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Review Article

The Third Trimester Human Fetus may be Protected from Prenatal Stress and Programmed Adult Mental Illness

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Abstract

There is evidence, primarily from animal models, that fetal exposure to drugs, endotoxins and infectious agents acting as physiological stressors lead to atypical adult behaviors. Maternal restraint and other "psychosocial" stressors also have been shown to induce aberrant behavioral phenotypes in the adult offspring. Translation to humans is supported by retrospective and prospective studies revealing increased risk of psychopathology in the adult children of women exposed to war, bereavement or other cognitively perceived stressors during their pregnancies, especially during the first and second trimesters. The presumed mechanism is the excess levels of corticosteroids from stressed mothers entering fetal circulation, binding the glucocorticoid receptor and promoting neural changes underlying psychiatric diseases. Collectively, the data support a fetal programming disease model that perinatal insults, including maternal stress, can predispose the individual to develop adult pathology, including mental illness. We propose that the animal findings of prenatal, psychosocial stress are best applied to the first and second trimester human fetus. Findings in the literature are highlighted to support our contention that the third trimester human fetus has evolved unique mechanisms that largely protect the fetus, rendering it resilient to maternal stress. The third trimester fetus is unlikely to experience later psychopathology from maternal exposure to psychosocial stress, thus limiting the reach of the fetal programming disease model.

INTRODUCTION

A ubiquitous concept in psychiatry recently is that maternal stress during pregnancy can modify the fetal human brain for later development of mental illness [1,2]. Most commonly, the mechanism is thought to be the role of excess glucocorticoids promoting low fetal growth and disrupting brain development [3]. The concept has been formalized as the fetal stress-programming model of adult disease. The tacit assumption is that exposure to prenatal stress raises the general susceptibility to psychopathology rather than directly inducing a specific form of psychopathology [4,5].

There are, however, reasons to question a broad application of the programming model. The literature often mixes psychosocial sources of stress during pregnancy with exposure to physiological stimuli. Many of the relevant review papers jump seamlessly between results with animal models and human fetuses as if species and timing of exposure were irrelevant [6]. Physiological stressor such as poor nutrition, oxidative stress, hypoxia, immune disturbances, endotoxins, exogenous hormones and drugs can have profound influences on fetal development [7-9].

But, can subjective, psychosocial stress to the pregnant female create similar damage in a fetus? There are empirical [10] and conceptual [11] reasons to believe that exposure to objective, physiological stressors differs from emotional distress. The latter release lesser amounts of stress hormone and are less disruptive to normal functions [12]. This review proposes limitations on the capacity of psychosocial stressors to program the CNS for later psychiatric disorders. We will demonstrate that the third trimester human fetus has evolved features independent of

maternal systems. The result is protection from many of the stressful agents to which the mother is exposed.

A critique of the prenatal psychosocial stress-programming model

Responses to psychological stressors such as job loss, divorce or bereavement, of course, are also physiologically based. Yet, psychosocial stressors can be distinguished as being subjective, cognitively perceived stimuli by an individual that activates the hypothalamic –pituitary – adrenal (HPA) axis and sympathetic adrenomedullary (SAM) system [13,14].

The programming concept places greater burden on the HPA axis. Maternal responses to physiological or psychosocial stressors during sensitive periods of fetal development are proposed to expose the fetus to excess glucocorticoids (CORT), i.e. cortisol in primates and corticosterone in rodents [1,15]. The emphasis on excessive CORT recognizes that glucocorticoids are necessary for the fetus. Typical hormone levels in the fetus serve as a developmental switch, driving changes in gene regulation for normal growth and differentiation of tissues and organs, including the fetal brain [16]. However, excessive quantities of CORT, either by physiological stressors or direct administration of CORT or metabolic inhibitors to pregnant experimental animals, increase the risk of aberrant behaviors in the offspring as adults [17, 18]. It is notable that experiments administering CORT most often use synthetic forms of the hormone. Similar findings are reported in children and young adults whose mothers were prescribed synthetic glucocorticoids during pregnancy [19]. This is important because the fetal rat or human responses to endogenous CORT are very different from responses to exogenous, synthetic glucocorticoids.

There is evidence pointing to a relation between psychological events in women and neural dysfunction and problem behaviors in the child, adolescent or adult [13,20]. An example is a study of large numbers of adult children of Danish women who had experienced the death of a close relative during pregnancy [21]. The researchers found an increase in diagnoses of schizophrenia in the offspring. Importantly for this review, the relation was statistically significant only for maternal stress occurring during the first trimester. There was no relation when the psychosocial stressor occurred later in pregnancy, particularly during the third trimester. Other studies have confirmed that the link of maternal emotional distress to offspring psychiatric disorders is most clearly observed during early pregnancy [22,23].

