout gestation but increase rapidly after birth, consistent with the postnatal development of brain in rat (8). After birth, MR reaches adult levels by the end of the first week of life (9,10). GR, however, is ~30% of adult values during the first few weeks of life, approaching adult levels by about 30 d of life (9–11). Both GR and MR are highly expressed in the developing brain with different and complex ontogenies to allow intricate brain development. Between postnatal d 4 and 14, neonatal rat pups have very low basal levels of corticosterone and the corticosterone response to stressors is blunted, the so-called stress hyporesponsive period (SHRP) (12). Recently, Schmidt (4) proposes that HPA axis during SHRP is caused by a peripheral inhibition at the level of the pituitary, *via* a high GR feedback signal, and at the adrenal level, *via* a low sensitivity to ACTH. In contrast to the periphery, the hypothalamus arcuate nucleus and paraventricular nucleus can exhibit profound responses to stress and release CRH.

Perinatal Programming

Prenatal life and early infancy are critical periods characterized by increased vulnerability to stressors (2,13). The process by which perinatal life events can have long-term effects on physiological system has been described as perinatal programming. During the perinatal period, the HPA axis is particularly susceptible to programming by glucocorticoids. Glucocorticoids are important for normal maturation in most fetal organs including the developing brain. A key regulator of

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Abbreviations: ADHD, attention deficit hyperactivity disorder; **CRH,** corticotrophin-releasing hormone; **DOHaD,** developmental origins of health and disease; **EPM,** elevated plus maze; **GR,** glucocorticoid receptor; **HPA,** hypothalamic-pituitary-adrenal; **MR,** mineralocorticoid receptor; **SHRP,** stress hyporesponsive period; **11β-HSD-2,** 11β-hydroxysteroid dehydrogenase type 2

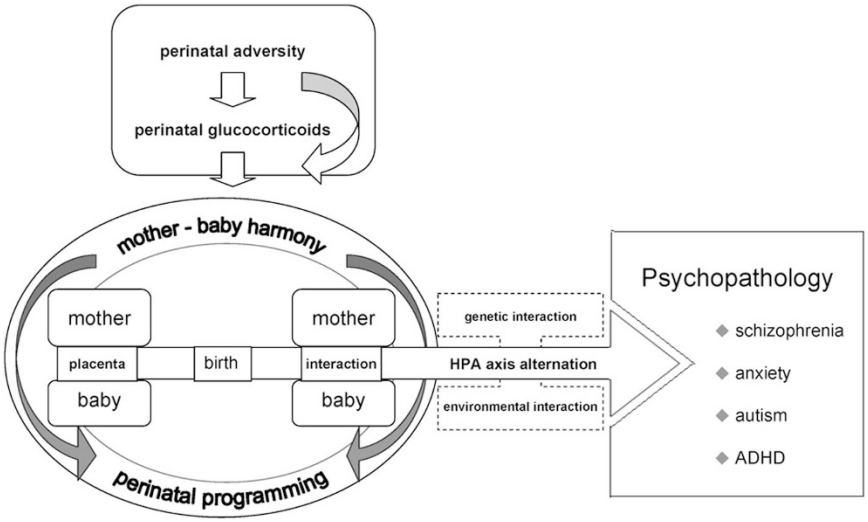

Figure 1. A simplified schematic representation of the route by which perinatal glucocorticoids exposure programs later psychopathology development. Perinatal adversity and perinatal glucocorticoids exposure act on either the mother or the baby, causing perinatal programming and persistent HPA axis alternation and susceptibility for later development of psychopathology.

human parturition is CRH, secreted by the placenta (14). Glucocorticoids increase placental CRH synthesis (15). CRH may in turn stimulate fetal and/or maternal cortisol synthesis, creates a positive feedback loop that again raises CRH concentrations and subsequently leads to delivery (14). Glucocorticoids are thus prime candidates for perinatal programming.

