

Original Research Article

Effects of Maternal Stress on Infant Neurodevelopment: A Non-Systematic Review

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ABSTRACT

Introduction: Since stress leads to changes in the secretion of endocrine and exocrine system hormones and these hormones leave their negative effects on the health of mothers and their fetuses and babies, and on the other hand, concerning the period of pregnancy is a stressful period and this stress affects the development of the nervous system of babies, so we decided to investigate the effects of the stress of pregnant mothers on the nervous development of babies in this review study.

Methods: This review study was conducted with the aim of explaining the role of stress on the development of the nervous system of infants. All review studies, clinical trials, and descriptive studies were searched to achieve the goals of this research. No time limit was applied to the studies and all published studies were evaluated in Persian and English languages.

Results: A number of articles were included in this review. The headlines of this study included stress and pregnancy, the effect of stress on pregnancy, childbirth, the effect of stress on the fetus and the baby, and the differences between male and female fetuses in being affected by maternal stress, which were fully explained.

Conclusion: Although the basal glucocorticoid level is necessary for fertility and fetal growth and development, its increase through high activity of the HPA axis (which leads to glucocorticoid production) or drug treatments with glucocorticoids can have negative effects on fertility and have the health of the fetus and its future life.

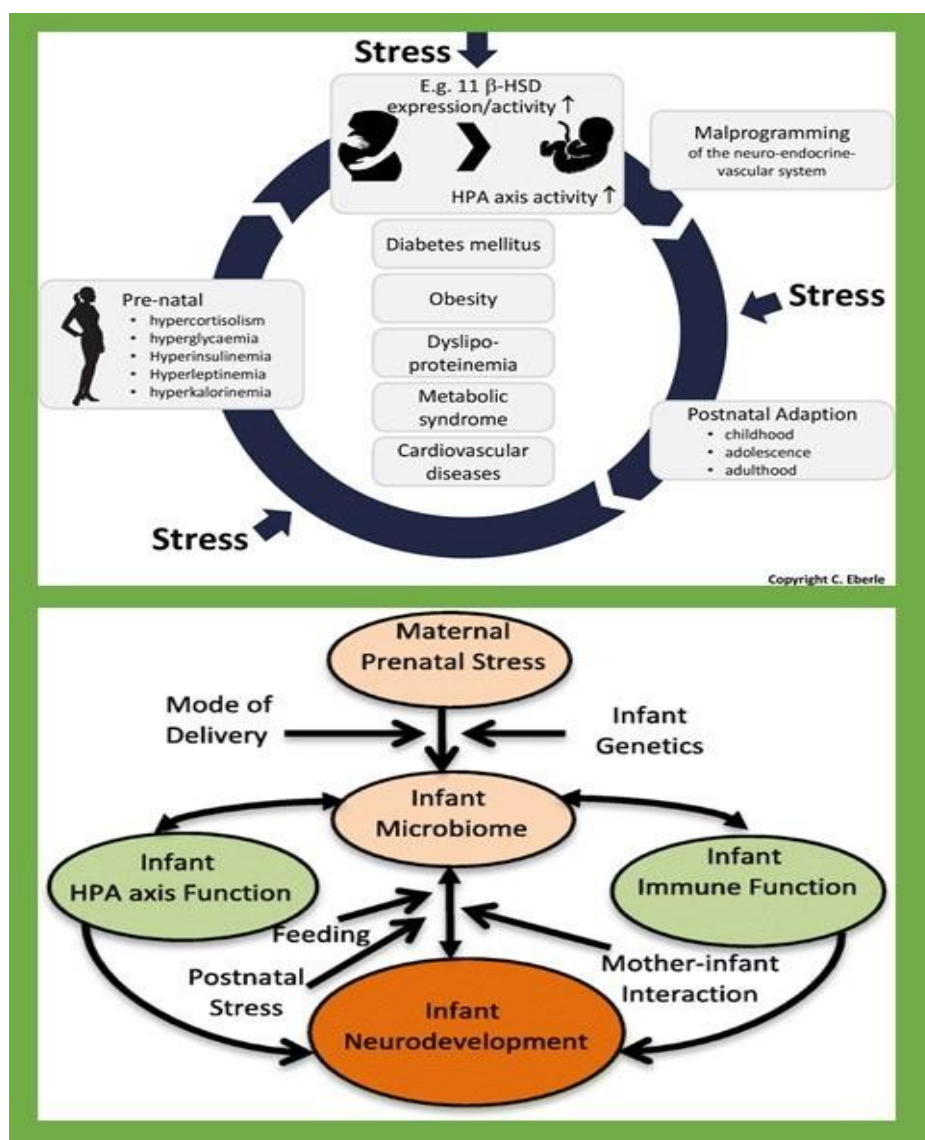
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GRAPHICAL ABSTRACT



