REVIEW ARTICLE

"SMALL BABY SYNDROME" AS A PREGNANCY-ASSOCITED GENERAL ADAPTATION SYNDROME (REVIEW)

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ABSTRACT

The aim: To analyze the current research literature devoted to the study of the mechanisms of the realization of stress factors during pregnancy.

Materials and methods: The article presents an analysis and summarizes the literature devoted to the study of the mechanisms of the realization of stress factors during the pregnancy, the pathogenetic aspects of violations of the feto-placental complex, "critical periods of vulnerability", the long-term consequences of the transferred prenatal stress.

Conclusions: The paper summarizes that the condition of the mother and the feto-placental complex play an important role in many aspects of fetal development, that determine baby's physical and emotional health, personality formation in the future.

KEY WORDS: stress, pregnancy, fetal programming, low birth weight, Barker's theory

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INTRODUCTION

"Small baby syndrome" is a pregnancy-associated general adaptation syndrome.

The essence of the general adaptation syndrome (stress) is that the influence of any external stimulus results in various defensive mechanisms aimed at counteracting it in order to preserve the integrity of the human body. They do not depend on the stress factor type; they are non-specific and common for everyone. Nonspecific adaptive response of the human body to stress includes more than 1,400 reactions involving all organs and systems of the body [1].

The mental and psychological well-being of a mother is extremely important for predicting a pregnancy outcome [2-4]. The conclusion regarding the influence of the functional state of the central nervous system (CNS) and the psyche of women on the frequency of obstetric pathology is unequivocal. It is based on the fact that in mentally ill pregnant women complications during pregnancy are 6 times more common than in the population [5].

THE AIM

The aim was to analyze the current research literature devoted to the study of the mechanisms of the realization of stress factors during pregnancy.

MATERIALS AND METHODS

Review and latest data analysis of scientific and medical literature.

REVIEW AND DISCUSSION

Stress during pregnancy can affect its course through psycho-emotional and pathophysiological components, as well as changes in the behavior of the expectant mother, such as: poor nutrition, decrease in physical activity, sleep disorders, bad mood, alcohol consumption or smoking [6].

As a result of chronic stressful situations, an impaired regulation of physiological systems occurs that jointly with the relevant lifestyle factors (i.e. diet, exercise, and social support) are expressed in allostatic load, which is a single indicator for measuring the total impact of "physical amortization" of the body[7]. It includes many subclinical physiological / physical parameters (e.g., diastolic and systolic blood pressure, heart rate, body mass index, immune markers, and cortisol level) upon reactivation and associated pathology, including pregnancy pathology. In particular, the general risks and possible adverse effects of stress during pregnancy are described including increased incidence of miscarriages and ectopic pregnancies, increased incidence of sexually transmitted infections, premature birth, low Apgar score, low birth weight, increased risk of stillbirth, additional use of medications, childbirth complications, the development of further postpartum depression, early refusal of breastfeeding, etc., which is further reflected in the health of their children [8].

To date, the degree of weight loss due to maternal stress during pregnancy has even been established: regardless of biomedical risk, each unit of maternal prenatal stress (from a possible sample range of 14.7 units) is associated with a birth weight loss of 55.03 g and a significant increase in

the probability of giving birth to a low birth weight baby (odds ratio = 1.32) [9].

Pregnancy cannot be considered in the narrow context of physical and psychological health of the expectant mother only. Pregnancy is a special condition that is equally important for both a woman and her unborn child. This is the time when they actually "share the same life" as they are a single neurohumoral organism. Therefore, the peculiarities of gestation, including the emotional state of a woman during this period determine the successful development of the fetus, the condition of the newborn and the subsequent adult health programming [10]. The condition of the mother and the uteroplacental complex play an important role in many aspects of fetal development, as well as in a number of key factors in the newborn's brain development, that therein determine baby's physical and emotional health, personality formation, etc.[11, 12]

The first epidemiological research on this subject was published in the late 1970s by Norwegian scientist *Forsdahl A*. [13]. However, it is considered, that the fundamental work was made by *Barker D.J*. who found that adult pathology can be programmed during the fetal period and its frequency is inversely proportional to the weight of the newborn [6].