The HPA axis is particularly sensitive to effects of prenatal exposure to excess levels of glucocorticoids. Prenatal programming effects derive from environmentally induced alterations of materno-fetal signaling. Prenatal glucocorticoid exposure, during the last week of gestation, permanently increases basal and stress-induced plasma corticosterone levels in adult offspring (16). Similarly, prenatal stress has been associated with altered adult offspring HPA function and chronic neuroinflammation (17), resulting in part from altered maternal and/or fetal glucocorticoid exposure.

Hippocampal MRs have a higher affinity for cortisol and are 80–90% occupied at basal levels of cortisol, maintain the HPA circadian rhythm. Hippocampal GRs become important during periods of increased glucocorticoid secretion, mediate most of the stress effects of cortisol (7). Because of the slow developmental profile of GR in the brain, the ability to "appropriately turn off" a stress response does not develop fully for several weeks after birth in rat (11,18). In a rat study, Weaver *et al.* (19) reported that low levels of maternal care programmed a permanent increase in DNA methylation of the GR promoter, leading to reduced expression of GR in the hippocampus. This discovery provides an important insight into how permanent disruption of GR function and a collateral HPA axis dysregulation can result from early life stress.

In terms of humans, the HPA system remains highly reactive and labile in early infancy (13). During the first year, sensitive and responsive caregiving becomes a powerful regulator of emotional behavior and neuroendocrine stress hormone activity in young children. The quality of caregiving that the child receives during early development predicts the emergence of later self-regulation abilities, with sensitive caregiving associated with better adaptive self-regulatory abilities and more optimal functioning of the child's HPA system (13). Figure 1 depicts the route by which perinatal HPA axis programs development of later psychopathology.

Physiology of Placental 11β-Hydroxysteroid Dehydrogenase Type 2 (11β-HSD-2)

Although steroids can easily cross the placenta, under normal circumstances fetal glucocorticoid levels are much lower than maternal levels (20). This is due to 11β-HSD-2, which is highly expressed in the placenta (21). Indeed, placental 11β-HSD-2 forms a functional barrier restricting the free transfer of cortisol between the maternal and fetal compartments by converting cortisol into its much less active 11-keto form, cortisone (21). In a rat study, it has been demonstrated that attenuation of placental 11β-HSD-2 activity may expose the placenta and fetus to inappropriately high levels of glucocorticoids and result in IUGR and fetal programming of adult disorders (22). This hypothesis is supported by the association observed between reduced human placental 11β-HSD-2 activity and deliveries complicated by IUGR (23).

Sustained elevation or depletion of glucocorticoid during fetal development can permanently modify brain structure and function (16). 11β-HSD-2 expression is dramatically switched off at the end of midgestation in the rat and mouse brain, coinciding with the terminal stage of neurogenesis (8). Similarly, in human fetal brain, 11β-HSD-2 seems to be silenced between gestational wk 19 and 26 (24). Thus, there appears to be a timed system preventing the developing brain from inappropriately exposure to glucocorticoids.

Dexamethasone is a poor substrate for 11β-HSD-2 and therefore readily passes across the placenta from mother to fetus (25). Similarly, betamethasone is a poor substrate for 11β-HSD-2. In contrast, 11β-HSD-2 rapidly inactivates prednisolone to inert prednisone, so this widely used steroid has less impact on the fetus *in vivo*.

Prenatal Exposure to Glucocorticoids

Mammalian organisms express relatively high levels of GRs during late fetal development. Glucocorticoids can penetrate the placental barrier, with 10–20% of maternal glucocorticoids reaching the fetus intact (21), and on reaching the fetal brain, they can influence brain development by promoting myelination and terminal maturation and affecting cell survival (25,26). Unlike endogenous glucocorticoids, synthetic glucocorticoids bind mainly to the GR because the MR has low affinity for synthetic glucocorticoids. Prenatal glucocorticoid administration delays maturation of neurons, myelination, glia and vasculature, and brain weight at birth (27–29) and programs the fetal brain (30).