1. Introduction

Unfortunately, nowadays, stress has become an integral part of modern life, and of course, it is not only mental and psychological stress that threatens human health in all its aspects, but it should be known that there are different types of stress [1]. In short, sleep disorder, blood sugar fluctuations, all kinds of allergies, and even the level of physical activity and exercise, etc. can have a similar effect to mental stress in the body

[2,3]. Therefore, if a person is managing stress, he should control all these sources of stress. The human body naturally has the ability to manage all types of stress, as long as it is not under chronic and continuous stress [4]. Chronic stress disrupts the functioning of the stress response system. In fact, the interesting thing is that the presence of the right amount of stress is good for the body. Glucocorticoids are important keywords to mention here [5].

As a result of stress (all types of stress) in the body, glucocorticoids are released into the bloodstream. One of the most important glucocorticoids is cortisol, which is known as one of the main stress hormones [6,7]. The reason for naming glucocorticoids is their important effect on glucose metabolism. This name is composed of three words (glucose + cortex + steroid). Glucose indicates that these hormones have an effect on glucose metabolism [8]. Cortex refers to these hormones being made by the cortex part of the adrenal glands. Steroid means that the structure of these hormones is steroid [9]. Glucocorticoids, which have many important effects on glucose metabolism, regulate a wide range of many important and vital functions in the body [10]. These hormones are responsible for the metabolic stability of the body, cardiovascular system, proliferation and survival of cells, growth, cognitive and behavioral functions, immune system and reproduction [11,12]. Because of these broad effects and having strong anti-inflammatory and immunosuppressive properties, they are widely used in clinical applications and even over-the-counter drugs [13]. In fact, it is estimated that 2.1% of the US population, approximately 3.6 million people, use glucocorticoid drugs [14]. Therefore, glucocorticoids are both secreted by the body in stressful situations and may be introduced into the body by drugs [15]. These hormones, like many natural substances in our body, have a balance level, and if they are out of balance, they will cause dysfunction in various body systems, including the reproductive system [16].

Stress usually refers to conditions that threaten the survival and stability of an organism in real or perceived form [17]. However, the body system of living organisms does not sit idle in the face of these conditions, which intend to upset their balance and stability, and shows a series of reactions, which is defined as the stress response [18]. This response actually tries to restore the stable conditions before the stress. This response

includes the activation of a wide range of the endocrine system, the nervous system and the immune system, which is called the body's response to stress [19]. During the body's response to stress, survival takes priority over less essential physiological activities such as growth and reproduction [20].

The system that is responsible for responding to stress in the body is the HPA axis (hypothalamic-pituitary-adrenal) [21]. This system consists of three hypothalamic, pituitary, and adrenal glands. The two hypothalamus and pituitary glands are located in the brain, and the adrenal glands are actually two very small glands located above the kidneys [22]. When this system is activated, the hypothalamus first secretes a hormone called CRH. This hormone signals to the pituitary gland and in the second step, the pituitary gland releases ACTH hormone. In the third stage, this hormone signals the adrenal glands to release a group of hormones into the bloodstream [23]. These hormones include glucocorticoids (cortisol hormone), mineralocorticoids (aldosterone) and adrenal androgens (androgens are sex hormones that are secreted from the adrenal glands). When the level of cortisol hormone in the blood reaches a certain level, the negative feedback loops instruct the hypothalamus and pituitary glands to reduce the secretion of CRH and ACTH and the body returns to the pre-stress state [24,25]. Since stress leads to changes in the secretion of endocrine and exocrine system hormones and these hormones leave their negative effects on the health of mothers and their fetuses and babies, on the other hand, considering that the pregnancy period and this stress affects the development of the nervous system of newborns, so we decided to investigate the effects of the stress of pregnant mothers on the nervous development of newborns in this review study.

