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The Importance of Prenatal Stress on the Development of ADHD in Children Literature Review 2019

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Abstract

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that affects children and often persists into adulthood. Research suggests that there is a link between maternal stress levels and the development of this condition. According to the Centers for Disease Control and Prevention (CDC), 6.1 million children living in the United States in 2016 had received a diagnosis of ADHD. The symptoms of ADHD can vary from person to person, but they typically include difficulties with concentrating, paying attention, and controlling impulses.It is not clear what causes ADHD, but scientists believe that genetics, certain environmental factors, and brain changes may play a role in its development. Researchers have also investigated the role of nutrients, such as vitamin D and hormone, such as prenatal testosterone. In this article, wewill reviewed the latest literature assessing the relationship between prenatal exposure to psychosocial stress during pregnancy and to the risk of developing behavioral problems related to attention deficit hyperactivity disorder (ADHD) in Childhood.

Keywords: Prenatal stress; Attention deficit hyperactivity disorder (ADHD); Vitamin D; Prenatal testosterone; Etiological factors.

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1. Introduction

Attention deficit hyperactivity disorder (ADHD) is one of themost common behavioral conditions, particularly among children [1]. According to World Health Organization (WHO) surveys, its prevalence averages 2.2% among children worldwide and is followed by adult ADHD in 57% of the cases, although prevalence of adult ADHD is likely to be underestimated [2]. ADHD typically starts in childhood and often persists throughout life [3]. The symptomsare inattention, hyperactivity, and impulsivity [4]. People with ADHD might reach lower education levels than healthy children and their occupational attainment and social level might be lower in adulthood, and this might have an economic burden to societies [5].The developmental aspect of ADHD must be taken into account when characterizingclinical presentation.The validity of ADHD among preschoolers has been an area of particularcontroversy in the literature. Although there is increasing evidence that ADHDconstitutes a valid diagnosis even before the age of 6, there are several challengesin making a diagnosis during this developmental period. For example, the difficulties associated with making observations across multiple settings for children notattending preschool – and subsequent lack of information about pervasiveness. In addition, hyperactivity and impulsivity are much more prominent at this stageand inattention might not be so evident due to there being less environmentaldemands on the child. Thus, it is not surprising that ADHD predominantly hyperactive/impulsive presentation is the most frequent presentation in preschoolers. Several studies have however shown that currently available criteria reliably identifyADHD in children as young as 3 years old and that these individuals haveclinically significant impairment across all relationships and settings [6] Years ago, ADHD was seen as a problem occurring only in little boys who werehyperactive. It is now clear that ADHD occurs in many individuals who are nothyperactive. Although it is more often recognized in males, it also is found in a significantnumber of girls and women. High intelligence is not a protection againstADHD. Many with ADHD are very bright, but still struggle a lot in exercisingexecutive functions described above which are essential for success in school, workand many activities of daily life. A very large percentage of children, teens and adults with ADHD have one ormore additional problems such as anxiety, depression, sleep difficulties, substanceuse disorders, obsessive compulsive disorder, autism spectrum disorders, and/orspecific learning disorders in reading, math or written expression. One of theseother problems may be identified first, possibly overlooking the underlyingADHD. Or the ADHD may be recognized while another underlying disorder isnot noticed or treated [7]. The causes of ADHD are not fully understood; however, several environmental (e.g., exposure to maternal stress during pregnancy, certain foods or inhalants) and genetic risk factors have been proposed [8]. Modern obstetrics has seen dramatic changes in the past decades. The fetus has become a patient and modern obstetrics has matured into feto-maternal medicine. The latest development is the advent of the new concept of ,,fetal programming'' which is based on the understanding that the intrauterine environment can impose postgenomic changes that can have far reaching consequences on health and wellbeing which can affect the individual in adulthood as well as subsequent generations. Understanding the concept of fetal programming requires the understanding of epigenetics, which in essence is the nonmutational manipulation of genes without affecting their basic structure. Fetal programming may create predisposition factors for adult disease and is also crucial for behavioral and cognitive normalcy or deviation thereof. The importance of fetal programming cannot be overstated. It is now common understanding that prenatal life is no safe haven for the fetus and that the environment in which the pregnant mother lives has a direct impact on the