Those human reports suffer from 1) reliance on retrospective measures, 2) failure to distinguish between prenatal and postnatal influences or 3) ignoring the likelihood a postnatal environment would reflect prenatal conditions [24,25]. The better, prospective studies [26] have other flaws including questionable assumptions related to the emotional states of the mother and status of the placenta. In one example, authors reached the conclusion that maternal anxiety suppressed enzymatic metabolism in the placenta. This was based on a single assessment of anxiety of the mother on the day before scheduled caesarian surgery and measurement of steroid enzymatic levels in the placenta after delivery [27]. Limitations on studying the human fetus and placenta has led to most of the work on the programming model being done with animal models, mostly rodents [28,29].

Two experiments from different animal laboratories illustrate this research. In both, pregnant rats were restrained repeatedly during the last week of gestation. Long-term brain changes were reported in the adult male offspring with increased glutamate NMDA receptors in prefrontal cortex, hippocampus and ventral striatum [30]. To control for intervening postnatal influences on adult NMDA receptors, Tavassoli and colleagues [31] sacrificed pups from stressed dams on different postnatal days (PND 2,6 or 15). Prenatally stressed males had elevated circulating corticosterone and increased expression of NMDA receptors in the right hemisphere. Collectively, the conclusion of the experiments was to point to a possible link between prenatal stress, glutamate and psychosis in humans [31]. Interestingly, there also were sex differences in prenatal influences that are often reported in the animal literature [32,33]. Specifically, female offspring experienced little of the neural changes found in the males. Few human researchers have attempted to distinguish sex differences in psychiatric outcomes with prenatal stress.

In summary, it is noteworthy that most of the evidence for prenatal programming by maternal stress is from rodent models. Rodent placenta and fetuses are comparable to the human fetus early in pregnancy. Data from prenatal rats and mice are, thus, likely an acceptable model for the first and second trimester human fetus [34,35]. The third trimester human (3^{rd}TH) fetus may be a quite different organism [36].

Uniqueness of the third trimester human fetus

Rodent neonates as an extension of fetal life: Humans belong to the group of animals that are incapable of independent survival at birth. The term used is altricial [37]. Degree of dependence on the mother differs among altricial species, and rodents are particularly altricial. Brains of primates & humans are more mature at birth than neonatal rodents [19]. The prenatal and immediate postnatal rodent, consequently, is comparable to the early human fetus. The level of maturity of the postnatal day 1-10 rat is more akin to the 3^{rd}TH fetus [38,39].

Sapolsky and Meaney [40] decades ago identified a stress nonresponsive period (SNRP) in neonatal rodents, suggesting a hyposensitive HPA axis. The SNRP was reported to persist from soon after birth to the second week of life, postnatal days 2-12. Later [41], there were reports that the SNRP is most applicable to pituitary – adrenal relations, thus applying primarily to CORT secretions.

Is it possible that the human fetus is similarly hyporesponsive to the CORT release to stress during the 3^{rd} trimester? Some researchers believe the answer is yes. Mellor *et al.,* [42] make an excellent case that the fetus is unconscious and unable to perceive pain. The authors concluded that there is no direct evidence that cortical or subcortical responses by the 3^{rd} TH fetus to presumably painful stressors can alone cause long-term adverse outcomes.

The Late Human Fetus

Our contention is that human fetuses in the first and second trimesters are more similar to the fetuses of experimental animals, including rats and mice. In that case, the data from animal models are more informative for early pregnancy