2. Method

This review study was conducted with the aim of explaining the role of stress on the development of the nervous system of infants. All review studies, clinical trials, and descriptive studies were searched to achieve the goals of this research; No time limit was applied to the studies and all published studies were evaluated in Persian and English languages

3. Results

3.1. Stress and pregnancy

Before we discuss the effect of stress on pregnancy and fetal development, we should initially talk about the maturation system of sexual organs and reproduction. This system is regulated by the HPG (hypothalamic-pituitary-gonadal) axis [26]. This axis consists of three glands: Hypothalamus, pituitary gland, and

gonads (in women, ovaries). In this axis, first the hypothalamus gland in the brain by releasing the GnRH hormone signals the pituitary gland to secrete two hormones, FSH and LH [27]. These two hormones also instruct the ovaries to secrete sex hormones (such as progesterone, estrogen, and testosterone) and regulate ovulation [28]. The important and basic thing is to know that hormonal health, getting pregnant, having a healthy pregnancy and fetal growth depend on the correct functioning of the HPG axis. The important point here is that stress has a negative effect on all levels of HPG axis functioning [29]. For example, the high level of glucocorticoids (for example, the hormone cortisol that is released in times of stress) in the blood inhibits the neurons that secrete GnRH, the pituitary gland, and the gonads and disrupts their function [30] (Figure 1).

