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FETAL PROGRAMMING: FETAL STRESS IMPACT ON THE DEVELOPMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN CHILDREN

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ABSTRACT

The purpose of this review was to examine the 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. Environmental exposures can alter maternal physiology in a manner that results in "programming" effects on the fetus. ADHD is one of the most prevalent neuropsychiatry disorders among children. The etiology of ADHD is complex and multifactorial. Genetic factors are critical determinants of ADHD, environmental factors are also thought to contribute to the emergence and severity of the disease. The role of nutrients and dietary factors in ADHD remains unclear. Vitamin D status during prenatal brain development may influence risk of ADHD symptoms in childhood. Sex hormones play many roles in the development and function of the human body and brain. Many studies support the hypothesis that prenatal testosterone exposure contributes to the development of ADHD in children.

KEYWORDS: Prenatal maternal stress, Fetal programming, ADHD, Etiology, Vitamin D, prenatal Testosterone.

INTRODUCTION

Environmental exposures can alter maternal physiology in a manner that results in "programming" effects on the fetus. This programming is understood in terms of adaptations to the prenatal environment, which may or may not be beneficial after birth. That is, the course of fetal development is altered as a function of critical environmental conditions in a manner that shapes growth and health outcomes into adulthood. According to some researchers,[1] offspring faces risk in the form of vulnerability to adversity and/or a lack or resilience if in utero programming is discordant with the postnatal environment. This programming effect was first noted in the context of undernutrition and is often referred to as "Barker's hypothesis," the "thrifty phenotype hypothesis," or the "fetal programming hypothesis," the central hypothesis guiding this approach is that the in utero environment shapes fetal development and subsequently sets probabilistic parameters for both adaptive and maladaptive outcomes. Barker and Osmond (1986)[2] relied on epidemiological data to ascertain that gestational undernutrition was correlated with adult onset heart disease. Multiple investigations have since identified fetal programming contributions to adult disorders,[3] and interest in developmental origins of health and disease continues to grow.[4] This review encompasses prenatal effects associated with exposure to stress, hormones, and nutrition. Fetal programming is thought to transform the structure and function of tissues/organs, shaping physiological outcomes associated with adult disease. Biological processes underling these programming effects represent a more recent emphasis, as DOHaD research has become increasingly concerned with the role of epigenetic mechanisms that alter gene expression.[1] Epigenetic mechanisms play a critical role in fetal programming, providing the basis for either healthy outcomes or disruption of physical and mental health. Environmental epigenetics encompasses a variety of environmental factors that serve to establish and maintain epigenetic modifications, influencing gene expression and the resulting phenotype. Fetal programming associated with maternal stress, toxicants, substance/psychotropic medication use, and nutrition reflects diverse biological pathways. All these exposures are nonetheless relevant to environmental epigenetics, as epigenetic processes provide conduits for conferring their effects to the gestating organism Consequences of fetal programming in humans have been documented most widely for physical health/medical outcomes,[5] with behavioral effects often examined in animal models.[6] Outcomes have not been typically framed as temperament per se, but rather discussed in terms of stress reactivity, susceptibility to anxiety, or impulsivity, without making

links to this overarching theoretical framework. Connecting these disparate findings under the umbrella of the psychobiological model of temperament makes it possible to view these in terms of their implications for social–emotional development and developmental psychopathology, and to provide prevention/intervention related recommendations.[7]

Throughout history, scholars have explored the idea that experiences early in life have a profound and persisting influence on health and well-being.[8] Over the past century, this idea has inspired the emergence of a vigorous field of research dedicated to understanding how the prenatal environment shapes long-term developmental outcomes. The foundation of this literature can be found in vanguard studies on fetal physiology dating back to the 1930s and 1940s.[9-12] Today, the convergence of diverse disciplines continues to fuel an expansion of research that has given rise to a conceptual paradigm called the developmental origins of health and disease.[13-14] Historically, the emphasis of DOHaD research has been on physical health outcomes, such as cardiovascular disease, obesity, and type 2 diabetes. More recent work examining neurobehavioral and clinical outcomes has provided compelling evidence of long-term educational, behavioral, and psychological sequelae of prenatal stress. Of note, the influence of developmental principles on the field of DOHaD research is increasingly visible, for example, in a growing interest in plasticity and the probabilistic nature of development (in contrast to "programmed" outcomes,[15] in the recognition of the bidirectional relationship between a pregnant woman and a fetus,[16] as well as in the recognition of pregnancy as a significant period of organization and development for a fetus and a woman, and in a mounting interest in the association between prenatal stress and adaptive outcomes and individual differences (and not only maladaptive outcomes) and what factors and processes may buffer stress effects and promote resilience. Despite the recent maturation and rapid growth of the DOHaD field of research, precisely how prenatal stress may alter developmental trajectories is not well understood.[17]