According to the *Barker's* hypothesis, the fetus requires a sufficient amount of nutrients, energy and oxygen for its normal growth and development. In case of their lack, the growth and development of the fetus slows down, and then changes its formation according to the "economical" or "hungry" phenotype. Thus metabolism reprogramming occurs, reducing the rate of metabolism and utilization of food substrates, inhibition of growth and fetal development, "sacrificing" tissues of liver, kidney and pancreas, as well as skeletal muscle, which allows redistributing and using nutrients for CNS which is critical for its vital function support [13].

The low weight of the fetus at birth is a very primitive indicator, but it reflects the interaction of many factors. Reducing fetal growth rate and nutrient use refers to the so-called "intrauterine survival strategy", which also includes accelerating maturation or termination of pregnancy in the form of miscarriage or premature birth in response to maternal stress [5, 14]. This is due to the phenomenon of phenotypic adaptation that is a process resulting in the body obtaining a previously absent resistance to a certain factor (or factors) of the environment and thus gets the opportunity to live in conditions previously incompatible with life, and solve problems that were previously unsolvable. It means the transition from "urgent adaptation", which occurs in response to the first action of the stress factor, to "long-term adaptation", which is formed by repeated stress factor actions, which provides resistance to it [15].

The most studied and, at the same time, the most controversial are the outcomes of the general adaptation syndrome during pregnancy on the central nervous system of the fetus, its role in distant behavioral disorders and psychiatric pathology. The CNS is a rather complex and dynamic structure, the maturation of which lasts a lifetime. The fetal period is the starting point for its formation that determines the importance of critical periods of vulnerability in its structural and functional development.

Prenatal experience is a subject that requires further extensive studies, but many modern studies show that the development of a child's mental and physical health begins in the prenatal period. However, the studies have shown the adverse effects of the mother's emotional stress on the outcome of pregnancy and childbirth, as well as the condition of the fetus, newborn and subsequent health of the individual [16].

Children born to mothers who have undergone stress during pregnancy in extreme conditions, in the short or long term have physiological and behavioral abnormalities: low birth weight, increased infant morbidity, mental retardation, speech disorders, problems associated with attention and learning, increased anxiety, the development of anxiety or affective disorders in adulthood [17].

Low birth weight is associated with a significantly higher risk of many physical and mental disorders, including low IQ and higher risk of mental disorders [7].

A prospective cohort study of 26-year-old patients in Norway found that low birth weight was a significant risk factor for adult psychiatric morbidity and reduced overall functioning. From adolescence to adulthood, children born with developmental delays had a significantly higher risk of mental disorders: 39% compared to 9% in the control group [18].

A large epidemiological study of 1.8 million full-term infants also found a relationship between low birth weight and a wide range of neurodevelopmental disorders: risk of cerebral palsy is 25 times higher, 16-fold increase in visual / hearing impairment occurrence, 7-fold increase in risk of schizophrenia, 5.4-fold increase in risk of epilepsy, 3.5-fold increase in risk of autism spectrum disorders and behavioral disorders, including hyperactivity disorder / attention deficit disorder [19].

One-third of adults with psychopathology who were prone to drug use had low birth weight [18].

Abel KM et al. analyzed the national registers of psychiatric treatment in Sweden (until December 31, 2002) and Denmark (until June 30, 2005), in which 5,445 cases of schizophrenia and 57,455 cases of any mental disorder in adults were recorded. They found that the risk of schizophrenia was related to birth weight. The attribution was not limited to body weight at birth less than 2,500 g, but there was a linear relationship between the increases in odds with a decrease in birth weight. Such dependence existed for any psychiatric diagnosis and for each of the categories of mental disorders [16].

Schizophrenia was described almost 100 years ago as a disorder of person's attitude to reality, as a polymorphic mental disorder or a group of disorders characterized by deviations in the perception or reflection of reality, associated with disorders of brain structure and function. To date, the issue of the disease causes has not been finally resolved. For example, studies of twins show a large role of hereditary factors. However, many scientists consider

schizophrenia as a disorder of early brain development under the influence of environmental factors that interact with many sensitive genes. It is perinatal factors and maternal stress that are given great importance [17].