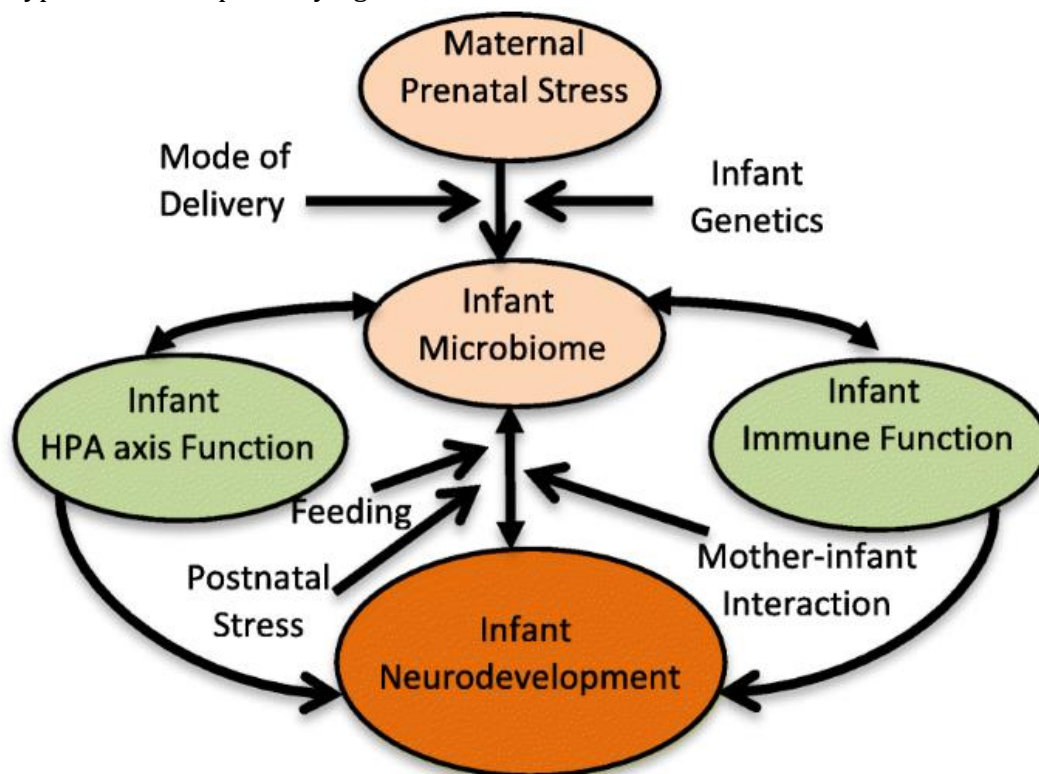


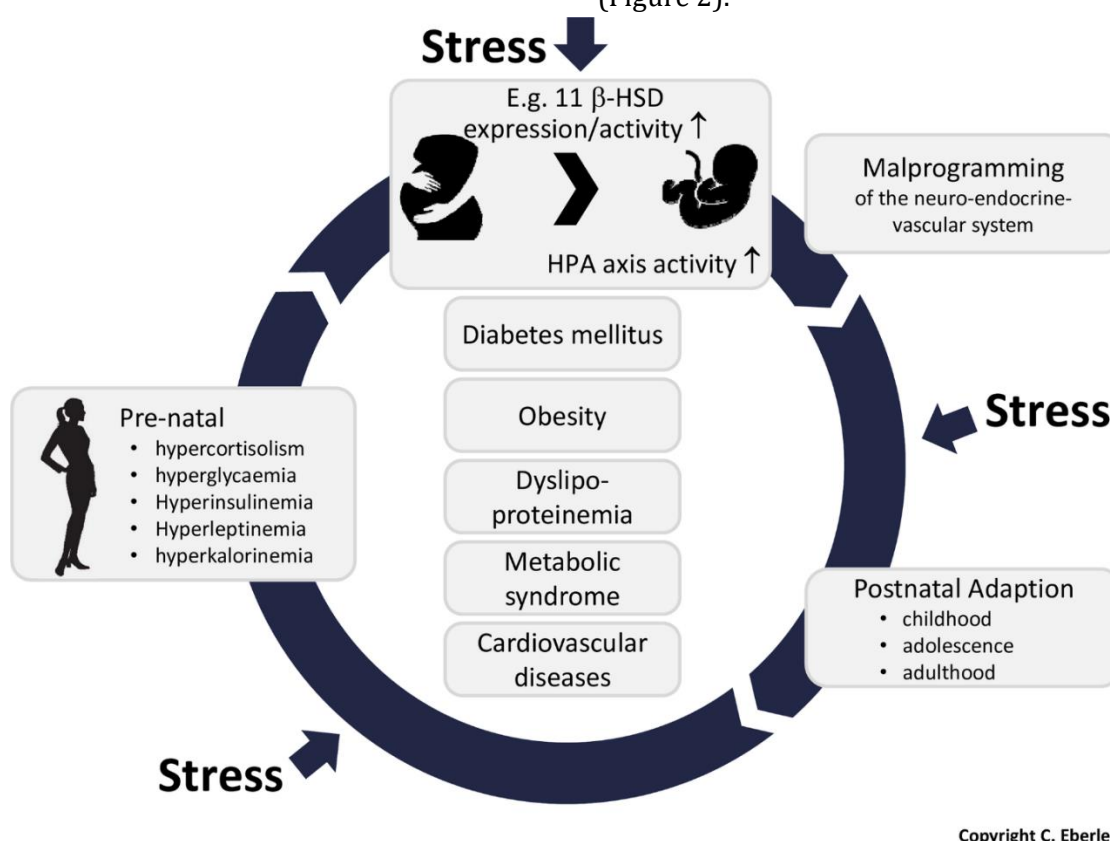
Figure 1. Maternal Stress and Infant Neurodevelopment

The health and proper functioning of the HPG axis is very important and key in sexual and

reproductive health. Research conducted on animals and humans has revealed that stress has

an inhibitory effect on the secretion of GnRH hormone and causes a decrease in the level of this hormone [31]. As mentioned, this hormone initiates the activity of the HPG axis, and any disturbance in it will disrupt the functioning of this axis [32]. Research conducted on sheep has shown that acute stress (caused by isolation, displacement, hypoglycemia, and cortisol injection) will suppress the GnRH hormone. Research shows that stress also affects other levels of the HPG axis and causes disruption of LH hormone secretion by the pituitary gland. As mentioned, the stimuli that the body perceives as stress do not only include mental stress [33].

