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Maternal stress in pregnancy and programming of the fetal brain: myth or reality?

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Maternal stress in pregnancy and programming of the fetal brain: myth or reality?

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"Não corro como corria, nem salto como saltava,
mas vejo mais do que via, e sonho mais que sonhava."

"O que impede de saber, não são o tempo nem a experiência,
mas, somente, a falta de curiosidade."

Agostinho da Silva

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"O caminho faz-se caminhando"

António Machado

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Resumo

Durante o período fetal, o desenvolvimento do cérebro ocorre rapidamente, e é extremamente sensível à programação pré-natal. Consequentemente, alterações no ambiente intrauterino podem causar um profundo impacto no neurodesenvolvimento fetal.

O stress pré-natal pode afectar várias áreas do cérebro, particularmente o córtex pré-frontal, o hipocampo, o hipotálamo e a amígdala. Além disso, o stress materno durante a gravidez tem sido associado a resultados desfavoráveis na descendência, incluindo o parto pré-termo e um baixo peso ao nascimento, assim como atrasos e défices sócio-emocionais e comportamentais durante a infância. O stress pré-natal também aumenta o risco para problemas crónicos de saúde, tais como a hipertensão e a diabetes, e está associado a défices intelectuais e de linguagem, sintomas de depressão/ansiedade ou transtornos afectivos na prole. É provável que alguns problemas de défice de atenção/hiperatividade, ou mesmo a esquizofrenia possam ter a sua origem durante a vida intrauterina.

Durante a gestação, níveis aumentados e sustentados de cortisol e da hormona libertadora de corticotrofina (CRH), estão associados a alterações na resposta do eixo hipotálamo-hipófise-adrenal (HPA) do feto. Além disso, níveis aumentados de cortisol, quer materno, quer fetal, estimulam a placenta a produzir CRH (pCRH) durante a gravidez. Tem sido documentada, em fetos, uma correlação positiva entre o cortisol e a testosterona, a qual contribui para a masculinização do cérebro e do comportamento, nos casos em que se verifica a ocorrência de stress pré-natal.

Tendo por objectivo esclarecer a relação entre o stress que ocorre durante a gestação, e as alterações morfológicas e do neurodesenvolvimento no cérebro do feto e da criança, foi realizada uma revisão bibliográfica baseada em estudos publicados entre janeiro de 2008 e fevereiro de 2019, disponíveis na base de dados PubMed, e elegíveis de acordo com uma estratégia de pesquisa estruturada.

Abstract

Brain development occurs rapidly during the fetal period and is extremely sensitive to prenatal programming. Consequently, insults to the intrauterine environment can cause profound impact on fetal neurodevelopment.

Prenatal stress may affect several areas of the brain, particularly the prefrontal cortex, hippocampus, hypothalamus and amygdala. Also, maternal stress during pregnancy has been associated with adverse outcomes of the offspring, including preterm birth and low birth weight, as well as socio-emotional and behavioural delays and deficits in childhood. Furthermore, prenatal stress increases risk for chronic health problems, such as hypertension and diabetes, and is associated with intellectual and language deficiencies, depression/anxiety symptoms or affective disorders of the offspring. It seems that some attention deficit/hyperactivity problems or even schizophrenia might have their origin during intrauterine life.

High and sustained levels of cortisol and corticotrophin releasing hormone (CRH) during gestation, are associated with modifications in the normal foetus hypothalamic-pituitary-adrenal (HPA) response. Additionally, increased levels of both maternal and fetal adrenal cortisol stimulate the placenta to produce placental CRH (pCRH) during pregnancy. A positive correlation between cortisol and testosterone in foetuses has been documented, contributing to the masculinization of brain and behaviour in cases of prenatal stress.

In order to clarify the relation between maternal stress during pregnancy and the morphological and neurodevelopment changes in the foetus and child brain, we undertake a review based on studies published between January 2008 and February 2019, available on PubMed database, eligible according to a detailed search strategy.

Keywords: prenatal stress; pregnancy; brain development; fetal programming; motor skills.

Abbreviations

5-HT	5-hydroxytryptamine (serotonin)
5-HTT	Serotonin reuptake transporter
11β-HSD2	11β-hydroxysteroid dehydrogenase type 2 enzyme
ADHD	Attention deficit/hyperactivity disorder
BDNF	Brain derived neurotrophic factor
CRH	Corticotrophin releasing hormone
E	Epinephrine
GCs	Glucocorticoids
GM	Grey matter
gw	Gestational week
HPA	Hypothalamic-pituitary-adrenal
IL-6	Interleukin-6
MAO A	Monoamine oxidase A
NE	Norepinephrine
OGT	O-linked-N-acetylglucosamine (O-GlcNAc) transferase
pCHR	Placental corticotrophin releasing hormone
SAM	Sympatho-adrenomedullary system
SSRIs	Selective serotonin reuptake inhibitors
TNF-α	Tumor necrosis factor alpha
WM	White matter

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1. Introduction

Prenatal or fetal programming, also known as the developmental origins of health and disease hypothesis,[1] is a model for understanding the impact of prenatal conditions and the associated quality of fetal development.[2] Maternal prenatal stress is one such condition that has been consistently linked with suboptimal developmental outcomes in the offspring,[3] effects that can persist through adolescence into early adulthood.[4]

Brain develops at an astonishing rate during the fetal period,[5] and the rapid growth and plasticity render the brain sensitive to intrauterine environment and can cause profound impact on fetal neurodevelopment.[6, 7] The effects on the fetal brain depend on gestational age.[8] It is noteworthy that the programming of the fetal brain, in response to maternal stress, may have been protective to human and animal ancestors, since many of the changes that we see as psycopathology today, may have enabled the offspring to detect and react more rapidly to real external danger such as the presence of predators.[9]