The etiology and timing of etiological factors in the implementation of autism in children are also debatable. Significant retrospective studies show that prenatal exposure to stressful events within pregnancy or a few weeks immediately before delivery is subsequently associated with an increased risk of developing autism spectrum disorders (ASDs) in children [20].

Chronic stress during pregnancy may play a role in the development of behavioral and emotional problems in the fetus with an increased risk of depression in offspring, which may be caused by cortisol changes in the hypothalamic-pituitary-adrenal axis [21].

Exposure to maternal stress during pregnancy may cause fetal brain changes that are the root cause of the risk of psychopathology, including associated depression, post-traumatic stress disorder, panic disorders, substance abuse, abnormal stress response, and other serious illnesses [22].

The problem of intrauterine growth restriction is associated with the programming of an appetite as a behavioral disorder in children in the postnatal period. Such children are prone to hyperphagia and rapid weight gain, a so-called "catching up". Newborn body weight gain over 100g within 1 week of life is considered rapid and is associated with a high risk of metabolic syndrome [23].

Maternal stress and malnutrition may also play a role in the development of Alzheimer's disease, a neurodegenerative disorder of the elderly characterized by progressive memory loss and cognitive deficits. Namely, the study of the mechanisms along which the stress factors in early period of pregnancy reprogram the fetal brain and contribute to the development of late periods of neurodegenerative disorders, becomes a new exciting field of study.

Prenatal stress also affects brain development in different ways, for example, it can cause delayed myelination, hypersensitivity of the amygdala to glucocorticoids (GCs), and abnormalities in the development of the dopaminergic system [24].

The researches with the use of brain imaging methods that study the effects of prenatal maternal stress on offspring brain development reveal structural and functional effects at birth and in adult offspring, particularly in several regions of the brain, including the prefrontal, parietal, and temporal lobes, cerebellum, hippocampus, and tonsils, as well as an increase in the index of local gyrification of the fetus in the frontal and temporal lobes (such results are found in adults with schizophrenia and in children with autism) [25].

The influence of birth weight on the global anatomical imbalance of the brain obtained by MRI in monozygotic twin pairs aged 9-10 years has been established. Low birth weight is associated with adolescent and adult mental disorders and may be caused by impaired morphological integration of the brain, which probably reflects disturbance of coordinated programs of nervous system development [26].

The effects of maternal stress can have different effects on different behavioral areas, such as motor or speech processes, and depend on the period of pregnancy when the effects occur. One historical example of an unfavorable stressful pregnancy is the so-called Dutch Hunger Winter of 1944-1945. Studies of birth outcomes have shown a significant increase in the risk of schizophrenia in the offspring of mothers who were in the first trimester of pregnancy, and an excessive increase in low-birth-weight newborns in women who were in the third trimester of pregnancy [16].

However, periods of prenatal sensitivity differ for different pathologies and also depend on the state of the placental system, which simulates the exposure of the embryo and fetus to biologically active substances. There are so-called "vulnerability windows", when it becomes less active and extreme levels of teratogens are more likely to affect the nervous system of the fetus -- that is the early gestational age, during 19-26 weeks of pregnancy (coinciding with the end of neurogenesis), and the final stages of pregnancy [27].

One approach to assessing the effects of stress on the fetus is the consideration approach based on the principles of general teratogenesis, in which any exogenous factor (teratogen) can cause even serious congenital anomalies, if the action occurs during the "sensitive periods" of pregnancy, but almost has no effect if it happens in other periods [28]. However, this approach has its flaws, as the so-called teratogenic effects of stress may be caused by psychotropic drugs taken by pregnant women who have psycho-emotional disorders.

Implementation mechanisms of stress factors are not completely clear in the context of further mental health, and have gender differences. In particular, women have affective disorders 2-3 times more often than men, who are more likely to have autism spectrum disorders. The incidence of schizophrenia and depression increases dramatically in adolescence: four times more often in boys than in girls, which is associated with the onset of major sex differences in brain maturation [29]. The male fetal brain is more sensitive to prenatal stress factors and neuroendocrine disorders of the mother than the female fetal brain [21].

That is associated with the different activity of sex hormones that act in different ways on the male and female brain in utero, as well as the difference in specific regions of the normal male and female brain in terms of structure, cell count, neuronal morphology, synaptic connections and connective fibers between structures [30].