development of the fetus. In effect, there is no other time throughout the life span of an individual where it is so intimately exposed to the environment. Whatever affects the pregnant mother may well affect her growing embryo and fetus, in many cases in a greatly amplified manner. The impact of exogenous toxins on the developing fetus is dependent on qualitative and quantitative factors and also on when they occur during the development of the fetus. First trimester exposure will generally have teratogenetic effects while second and third trimester exposure will more often be expressed in growth restriction and organ failure [9]. The importance of development during the fetal period is well established with regards to the association between the baby's growth in the womb, and later vulnerability to physical disorders such as cardiovascular disease and other aspects of metabolic syndrome [10]. It is now clear that environmental effects on fetal development are important with respect to emotional, behavioural and cognitive outcomes too. Many groups around the world are studying how the emotional state of the mother during pregnancy can have long-lasting effects on the psychological development of her child [11-12]. Some are using large population cohorts, which have the advantage of being able to statistically allow for many confounding factors including postnatal maternal mood. [13] Others are smaller observational studies which can examine the child in more detail [14]. Stress is a generic term which includes anxiety and depression, but also includes distress due to poor relationships or the response to an acute disaster. All these have been shown to be associated with altered outcome for the child. Many independent prospective studies have now shown that if a mother is stressed, anxious or depressed while pregnant, her child is at increased risk for having a range of problems, including emotional problems, ADHD, conduct disorder and impaired cognitive development. Both altered brain structure [15] and function [16] have been shown to be associated with prenatal stress, and also the mother's experience of early childhood trauma [17]. While genetic transmission and the quality of postnatal care are likely to contribute to some of these findings of association, there is good evidence that there is a causal influence of the mother's emotional state while pregnant also. Some studies have found stronger associations with prenatal maternal mood than paternal [18]. Several large cohort studies have found associations independent of possible confounding factors, such as birthweight, gestational age, maternal education, smoking, alcohol consumption, and most importantly, postnatal anxiety and depression [13]. Thus, although the mother's postnatal emotional state and the quality of early postnatal care are clearly important for many of these outcomes, the evidence suggests that there are substantial prenatal effects also. Within a normal population, the children of the most anxious mothers during pregnancy (top 15%), had double the risk of emotional or behavioural problems, compared with the children of the less anxious mothers [13]. Most children were not affected, and those that were, were affected in different ways. However a doubling of risk is of considerable clinical significance. Several studies are finding that boys and girls can be affected in different ways [11]. There are gene environment interactions too, in that a child with a specific genetic vulnerability is more likely to be affected in a particular way [19]. It is clear that it is not just toxic or extreme prenatal stress that are important, as several studies have shown that problems such as daily hassles, pregnancy specific anxiety or relationship strain [14] can have an adverse effect on the developing fetus. Effects of acute disasters such as [16-18,20] have also been demonstrated. Different studies have shown different gestational ages of vulnerability. This may vary for different outcomes. Increased vulnerability to schizophrenia has been found to be associated with extreme stress in the first trimester [21]. The risk for other outcomes, such as ADHD, has been found to be associated with stress later in pregnancy [13,22]. When discussing causation, studies of DNA risk variants have a clear advantageover studies of the environment. Our