It is now widely accepted that maternal stress during pregnancy is a risk factor for a range of adverse birth outcomes, including preterm birth and low birth weight,[10] two common causes of neurocognitive, as well as socio-emotional and behavioural delays and deficits in childhood.[7, 11] Furthermore, prenatal stress has been associated with executive functioning (e.g., problems with learning, memory and language),[12] and also with depression/anxiety symptoms, affective disorders,[13] and delayed motor development on offspring.[14] It is also well established that prenatal stress increases risk for chronic health problems, like hypertension, diabetes,[15] asthma[16] and allergic diseases.[17] Additionally, it seems that some neurodevelopmental disorders, including attention deficit/hyperactivity (ADHD),[18] autism or even schizophrenia,[19] might have their origin during intrauterine life.

It is also important to point out that prenatal stress may indeed lead to structural and functional changes in several brain regions, namely the prefrontal, parietal, and temporal lobes, as well as the cerebellum, hippocampus, hypothalamus and amygdala.[20-22] It is generally accepted that behavioural problems, and susceptibility to neurodevelopmental and psychiatric disorders are driven by alterations in functional connectivity of amygdalar-thalamus networks, and in intrinsic brain circuitry including default mode and attention networks.[22]

Despite the growing literature concerning the effects of maternal stress during pregnancy, the specific mechanisms through which prenatal stress impact brain development and later child outcomes are not yet fully understood.[7, 23] In the last decades, the stress hormones have been intensely studied in the animal model and in the human being.[3, 24] Thus, we are starting to understand some of the biological mechanisms that are underlying this fetal programming,

including the hypothalamic-pituitary-adrenal (HPA) axis, the sympatho-adrenomedullary system (SAM), the role of the placenta, cytokines and serotonin, changes in the fetal brain, as well as the importance of gene-environment interactions and epigenetics.[8, 24]

The high prevalence of prenatal stress and the increased risk for an adverse outcome in the offspring is a growing global public health concern.[25] Women who experienced stress during pregnancy are less likely to seek out prenatal care, and have been reported to have poorer overall physical as well as psychological health, which may have implications in fetal development.[26] Moreover, prenatal stress may also be strongly associated with other prenatal risk factors such as smoking, alcohol use, socio-economic deprivation, and adverse life conditions.[27] Thus, interventions designed to reduce stress during pregnancy, by providing the mother with enhanced coping skills and/or emotion-regulation strategies, may grandly influence mother-child interactions postnatally, and therefore improve the outcome.[24] It is likely that investing in maternal prenatal stress preventive interventions will have broad reaching beneficial effects on the health of mothers, children and their relationship.[7]

The main objective of this review is to provide a synthesis of studies that relate the maternal stress during pregnancy with morphological changes on foetus and child brain, and offspring neurodevelopment, with emphasis on motor development.

2. Materials and Methods

2.1. Search strategy

A systematic search was performed on online PubMed database between January 2008 and February 2019. The following strategy using MeSH words combinations were used: ((prenatal stress AND pregnancy) AND brain development OR fetal programming OR motor skills)); ((prenatal stress AND brain development) AND fetal programming OR motor skills)); ((prenatal stress AND fetal programming) AND motor skills)); ((pregnancy AND brain development) AND fetal programming OR motor skills)); ((pregnancy AND fetal programming) AND motor skills)); ((brain development AND fetal programming) AND motor skills)).

We limited the results to studies published in English. The primary search returned 3870 articles, after the exclusion of duplicates. Thereafter, the authors screened the titles and abstracts for all articles, in order to identify studies that potentially meet the inclusion criteria outlined below. The full texts of relevant articles were examined in order to select each study for review. Eligible studies were collected and processed using the software Endnote X9®.

2.2. Inclusion and exclusion criteria

Study eligibility was determined based on the following inclusion criteria:

1. Prenatal maternal stress defined as any type of stress, such as natural disasters, significant life events, anxiety and depressive feelings or traumatic stress;
2. Prenatal maternal stress measured validated by self-reported questionnaire, physiological parameters (e.g., hormone levels), interview, and objective measures of stress and population level events;
3. Studies that measured some form of offspring health or development as an outcome, with no restrictions on offspring age;
4. Studies evaluating women who have experienced any type of stress at any time during pregnancy;
5. Studies limited to human-subject;
6. Studies published in peer-reviewed journals.

Studies were excluded if they were published in any other language than English; if they included the effects of psychological distress specific to psychotropic medication, substance abuse or resulting from severe psychopathology (e.g., bipolar disorder, psychosis); if the studies did not refer to prenatal stress exposure or child health outcome; and if the articles were not peer-reviewed.

Applying these inclusion and exclusion criteria, 46 publications were selected to this revision. In addition, the reference lists of all eligible studies were hand-checked, to identify further relevant articles for inclusion, ending up with 92 publications being analysed for this review (Fig. 1).