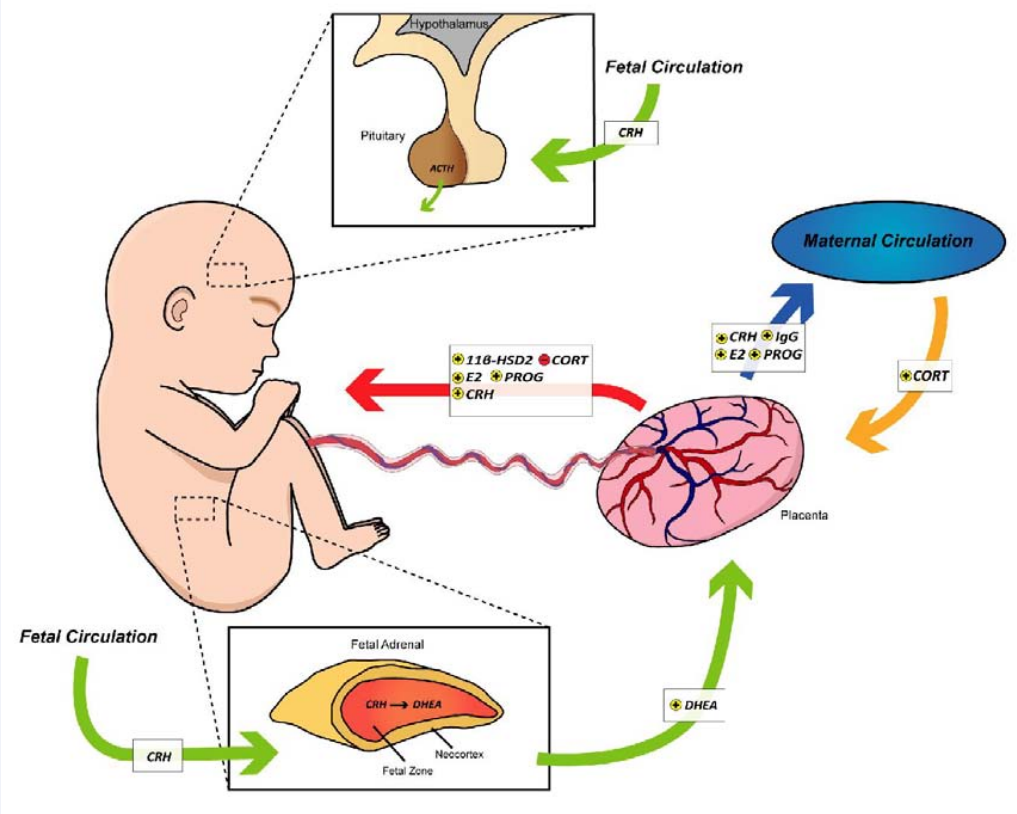

Figure 1 Representation of the third trimester fetus and the hormone flux from the placenta to fetal circulation (red arrow), placenta to the maternal circulation (blue arrow) and reciprocal exchanges (orange arrow). Green arrows indicate metabolic processes in the fetus and subsequent interactions with the placenta. (+) represents the addition of a substrate to the target region, while (-) indicates a reduction in synthesis.

while the 3rd TH fetus is unique and uniquely protected from maternal stress and excess CORT. Studies frequently cited in the programmed stress literature are of the relation between maternal bereavement stress and the risk for developing schizophrenia [21,43,44]. In each of those reports, it is only the first or second trimester fetus that is found to be at a higher risk for psychiatric disease. Thus, those data are consistent with the findings of antenatal programming in the rodent animal model. It is important to recognize that the fetus is an individual organism, only genetically similar but not identical to the mother. Although highly dependent upon the mother, it is intuitive that the fetus would have evolved independent survival mechanisms. The 3rdTH fetus is testament to the evolution of survival mechanisms that differ between mother and fetus. An example is that basic neurophysiology differs between the 3rdTH fetus and the human neonate. The neurotransmitter GABA is the major inhibitory transmitter with the other amino acid, glutamate serving as the main excitatory transmitter in adulthood. In the fetus, GABA ergic neurons and synapses are excitatory and a principal source of neuronal activity. At parturition with enhanced maternal oxytocin levels, there is an abrupt change so that the hyperpolarizing action of GABA protects embryonic neurons from anoxic insults [45]. There are many other examples of the unique physiology of the 3rdTH fetus. Most are clearly designed to protect the fetus from insult and prepare for a healthy parturition and postnatal life. The first-line of defense is provided by the placenta, and by the third trimester, the placenta is well positioned to protect the fetus.

Placenta

The placenta is a lipid-soluble barrier that plays a crucial role in monitoring and controlling nutrient absorption, waste elimination, and gas exchange between the mother and the fetus. By the end of the first trimester, the placenta has established functional units or cotyledons. Cotyledons are the primary area of exchange between the maternal and fetal systems. Like other biological lipid-soluble membranes, the placenta is selectively permeable and serves as a barrier to various substances in the maternal bloodstream. However, the placenta readily transfers lipophilic steroids such as CORT from maternal and fetal circulation, but also from fetus to maternal circulation [46].