Prenatal exposure to maternal stress, anxiety, and depression can have lasting effects on infant development with consequences for risk of psychopathology. Though the impact of prenatal maternal distress has been well documented, the potential mechanisms through which maternal psychosocial variables shape development have yet to be fully elucidated. Advances in molecular biology have highlighted the role of epigenetic mechanisms in regulating gene activity, neurobiology, and behavior and the potential role of environmentally-induced epigenetic variation in linking early life exposures to long-term biobehavioral outcomes.

The developmental origins of disease risk have been established through epidemiological studies in humans and illustrate the profound impact of early life adversity. During prenatal development, the fetus is particularly vulnerable to the effects of a broad range of environmental exposures, with consequences that can persist into infancy, adolescence, and adulthood. In particular, maternal distress during pregnancy, in the form of exposure to chronic or acute stressors, depression, and/or anxiety, can influence both fetal and infant behavioral and physiological outcome measures.[18]

Since ancient times, scientists have written about beliefs that the emotional state of the pregnant mother may affect her unborn child. Today, both animal and human studies support the notion that maternal stress and anxiety during pregnancy can have both immediate and long-term effects on her offspring. However, studies vary substantially in terms of their methodologies and results. Some studies examine isolated stressors, such as death of a spouse or natural disaster, while others look at stressful feelings and daily hassles during pregnancy.

Prenatal stress and infant outcomes—Prospective studies have shown that maternal stress and anxiety during pregnancy are related to infant outcomes such as: temperamental problems and increased fussiness, problems with attention, attention regulation, and emotional reactivity, lower scores on measures of mental development.

Prenatal stress and child outcomes—a recent large-scale epidemiological study confirmed some of the infant outcomes above and showed associations between prenatal stress and anxiety and: hyperactivity and inattention in boys, emotional problems in girls and boys, conduct problems in girls.

Prenatal stress and adult outcomes—a number of retrospective and epidemiological studies have linked severe stress during pregnancy (such as experiencing famine, a major earthquake, or other natural disasters) to higher incidences of mental illness in adult offspring, such as schizophrenia and severe depression.

Moderate stress versus chronic or severe stress—some studies have shown that mild to moderate levels of stress during pregnancy might actually be good for the baby, resulting in healthier immune systems and better motor development. More research is needed before firm conclusions can be drawn, but it may be that mild to moderate amounts of stress during pregnancy help prepare the baby for later stressors, such as birth.[19]

Attention-deficit/hyperactivity disorder (ADHD) is a childhood-onset neuropsychiatric disorder characterized by persistent and impairing inattention, hyperactivity, and impulsivity. The symptoms of ADHD often persist into adulthood. Early comorbidities concurrent with ADHD may include tic disorder, anxiety disorder, autism spectrum disorder, communication and specific learning

or motor disorders (eg, reading disability, developmental coordination disorder), and intellectual disability. Long-term follow-up studies from childhood to adulthood found that children with ADHD, compared with those without ADHD, were more impaired in psychosocial, educational, and neuropsychological functioning and had higher risks for antisocial disorders, major depression, and anxiety disorders as adults. The American Psychiatric Association states in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition that 5%of children have ADHD, based on previous worldwide estimates in earlier years. The prevalence of ADHD varies across different countries, with a significantly higher prevalence in the United States than in European countries. Moreover, the prevalence of ADHD has changed over time. Several previous studies in the United States have shown an increase in ADHD prevalence over the past years. For example, an analysis of the National Health Interview Survey (NHIS) reported a 33% increase in ADHD prevalence from 1997-1999 (5.7%) to 2006-2008 (7.6%) among children and adolescents aged 3 to 17 years. Similarly, the National Survey of Children's Health showed a 42%increase between 2003 and 2011 in the prevalence of diagnosed ADHD among children and adolescents aged 4 to 17 years.[20]