3. Types and timing of prenatal stress

Prenatal stress, described more accurately as 'maternal prenatal psychosocial stress', refers to a status of low or negative well-being experienced during pregnancy, as well as physiological or neuroendocrine stress responses in the body of the expecting mother.[2] A wide range of different types of stressors can influence child development, including maternal anxiety, pregnancy-specific anxiety, depressive feelings and negative life events.[8, 24, 28] Stressful life events vary from mild daily stressors to high stress perception at individual level, and may also include severe and massive stress events like the exposure to acute natural disasters,[28] such as Canadian ice storm and Louisiana hurricane,[29-31] or human made disaster such as Chernobyl and the September 11 terrorist attacks.[32, 33] Several studies reported that maternal exposure to significant life stressors

such as daily hassles, bereavement, job loss, trauma, divorce and domestic abuse, at critical periods during pregnancy, might increase offspring psychopathology.[8, 28] The associated outcomes depend on each individual's cognitive evaluation of the event, and the sufficiency of their coping and social support resources.[34]

It is quite intuitive that the greatest negative effects arise from severe and chronic stressful conditions, and the most positive effects result from mild to moderate stress.[24] Different types of stress during pregnancy have been related with different areas of child development, including birth outcomes (such as weight, length, and head circumference),[35] delayed play, motor and language development, lower cognitive performance, and poor temperament, sleep problems and increased fearfulness.[28, 36] However, some studies revealed differential effects, where stressors are associated with one area of development but not another.[36] It is possible that anxiety and depression, two stressors that are quite comorbid, can affect outcome in somewhat different ways,[28] and the same is true for prenatal stress.[36] Important to note, though, is that multiple stressors frequently co-occur, and it is hard to disentangle their effects.[24] Interestingly, other studies report that low to mild prenatal stress was found to positively affect infant motor development and cognitive ability.[37, 38]

Every moment in pregnancy represents a window of vulnerability for some form of development.[31] Fetal organs and systems mature at different times, and so periods of vulnerability vary, reason why stress at a specific time can influence different areas of development.[31, 36, 38, 39] In Project Ice Storm, objective exposure to prenatal stress in early gestation predicted lower cognitive development. Also, in this Project, maternal subjective distress perceived during the second trimester predicted greater dermatoglyphic asymmetry.[31] In addition, higher maternal cortisol levels early in gestation predicted lower mental development, but a better child mental development when it occurred late in gestation.[39] There is also evidence that exposure to stress during the first trimester, rather than later in gestation, increases the risk of schizophrenia.[40] On the other hand, the third trimester exposure was key for motor development,[41] and the later in gestation girls were exposed to the ice storm the lower their bilateral coordination and visual motor integration scores at age 5 ½. This period also appears to be sensitive for the development of emotional, behavioural and attention problems.[31] Moreover, it seems that exposure to prenatal stress in mid to late gestation increased the risk of autism.[30]

Both animal and human studies demonstrate sexually dimorphic responses to prenatal adversity.[25] This may be due to different responses to elevated glucocorticoids by male and female fetuses and placentae.[42] It is believed that male foetuses prioritize growth and physical development in the presence of intrauterine adversity, whereas female foetuses modulate

growth to improve viability.[42, 43] These different adaptive strategies render the male foetus more susceptible to morbidity and mortality,[25] and females increase both viability and subsequent vulnerability to psychopathology.[43] On the other hand, internalizing problems such as anxiety, depression, and affective disorders are more prevalent among females.[44] Also, girls appear more vulnerable than boys to the effects of late gestation exposures on motor functioning.[31] Despite some controversial results, studies that do not account for the sex of the child may overlook important relationships.[36]

Concluding, stress definitely influences the developing human fetus, with consequences that persist into childhood and probably for the entire lifespan.[45]

4. Animal and human studies

Animal models provide undeniable evidence for preconception stress effects on offspring neurodevelopment.[3] Exposure to a range of highly adaptable prenatal stressors (e.g., overcrowding, temperature, restraint, bright lights, social isolation and pain stress), cause negative effects in a number of developmental areas in offspring such as neurodevelopment, cognition, attention, behavior, motor development, immune and metabolic functioning, effects which have been shown to persist into adulthood, and may even be passed on to subsequent generations.[3, 26] However, despite the similarity, results obtained by animal studies cannot be precisely translated to human populations.[46]

Prenatal stress research in human populations is mainly observational rather than experimental, since it is neither ethical nor desirable to place pregnant women under stressful circumstances.[47] Studies using stress that may occur as part of ordinary life, such as mental health problems or stressful life experiences,[36] turn difficult to make causal attributions between prenatal maternal stress and child development, or to isolate a single attributable variable.[47] Furthermore, these types of stress are not randomly assigned, and can be partly due to maternal temperament and personality, and thus impact self-ratings of subjective stress. In addition, maternal psychological distress like, for example, depression, may have a genetic component that can be shared by the child.[28, 38, 47] Thus, the limitations of these studies can be partly overcome by using extraordinary events, such as natural disasters or terrorist attacks.[28]

Population-based disasters may provide insight into prenatal stress effects on postnatal plasticity, due to their random nature and independence of maternal characteristics.[24, 31] Moreover, it is possible to more accurately determine the timing of stress exposure and measure the intensity of the stressor during gestation when using a disaster as a stressor.[38, 48] While the

use of a natural disaster reduced the influence of some potential confounders, such as heritability, other confounding factors may still be present, such as individual variation in maternal stress reactivity. Thus, maternal stress should be measured at multiple time points during pregnancy, in order to avoid potential recall bias and to better understand continuous longitudinal effects, allowing subsequent incorporation of postnatal caregiving procedures with beneficial effects.[36, 48]

5. Underlying biological mechanisms to explain prenatal stress effects on offspring

There is still paucity of studies examining the mechanisms of fetal programming by prenatal stress. The numerous possible mechanisms that could potentially justify enhanced developmental plasticity include, for example, effects in the fetal intestinal microbiome,[8] and neuroinflammation processes,[2] that will not be considered in this report. In this chapter, we will refer to some of the most important potential mechanisms of transmission of prenatal stress in the developing fetus.