Thus, the most studied and, at the same time, the most controversial issues of the pregnancy-associated general adaptation syndrome are the effects of prenatal stress on the central nervous system of the fetus. It is a rather complex and dynamic structure, the maturation of which lasts a lifetime. The fetal period is the starting point for its formation that determines the importance of critical periods of vulnerability in its structural and functional development.

In the pathogenesis of disorders the following factors are considered: the key role of neuroendocrine, immune pathways of damage to the mother-placenta-fetus system,

as well as more subtle processes including epigenetics, mitochondrial biology and maternal and child microbiome.

The nature of the stress affecting woman may be different, but the main outcome of any stress is an adverse effect on the fetus caused by the activation of the hypothalamic-pituitary-adrenal system with increased levels of glucocorticoids. It is glucocorticoids, and cortisol in particular, that are most often attributable to have a negative effect on the fetus.

However, even during a physiological pregnancy, it is normal for the level of this hormone to increase in several times, so the hormone is considered problematic in terms of the assessment of its effect on the fetus, and thus it cannot be used as a stress marker during pregnancy. It has also been shown that maternal glucocorticoids do not penetrate the placenta [14].

The direct effect of maternal cortisol on the fetus is offset by the placental enzyme 11β-HSD2 that oxidizes cortisol to an inactive form of cortisone and inactivates it [31]. Therefore, the concentration of maternal cortisol does not correspond to fetal one. However, with prolonged stress, the above-mentioned disorders change the permeability of the placental barrier and create conditions for damaging the fetus. Hypoxia may be a factor that may lead to decreased 11β-HSD2 expression. This effect has been described in the placenta during pregnancy complicated by preeclampsia and intrauterine growth retardation [32].

Hypoxia, oxidative stress due to changes in the metabolic activity of placental mitochondria, nitrative stress (which causes covalent modification and changes in protein activity) alter the development of the placenta. They are the pathogenetic mechanism underlying the altered function of the placenta with the programming of fetal pathology [6].

Thus, the placenta has a clearly organized cascade development during gestation. Its malformation can lead to abnormal development of the vascular placenta or trophoblast, which is reflected later in its functional activity and, as a result, the programming of the fetus. The placenta can adapt to the factors that alter its development, including hypoxia, stress, and maternal malnutrition, by changing the expression and activity of the transporter to support fetal growth or by epigenetic regulation of placental gene expression [33]. The implementation of the prenatal stress effects on the placenta is reflected in its morphology: the formation of placenta abnormal weight (placental hyperplasia in malnourished fetus is of particular importance), short umbilical cord, macrophage infiltration of decidual tissue, chorioamnionitis and neutrophilic infiltration of amniotic fluid.

As we have noted, cortisol in the mother's body is mainly inactivated by the placenta to protect the fetus, but it can stimulate placental corticotropin-releasing hormone (CRH), which acts directly on the fetus. This encourages the fetus to synthesize its own cortisol, which stimulates the placenta to further synthesize CRH, creating a vicious circle of self-harm by its own fetal stress hormones [10]. CRH has a direct effect on the uterus and cervix, potentiates the effect of estrogen on them, interacts with both prostaglandins and oxytocin that are the two main uterotonics responsible for stimulating and maintaining the contractile ability of the myometrium during childbirth [34]. It is a "placental clock" that determines the duration of pregnancy and is one of the pathogenetic mechanisms of its prematurity and the birth of underweight children.

Placental CRH is released into the maternal and fetal bloodstream during the eighth week of gestation and increases exponentially during gestation to regulate fetal maturation, metabolic functions and time of birth, which determines its role in prenatal pathology under stress [22, 31, 33].

Dysregulation in this system due to excessive strength or duration of stress leads to increased synthesis of placental corticotropin-releasing hormone, which is known to act on the embryonic axis of regulation of the hypothalamic-pituitary system, stimulates the biosynthesis of adrenocorticotropic hormone and adrenal steroids in the fetus (stimulates the secretion of DHEA-S). GCs act as regulators of functional tissue maturation and adaptation of the fetus to the conditions of existence both in utero and after birth [31]. It is proved that glucocorticoids can underlie the connection between low birth weight and the development of programmed pathology in adulthood [6, 11].