Animal studies. In the rat, daily exposure to synthetic glucocorticoids in either the third week of gestation or throughout the gestation period was found to result in adult male offspring having elevated basal plasma corticosterone levels and a significant decrease in GR and MR mRNA levels in specific hippocampal subfields (31). Alterations in MR and GR expression, therefore, influence basal and stress-induced increases in HPA activity. In addition, prenatal dexamethasone exposure on gestational d 17, 18, and 19 resulted in adult male offspring with elevated blood corticosterone levels and enhanced behavioral activities related to stress (32). In primates, dexamethasone-treated offspring also have been shown to demonstrate higher basal cortisol levels and higher plasma cortisol levels after stress (33). Prenatal glucocorticoid exposure resulted in adult male offspring with reduced exploratory behavior in an open field and reduced exploration in an elevated plus maze (EPM) (34). The open field test is a paradigm for measurement of anxiety like, explorative, and locomotor behavior in rats. The EPM has two open and two closed arms, presenting the rat with a conflict between the desire to explore a novel situation and its fear of height and open spaces. Furthermore, transgenic mice with selective loss of GR gene expression in the brain show markedly reduced anxiety (35).

The amygdala functions to control fear responses and the formation of emotional memories. Prenatal glucocorticoid exposure increases adult CRH levels specifically in the central nucleus of the amygdala—a key locus related to fear and anxiety (34). Similarly, prenatal stress causes increased anxiety-related behaviors with elevated CRH in the amygdala (36).

Prenatal glucocorticoid exposure also affects the developing dopaminergic system, suggesting a developmental relevance to schizo-affective disorders. Diaz *et al.* (37) showed that offspring born to corticosterone-treated mothers displayed enhanced spontaneous locomotor activity in the adulthood, when compared with control offspring (37). These abnormalities were already present at the prepubescent stage of development and persisted into adulthood. Long-lasting alterations in apomorphine-induced motor activity were also exhibited, which suggested reductions in dopamine receptor sensitivity and/or in the cellular and motor network mechanisms controlled by dopamine receptors. Shalev and Weiner (38) found that prenatal corticosterone administration during the last week of gestation led to a disruption of selective associating learning. This was evident from the form of loss of the latent inhibition effect in adulthood. In addition, programming of the HPA axis may also be regulated through the serotonergic system, which has been linked to hippocampal GR programming (31).

Using pharmacological blockage of 11β-HSD-2 by carbenoxolone in rats, Welberg *et al.* (39) found reduced immobility in a forced swim test in exposed offspring, indicating permanent anxiety-like behavior in aversive situations. In addition, 11β-HSD-2 ($-/-$) mice exhibited greater anxiety in the EPM test than both 11β-HSD-2 ($\pm$) and 11β-HSD-2 ($+/+$) littermates (40). In summary, available evidence in animal studies indicates that prenatal exposure to glucocorticoids leads to altered HPA axis activity, anxiety, and schizo-affective disorder.

Human studies. With regard to prenatal exposure to glucocorticoids, relatively few studies have been conducted in humans. Seminal work by Liggins and Howie (41) led to the worldwide use of prenatal glucocorticoid therapy to prophylactically impede morbid symptoms associated with preterm delivery, such as RDS and intraventricular hemorrhage. This treatment has been shown to increase the survival rate of preterm infants, but current evidence suggests that fetal exposure to synthetic glucocorticoids has detrimental effects on human birth outcome, childhood cognition, and long-term behaviors (42).

In 2001, the US National Institutes of Health recommends single course of antenatal corticosteroid treatment for fetal maturation. Repeated courses of antenatal glucocorticoid may have some benefits for lung function of the preterm newborn, but ongoing concerns for long-term health preclude their use at the present time (43). However, a recent survey showed that the proportion of women receiving antenatal corticosteroids had increased consistently over a 7-y time period for those deliveries between 24 and 35 wk (average increase rate 12% per year, $p < 0.001$) and for those deliveries after 34 wk (average increase rate 21% per year, $p < 0.001$) (44). Therefore, many fetuses likely still are exposed to multiple courses of antenatal corticosteroids.