These features help define the placenta as an endocrine and immune organ. However, it is an organ more genetically compatible with the fetus than with the mother. The role of the placenta is primarily to serve the developmental needs of the fetus. An anthropomorphic interpretation is that the placenta is focused on the fetus and interested in the welfare of the mother only to the extent that she can enhance fetal viability. As an example, the human placenta physically embeds itself into the uterine wall, causing what has been described as a significant wound to the uterus [36]. The maternal immune system reacts to the insult, and the woman may feel ill during the early weeks of

pregnancy. Once the wound has healed, the mother is now able to provide the nutritional needs for the fast-growing fetus [47]. The third trimester is characterized by the mother, placenta and fetus in a symbiotic relation. Although the singular goal of all three is an uneventful birth of a healthy neonate, the fetus has more to lose. The placental – fetal relation is unique.

Continuing the anthropomorphic perspective, the eye of the placenta is firmly on healthy fetal development even when it is detrimental to the mother [48]. Fetal leukocytes can leak into the maternal bloodstream causing her immune system to react to paternal antigens. The high rates of depression in pregnancy may have its genesis, in part, from placental synthesis of monoamines, proteins and HPA hormones underlying mood [26].

More often, it is clear that the placenta and fetus are active partners in contributing to the health of the mother during pregnancy progression. Trophoblasts, the cellular unit of the placenta, produce substances that influence the maternal immune system for the purposes of maintaining and guarding the pregnancy [47,49]. At the same time, the 3rdTH fetus synthesizes an immunoglobulin (IgG) receptor that allows the placenta to transfer maternal IgG to the fetus. Indeed, at birth the neonate has higher levels of immunoglobulin than the mother. Finally, the placenta helps down-regulate the autoimmune sensitivity of the maternal immune system that could induce rejection of the fetus. The 3rdTH placenta uses the prodigious amounts of DHEA, a precursor of sex steroids, released from the fetal adrenal glands to synthesize estrogens. The extraordinarily high levels of estradiol in a pregnant woman come almost exclusively from the placenta. Her ovaries synthesize little estrogen [47].

Throughout most of a normal gestation, the placenta also produces large amounts of progesterone. The hormone restrains the adaptive immune system responses that would identify the fetus as an antigen and risk rejection [49]. Progressively increasing amounts of progesterone in maternal and fetal circulation also ensure high levels of the progesterone metabolite, allopregnanolone. Allopregnanolone protects the fetus from harmful levels of maternal glucocorticoids. In addition, allopregnanolone plays other roles in development and neuroprotection of the fetal brain, e.g., helping regulate the release of oxytocin and prevent preterm delivery [50]. Obstetric medicine takes advantage of that feature and uses exogenous progesterone to prevent preterm births. In a study of pregnant women administered synthetic progesterone [51], markedly lower levels of the drug were found in umbilical cord fluid than in maternal circulation. The authors suggested it is possible the placenta is particularly effective in metabolizing the steroid. Alternatively, they propose another mechanism that is likely at work with other steroids, efflux transporters in the placental returning hormone to maternal circulation [52].

Finally, a critical function of the placenta is to protect the fetus from excess levels of CORT. The main mechanism is the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD2). There are large quantities of the enzyme in the placenta to metabolically convert high levels of cortisol from the mother's circulation to an inactive form before being delivered to the fetus [53]. Other placental steroidal metabolizing enzymes in the 3rdTH fetus may also contribute to decrease the level of fetal CORT [54], but clearly 11β-HSD2 is primary. There are several fine reviews of the 11β-HSD2 [55,56], and we will only note a few features of the enzyme in the placenta. Most important is that 11β-HSD2 metabolizes the endogenous CORT to biologically weak metabolites. However, it is metabolically ineffective with synthetic analogs of CORT. Dexamethasone, prednisone or betamethasone pass the placenta with ease, dramatically raising the levels of CORT in the fetus [57].

The effectiveness of 11β-HSD2 is illustrated in titers of endogenous CORT being double or more in maternal circulation than the levels in the fetus. It is notable that the activity of the enzyme changes during pregnancy with greater metabolic activity during the third trimester [58]. Reports in the literature have indicated reductions or disruptions to 11β-HSD2 in the fetus to psychosocial maternal stress [59]. These studies are generally with rodents that generalize better to human fetuses during early pregnancy than to the 3rdTH fetus.

Along with the placenta and its 11β-HSD2 enzyme, the fetal HPA helps control excess CORT in the 3rdTH fetus. Most of the CORT found in fetal circulation during the first half of pregnancy is from the mother. By the onset of the third trimester, the fetal HPA decreases its release of CRH and adrenocorticotropin hormone (ACTH) in response to negative feedback mechanisms that are now beginning to develop. The 3rdTH fetus also controls bioactivities of excess CORT by synthesizing receptors for glucocorticoids (GR) and mineralocorticoids (MR). The two receptors work in tandem in that the higher affinity of the MR binds much of the excess CORT, preventing binding with the GR that can be detrimental.