genome comes into existence prior to ourbirth. So, when scientists discover an association between ADHD and a DNA variant,it is clear that having ADHD cannot "cause" one to have a specific DNA variantbut that having a DNA variant could logically increase risk for ADHD. Studiesof the environment are less clear-cut. For example, if a study documents thatpoverty is associated with ADHD, that could mean that poor nutrition, stress andother concomitants of poverty increase the risk for ADHD. But it is also possiblethat having ADHD leads to lower levels of education, poorer job performance andthereby increases the risk for parents with high genetic risk for ADHD to live inpoverty. Thus, one must always keep in mind the potential for such 'reverse causation'when evaluating environmental risk factors and evaluate whether these havebeen considered by the relevant studies. That said, keep in mind that when onemember of an identical twin pair has ADHD, the risk to the co-twin is only about50%. Thus, environmental risk factor must contribute to the etiology of ADHD [7]. Some environmental risks are due to exposures to toxins, lack of nutrients ortrauma. Many studies have examined the effects of iron and zinc on ADHD becauseboth of these elements are essential for producing norepinephrine and dopaminein the brain. In a meta-analysis, Scientist [23] reported that measuresof iron deficiency were associated with ADHD. They also found that ADHD wasassociated with low levels of zinc in the blood. Among the many toxins studied in ADHD patients, the strongest evidence implicates lead contamination. In their meta-analysis, they found that compared with controls, ADHD caseswere more likely to have been exposed to lead. Many studies have tested the idea that pregnancy and delivery complications(PDCs) might cause ADHD by harming the brain at early stages of its development.Although the literature presents conflicting results, it tends to support theidea that PDCs are risk factors for ADHD. When PDCs have been implicatedin ADHD they typically lead to oxygen deprivation and tend to involve *chronic*exposures to the fetus, not *acute* events. Among the most investigated PDCs, prematurity and low birth-weight are the most studied. A recent meta-analysis ofthe literature on the association between both very-premature and/or very low--weight babies and ADHD showed a 3 times increased risk for those infants tohave ADHD in the future [24]. However, it is important to note that prematurity andlow-birth weight are risk factors to other mental disorders. Anyhow, wheneverassessing very premature and/or very low birth weight children, clinicians mightconsider assessing for ADHD. Maternal smoking during pregnancy has been widely studied as a risk factorfor ADHD. It is well documented that smoking during pregnancy places the fetusat risk for birth complications, including low birth weight, which has been associatedwith ADHD. Maternal smoking also places the fetus at risk for a hypoxia,which has been associated with ADHD. Although one groups of scientist's [25] meta-analysisconcluded that children whose mothers' smoked during pregnancy had a 2.4 foldincreased risk for ADHD, this is still an area of debate because ADHD and itspolygenic risk are known to be associate with smoking behaviors. Thus, mother with ADHD might smoke more than mothers without ADHD and the risk is associated to genetic factors related to ADHD and not to smoking. Those who favorthe maternal smoking hypothesis point out that it is a plausible risk factor becausenicotine regulates the activity of the dopamine transporter, the site of action of thestimulant drugs that treat ADHD. People who experience mild traumatic brain injuries (mTBIs) are at risk fordeveloping ADHD. This was the conclusion of a meta-analysis which showed thatmTBI associated with ADHD.[26] Another well-documented environmental riskfactor is severe institutional deprivation in early childhood. We know this fromstudies of children who spent the early years of life in Romanian orphanages thatoffered poor nutrition and nearly no human contact. Many of these children developed ADHD later in life [27]. Environmental risk factors for ADHD that have been confirmed by meta-analysesinclude: preterm birth [28], prenatal exposure to maternal