A study on postmenopausal women has demonstrated that severe diseases and brain injuries cause a decrease in two hormones, FSH and LH. All of these cases show that stress in all its forms causes a malfunction in the reproductive system [34]. The balance of FSH and LH hormones is very important in hormonal health and fertility. Research conducted on mice shows that the use of glucocorticoid drugs increases this ratio by increasing FSH and decreasing LH. In fact, the high activity of the HPA axis (which happens due to the increase in the rate of stress applied to the body) causes disruption in the functioning of the HPG axis [35] (Figure 2).



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Figure 2. Stress and HPA

It was mentioned that the activity of the HPA axis starts with the release of the CRH hormone by the hypothalamus. In fact, the more the activity of this axis increases and goes out of balance, the more CRH will be secreted [36]. Some studies

have investigated the effect of increasing CRH on fertility. High levels of glucocorticoids (whether caused by stress or glucocorticoid drugs) are also associated with ovulation disorders [37]. During a study, a relationship was found between the

level of glucocorticoids and the maturation of eggs and successful conception in women who underwent *in vitro* fertilization. In fact, high levels of glucocorticoids have negative effects on the ability of eggs to be fertilized [38].

3.2. The effect of stress on pregnancy and childbirth

During pregnancy, processes occur in the body that are not seen in non-pregnant women. One of these processes is the production of CRH hormone (initiator of HPA axis activity) in the fetal placenta, which is at its highest level at the time of delivery [39]. In fact, the level of CRH hormone in pregnant women is 1000 to 10000 times that of non-pregnant women. There is a hypothesis that the increase in CRH level acts as a "fetal clock". The mechanism that is responsible for the pregnancy duration and the contractile processes before birth. Although the extra CRH hormone is secreted in the body of pregnant women through the placenta, the interesting thing is that this hormone can stimulate the ACTH production in the pituitary gland and increase the amount of glucocorticoids in the blood [40].

On the other hand, it has been shown that glucocorticoids can increase CRH produced by the placenta! These results show that there is a positive feedback loop that if the amount of glucocorticoids in this loop is out of adjustment, it can lead the system to instability! That is, if the glucocorticoids caused by various sources of stress for the body increase, they can disrupt the body's settings for the timing of delivery and cause premature delivery [41]. The premature birth is the main cause of infant mortality, and despite the resources allocated to this field, its rate has not decreased in the last 25 years [42].

Although preterm birth has various causes, maternal stress is recognized as a potential factor for preterm birth. In a study of 9,350 mothers (and fetuses) in the United States, the occurrence of a stressful event that occurred before pregnancy was associated with a 4-fold increase

in the risk of preterm birth [43]. Another study conducted in Denmark showed a relationship between the occurrence of a stressful event in the six months before pregnancy and premature birth. In a small study of African-American women, childhood stress was associated with preterm birth, independent of adult stress [44]. The important point is that although several studies have shown the relationship between stress and preterm birth, stress before pregnancy, or during pregnancy does not necessarily predict preterm birth, and in fact, the basic mechanisms of the relationship between stress and preterm birth are still unknown. Some researchers have reported an increase in HPA axis activity and an increase in CRH and cortisol levels in the pregnant mothers. Cortisol levels naturally increase at the end of pregnancy and at the time of delivery [45]. This increase is necessary to start the labor process, but if stress causes more cortisol in the body, the natural settings of this hormone are out of balance and may cause premature labor [46].

3.3. The effect of stress on the fetus and newborn

Glucocorticoids play a fundamental role in our body and are essential for our body and the fetus. These hormones are very important during fetal development for the functional maturation of the respiratory system [47]. Therefore, when premature birth occurs, glucocorticoids are used to prevent respiratory distress syndrome. Although glucocorticoids are essential for our health and survival, increasing them either through stressful sources for the body or through glucocorticoid medications can lead to long-term effects in offspring. The excess glucocorticoids direct bad environmental conditions from the mother's body to the fetus, causing changes in their development and permanently affecting the functioning of their tissues and organs [48]. Several studies across a wide range of species have shown that maternal stress or exposure to

high levels of glucocorticoids before and during pregnancy is associated with reduced birth weight. These children are at greater risk for cardiovascular and metabolic diseases, HPA axis dysfunction, and emotional disorders. In addition, the recent research has shown that the effects of exposure to glucocorticoids (either through stress or through drugs) may persist for several generations [49].