Also according to other sources previous estimates of the prevalence of attention-deficit /hyperactivity disorder (ADHD) in the United States suggested that the prevalence was increasing. The incidence of ADHD increased with age (7.7% among children aged 4 to 11 years, 13.5% among children aged 12 to 17 years). The prevalence of an ADHD diagnosis increased over time (6.1% in 1997-1998, 10.2% in 2015-2016), a trend that was statistically significant. The trends were noted in both age groups but the increase (from 7.2% to 13.5%) was highest in children aged 12 to 17. The prevalence of the diagnosis among boys increased from 9% to 14% over the years studied. Among girls, it increased from 3.1% to 6.3% over the same years. Every racial or ethnic subgroup likewise experienced significant increases over time. The rising prevalence occurred regardless of family income measures or geographic region. The conclusion of the study is that the estimated prevalence of ADHD/ADD has increased between 1997 and 2016.[21]

Information about the current prevalence of ADHD and its long-term trends over the past decades is needed to inform future research, clinical care, and policy decision making on ADHD.

The prevalence of ADHD is substantially different between the sexes: reported ratios of boys to girls range from 4:1 to 9:1.[20]

The etiology of ADHD is complex and multifactorial. While twin and adoption studies indicate that genetic factors are critical determinants of ADHD, with a heritability estimate of 76%,[22] environmental factors are also thought to contribute to the emergence and severity of the disease. Many of these factors seem to cluster around pregnancy and birth, including obstetrical complications, maternal smoking, alcohol use and stress during pregnancy.[23-24] Other environmental contributing factors include parental mood disorders, psychosocial adversity and parenting style.[25]

Prenatal stress has been associated with negative outcomes in children from infancy to school age. Epidemiological studies have shown that prenatal stress increases the rate of spontaneous abortions, fetal malformations, and preterm birth.[26] Toddlers born to stressed mothers have worse general intellectual and language functioning.[27] In a large-scale community, O'Connor et al.[28] found a robust link between prenatal stress and externalizing problems in children at four and six years.[29]

General prenatal stress and stressful life events during pregnancy increase the risk of having a child who develops ADHD. Prenatal exposure (especially during the first trimester) to perceived general stress was associated with an increased risk of ADHD diagnosis, especially in boys.[30] In a retrospective case-control study, maternal stressful events during pregnancy were significantly associated with ADHD compared to an unaffected sibling, with males more likely than females to be affected. Examining a large Danish cohort,[31] researchers found that severe bereavement stress was associated with an increased risk of ADHD. Similarly, an earlier study of Danish children born between 1987 and 2001 found that boys born to mothers who experienced the unexpected death of a child or a spouse during pregnancy had a 72 % increased risk of a hospital diagnosis of ADHD or receiving ADHD medication.[32] However, unlike the findings with maternal perception of general stress levels during pregnancy,[33] there was a trend for the risk of ADHD to be greatest if the loss of a first-degree relative was during the third trimester. The death of a non-first-degree relative did not increase the risk. In addition, the risk was gender specific such that it is only applicable to males. Neither of the bereavement studies measured the mother's subjective response to her loss or the impact of maternal exposure to less aversive stressors. In a small retrospective case-control study, positive life events and marital satisfaction were significantly lower during pregnancy in mothers who gave birth to children who were later diagnosed with ADHD.[34] A prospective cohort study found that maternal-state anxiety at 12–22 weeks of gestational age (but not later in pregnancy) was related to ADHD symptoms in 8 and 9-year-old children.[35] In contrast, maternal anxiety diagnosis was not related to the later development of ADHD in another study of a larger sample of women and their offspring.[36] These studies further emphasize the potential interaction between timing of adversity, severity of the stressor, and sex of the offspring in the programming of risk for mental disorders.[37]

Activity of the hypothalamic-pituitary-adrenal (HPA) axis is thought to play a key role in mediating the effects of maternal stress on the fetus. Activation of the HPA axis, in response to physical or psychological stress, results in the release of circulating cortisol. In highly stressful situations, elevated maternal cortisol could exceed the placental capacity to degrade it, cross the placental barrier and influence the developing brain and/or 'programm' the fetal HPA axis.[38] Alternatively, maternal stress could cause a constriction of the uterine artery, leading to decreased blood flow to the fetus. The resulting fetal hypoxia may hinder fetal development and predispose the child to problems later in life.[39]