5.1. The role of the HPA Axis and Cortisol

The hypothalamic-pituitary-adrenal (HPA) axis is widely considered to be a pathway by which maternal distress may influence the development of the fetus. In a non-pregnant state, the release of corticotrophin releasing hormone (CRH) from the hypothalamus, initiates a cascade of hormones, which leads to the production of cortisol from the adrenal gland.[25] However, during pregnancy, the regulation of the HPA axis changes considerably, as the placenta also starts producing and releasing CHR (pCRH), from 8 to 10 weeks of gestation, which causes an increase in maternal cortisol (2-4x fold, mainly in the 3rd trimester).[2, 25, 28] When pregnant women experiences anxiety or stress, the HPA axis increases reactivity, contributing to an increased amount of cortisol and CRH across the placental barrier, which can potentially disrupt neuronal development, enhancing the risk of long-term alterations in child developmental areas such as cognition.[39]

Glucocorticoids (GCs) shape some of the brain structures involved in emotion regulation and cognitive function, such as hippocampus and amygdala.[49] Studies evaluating the impact of treatment with a high dose of synthetic GCs, in pregnant women at risk of preterm delivery to enhance fetal lung maturation, revealed deregulation on the fetal HPA axis and impact in infant behavior.[2] However, altered programming of the fetal HPA axis in response to maternal stress

can be advantageous if the postnatal environment is stressful, but can result in an elevated risk of disease or developmental disadvantage if there is a mismatch between the prenatal and postnatal environment.[50]

Unlike in adults, a positive correlation also exists between fetal cortisol and testosterone levels.[24, 41] Thus, increased fetal cortisol levels triggered by increased maternal cortisol levels, could heighten the foetus exposure to testosterone, and influence cognitive functioning such as mental imagery and visuospatial perception.[41] Numerous studies have demonstrated the effects of prenatal stress on masculinization of brain and behaviour, especially in females.[24]

It is important to point out that the maternal HPA axis becomes gradually less responsive to stressors as pregnancy progresses, and it thus seems unlikely that an increase in maternal cortisol is the mediating mechanism between prenatal maternal stress in later pregnancy and altered fetal outcome.[28]

5.2. Placental functioning

The placenta is an organ that serves as a bidirectional interface between the mother and her fetus.[24, 25] On one hand, the placenta affects HPA axis regulation in both the mother and foetus, since exposure to increased levels of maternal and fetal adrenal cortisol, stimulates the placenta to produce more pCRH during pregnancy. In fact, pCRH levels may be considered a more accurate indicator of fetal exposure to prenatal stress than maternal cortisol only, and was associated with greater child internalizing problems such as, for example, fear and distress if greater pCRH levels during mid-gestation.[51]

Another mechanism by which the foetus could become overexposed to glucocorticoids is through the placental barrier enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2).[8, 24, 28] Particularly in early pregnancy, the placenta serves as a protective factor against maternal cortisol by using 11β-HSD2, which converts 80-90% cortisol into its inactive form, cortisone.[2, 3, 8, 24, 28] The activity of 11β-HSD2 increases during the second and third trimesters, but decreases near the end of pregnancy,[2, 8] to ensure that enough cortisol reaches the foetus, especially during the critical phase of lung maturation.[2] Additionally, the foetus is ready for birth when maternal cortisol levels are very high, being referred to as a normal hypercortisolaemic status.[52]

Prenatal stress exposure results in the downregulation of both the expression and activity of 11β-HSD2, which in turn exposes the foetus to higher levels of maternal cortisol,[53] independently of any change in the maternal cortisol level.[8] With stress, the placenta becomes more permeable and, thus, increases fetal exposure to cortisol and other hormones, at any

gestational age.[8, 24] However, fetal cortisol levels are correlated with maternal levels, since if the mother has higher basal levels of cortisol, then the amount of fetal exposure will be higher too.[9] Moreover, the decrease in placental 11β-HSD2 activity is associated with the early development, including fetal growth restriction, prematurity and low birth weight.[24]

Recent studies suggest that sexually dimorphic fetal and placental responses to prenatal stress may lead to sex differences in risk pathways that contribute to later psychopathology.[25]

In summary, it appears that the placenta plays a critical role in modulating fetal exposure to stress via production of pCRH and 11β-HSD2.[24]

5.3. Sympatho-adrenomedullary system

Although less studied than the HPA system, the sympatho-adrenomedullary system (SAM) is another important component of the stress response, involving the release of catecholamines such as norepinephrine (NE) and epinephrine (E).[24] Enzymes present in the placenta metabolize the vast majority of catecholamines, but some are still transferred from the mother to the foetus. Furthermore, the foetuses can produce their own catecholamines in response to maternal stress.[24] Because of the tight link between NE and the CRH stress-response system, high NE activity is augmented by stress, and together, these interacting systems regulate emotional arousal.[54]

Higher maternal NE levels during mid-gestation were associated with greater report of infant soothability, and only for boys, predicted less child activity. In turn, higher maternal E levels were associated with lower ratings of infant soothability, and also only for boys, predicted greater distress to limitations.[55] However, a recent work underlines the importance of NE in the regulation of developmental plasticity. The authors reported that high NE reactivity, in aversive contexts, might enhance the effect of stressors on psychological outcomes, perpetuating overarousal and hypervigilance that would drastically impair cognition and focused attention, whereas lower NE function might convey resilience to the effects of chronic stress. Nonetheless, high NE functioning, in contexts of copious resources and positive stimulation, may yield optimal levels of focused attention.[54]