The effects that high glucocorticoid levels caused by various types of stress or the administration of glucocorticoid drugs can leave in the body of the fetus in utero include the following:

1. Physical effects: Loss of birth weight, size reduction, late puberty, and high risk of contracting some diseases such as diabetes. **2. Cardiac effects:** Increased blood pressure in response to stress and increased risk for coronary artery disease. **3. Other effects:** Poor managerial and executive functions, decreased secretion of GnRH hormone (initiator of the HPG axis, which is related to the health of the sex hormone system), increased irritability and immune system activity, and increased anxiety [50].

Research has shown that mothers who were pregnant at the time of disasters, their children had developmental disorders. During the Dutch Famine (1944-1945), babies who were exposed to famine in mid or late pregnancy were lighter, shorter, thinner, and had smaller head circumferences than babies who were not exposed to famine. These children have also faced an increased risk of certain diseases such as coronary artery disease and type 2 diabetes, increased blood pressure in response to stress, poor cognitive functions, and an increased risk of schizophrenia and depression [51,52]. Genome analysis of these children showed that methylation was done differently in different areas of their DNA. All these studies revealed that women who experience various types of stress during pregnancy may create an unfavorable environment before birth, which leads to

deficiencies in children. Mother's stress during pregnancy can manifest itself in children's childhood in a wide range of developmental areas, including temperament, cognitive abilities, language skills, and motor functions [53].

Effects of fetal exposure to synthetic glucocorticoids on children's susceptibility to social-demographic adversities after birth have been further investigated. Children who have been exposed to both prenatal stress hormones and social-demographic abnormality have shown poor performance in standard tests of long-term memory performance, and these results are independent of maternal intelligence and concurrent maternal depression [54]. These findings suggest that exposure to synthetic stress hormones (glucocorticoid drugs) may be associated with increased susceptibility to social-demographic problems after birth and have consequences on cognitive functions that persist six to 10 years after birth [55].

3.4. Differences between male and female fetuses in susceptibility to maternal stress

Research revealed that the placenta and umbilical cord blood of infants born to mothers with lower socioeconomic status, which is associated with psychological stress, cortisol dysregulation, and poor environmental conditions, show a transcriptional profile of higher immune system activity and delayed puberty. Likewise, this means that uterine response to stress leads to the molecular signaling changes. Furthermore, evidence suggests that male and female fetuses differ in their response to prenatal stress [56].

Things like cytokine expression, IGF axis, adrenal gland function, growth, etc. are greatly affected by cortisol hormone. Research has revealed that the female placenta responds to changes in glucocorticoid concentrations with changes in cortisol metabolism, cytokine expression, IGF-axis signaling, adrenal gland function, and growth, whereas the male placenta appears to be

glucocorticoid resistant, as those normally cortisol response such as cytokine expression, IGF axis, adrenal function and growth remained unaffected [57]. In fact, studies revealed that maternal stress before birth can have different results for each gender after the neonatal period. The effects of exposure to stress for female fetuses continue until pre-adolescence and are manifested in the form of increased levels of anxiety, impaired executive functions, and neurological markers related to these behaviors [58].

In addition, female fetuses, and not male fetuses, that were exposed to increased maternal cortisol levels in early pregnancy, had significantly enlarged amygdala brain and increased anxiety levels in childhood [59]. These results show that when the mother is exposed to an excess amount of glucocorticoids (either in the form of stress or in the form of drugs), it will have different consequences on the male and female fetus [60].

4. Conclusion

Although the basic glucocorticoid level is necessary for fertility, fetal growth, and development, its increase through high activity of the HPA axis (which leads to glucocorticoid production in the last stage in this axis) or drug treatments with glucocorticoids can have negative effects on fertility and fetal health. It has a future life. The increased HPA axis activity (read chronic stress) is associated with changes in hypothalamus, pituitary, and gonads. In addition, children of mothers who are under stress can have abnormalities such as low birth weight, higher anxiety levels, higher levels of HPA axis function, and are at greater risk of developing various physiological diseases. Reproductive dysfunction as a result of stress or exposure to glucocorticoid drugs has been documented at several levels of the HPG axis, and the mechanisms at some of these levels have been investigated, but the results of research in this

area are still incomplete and require further studies.

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