The American Academy of Pediatrics recommends exclusive breastfeeding of infants for around 6 months given the various known benefits, including reduced risk of allergic diseases, sudden infant death syndrome, and childhood obesity.[40-42] While overall breastfeeding rates have increased, the literature has identified significant disparities in breastfeeding among postpartum women. Such disparities may be related to social norms, cultural factors, and maternal socioeconomic status. In some studies, black women and women with lower education levels were less likely to achieve their breastfeeding goals. Life events are environmental stressors that may negatively impact health outcomes. Epidemiologic studies suggest that psychosocial stressors, such as conflict, bereavement, and high perceived stress during pregnancy, are associated with low birth weight, preterm birth, and adverse neurodevelopmental outcomes in children. In separate studies among postpartum women, researchers[43] showed that perceived life stress was associated with increased odds of preterm birth. One of them[44] also demonstrated that for each unit increase in perceived life stress during early pregnancy, there was a nearly 100 g decrease in infant birth weight. It is well established that maternal mental health and perceived social support can affect maternal breastfeeding attitudes and behaviors. There is limited information available, however, regarding the relationship between other environmental stressors and breastfeeding outcomes.[45]

The role of nutrients and dietary factors in attention-deficit hyperactivity disorder (ADHD) remains unclear. Vitamin D deficiency is a common condition worldwide. Although exposure of the skin to sunlight leads to vitamin D production from cholesterol, vitamin D deficiency is common, also in areas rich in sunshine.[46-47] Several hypotheses concerning the importance of vitamin D for brain development, especially prenatally and during the early neonatal period, have been formulated.[48-49] It has been proposed that vitamin D deficiency could be a risk factor for developing attention deficit/hyperactivity disorder (ADHD).[50-51] Results from two recent studies on the association between vitamin D status and ADHD diagnosis showed an association between low levels of D vitamin and an ADHD diagnosis. In these studies D vitamin levels were not assessed at pregnancy or birth but in children 5–18 years of age. Three studies measuring D vitamin levels in the mothers at pregnancy have not found any association between low levels of D vitamin in pregnancy and that ADHD in the offspring.[52-54] These studies have assessed D vitamin levels in the mothers at pregnancy, but not the actual D vitamin levels of the child at birth. Even if it is probable that the vitamin D levels of the mother is close to the levels of the foetus, it is of interest to compare these results with a study of vitamin D levels in the child as a hypothetical risk factor for later development of ADHD. The levels of vitamin D at birth should be a good estimate of the child's vitamin D levels, at least in the later part of the gestation.

Another study fails to support the hypothesis that low levels of vitamin D during pregnancy are a risk factor for ADHD in the offspring. No other study of vitamin D levels in children, with a prospective or pseudo-prospective design, has previously been performed. In a study from Qatar, vitamin D in serum was determined in 1331 ADHD children age 5–18 years and in the same number of controls. The ADHD children had lower levels than the controls. In a study from Turkey, 60 ADHD children 7–18 years of age were compared with 30 children without a diagnosis. That study also showed that children with ADHD had lower levels of vitamin D in serum. These results are contradicted by Tolppanen et al.[55] who, in a large English study, found no association between low levels of vitamin D and behavioural problems, including inattention and hyperactivity. Mc Cann et al.[56] reviewed the animal research literature and concluded that there are indications of behavioural effects of vitamin D inadequacy, but that the evidence is weak. Human studies have indicated that vitamin D deficiency is associated with an increased risk of developing many diseases and disorders, like Parkinson's disease, epilepsy, depression, multiple sclerosis, schizophrenia, autism, and autoimmune diseases like rheumatoid arthritis and type I diabetes mellitus. From a theoretical point of view, in foetal life and during early childhood, the immature brain should be more vulnerable to environmental influences like vitamin D deficiency. The studies by Gale et al.[57] and by Whitehouse et al.[58] showed that the mother's vitamin D status during pregnancy had no association with behavioural problems in the offspring, including symptoms of ADHD, several years later. Strøm et al[59] made a follow-up study of children up to 22 years after birth and did not find an association between low D vitamin levels in the serum of the mothers at week 30 of the pregnancy and ADHD in the offspring. While Strøm et al have analysed the levels of D vitamin in the serum from the mothers at pregnancy, in other studies D vitamin levels have been analysed in the serum collected from the child at birth, which should reflect the prenatal vitamin D status of the child. Then the children who later received an ADHD diagnosis were compared with controls. This means that that study, like the studies by Strøm et al., Gale et al., and Whitehouse et al but unlike the recently published studies in Quatar and Turkey, has a prospective design

where vitamin D levels are measured at a time before the child receives a diagnosis. ADHD has a heritability of about 80%, but genetically mild forms of ADHD may be sensitive to environmental factors augmenting the symptoms. Vitamin D deficiency acquired at a later age could possibly enhance ADHD symptoms, so that an otherwise mild form of ADHD develops into overt symptoms. Other hypothetical explanations of the findings in the studies from Qatar and Turkey are that children with ADHD eat more junk food, take medication that decreases their appetite, spend more time indoors with computers and are often awake late at night. Such lifestyle factors could lead to lower levels of vitamin D.[60]

