REVIEW ARTICLE

Prenatal Stress-induced Behavioral, Cognitive, and Psychopathological Modifications: A Mini Review of Literature

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Abstract

Background: Prenatal stress (PNS) can influence the development of the progeny, which undergoes complex physiological changes during intrauterine and early postnatal life, thus causing them to experience far-reaching undesirable consequences. Prenatal stress is particularly a challenging issue because, by reacting to the mother's stress through a sequence of biological mechanisms, the fetus is placed under risk of several neurobiological variations that give rise to behavioral and emotional alterations in the offspring. Various studies have been conducted over the last two decades, not only on various stressors that give rise to negative emotions during pregnancy but also on their impact on offspring's mental health during the entire course of their development.

Objective: This review aims at discussing various studies on the effect of prenatal stress in animal models and human subjects, and to explore some of the controversies arising in this field.

Materials and methods: We searched PubMed and Scopus for English language abstracts published from 1992 to 2021. Search terms were related to prenatal stress, infant or child cognitive and motor development, and developmental psychopathology.

Results and conclusion: A vast number of studies have reported negative neurobiological outcomes in the offspring subjected to PNS, although a clear understanding about the underlying biological mechanisms is not available. Methodological challenges do exist in PNS research which has not been successfully overcome. At present, however, there is a definite need to identify, advise, and support pregnant women with some degree of stress with a hope to minimize any adverse consequences in the progeny.

Keywords: Behavior, Cognition, Motor development, Prenatal stress.

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Introduction

Prenatal stress refers to any negative environmental variation experienced during pregnancy that can negatively influence the development of the progeny. Since several complex physiological changes occur during intrauterine and early postnatal life, prenatal/perinatal stress influences these modifications and causes far-reaching undesirable consequences. Prenatal stress is particularly a challenging issue because, by reacting to the mother's stress through a sequence of biological mechanisms, the fetus is placed under risk of several neurobiological variations that give rise to behavioral and emotional alterations in the offspring.[1,2] Gestational stress can cause strong activation of the HPA stress response leading to increased production of corticotropin-releasing hormone (CRH).[3] These alterations could have undesirable ill effects on maternal health and, thereby, fetal developmental parameters when they reach a sufficient magnitude.[4] Studies have been conducted for the last two decades, not only on various stressors that give rise to negative emotions during pregnancy but also on their impact on offspring's mental health during the entire course of their development.[5] Existing knowledge on both immediate and long-lasting effects of PNS in the progeny derives mostly from animal studies. This review aims at discussing various studies on the effect of PNS in animal models and human subjects, and to address some of the controversies arising in this field.

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Materials and Methods

Our search targeted studies reporting an association between prenatal stress and any child's developmental outcome. We searched studies conducted in experimental animals and observational studies conducted in human volunteers. We searched PubMed and Scopus, for English language abstracts published from 1992 to 2021. Search terms were related to prenatal stress; infant or child cognitive and motor development, and developmental psychopathology.

Results and Discussion

Animal Studies

Effects of Prenatal Stress on Behavioral Measures: Cognition, Learning, and Memory

Experiencing unavoidable stress at the time of pregnancy results in various neurophysiological and behavioral modifications, which may be observed during juvenile stage or may persist through adulthood and sometimes even later towards aging. The wealth of literature is now available from animal studies, stating both short-term as well as lasting effects of prenatal stress on cognitive aspects in the posterity. Long-term effects of prenatal stress on cognitive and neurophysiological aspects in adult offspring are widely studied.[4,5] Exposure of pregnant monkeys to noise stress during early gestational periods, the time when neuronal migration takes place, resulted in their offspring having a lower attention span.[6] Restrain stress throughout gestation in mice resulted in impairment of hippocampus associated spatial learning and memory and a significant decrease in hippocampal N-methyl-D-aspartate (NMDA) receptor expression in adult offspring[7] although few other physiological parameters did not vary in comparison with non-stressed group. Juvenile rats born to mothers subjected to restrain stress,[8] and immune stress[9] during the last week of gestation, exhibited reduced performance in the prefrontal cortex-associated object recognition task. Similarly offspring of mothers exposed to various other kinds of stress during pregnancy displayed defective spatial learning and memory tasks.[10–12] One-month-old juvenile female offspring of rats imperiled to 90 minutes unpredictable stress during late gestation, suffered from long-term as well as short-term memory loss.[13] Unpredictable restrain stress during late gestation resulted in learning and memory disabilities in both male and female offspring at 1 month of age; and only in female offspring at 3 months of age.[14] Furthermore, spatial learning and memory were negatively affected in young offspring of rats stressed by unpredictable foot shock during second half of pregnancy.[15] Offspring of rats subjected to late gestational restrain stress suffered fear-related learning and memory in a condition avoidance test.[16]