The adaptive role of glucocorticoids, as well as other steroids, is connected with the fact that they are characterized by a prolonged organizing effects, i.e., during critical periods of development they are able to cause internal changes in target cells, tissues, organs and systems that are virtually unaffected by further manipulations with these hormones. Therefore, today it is believed that among the hormones that control fetal development, GCs are the most important for in utero programming of phenotypic traits of the body before and after birth [22, 31]. Many studies have shown that elevated prenatal glucocorticoid levels lead to basal GC secretion higher than normal and secretion is decreased in response to stress even in the postnatal period, such as it was noted in children of women who survived the September 11 attacks on the World Trade Center in the United States in 2001 [35].

Maternal stress is a trigger for the secretion of not only cortisol but also for another stress-attributed hormone, namely adrenaline. Catecholamines mediate short-term behavioral, metabolic, and immunological responses to environmental stressors. Adrenaline and adrenaline-like hormones cause uterine contractions, which directly affect the fetus by increasing vascular resistance and spasm of its vessels, disrupting the blood supply through the placenta and the supply of oxygen to the fetus, triggering placental oxidative stress. Oxygen imbalance for the fetal brain during pregnancy is defined as a risk factor for schizophrenia [36].

Thus, genetically programmed sex features and individual peculiarities of brain microstructure, behavior, central regulation of the hypothalamic-pituitary-adrenal system and reproductive system of the individual are also modified under the influence of the general adaptation syndrome of the maternal organism [37].

The negative impact of prenatal stress on the central nervous system during its development can manifest itself in the form of pathological expansion of the normal process of epigenetic programming. In a normal gestational environment, the level of glucocorticoids in the developing fetus is released in proportion to the disorders of the fetal environment. When the environment is more complex than usual, the flow of maternal stress hormones to the fetus increases allowing the offspring to adapt to more difficult conditions. However, maternal exposure to prolonged or severe stress can lead to the development of pathological, lifelong hyperactivation of the pituitary-adrenal system, as well as increased levels of stress hormones [1, 13].

Thus, according to Barker's hypothesis, the reprogramming of neurodevelopment causes adaptation to the early environment in anticipation of similar postnatal environment. If there is a mismatch between the two environments, such reprogramming may increase the risk of a disease. For example, if the mother experiences increased stress during pregnancy, but the postpartum environment does not cause stress, the brain of the offspring may continue to respond inadequately to stressors throughout his/her life [37].

The functional changes that occur in response to stress factors, which include changes in gene expression, metabolism, differentiation and cell organization have been described. They are often so weak that they are detected by special morphological examination only. Epigenetic changes may have a permanent effect on the promoter regions of specific genes, which do not appear until a certain time when there are appropriate stimuli for their expression, for example, the presence of transcription factor levels. However, they can be identified at birth, making them effective biomarkers that can indicate not only prenatal problems but also potential further responses to disease risk factors [38].

Manipulation of epigenetic mechanisms during pregnancy may represent promising intervention strategies. Several animal studies have shown promising data based on the use of DNA methylation inhibitors and other agents such as the plant derivative isoflavone genistein, leptin, folate, fish oil, omega-3 and vitamin D. These treatment methods may modify the corresponding abnormal epigenetic changes and mitigate the adverse effects of programming caused by prenatal stress [39].

Initial research on this issue was mostly retrospective, but modern research includes cohort studies. They try to establish potential biomarkers of pathology (primarily epigenetic), as well as a possible specific period that has become critical in this case.

CONCLUSIONS

Thus, maternal prenatal stress largely determines the outcome of pregnancy and childbirth, and can determine the prognosis of further health of the child, including mental health [1, 16]. Low fetal weight at birth is not just an obstetric problem, as it is a marker of the general adaptive syndrome. Despite the more than 30-year period since the beginning of the first studies, the mechanisms of intrauterine programming of adult diseases are still insufficiently studied. The main vector of modern research in this area should be aimed at studying its pathways at the cellular and molecular levels, and expanding the list of intrauterine "programmed" pathology. Given the possible manifestation of pathology in adulthood, its study should be multidisciplinary with the involvement of specialists in various fields.

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