Sex hormones play many roles in the development and function of the human body and brain. Organizational effects of hormones are believed to play an important role in the structural organization of the brain and body with subsequent effects on sex-typed behavior.[61] Specifically, work in animals suggests that this sexual differentiation (ie., masculinization/de-feminization) of behavior is primarily due to the effects of prenatal testosterone exposure which is higher in males than in females.[62-63] High levels of prenatal testosterone appear to masculinize parts of the brain, particularly the dopaminergic system, with downstream effects on sex-typed behavior relevant to DBD such as rough-and-tumble play.[64-65]

More specifically, high levels of prenatal testosterone appear to lead to increased cell death within the brain, increased neural lateralization, slower development of the brain, and differential modulation of neurotransmission including dopamine.[66-67] In boys, the dopamine system may be especially sensitive to these hormonal effects because it is slower to develop prenatally. This slowed development may provide a longer period of time where hormone exposure can influence prenatal dopaminergic gene expression.[68-69]

Importantly, these early prenatal hormone, or organizational, effects are touted as stable, irreversible, and early-emerging.[70] Thus, organizational theory of prenatal testosterone effects on behavior suggests that prenatal testosterone might influence early-emerging DBDs that are more common in males by altering the dopaminergic neurotransmission system that underlies these disorders, leading to masculinization of traits (e.g., disinhibition) and behaviors (e.g., aggression) that are associated with DBD.[64-65,71]

Postnatal T activation from childhood to puberty potentially influences behavioral and physiological change, as well as neurodevelopment. Postnatal T levels are usually determined by analyzing the current (activational) T concentration in saliva or peripheral blood. Several studies have investigated the relationship between current T level and ADHD. For example, Herguner et al[72] reported that women with polycystic ovary syndrome (an endocrine disorder that manifests hyperandrogenism) had more ADHD symptoms than did control subjects. Furthermore, higher T levels in saliva or in plasma have been observed in children with aggressive tendencies compared with those without aggressive tendencies. In contrast, Dorn et al[73] suggested that no significant association is found between salivary T levels and children's disruptive behavior disorders (DBD). To date, evidence about the connection of current T levels to the pathogenesis of ADHD remains scarce and inconsistent.

Peripheral T levels are similar among boys and girls during early childhood, but T levels notably increase in prepubertal boys. During this period, the activation of preformed brain structures leads to sexually dimorphic, physical, behavioral, and cognitive alterations. Therefore, T may be involved in the pathogenesis of sex-biased neuropsychiatric disorders, such as ADHD. However, few studies have simultaneously investigated the potential roles of prenatal and postnatal T exposure on the clinical features of ADHD. In addition, how T influences the neurocognitive function in patients with ADHD and whether there is a sex difference in the relationship between T and ADHD presentations remains poorly understood.

Many 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 T exposure and ADHD features or externalizing behavior problems in children. In sum, whether prenatal T exposure plays a role in the etiology of ADHD is still open to debate.[74]

Although Attention-Deficit/Hyperactivity Disorder shows (ADHD) male predominance, females are significantly impaired and exhibit additional comorbid disorders during adolescence. However, no empirical work has examined the influence of cyclical fluctuating steroids on ADHD symptoms in women.[75]

Prenatal exposure to higher levels of fluoride not only impairs cognitive development but also significantly increases the incidence of attention-deficit/hyperactivity disorder (ADHD) in children, new research shows. In addition to water fluoridation, fluoride is also added to dental products, and a range of foods contain it in varying quantities. One consequence of excess fluoride consumption is dental fluorosis, discoloration or pitting of teeth.

The Centers of Disease Control and Prevention (CDC) notes that from 1999 to 2004, about 33% of 6- to 11-year-olds had experienced some form of dental fluorosis.