In the North American TSH-Releasing Hormone Trial, infants who were exposed to three or more courses of antenatal glucocorticoids had lower plasma levels of cortisol at 2 h of age, suggesting suppression of the HPA axis activity by repeated antenatal glucocorticoids (45). Davis *et al.* (46) showed that infants of whose mothers were exposed to repeated courses of betamethasone exhibited a blunted salivary cortisol response to a heel-stick stressor at both 1 and 34 wk postnatally. In contrast, in an observational study, plasma cortisol and ACTH levels were similar in 86 2-d-old infants who had been exposed to single or multiple courses of antenatal glucocorticoids; this finding suggests no alternation of the HPA axis by repeated antenatal glucocorticoids (47).

Premature exposure of the fetus to glucocorticoids may program the child to perceive the world as hostile (2,5). Psychological assessments were performed on 541 of the infants enrolled in the Western Australian preterm birth cohort at periodic intervals up to 6 y of age. Children exposed to three or more courses of antenatal glucocorticoids exhibited significantly higher relative risks of externalizing behavioral disor-

ders and distractibility at 3 and 6 y of age. There were no effects on intelligence quotient or measures of internalizing behaviors (48). Similarly, Crowther *et al.* (49) reported that 521 children who had been exposed to repeated doses of glucocorticoids *in utero* were characterized by higher levels of attention problems at 2 y of age.

A recent report of follow-up in the antenatal betamethasone trial indicates that there are no clinical effects on cognitive functioning, working memory and attention, psychiatric morbidity, handedness, or health-related quality of life at 31 y of age (50). In summary, available evidence in human studies indicates that prenatal glucocorticoids exposure leads to behavioral problems in early childhood. If prenatal glucocorticoids exposure has persistent effects on human neuroendocrine function and susceptibility to psychiatric disorders is a question, then that cannot be answered until the results of large randomized controlled trials are available and follow-up of the offspring is completed.

Postnatal Exposure to Glucocorticoids

Postnatal administration of glucocorticoids can have deleterious effects on brain development. Previous studies in rodents demonstrate that during postnatal d 2–14 normal maternal behavior ensures a quiescent stress response in the pup, the so-called SHRP, when neonatal rats have very low basal levels of corticosterone and the corticosterone response to stressors is blunted (12). In this period, rates of neurogenesis, neuronal migration, and cell death reach maximal levels while circulating corticosterone is low (51). Acute administration of glucocorticoids during this period causes an irreversible decrease in brain weight and myelination of fibers (52). In the dentate gyrus, acute postnatal glucocorticoid treatment during this period reduces cell death in the granular layer of the dentate gyrus and, in contrast, increases cell death in the hilus (51).

Similarly, in human infants, there is a developmental period that shows decreased responsiveness of the HPA axis to stressors (53). Chronic lung disease remains a major morbidity in preterm-born infants and dexamethasone is widely used for preventing or treating it. The almost routine use of dexamethasone continued until 1998, when Yeh *et al.* (54) demonstrated a significant increase in neurodevelopmental dysfunction in neonates treated with dexamethasone compared with controls. However, a prospective evaluation of postnatal steroid administration in California from April 2002 to March 2003 showed that 19.3% of the very low birth weight infants (<1500 g) still received steroids for chronic lung disease, hypotention, or extubation stridor (55). Therefore, it is important to continue evaluating all of its developmental consequences.

Animal studies. Using a tapering course of dexamethasone treatment between postnatal d 3 and 6 in rat pups, Flagel *et al.* (56) demonstrated an association between dexamethasone exposure in the neonatal rat pups and changes in HPA function in the adolescent. This was evident in the form of increased anxiousness in the light-dark test of anxiety and in response to a mild novelty stress, as measured by a blunted corticosterone response. The light-dark test in rodents is based on a conflict between the innate aversion to brightly illuminated areas and spontaneous exploratory activity. The authors concluded that the dissociation between behavioral and hormonal stress responsiveness suggested that neonatal dexamethasone exposure permanently alters brain function, particularly within the neuroendocrine stress axis (56). Using the same dexamethasone regimen, Neal *et al.* (57) showed increased anxiety-like behaviors in single-housed dexamethasone animals in the EPM and open field, however, they found no differences between groups in the light-dark test. Although the animals exhibited increased anxiety-like behavior in threatening environments, they demonstrated no such behavior when placed in a less-threatening novel environment. Basal corticosterone levels were no different between adult males and female groups. In response to crowding stress, animals in the dexamethasone groups demonstrated an adequate corticosterone response but exhibited a slower termination to baseline. The animals could mount a response, but they were unable to turn it off appropriately, even up to 120 min after crowding stress was initiated (57).