Progesterone can bind and antagonize the GR. Placental 11β-HSD2 may regulate competition of progesterone-glucocorticoid GR receptor and modify activity of both steroids in the placenta and fetus [60]. Because the fetal programming model of mental illness focuses on CORT as the mechanism, it is of special interest to consider the 3rdTH fetus capacity to oppose excess levels of CORT. Along with the placenta, development of the HPA during the third trimester is a key.

The Fetal HPA

Another unique feature of the 3rdTH fetus is a prenatal adrenal gland that is structurally and functionally unlike the postnatal adrenal. The adult adrenal cortex is comprised of three zones that synthesizes androgen precursors such as DHEA (zona reticularis), mineralocorticoids (zona glomerulus) and CORT (zona fascicularis). The fetal adrenal is much larger relative to body size and is comprised of a neocortex that will become those zones and a significantly larger, unique "fetal zone." Soon after birth, the fetal zone undergoes involution while the neocortex differentiates into the adult three zones [61].

The fetal zone is a highly active endocrine gland synthesizing large amounts of DHEA. Indeed, only in humans and a few primates do the fetal or adult adrenals secrete much DHEA and its sulfate DHEAS [62,63]. In the human fetus, the placenta converts DHEA into estrogens via the aromatase enzyme that is shuttled into fetal and maternal circulation. The rodent placenta lacks aromatase and all estrogen is from the mother [63]. Also different from the rodent placenta in which progesterone and estrogen are

inversely related, both hormones remain high during pregnancy in humans [64].

The 3rdTH fetus has an extraordinary capacity to respond to emergency conditions occurring during development. This can be observed in the development of the HPA and factors in perirenal adipose tissue in response, for instance, to hypoxia. Both maturational changes in the 3rdTH serve the same role, providing the fetus with the means to respond to intrauterine hypoxia and other stressors from either physiological or psychosocial sources [65].

Yet another unique feature of the 3rdTH fetus is the development of a functional HPA axis. But, the 3rdTH HPA behaves differently than the adult HPA [64]. The placenta synthesizes CRH to be released into maternal and fetal circulation. Unique to humans and a few great apes, the levels of CRH increase progressively from mid-pregnancy until parturition. Placental CRH is as biologically active in the fetal HPA as CRH produced by the adult hypothalamus. Placental CRH stimulates ACTH production and release from the fetal pituitary and, subsequently, synthesis of CORT [66]. Placental CRH thereby provides a means for the fetus to regulate its own pituitary-adrenal axis independent of hypothalamic CRH, and thus exercises control of CORT levels in fetal circulation [36].

In addition, the fetal CRH forms a positive feedback loop with the placenta producing increasing amounts of DHEA and, thus, estrogen. Indeed, the maturing 3rdTH fetal HPA has a unique function to regulate the amounts of various hormones to maintain the fetus until term and, likely, also plays an important part in determining parturition.

CONCLUSION

There is little doubt that the experiences of the fetus can have a lasting impact on the individual as an adult. We have no quarrel with physiological stressors such as drugs, infection or toxins having the capacity to program expression of the genotype, revealing itself as an adult phenotype. All too often, the individual is programmed for adult pathology, including psychopathology. However, we have questioned the capacity of psychosocial stressors to do the same. We also acknowledged that the mother and fetus are in a symbiotic relation beneficial to both. However, many authors place sole emphasis on the mother. Such an emphasis underestimates the role played by remarkable placental – fetal interactions that protect the fetus, especially the third trimester human fetus.

Our emphasis on the 3rdTH fetus does not diminish the importance of data from animal models. It is only that findings with animal models best apply to the initial two trimesters of the human fetus. Similar to laboratory animals, those early phases of fetal development are particularly vulnerable to outside influences. By the third trimester, the fetus possesses unique mechanisms that allow it to resist physiological changes that would lead to neurological and peripheral injury or death [67]. We contend this resistance applies particularly to excess maternal corticosteroids from psychosocial stress programming of later mental illnesses.