5.4. Serotonin and Dopamine

Serotonin, or 5-hydroxytryptamine (5-HT), is a neurotransmitter that has been proposed as a possible mediator when considering programming effects induced by prenatal stress.[2, 28]

Serotonin is crucial for neuronal development from fetal life onward, as it acts as a trophic factor by regulating important brain growth-related processes, including cell division and differentiation, migration, and synaptogenesis.[56] During early fetal development, 5-HT also acts as a growth factor, regulating its own development and other closely related neurotransmitter systems, such as GABAergic, glutamatergic and dopaminergic systems.[2, 24, 57] Moreover, since 5-HT and HPA systems are cross-regulated, it is not surprising that prenatal maternal stress produces alterations in the 5-HT system, and so can cause impaired development, thereby contributing to neurocognitive and behavioural disorders on offspring.[2, 24]

Serotonin produced by the placenta is responsible for the development of the neurons in different parts of the brain, and is required to maintain normal levels of 5-HT during initial stages of forebrain development.[58]

Researches on animal studies have shown that increased exposure to 5-HT during gestation can alter fetal neurodevelopment, leading to long-term dysfunction of circuits underlying mood and emotion.[28, 58] Prenatal maternal stress is associated with reduced methylation in the promoter region of maternal and child *SLC6A4*, the gene which codes for the serotonin reuptake transporter (5-HTT) protein. Individuals with short allele may be more vulnerable to prenatal adverse exposures, since there is a reduction in the availability and function of the 5-HTT protein.[56] Moreover, it is well established that maternal stress is associated with a reduction in placental monoamine oxidase A (MAO A) expression, the enzyme that metabolizes serotonin, with a subsequent increase in fetal exposure to 5-HT.[59]

Studies examining the use of selective serotonin reuptake inhibitors (SSRIs) by depressed women during pregnancy, revealed fetal disrupted sleep patterns and increased motor movements [60], as well as reduced fetal breathing and reduced fetal heart rate variability.[61] Thus, a proper control of 5-HT signaling, through the number and/or type of 5-HT receptors activated, may be of particular interest for normal brain development.[57]

Recent and promising studies, although only provided by animal research, have shown that dopaminergic system is also related to prenatal exposure to stress.[2] Dopamine has an important role in the development of fetal brain, regulating neuronal differentiation, migration, and axonal and dendritic growth; in the adult brain, serves a variety of functions, including control of movement.[62] Particularly limbic area seems to be more vulnerable than motor areas to the deleterious effects of prenatal stress insults.[63] Dopamine system anomalies have further been associated with severe neurological and psychiatric disorders, such as schizophrenia, Parkinson disease, attention-deficit and hyperactivity disorder and drug abuse later in life.[62, 63]

5.5. Cytokines

Exposure to early life stressful events can alter the fetal immune system function over the entire life span,[8] in addition to the direct effects of maternal immunological changes on fetal brain development.[2] Numerous studies demonstrated that symptoms of anxiety and depression during pregnancy, or psychosocial stress, such as exposure to intimate partner violence, has been associated with altered cytokine patterns, namely high levels of interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α).[64-66] Nevertheless, how cytokines affect placental function or the development of fetus remains to be determined.[8, 28] The effects of both immune system deregulation and alterations in the developing brain may heighten the risk for neurodevelopmental disorders, including autism and schizophrenia.[6]

5.6. Novel directions

Over the last decade, there is growing interest in the potential role of epigenetics as underlying mechanism by which prenatal stress may cause long-term effects on the development of the brain of the fetus and child.[2, 8] Epigenetic patterns are generated during development, particularly throughout critical periods, and are essential for processes including placentation, cell fate determination, genomic imprinting and X-inactivation.[67] Epigenetic modifications fix the effects of early environmental events, ensuring sustained responses to transient stimuli that result in modified gene expression patterns and phenotypes later in life.[57, 67] However, in some cases, epigenetic changes can also be reversed.[8]

The three major epigenetic mechanisms include microRNA (changes in small non-coding RNAs with post-transcriptionally regulate gene expression), histone modification (acetylation, methylation, phosphorylation, ubiquitination), and DNA methylation (covalent modification of cytosine with a methyl group).[2, 6, 28, 68] In fact, DNA methylation is considered one of the most well-characterized mechanisms involved in the long-lasting effects of *in utero* stress exposure,[68] since it regulates the degree to which a gene is expressed or repressed.[8]

For example, evidence for epigenetic programming induced by prenatal stress was provided by a study showing that mothers exposed to war trauma and chronic stress, in the Democratic Republic of Congo, presented differential methylation patterns across multiple genes, shown to regulate the HPA axis: *CRH*, which codes for corticotrophin releasing hormone; *CRHBP*, coding for CRH binding protein; *NR3C1*, coding the glucocorticoid receptor; and *FKBP5*, coding for FK506 binding protein.[69] Interestingly, there is also evidence that maternal stress at early stages of pregnancy seems more significant for epigenetic changes than that trigged at later stages of

pregnancy.[68]

Alterations of placental gene expression, downstream function, and signaling during fetal development, have the potential for significant changes in developmental programming.[57] A recent study showed that high levels of maternal self-reported perceived stress were related to increase *11β-HSD2* and *FKBP5* gene methylation, which play an important role in explaining preterm birth and neonatal neurodevelopmental alterations.[70] Another promising placental biomarker of maternal stress exposure is represented by O-linked-N-acetylglucosamine (O-GlcNAc) transferase (OGT), an X-linked gene important in regulating proteins involved in chromatin remodeling. Levels of OGT were significantly lower in males, and further reduced by prenatal stress.[71] The sex difference in DNA methylation is probably responsible for divergences in gene expression in the placenta, and may relate to sex-biased sensitivity to insults and outcomes in neurodevelopment.[57, 71]