Using a tapering course of dexamethasone treatment between postnatal d 1 and 3 in rat pups, Kamphuis *et al.* (58,59) showed that neonatal treatment with dexamethasone not only resulted in long-lasting behavioral changes but also a reduction of the HPA axis activity to novelty stress in adults. In addition, Roskoden *et al.* (60) showed that early postnatal corticosterone treatment led to a higher locomotor activity as indicated by more entries into closed arms of the EPM, and a lower number of CRH-immunopositive neurons in the central nucleus of amygdala. Moreover, Slotkin *et al.* (61) demonstrated that dexamethasone administered during the critical neurodevelopmental stage elicited selective changes in serotonergic and dopaminergic synaptic function, implying that adverse neurobehavioral consequences may be inescapable in glucocorticoid therapy of preterm infants. In summary, available evidence in animal studies indicates that postnatal exposure to glucocorticoids leads to altered HPA axis activity and anxiety.

Human studies. Systemic corticosteroid therapy has been increasingly prescribed for ventilator-dependent infants since the 1980s. A recent series in the Cochrane Database of Systematic Reviews has concluded that the benefits of early postnatal corticosteroid treatment (<7 d of age), particularly dexamethasone, may not outweigh the known or potential adverse effects of this treatment (62). Long-term follow-up studies suggest an increased risk of abnormal neurological examination and CP (62). However, postnatal corticosteroid treatment for chronic lung disease initiated after 7 d of age may reduce neonatal mortality without significantly increasing the risk of adverse long-term neurodevelopmental outcomes (63). In February 2002, the American Academy of Pediatrics and the Canadian Pediatric Society advised that postnatal corticosteroids therapy should be limited to exceptional situations (64).

Few clinical studies have examined the effects of premature neonate exposure to glucocorticoids on the HPA axis and on long-term behavioral outcomes have been few. Ng *et al.* (65) assessed longitudinal hypothalamic, pituitary, and adrenal response in a cohort of ventilated infants exposed to systemic dexamethasone treatment. The results of the study suggested

that hypothalamic function was suppressed during systemic corticosteroid treatment but partial recovery occurred 4 wk after therapy had ended. Yeh *et al.* (66) examined 146 children and found that early postnatal dexamethasone treatment was associated with adverse effects on neuromotor and cognitive functions in school-age children.

Using the Child Behavioral Checklist, Karemaker *et al.* (67) assessed behavioral outcomes in school-age children who were neonatally exposed to dexamethasone or hydrocortisone. The checklist consists of items relating to anxiety, depression, aggressive behavior, social problems, and thought and attention problems. Karemaker *et al.* (67) reported that infants treated postnatally with hydrocortisone had behavioral outcomes similar to control samples, whereas postnatally dexamethasone-treated girls exhibited poorer performances on behavioral scales than girls in the control group. In a subsequent study, Karemaker *et al.* (68) demonstrated for the first time that HPA-axis activity in school-age children was decreased in prematurely born children treated with dexamethasone during the neonatal period. However, no changes in HPA were observed when children had been treated neonatally with hydrocortisone. Together, in the same cohort of children, dexamethasone-treated girls displayed more behavioral problems, such as attention problems and social problems associated with alternations in the HPA axis.