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REFERENCES

1. Harris A, Seckl J. Glucocorticoids, prenatal stress and the programming of disease. Horm Behav. 2011; 59: 279-289.
2. Goldstein JM, Handa RJ, Tobet SA. Disruption of fetal hormonal programming (prenatal stress) implicates shared risk for sex differences in depression and cardiovascular disease. Front Neuroendocrinol. 2014; 35: 140-158.
3. Raikkonen K, Pesonen AK, O'Reilly JR, Tuovinen S, Lahti M, Kajantie E, et al. Maternal depressive symptoms during pregnancy, placental expression of genes regulating glucocorticoid and serotonin function and infant regulatory behaviors. Psychological Medicine. 2015; 45: 3217-3226.
4. Beijers R, Buitelaar JK, De Weerth C. Mechanisms underlying the effects of prenatal psychosocial stress on child outcomes: beyond the HPA axis. Eur & Adolesc Psychiatry. 2014; 23: 943-956.
5. Taylor GT, Maloney S, Dearborn J, Weiss J. Hormones in the mentally disturbed brain: Steroids and peptides in the development and treatment of psychopathology. Cent Nerv Syst Agents Med Chem. 2009; 9: 331-360.
6. Mesquita AR, Wegerich Y, Patchev AV, Oliveira M, Leão P, Sousa N, et al. Glucocorticoids and neuro- and behavioural development. Semin Fetal Neonatal Med. 2009; 14: 130-135.
7. Duthie L, Reynolds RM. Changes in the maternal hypothalamic-pituitary-adrenal axis in pregnancy and postpartum: influences on maternal and fetal outcomes. Neuroendocrinology. 2013; 98: 106-115.
8. Oliveira M, Leao P, Rodrigues AJ, Pego JM, Cerqueira JJ, Sousa N. Programming effects of antenatal corticosteroids exposure in male sexual behavior. J Sex Med. 2011; 8: 1965-1974.
9. St-Pierre J, Laurent L, King S, Vaillancourt C. Effects of prenatal maternal stress on serotonin and fetal development. Placenta. 2015.
10. Nazeri M, Shabani M, Ghotbi Ravandi S, Aghaei I, Nozari M, et al. Psychological or physical prenatal stress differentially affects cognition behaviors. Physiol Behavior. 2015; 142: 155-160.
11. Sapolsky RM. Stress, the Aging Brain, and the Mechanisms of Neuronal Death. Cambridge, MA: The M.I.T. Press; 1992.
12. Graignic-Philippe R, Dayan J, Chokron S, Jacquet AY, Tordjman S. Effects of prenatal stress on fetal and child development: a critical literature review. Neurosci Biobehav Rev. 2014; 43: 137-162.
13. Charmandari E, Kino T, Souvatzoglou E, Chrousos GP. Pediatric stress: hormonal mediators and human development. Horm Res. 2003; 59: 161-179.
14. Koenig JI, Walker CD, Romeo RD, Lupien SJ. Effects of stress across the lifespan. Stress. 2011; 14: 475-480.
15. Zagron G, Weinstock M. Maternal adrenal hormone secretion mediates behavioural alterations induced by prenatal stress in male and female rats. Behav Brain Res. 2006; 175: 323-328.
16. Moisiadis VG, Matthews SG. Glucocorticoids and fetal programming part 1: Outcomes. Nat Rev Endocrinol. 2014; 10: 391-402.
17. Barbazanges A, Piazza PV, Le Moal M, Maccari S. Maternal glucocorticoid secretion mediates long-term effects of prenatal stress. J Neurosci. 1996; 16: 3943-3949.

18. Welberg LA, Seckl JR, Holmes MC. Inhibition of 11beta-hydroxysteroid dehydrogenase, the foeto-placental barrier to maternal glucocorticoids, permanently programs amygdala GR mRNA expression and anxiety-like behaviour in the offspring. Eur J Neurosc. 2000; 12: 1047-1054.

19. Matthews SG. Antenatal glucocorticoids and programming of the developing CNS. Pediatr Res. 2000; 47: 291-300.

20. Welberg LA, Thrivikraman KV, Plotsky PM. Chronic maternal stress inhibits the capacity to up-regulate placental 11beta-hydroxysteroid dehydrogenase type 2 activity. J Endocrinol. 2005; 186: 7-12.

21. Khashan AS, Abel KM, McNamee R, Pedersen MG, Webb RT, Baker PN, et al. Higher risk of offspring schizophrenia following antenatal maternal exposure to severe adverse life events. Arch Gen Psychiatry. 2008; 65: 146-152.

22. Ghaemmaghami P, Dainese SM, La Marca R, Zimmermann R, Ehlert U. The association between the acute psychobiological stress response in second trimester pregnant women, amniotic fluid glucocorticoids, and neonatal birth outcome. Dev Psychobiol. 2014; 56: 734-747.

23. Zhu P, Tao F, Hao J, Sun Y, Jiang X. Prenatal life events stress: implications for preterm birth and infant birthweight. Am JObstet Gynecol. 2010; 203: 34-38.

24. O'Connor TM, O'Halloran DJ, Shanahan F. The stress response and the hypothalamic-pituitary-adrenal axis: from molecule to melancholia. QJM. 2000; 93: 323-333.