Other significant biological pathways involved in epigenetic process to response to stress, such as *BDNF* (Brain Derived Neurotrophic Factor) and serotonergic signaling pathways, have been investigated since they are involved in neurodevelopmental processes, and have been considered epigenetic markers of exposure to early life adversity.[68]

Thus, sex-dependent molecular memories of the prenatal environment can be encoded by the fetal epigenome, involving multiple gene networks, and when incorporated into the germ line, could propagate to the future generations.[6, 68]

6. Prenatal stress and brain development

During the embryonic and fetal life, brain development comprises complex processes and interactions between genetic, epigenetic and environmental factors, responsible for the construction of its architecture, which is dynamically changed during the whole life span.[22] The major aspects of development, such as proliferation, migration and differentiation are not entirely programmed genetically, being also subjected to diverse extrinsic factors occurring in the prenatal and early postnatal period, which enable changes in spatiotemporal expression of gene patterns, and so influence the structure and function of the brain.[22, 57]

Prenatal brain development undergoes two major stages: ballooning and gyrification. The ballooning phase (gestational week 3 to 15) involves the proliferation and migration of neurons in a spatiotemporal specific way, forming the cortical layer structure. After gw 15, the processes involved in the building of grey matter (GM) and white matter (WM) include the production and expansion of astrocytes, oligodendrocytes, and microglial cells; the growth of neuronal dendrites

and axons; the formation of synapses and the development of the vasculature system; as well as the formation of the layers in the cortex. The gyrification processes occurs in synchrony with neuronal connectivity, between gw 17 and 47, when all neurons have moved to their final position.[22, 72] Alterations either in the gene network (e.g., *de novo* mutations in transcription factors), or in the epigenetic gene regulatory networks, may result in varying folding pattern that can be measured even in the adult brain.[72] Thus, changes in the brain function, structure, and connectivity may have their origins in the early prenatal period, and are seen as potentially mediating the link between maternal distress in pregnancy, and offspring behavioral, cognitive, and emotional problems. The functional and structural measures of brain regional connectivity, has been increasingly recognized as biomarkers of prenatal stress, altering risk or resilience for neurodevelopmental and psychiatric disorders.[22]

Some studies have evaluated the effects of prenatal stress using noninvasive measures of growth and macrostructure of the perinatal brain, and reported delayed overall brain growth, limbic-specific volumetric changes, and white matter abnormalities.[73, 74] Neuronal and synaptic changes induced by prenatal stress are highly region-specific, and this may be related to the different maturity of offspring sensory, prefrontal and limbic system (including the amygdala, hippocampus and hypothalamus) during stress exposure, regions which are involved in cognitive, behavioral and psychosocial functions.[75, 76] In particular, the amygdala plays a critical role in memory and emotions, and has been considered as a key regulator of the HPA axis,[24] since it contains glucocorticoid and mineralocorticoid receptors that, when activated, have positive feedback loops on the hypothalamus and thus, regulate stress response.[20] Moreover, the amygdala is fundamental to moderating the perception of emotionally relevant events, which determines whether HPA axis initially becomes activated.[24]

Prenatal maternal distress and high maternal cortisol levels were associated with a larger right amygdala volume in female preschoolers,[49, 77] and with changes in the WM microstructure,[74, 78] as well as GM volume reduction in both amygdalae in adulthood. Such altered GM was observed in several cortical areas in childhood, including the prefrontal cortex, the premotor cortex, the medial and lateral temporal cortex, and the cerebellum.[79] Another study found that elevated prenatal maternal cortisol predicts stronger amygdala functional connectivity to other brain regions and to sensory processing, during the neonatal period, and higher internalizing symptoms in girls, but not boys.[80] In addition, it is important to point out that greater activity in the amygdala may be a mechanism for plasticity, rather than just an early response to postnatal stress.[24] Also, reduced hippocampal volume is induced by stress exposure during early developmental periods, with accompanying increases in fearfulness and increased stress reactivity.[73]

Structural brain alterations induced by prenatal maternal stress were observed in the neonate until adulthood, and are different for males and females with implications for sex-specific psychopathology.[22, 25] However, because offspring brain and behavior are commonly assessed years after birth, the timing of such maternal effects is unclear.[74] Understanding the timing of potential neurobiological alterations holds inherent value for the development and evaluation of future therapies and interventions.[78]

7. Types of outcomes and motor development

There is a growing number of studies investigating associations between prenatal exposure to maternal stress during pregnancy, and offspring outcomes from birth until adulthood. Severe stress in the first trimester of pregnancy has been found associated with an increase in congenital malformations at birth.[28] In turn, moderate stress is associated with adverse birth outcomes, including preterm birth and low birth weight.[10] Also, as mentioned above, prenatal stress increases risk for chronic health problems such as hypertension, diabetes, asthma and allergic diseases.[15-17] Moreover, adverse behavioural outcomes are associated with higher maternal stress during pregnancy and include, for example, difficult temperament, sleep problems and fearfulness. Many studies have found an association between prenatal stress and increased risk for child emotional problems, especially anxiety and depression, and for neurodevelopmental and psychopathological disorders, including cognitive and intellectual impairment, attention deficit/hyperactivity (ADHD), autism or even schizophrenia.[7, 11, 13, 18, 19, 22, 76, 81] However, few studies have focused on the effect of prenatal maternal stress on motor development.[14, 36, 41]