Emotionality, Anxiety and Fear

Several studies have reported anxiety like behavior and depression in offspring of dams exposed to stress of different nature, timing, and intensity. Increased anxiety-like behavior was observed in prenatally stressed pups of rhesus monkeys[6] and in adult rat offspring[17] exposed to prenatal social stress. Piglets exposed to prenatal social stress during the second and third trimesters of gestation showed lower coping to maternal isolation stress at weaning and also exhibited long-lasting effects on behavioral patterns that included an abnormal maternal behavior.[18] Rats exposed to psychological stress during the last week of pregnancy displayed heightened anxiety in the open field environment and depression-like behavior in forced swim test, as observed by Abe and coworkers.[19] Contrary to this finding, it was observed in a study that female offspring prenatally stressed by social stress during late gestational period were not affected in terms of emotionality,[17] however, when combined with restrain stress during mid-gestation, the female offspring did exhibit anxiety behavior.[20] Gender-specific differences in anxious behavioral responses, as a consequence of prenatal stress, were also observed in few other studies.[21] In contrast to these findings, female rat offspring of dams restrained during last week of pregnancy exhibited lower anxiety in the EPM and better learning in the Morris water maze.[22] Stress during the last week of pregnancy resulted in higher level of anxiety in elevated plus maze, equally in both male and female offspring.[23] Offspring of rats exposed to late gestational stress exhibited increased anxiety-like behavior during the early growing period as demonstrated by greater time spent in a dark area of a dark bright arena. Increased rearing near the walls of open field and a greater number of fecal pellets in the open field was also suggestive of enhanced anxiety.[24]

Neuromotor Development

In the Rhesus monkey model, the offspring subjected to prenatal stress were observed to have lower neuromotor skills during the first month of their life, and this effect was relatively higher in offspring subjected to early prenatal stress rather than to stress during latter half of pregnancy. Locomotion and exploratory behaviors were also seen to be reduced in these animals.[6] Loss of locomotor activity was observed in 4-week-old male offspring, as a result of sound stress combined with forced swim stress their mothers went through, during their late gestation period.[25] Recurrent mental stress in squirrel monkeys throughout gestation, led to diminished motor skills, reduced balance responses, and decreased post-rotary nystagmus in their infants.[26]

Relatively, the larger number of studies have suggested that the late gestational period is more sensitive to emotional stress-induced effects on the offspring. Oxidative stress is more apparent in mothers exposed to stress during later stages of pregnancy,[27] however, both early and late gestational stress in rats showed oxidative stress in the developing brain during early postnatal development.[28] Larger number of human studies is needed to draw conclusion regarding the sensitive period during pregnancy so that timely preventive measures can be designed.

Effect of Prenatal Stress on Behavioral Measures: Human Studies

Fetal programming has long been proven through various studies to be a crucial element for neurodevelopmental as well as psychiatric outcomes. As a women goes through her pregnancy, recurrent alteration in her physiology related to mood, disturbs the neurobehavioral developmental patterns.[29] It is now evident from numerous reports of epidemiological studies that offspring who have developed less well in utero are more likely to suffer a range of behavioral complications later in life. Few authors stress on the role that prenatal environment might play in the pathophysiology of anxiety and depression. Several different studies have documented that the child of a mother undergoing stress through pregnancy is at greater risk of anxiety. Exposure to in-utero stress may result in a variety of adverse outcomes in the progeny depending on the nature of stress, time of exposure, its duration, and intensity. Child of a mother living through stress during gestation is at a higher risk of anxiety,[30,31] attention-related

disorder(ADHD),[30–32] and behavioral alterations.[31,33] Prenatal exposure to various stressors like bereavement, natural disasters, and common everyday hassles have been related to major modifications in development of nervous system of the child leading to issues like autism, mixed-handedness, delayed cognition, etc.[34] The influence of gestational stress-associated psychoneuroendocrine processes on health and development of the fetus may persist as temperamental and behavioral complications in the first few years after birth.[35] It was reported from a community-based prospective study that antenatal anxiety during late pregnancy rather than depression caused behavioral and emotional problems in their children at 4 years of age.[36] They also found that postnatal depression added to the risk of this prenatal anxiety induced behavioral problems. In another study by the same authors, it has been found that, higher level of antenatal anxiety resulted in higher levels of emotional problems in children that lasted till the age of 47 and 81 months, suggesting that prenatal stress induced effects may last at least till the middle childhood stage.[31] This is in line with similar kind of findings from animal studies where prenatal stress produced enduring negative effects in the offspring. In another study, researchers observed that, adolescent children of 14–15 years of age, born to mothers who were highly anxious during 12–22 weeks of pregnancy were significantly more impulsive, completed the given task more quickly but with more errors when compared to children of low anxious mothers. They also reported that female offspring rather than males suffered from depressive symptoms as a consequence of prenatal stress.[37] Similarly, depressive and attention deficit hyperactivity disorder symptoms were observed in 14 year olds exposed to prenatal anxiety due to Chernobyl disaster during second trimester of pregnancy[32] and also low mental and delayed motor development were seen in 8-months-old infants exposed to in-utero stress during mid-pregnancy.[38] Early pregnancy stress has been shown to cause temperamental problems in young infants at 3 and 8 months of age and low mental development at 8 months of age[38] which could lead to psychopathological problems later in life. Amniotic fluid cortisol level estimated during mid-pregnancy correlated negatively with cognitive development assessed by Bayley Scales in 17-months-old infants, although this deficit was eliminated by a positive infant–mother relationship.[36] Moreover, postnatal parental caregiving can also reverse the prenatal stress-induced fearfulness in children.[39]