A recent study by Spittle *et al.* (69) examined 188 very preterm infants (GA $<$30 wk or birth weight $<$1250 g) at 2 y of age. They demonstrated that at 2 y, very preterm children exhibited significantly higher internalizing and dysregulation scores and lower competence scores than peers born at term. In addition, postnatal corticosteroids exposure was significantly associated with lower competence scores in the very preterm group.

In summary, available evidence in human studies indicates that postnatal glucocorticoids exposure leads to altered HPA axis activity and behavioral problems in childhood. If postnatal glucocorticoids exposure has persistent effects on human neuroendocrine function and susceptibility to psychiatric disorders is a question, then that cannot be answered until the results of large randomized controlled trials are available and follow-up of the offspring is completed.

Developmental Origins of Psychiatric Disorders

The Barker hypothesis states that low birth weight is associated with adverse adult outcomes, such as coronary heart disease, stroke, high blood pressure, and type 2 diabetes (70). These observations show that early life influences can alter later disease risk, leading to the concept of developmental origins of health and disease (DOHaD) (71). The concept of DOHaD proposes that the fetus forecasts the future and elicits biological programming according to the environment that is likely to prevail after birth. Under this concept, birth weight is an epiphenomenon that reflects the nutrients availability *in utero* (3,71). The concept of DOHaD also applies to psychiatric disorders (1,5,72).

Schizophrenia is a complex neurodevelopmental disorder, which is characterized by psychosis, apathy and social withdrawal, and cognitive impairment (73). Perinatal adversity has been associated with the development of schizophrenia (74). The support for the neurodevelopmental hypothesis of schizophrenia is derived from epidemiological studies assessing the effects of prenatal stress on schizophrenia risk (75,76).

Anxiety is defined as a state of cognitive and behavioral preparedness that an organism mobilizes in response to a state of uneasiness and apprehension. A developmental approach is relevant to anxiety disorders (77) as the mean age of onset for anxiety disorder is 11 y (78). This early onset implies that individual levels of trait anxiety are early developmental processes or events that wire the developing brain. Birth cohort studies have identified maternal immune and stress responses as significant risk factors for major depressive disorder (79). A famous example is the Dutch Winter Famine study, which showed that second or third trimester exposure to famine was associated with an increased risk of admission for mood disorders in later life (80). Analysis of database has shown that adults exposed to child abuse and/or neglect are at greater risk for the development of affective disorders (81).

Autism disorders are not uncommon, the prevalence of autism today is estimated at 13 per 10,000 (82). Autism is a neurodevelopmental disorder that is characterized by abnormal social interaction, patterns of interests, speech development, and patterns of behavior. Empirical evidence suggests that prenatal stress may play a significant role in the etiology of autism disorders (82). Recently, in a study of prenatal exposure to hurricanes and tropical storms in Louisiana, the prevalence of autism increased in dose-response fashion from 3.72/10,000 births for the low-exposure group, to 9.65/10,000 births for the intermediate-exposure group, and further to 26.59/10,000 births for the high-exposure group, especially for cohorts exposed during the 5–6 and 9–10 mo of gestation (83).

Attention deficit hyperactivity disorder (ADHD) manifests in childhood and is characterized by symptoms of developmentally inappropriate inattention, impulsivity, and hyperactivity. Some evidence from brain imaging studies using positron emission tomography (84) and magnetic resonance spectroscopy (85) support the notion of developmental origin of ADHD. Froehlich *et al.* (86) demonstrated that prenatal tobacco and childhood lead exposures were associated with ADHD in US children, especially among those with both exposures. In addition, low birth weight was associated with features of hyperactivity and reduced attention in preschoolers (87).

Conclusions

The evidence of perinatal programming of psychiatric disorders is clear. Extensive evidence in animal studies has shown the link between perinatal glucocorticoids exposure and later psychopathologies; however, caution should be exerted in extrapolating these findings from animals to humans. Although direct evidence is lacking in humans, preliminary observations suggest an important role of glucocorticoids for perinatal programming of psychiatric disorders. Because glucocorticoids have been widely used during the perinatal period in recent decades, long-term follow-up of infants enrolled in randomized controlled trials are needed in future research.

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