During the infancy, motor development is extremely important because increased mobility functions as an opportunity to other developmental experiences.[36] The transition periods (e.g., from crawling, to standing without support, to walking), reflects a new way for infants interact with their environment, and to gather information and interrelate with others, with advances in a range of cognitive and social-emotional domains.[82] Thus, it seems consensual that delays in motor development may cause delays in other developmental areas, such as cognition, language, eye-hand coordination, attention and academic achievement.[36, 82] As the brain is highly plastic, and its development continues after birth, postnatal events have a major influence on neuromotor function. Therefore, negative experiences may not allow the development of all potential brain circuits, yet a stimulating environment can improve outcomes, thus providing a window of opportunity for early interventions.[36]

As with other areas of development, the relationship between prenatal maternal stress and

child motor skills appears highly dependent on the types and timing of stressors.[36] Previous studies demonstrate that stress associated with daily life is not generally significant as a predictor of motor development,[39] but stressful events experienced in late pregnancy were negatively related with offspring motor functioning, while earlier stressful events had no significant impact.[83] However, one study found a positive relationship between mid pregnancy related stress and child motor skills at 2 years aged.[37]

Recent studies examined the magnitude to which *in utero* exposure to prenatal maternal stress resulting from a natural disaster (e.g., the 1998 Quebec Ice Storm - Canada and the 2011 Queensland Flood - Australia) influenced motor development during childhood.[14, 36, 41] Findings from these projects showed that more severe prenatal maternal stress predicted poorer motor functioning, and that disaster-related objective hardship and subjective distress, explained variance in child fine and motor development.[14, 41] In general, gross motor development was negatively affected by both objective and subjective stress, whereas fine motor skill was negatively affected by objective, but not subjective stress.[14] In particular, prenatal exposure to the ice storm was associated with lowered bilateral coordination and visual motor integration, but not balance, abilities.[41] Additionally, the timing of exposure in gestation and the sex of the child influenced motor development. The later the storm occurred in pregnancy, the poorer the motor functioning in girls, whereas timing in pregnancy had no effect on boys.[14] Sex differences might be explained, in part, by variations in maternal cortisol levels which depending on gestational week and sex of the fetus. Thus, in early pregnancy, maternal cortisol levels were higher in women carrying a male fetus, but around 30 weeks, a cross-over occurred and cortisol levels were higher in women carrying a female fetus, and at the end of pregnancy, cortisol levels were similar regardless of fetal sex.[41] Later pregnancy exposure to prenatal stress, together with carrying a female foetus, may cause an additional increase in maternal cortisol levels, and consequently may disrupt optimal development of the cerebellum, structure implicated in motor control and coordination.[14, 41]

It is important to point out that stress in pregnancy, did not affect motor development in the same way at all ages. For example, motor development was positively associated with prenatal stress at 2 months of age, but it was negatively associated at 6 months. These age-related changes may be due to the fact that effects become more evident at times of major motor transitions, such as the emergence of independent locomotion, and could also be due to “silent vulnerability”, which is characterized by developmental deficits that occur in close proximity to an insult, that then disappear for long periods, and re-emerge later in development.[14]

The Quebec Ice Storm and Queensland Flood projects were considered less traumatic events and small-scale models of prenatal maternal stress resulting from major recent natural

(Hurricane Katrina, South-East Asian Tsunami) or man-made (World Trade Center attack) catastrophic events.[41] Since prenatal maternal stress can manifest longitudinally over the lifespan, longer-term follow-up of natural disasters cohorts will assess whether these effects in different areas of development, will persist into the child and adulthood.

8. Prenatal stress: what should be done?

There is extensive evidence that maternal stress, anxiety, and depression during pregnancy increases the risk for neurodevelopment and psychiatric disorders in offspring, which constitute a major burden to society.[84] This suggests that better emotional care of pregnant women should reduce psychopathology in the next generation.[8] Up to 30% of pregnant women experience high stress during pregnancy,[85] so prenatal origins of conduct disorder, cognitive and social-emotional dysfunction have important public health implications, since prenatal environmental risk factors can potentially be modified.[86] A better knowledge of these risk factors allow increased screening and early intervention for children exposed to prenatal maternal stress, with the purpose of improving their long-term neurodevelopmental outcome.[81] Therefore, the prenatal period is a crucial target for primary preventive interventions.[22]

Many types of individual, family, or group-based therapies, such as cognitive-behavioural therapy, have been shown to lessen maternal distress levels, with benefits for the offspring in infancy.[87] There is strong evidence that appropriate music, specially composed songs for pregnancy, showed promise in reducing prenatal symptoms of anxiety and depression.[88, 89] The potential benefit of maternal relaxation has been shown to improve indices of fetal neurobehaviour, by reduction of both maternal cortisol and noradrenaline levels.[90] Other interventions, such yoga, indicate lower incidences of prenatal disorders (preeclampsia and pregnancy-induced hypertension) and small gestational age, lower levels of pain and stress, and higher score of relationship.[91] Also, prenatal yoga significantly reduced pregnant women's cortisol, and enhanced their immune function.[92] Moreover, yoga is considered a safe and more effective intervention than walking or standard prenatal exercises.[91]

It is clear that interventions should be started as early as possible, but later interventions also seem to be beneficial.[28] The interesting point of these interventions is that they serve a double purpose: 1) enhancing our insight on putative mechanisms that regulate stress, and 2) offering a protective tool for the future generation.[2]