smoking [29] prenatal methylmercury exposure from maternal fish consumption [30] exposure to lead [31] andperinatal vitamin D deficiency [32]. From meta-analyses, we can also exclude some environmental factors as increasing the risk for ADHD. These include: sugar consumption [33]. methylmercury in vaccines [30], maternal thyroid hormone insufficiency [34], sleep restriction [35], cesarean section [36] and solar intensity [37]. It is easy to see how toxic exposures, pregnancy and delivery complications,traumatic brain injuries and severe institutional deprivation could affect the developing brain and increase risk for ADHD. In addition to such biological adversity,studies have also implicated adverse psychosocial experiences as risk factors forthe disorder. Examples of psychosocial stressors that affect children are maritaldistress, family dysfunction and low social class. Other potential risk factors for ADHD are low maternal education, low socialclass, and single parenthood. Several studies show that the mothers of ADHDchildren have more negative communication patterns, more conflict with theirchild and a greater intensity of anger than do control mothers and that families ofADHD children are more likely to have higher levels of chronic conflict, decreased family cohesion, and exposure to parental psychopathology. However, most ofthe environmental factors might act more as unspecific triggers for mental healthproblems in general than specific environmental risk factors for ADHD. An association between vitamin D and attention deficit hyperactivity disorder (ADHD) has been proposed by several researchers in recent years;however, the investigations have led to inconsistent results. It has been suggested that dietary interventions such as ω-3 FA [38] and vitamin and mineral supplementation [39], restriction diets, and the avoidance of synthetic food color additives [40] might affect ADHD symptoms [41]. Recently a number of studies have proposed that vitamin D might play a role in ADHD pathogenesis. The mechanisms by which vitamin D might affect a number of neurological diseases, including ADHD, are not clear. Nevertheless, there is evidence demonstrating the widespread presence of vitamin D receptors and 1α-hydroxylase (the enzyme responsible for the formation of the active vitamin) in the human brain; therefore, it is suggested that vitamin D might have neurohormonal properties in the human brain [42]. Furthermore, a recent study proposed that vitamin D directly upregulates expression of tyrosine hydroxylase (a rate-limiting enzyme in dopamine synthesis) by binding to the nuclear vitamin D receptor [43]. It is also suggested that this vitamin is involved in the synthesis of serotonin in the brain [44]. Several observational studies have examined the association between vitamin D status and ADHD in children andadolescents in recent years; however, they have achieved inconsistentresults [45-48]. Themajority of case-control studies have revealed that serum vitamin D concentrations arelower inADHDchildren than in healthy controls [46,47, 49-51]. However, a study done by other scientists [45] couldnot show the same association. Moreover, in a cohort study, researchers [48] reported that there is no difference in cordblood vitamin D concentrations at birth between childrenwithADHDand healthy controls. In contrast, another cohortstudy conducted byother group of researchers[52] revealed that highermaternal circulating concentrations of 25-hydroxyvitamin D[25(OH)D] in pregnancy might be associated with a lowerrisk of developing ADHD-like symptoms in offsprings.Although the findings of a connection between vitaminD status and ADHD have been controversial [53]. On the basis of observations of sex differences, many researchers have raised questions with respect to the potential roles of the neuroendocrine system in the etiology of ADHD [54-56]. The male gonad commences testosterone secretion as early as the 7th week of pregnancy. Testosterone levels peak around 14-18 weeks of gestation and testosterone levels in the developing male fetus may become close to adult levels. Testosterone exerts manifold effects on the developing organism, like sex-specific development of genitalia and growth rate. The effect of fetal sex steroids on

mammalian brain development is most striking. Dependent on the availability of testosterone receptors, testosterone affects cell apoptosis and is involved in the establishment of neural connectivity. The results of this development are far reaching and are of crucical importance for „male'' behavior after birth and throughout life, including childhood play behavior, and may also be involved in the establishment of sexual orientation and sexual identity. High exogenous or endogenous testosterone levels in female embryos (or neonates) will lead to behavior patterns typical of males [57]. High levels of prenatal T may affect the dopaminergic neural circuitry and decelerate neural development globally [58]. Excessive prenatal exposure to testosterone has been implicated in the development of dyslexia and autism [59]. On the other hand, reduced levels of fetal testosterone can be found in situations where the pregnant women is under acute and chronic stress, such as in times of war or when exposed to natural or personal disasters. Prenatal maternal stress and anxiety have been shown to be associated with impaired neurodevelopmental outcomes, including attention deficit and hyperactivity in boys [60]. Several studies support the hypothesis that prenatal T exposure contributes to the development of ADHD in children. However, some researchers have not found associations between prenatal testosterone level and ADHD features or externalizing behavior problems in children [61-63]. In sum, whether prenatal T exposure plays a role in the etiology of ADHD is still open to debate. Individuals with ADHD have at least 1.5 times the average risk of developing dependence on nicotine, alcohol, marijuana, cocaine, and other drugs [64], and tend to have earlier onset, faster progression, and less remittance of substance use disorders (SUDs) [65-66]. They also have higher rates of obesity [67] and three times higher rates of binge eating than individuals without ADHD [68]. Furthermore, ADHD is associated with unsafe sexual behavior, including earlier sexual activity and more partners [69-70]. ADHD youth are also less likely to use contraception, leading to higher rates of sexually transmitted infections (STIs) and unintended pregnancies [70]. SUDs, obesity, and STIs are directly associated with chronic health problems as well as morbidity and mortality. SUDs also increase rates of violence, accidents, and unprotected sex. These difficulties, along with unintended pregnancies, additionally reduce socioeconomic attainment and quality of life. In light of the high prevalence of ADHD and associated risks, health promotion efforts for this population are much needed and have the potential for substantial public health impact. Future research questions and implications for clinicians are - when and how medical practitioners may optimally intervene to avoid the development of ADHD in children and how improve child health through early screenings, increasing medication adherence, and treating psychosocial impairments.

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