25. Weinstock M. Gender differences in the effects of prenatal stress on brain development and behaviour. Neurochem Res. 2007; 32: 1730-1740.

26. Reynolds RM, Pesonen AK, O'Reilly JR, Tuovinen S, Lahti M, Kajantie E, et al. Maternal depressive symptoms throughout pregnancy are associated with increased placental glucocorticoid sensitivity. Psychol Med. 2015; 45: 2023-2030.

27. O'Donnell KJ, Bugge Jensen A, Freeman L, Khalife N, O'Connor TG, Glover V. Maternal prenatal anxiety and downregulation of placental 11β-HSD2. Psychoneuroendocrinology. 2012; 37: 818-826.

28. Lajud N, Torner L. Early life stress and hippocampal neurogenesis in the neonate: sexual dimorphism, long term consequences and possible mediators. Front Mol Neurosc. 2015; 8: 3.

29. Maccari S, Krugers HJ, Morley-Fletcher S, Szyf M, Brunton PJ. The consequences of early-life adversity: neurobiological, behavioural and epigenetic adaptations. J Neuroendocrinol. 2014; 26: 707-723.

30. Berger MA, Barros VG, Sarchi MI, Tarazi FI, Antonelli MC. Long-term effects of prenatal stress on dopamine and glutamate receptors in adult rat brain. Neurochemical Research. 2002; 27: 1525-1533.

31. Tavassoli E, Saboory E, Teshfam M, Rasmi Y, Roshan-Milani S, Ilkhanizadeh B, et al. Effect of prenatal stress on density of NMDA receptors in rat brain. Int J Dev Neurosci. 2013; 31: 790-795.

32. Glover V, Hill J. Sex differences in the programming effects of prenatal stress on psychopathology and stress responses: an evolutionary perspective. Physiol Behav. 2012; 106: 736-740.

33. Lerch S, Dormann C, Brandwein C, Gass P, Chourbaji S. The scent of stress: Environmental challenge in the peripartum environment of mice affects emotional behaviours of the offspring as adults. Lab Anim. 2015.

34. Goel N, Bale TL. Examining the intersection of sex and stress in modelling neuropsychiatric disorders. J Neuroendocrinol. 2009; 21: 415-420.

35. VandenBergh BR, Van Calster B, Smits T, Van Huffel S, Lagae L. Antenatal maternal anxiety is related to HPA-axis dysregulation and self-reported depressive symptoms in adolescence: a prospective study on the fetal origins of depressed mood. Neuropsychopharmacology. 2008 ;33: 536-545.

36. Coe CL, Lubach GR. Vital and vulnerable functions of the primate placenta critical for infant health and brain development. Front Neuroendocrinol. 2014; 35: 439-446.

37. Tottenham N. The importance of early experiences for neuro-affective development. Curr Top Behav Neurosci. 2014; 16: 109-129.

38. Clancy B, Darlington RB, Finlay BL. Translating developmental time across mammalian species. Neuroscience. 2001; 105: 7-17.

39. Semple BD, Blomgren K, Gimlin K, Ferriero DM, Noble-Haeusslein LJ. Brain development in rodents and humans: Identifying benchmarks of maturation and vulnerability to injury across species. Prog Neurobiol. 2013; 106-107: 1-16.

40. Sapolsky RM, Meaney MJ. Maturation of the adrenocortical stress response: Neuroendocrine control mechanisms and the stress hyporesponsive period. Brain Research Reviews. 1986; 11: 65-76.

41. Schmidt M, Levine S, Oitzl MS, vanderMark M, Muller MB, Holsboer F, et al. Glucocorticoid receptor blockade disinhibits pituitary-adrenal activity during the stress hyporesponsive period of the mouse. Endocrinology. 2005; 146: 1458-1464.

42. Mellor DJ, Diesch TJ, Gunn AJ, Bennet L. The importance of 'awareness' for understanding fetal pain. Brain Res Brain Res Rev. 2005; 49: 455-471.

43. Huttunen MO, Machon RA, Mednick SA. Prenatal factors in the pathogenesis of schizophrenia. Br J Psychiatry Suppl. 1994; 23: 15-19.

44. Malaspina D, Corcoran C, Kleinhaus KR, Perrin MC, Fennig S, Nahon D, et al. Acute maternal stress in pregnancy and schizophrenia in offspring: a cohort prospective study. BMC Psychiatry. 2008; 8: 71.