9. Final remarks

In this review, we present strong evidence that prenatal stress programs postnatal plasticity, especially in what concerns neurodevelopmental outcomes, potentially leading to later psychopathology in child that persists throughout adulthood. The biological mechanisms underlying such fetal programming are being gradually uncovered, and include numerous neuroendocrine actions and increased activity in the amygdala. It is also important to highlight the role of the placenta as a biomarker of maternal stress, and its potential for determining the structure and function of the developing brain. Novel directions in research have emerged in the past decade, including epigenetics and neuroimaging. However, more comprehensive and detailed studies aided by modern technology are needed to better characterize the mechanisms underlying prenatal stress effects on fetal and offspring outcomes. Moreover, a clear understanding of the mechanisms mediating transgenerational programming of stress responses and pathologies is extremely important to determine which populations are exposed to long-term adversity, and to design effective interventions during pregnancy, that will benefit future generations.

Natural or man-made tragic disasters are opportunities to better study the effects of *in utero* exposure to maternal stress, on the development of biological, cognitive and behavioural difficulties in early infancy, that probably persists into adulthood.

The evidence that postnatal factors such as positive parenting, maternal-child attachment and family cohesion as well as physical exercise, music and relaxation, can reduce the consequences of prenatal maternal stress on child risk for psychopathology, and therefore social measures should be undertaken. The development of public health initiatives that communicate the importance of reduction of stress and improve stress regulation during pre and postnatal period, are fundamental to promote offspring health and reduce psychopathology in the next generations.

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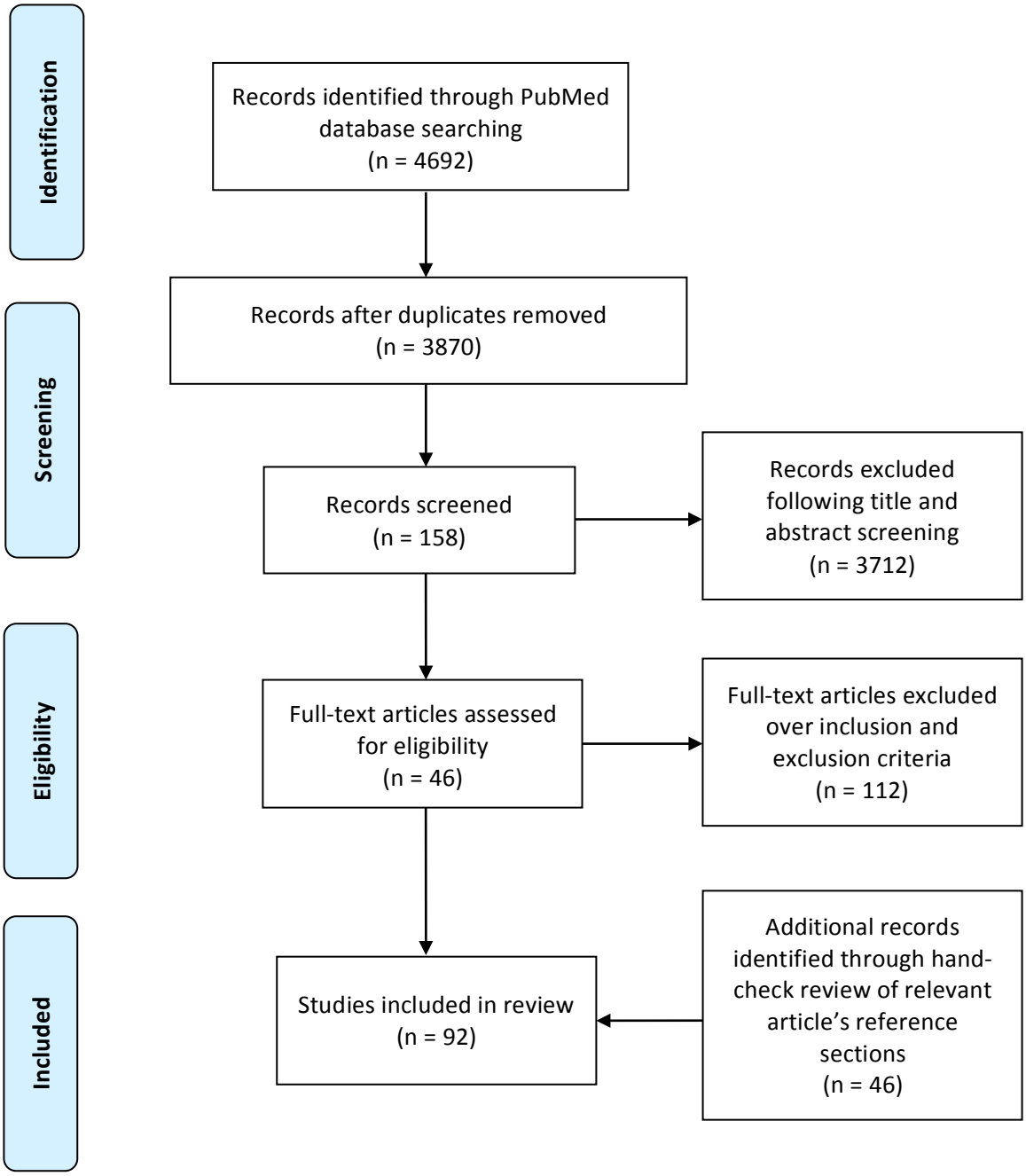

Figure 1. Diagram for selection of review articles.

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