The CDC has suggested measures to protect children. It has recommended that families with children younger than 8 years consider using alternate sources of drinking

water or, if they live in an area where fluoride levels are higher than 2 ppm, filtering their water.[76]

A large Danish population-based study provides strong evidence of an association between childhood infection, antibiotic treatment, and subsequent neuropsychiatric disorders.

Investigators found that the risk of developing a mental disorder increased by more than 80% after hospitalization for severe infection. The use of anti-infectives, specifically antibiotics, to treat the infection was associated with about a 40% increased risk for a subsequent mental disorder.[77]

Some prior research has also linked infections with the development of mental disorders. Infection treated with an antibiotic was associated with a 41% increased risk for mental disorders and a 22% increased risk for use of psychotropic medication.

Schizophrenia spectrum disorders, obsessive-compulsive disorder, personality and behavior disorders, mental retardation, autism spectrum disorder, attention-deficit/hyperactivity disorder, oppositional defiant disorder, conduct disorder, and tic disorders were associated with the highest risks following a severe infection.

The risk for a mental disorder after a severe infection increased with the number of infections and with the temporal proximity of the last infection. The biggest increase in risk was observed 0 to 3 months after infection. Results of the primary analyses were supported by analyses that included different reference groups and siblings.[78]

Rates of attention deficit–hyperactivity disorder (ADHD) diagnosis in children have increased over the past 2 decades, but they vary geographically. State differences in arbitrary birthday cutoffs for kindergarten entry (i.e., being 5 years old by September 1) mean that some children will be up to a year younger than classmates, which may manifest as more social-emotional immaturity. According to conducted studies we often see in children (particularly boys) with summer birthdays entering kindergarten whose teachers may perceive them as having more behavioral or academic difficulties. Completing a year of "Young 5s" before kindergarten, where available, is helpful for these children. Yet, when seeing a young kindergartener with problems regulating behavior or attention, it is worth getting parent/teacher Vanderbilt scales, since an official ADHD diagnosis can help the child obtain school accommodations and behavioral therapy, which are recommended before stimulant treatment.[79]

Maternal stress during pregnancy increases the risk of the child having a range of altered neurodevelopmental outcomes. The stress can be of different types, and at least for some outcomes, there seems to be a linear dose response effect. Not all children are affected, and those that are, are affected in different ways. The gestational age of vulnerability probably differs for different outcomes. It is of interest to view all this in terms of our evolutionary history. In a stressful environment it may have been adaptive for our ancestors to have children who were more vigilant (anxious) or with readily distracted attention (ADHD), and possibly with more rapid motor development. But in our modern world several of these changes can be maladaptive, and cause problems for the child and their family.[80]

Most of the information about prognosis in children with ADHD is derived from small cohort studies of male patients who were evaluated and treated for ADHD in psychiatric clinics. The generalizability of the information to other patient groups is limited. Long-term follow-up (six to eight years) of the Multimodal Treatment study of children with ADHD (MTA) study cohort suggests that functioning during adolescence is predicted by the initial clinical presentation (including severity of symptoms and comorbid conduct problems), intellect, social advantage, and the strength of ADHD response to any mode of treatment. Follow-up into early adulthood (approximately 16 years after enrollment at a mean age of approximately 25 years) suggests that functioning in early adulthood is predicted by persistence of symptoms, baseline ADHD severity, intelligence quotient, and comorbidity. Early and effective management and support may be helpful in improving adult outcomes.[81]

Importantly, studies are beginning to examine what factors might help buffer the effects of stress during pregnancy. One important factor seems to be the mother's level of social support. Other protective factors may include: gaining some control of stressful situations, consistent prenatal care, regular light exercise, adequate rest, healthy eating habits, and avoiding alcohol, tobacco, and other drugs.[19]

The implications of this research are that if we want the best outcomes for our children we need to provide the best possible emotional care for pregnant women. There needs to be more public health education about this issue, and pregnant women encouraged both to look after themselves emotionally, and to seek help if needed. At present most anxiety and depression in pregnant women is undetected and untreated. We need to make sure that pregnant women are sensitively questioned when they first come into contact with health professionals about their emotional history and current state. It is important to note that it is not just diagnosable disorders that can affect fetal development, but a range of symptoms of stress, anxiety and depression, including a poor relationship with the partner. Appropriate personalized help should be instituted for each woman. This has the potential to prevent a range of neurodevelopmental

problems arising in a clinically-significant proportion of children.[80]

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