Cognitive Impairment

Besides behavioral alterations, prenatal stress-induced cognitive impairment has been reported by a significant number of studies. For example, exposure of pregnant women to unfavorable conditions results in increased propensity of their children for mild intellectual deficit along with behavioral alteration.[40,41] Exposure of pregnant women to ice storm crisis in the Canadian province led to lower IQ measures and language abilities in their offspring at 5½ years of age.[40] Prenatal stress due to problems in partner relationship is one of the important aspects leading to developmental issues in the offspring. A study conducted in Queen Charlotte's and Chelsea Hospital, London, assessed the impact of partner relationship strain during pregnancy and found this to cause fearfulness and delayed mental growth in children at 14 and 19 months of age.[39] Prefrontal cortex-dependent working memory performance was compromised in adult offspring of about 25 years of age, born to mothers who were exposed to a major negative crisis during their pregnancy.[42]

Exposure to not only severe, but even moderate levels of psychological distress during early pregnancy has shown to decrease the male to female sex ratio.[43] The number of studies have documented that the neurodevelopmental problems associated with exposure to prenatal stress occurs in 3–16-year-old children rather than in infants and adults.[44]

Motor Development

Motor development in the fetus is also assumed to be associated with the psychological status of the pregnant woman. For example, fetal heart rate variability and motor activity were assessed during third trimester of pregnancy and it was found to be negatively influenced by pregnancy-related stress.[45] A pilot study conducted many years ago has documented that fetuses of women with high anxiety scores spent more time in quiet sleep and were less active in terms of eye and body movements when assessed during 38 and 40 weeks of pregnancy.[46] Exposure during third trimester of pregnancy to psychological distress may impede the development of brain lopsidedness leading to mixed-handedness in children.[47] Late gestational stress assessed by early morning higher cortisol levels caused delay in motor and mental growth in 3-months-old offspring but delayed only the motor development in 8-months-old infants.[38] Interestingly, contrary to the reports available from the above studies, mild to moderate stress during pregnancy has shown to be positively related to motor development of the fetus.[48] Such behavioral modifications induced by chronic stress have been assumed to create better awareness of the fetus to future unfavorable environmental conditions. This awareness may be needed for one's survival in spite of these behavioral changes having lasting effects.[49] However, if the anticipated postnatal milieu does not match with the actual one, the offspring bear a risk of increased vulnerability to develop diseases of various kinds later in life.[50]

Developmental Psychopathology

The common notion held since earlier days, that the emotional state of a mother during her pregnancy could very well influence the fetus, has been validated by a significant number of scientific studies. This influence is apparently more significant on the neuropsychological development of the fetus. Various studies have attempted to find correlation between stressful experiences during pregnancy and psychopathological development in the offspring. Association of prenatal stress with autism,[51–56] and attention-deficit hyperactivity disorder (ADHD)[51,52,55,57] children; whereas, depression and schizophrenia[55] in adults have been documented.

Clinical research dating back many years have tried to associate early life stress to schizophrenia in offspring later in life,[58] which is supposed to be a long-lasting, serious, disorder caused by defective organization and function of the brain. Early life events that cause abnormal development of brain particularly the medial temporal lobe may predispose to schizophrenia. This condition is known to be associated with reduced volume of amygdala and hippocampus.[59] Association of prenatal stress due to food scarcity during the first trimester of gestation in Dutch hunger winter episode,[60] and exposure to atom bomb explosion during the second trimester of pregnancy,[61] with chances of offspring developing schizophrenia have been examined, in which positive link was obtained. Severe stress in the first trimester due to incidences like death of a relative proved as a risk factor for developing schizophrenia.[41] However, maternal stress during the six days Israel war did not show evidence of any link with schizophrenia in the progeny.[62] One earlier study

documented increased prevalence of autism in children born to mothers who experienced stress due to severe storm episode, during the middle and last stage of pregnancy,[54] thus proving that stress during sensitive periods of gestation may contribute to psychopathological disorders. However no positive link was found between prenatal stress and development of autism in childhood, in a population based cohort study conducted to assess the effect of maternal bereavement due to death of close relative during different prenatal periods (7–12 months before pregnancy, 0–6 months before pregnancy, first trimester, second trimester, and third trimester).[52]

Conclusion

There is a definite need for improvement of stress research by improving methodology and involving larger number of patients. Methodological challenges do exist in prenatal stress research which has not been successfully overcome. However, results from animal and human studies do suggest that undesired neurobiological consequences could result from stress during pregnancy and, therefore, pregnant women with some degree of stress need to be identified, advised, and supported not only to prevent potential direct harm for the developing fetal brain but also to address possible consequences of prenatal stress that can indirectly impair neurodevelopment of the child later on.

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