45. Ben-Ari Y, Spitzer NC. Phenotypic checkpoints regulate neuronal development. Trends Neurosci. 2010; 33: 485-492.

46. Ewing G, Tatarchuk Y, Appleby D, Schwartz N, Kim D. Placental transfer of antidepressant medications: implications for postnatal adaptation syndrome. Clin Pharmacokinet. 2015; 54: 359-70.

47. Mor G, Cardenas I. The immune system in pregnancy: a unique complexity. Am J Reprod Immunol. 2010; 63: 425-433.

48. Kane HS, Dunkel Schetter C, Glynn LM, Hobel CJ, Sandman CA. Pregnancy anxiety and prenatal cortisol trajectories. Biol Psychol. 2014; 100: 13-19.

49. Schminkey DL, Groer M. Imitating a stress response: a new hypothesis about the innate immune system's role in pregnancy. Med Hypotheses. 2014; 82: 721-729.

50. Brunton PJ, Russell JA, Hirst JJ. Allopregnanolone in the brain: protecting pregnancy and birth outcomes. Prog Neurobiol. 2014; 113: 106-136.

51. Caritis SN, Sharma S, Venkataramanan R, Hankins GD, Miodovnik M, Hebert MF, et al. Pharmacology and placental transport of 17-hydroxyprogesterone caproate in singleton gestation. Am J Obstet Gynecol. 2012; 207: 398.

52. Iqbal M, Audette MC, Petropoulos S, Gibb W, Matthews SG. Placental drug transporters and their role in fetal protection. Placenta. 2012; 33: 137-142.

53. Fowden AL, Forhead AJ. Endocrine mechanisms of intrauterine programming. Reproduction. 2004; 127: 515-526.

54. Benediktsson R, Calder AA, Edwards CR, Seckl JR. Placental 11 beta-

hydroxysteroid dehydrogenase: a key regulator of fetal glucocorticoid exposure. Clin Endocrinol (Oxf). 1997; 46: 161-166.

55. Chapman K, Holmes M, Seckl J. 11β-hydroxysteroid dehydrogenases: intracellular gate-keepers of tissue glucocorticoid action. Physiol Rev. 2013; 93: 1139-1206.

56. Wyrwoll CS, Holmes MC, Seckl JR. 11β-hydroxysteroid dehydrogenases and the brain: from zero to hero, a decade of progress. Front Neuroendocrinol. 2011; 32: 265-286.

57. Murphy VE, Fittock RJ, Zarzycki PK, Delahunty MM, Smith R, Clifton VL. Metabolism of synthetic steroids by the human placenta. Placenta. 2007; 28: 39-46.

58. Pepe GJ, Albrecht ED. Actions of placental and fetal adrenal steroid hormones in primate pregnancy. Endocr Rev. 1995; 16: 608-648.

59. Jensen Peña C, Monk C, Champagne FA. Epigenetic effects of prenatal stress on 11β-hydroxysteroid dehydrogenase-2 in the placenta and fetal brain. PLoS One. 2012; 7: 39791.

60. Burton PJ, Waddell BJ. Dual function of 11beta-hydroxysteroid dehydrogenase in placenta: modulating placental glucocorticoid passage and local steroid action. Biol Reprod. 1999; 60: 234-240.

61. Auchus RJ, Parker KL, Rainey WE. The adrenal glands. In: Kovacs WJ, Ojeda SR, editors. Textbook of Endocrine Physiology. New York: Oxford University Press; 2012; 346-80.

62. Collier AC, Miyagi SJ, Yamauchi Y, Ward MA. Assisted reproduction technologies impair placental steroid metabolism. J Stero Biochem Mol Biology. 2009; 116: 21-28.

63. Ferrari E, Cravello L, Muzzoni B, Casarotti D, Paltro M, Solerte SB, et al. Age-related changes of the hypothalamic-pituitary-adrenal axis: pathophysiological correlates. Eur J Endocrinol. 2001; 144: 319-329.

64. Power ML, Schulkin J. Functions of corticotropin-releasing hormone in anthropoid primates: From brain to placenta. Am J Hum Biol. 2006; 18: 205-212.

65. Newby EA, Others X. Fetal endocrine and metabolic adaptations to hypoxia: the role of the hypothalamic-pituitary-adrenal axis. Am J Physiol: Endocrinol Metab. 2015; 100: 1-10.

66. Rainey WE, Rehman KS, Carr BR. Fetal and maternal adrenals in human pregnancy. Obstet Gynecol Clin North Am. 2004; 31: 817–35.

67. Sandman CA, Davis EP, Glynn LM. Prescient human fetuses thrive. Psychol Sci. 2012; 23: 93-100.

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