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Perinatal Factors of Developmental Attention Deficit Hyperactivity Disorder in Children

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Abstract

Background: Attention deficit hyperactivity disorder is a common pediatric neurobehavioral disorder often treated in the primary care setting. It shows a high and chronic level of inattention, impulsivity/hyperactivity and/or both, and can affect more than 2 million school-age children. The researchers are not sure about the exact causes of the disorder, but it seems that apart from genetic factors, perinatal factors seem to dynamically contribute to the development of the disorder. Purpose: The aim of this review was to investigate the perinatal and obstetric factors related to the development of the attention deficit hyperactivity disorder in childhood. Method: An online review of English language studies published from 2002 to 2020, using the Embase, PsychINFO, PubMed and Google Scholar databases. From 1100 studies only 17 were included in the review since they met the inclusion criteria. Conclusions: The results of the review showed that apart from heredity and genetic factors, various conditions in pregnancy or the mother's way of life in pregnancy, adverse conditions in labor and infancy can contribute on their own or in combination to the development of the attention deficit hyperactivity disorder in childhood. Obstetric vigilance to detect risk factors in pregnancy in combination with the prevention of obstetric complications is the key in preventing attention deficit hyperactivity disorder.

Keywords

Attention Deficit Hyperactivity Disorder, Perinatal Factors, Postnatal Factors

1. Definition, Symptoms and Diagnosis of Attention Deficit Hyperactivity Disorder

Attention deficit hyperactivity disorder (ADHD) is "one of the best-researched

disorders in medicine, and the overall data on its validity are far more compelling than for most mental disorders and even for many medical conditions" [1]. Despite the on-going research, there is a lack of knowledge about the causes of ADHD. ADHD is a chronic disorder, manifested in childhood and affecting about 5% of the children and adolescents globally, irrespective of their country of living [2] (**Figure 1**) and lasting until early adulthood in about 65% - 75% of the cases [3].

In terms of gender, boys are more often affected by the disorder compared to girls, 34:1, and although the family's socioeconomic class does not seem to be a burdening factor, it seems that children with ADHD mainly come from disharmonious families with parental psychiatric pathology or alcoholism [4]. ADHD symptoms are responsible for severe social dysfunction, such as low educational level because of school-leaving and family life problems, up to low self-esteem and decreased emotional growth [5]. People with ADHD also run a significant risk of simultaneous or future mental comorbidity, such as behavior disorder, stress and mood disorders, antisocial conduct and substance abuse [3].

ADHD is diagnosed using reliable clinical criteria. In 2013 the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5th edition (DSM-5) was revised to increase the reliability of diagnosis. The key characteristic of the disorder is a combination of inattention, hyperactivity and impulsivity and is essential for the diagnosis [6]. The ADHD definition has developed since 1900 from "hyperkinetic disease" to minimal brain dysfunction (DSM-I) in the 1970s. The disorder was renamed as "hyperactive reaction" of childhood (DSM-II); then as "deficit disorder with or without hyperactivity" (DSM-III), as "deficit disorder" and currently as ADHD (DSM-V). Maintaining the 18 key ADHD symptoms in DSM-V reflects the significance of the definition of (ADHD) DSHD-IV and has endured over time [7].

Many studies have shown that ADHD-related symptoms remain up to adulthood in half of the sample cases [8]. Hyperactivity/impulsivity symptoms in children may be reduced over time, but inattention symptoms seem to remain to a high degree in adulthood [3] [9] [10]. A key phenomenon also of ADHD is comorbidity. ADHD usually co-exists with specific and global developmental

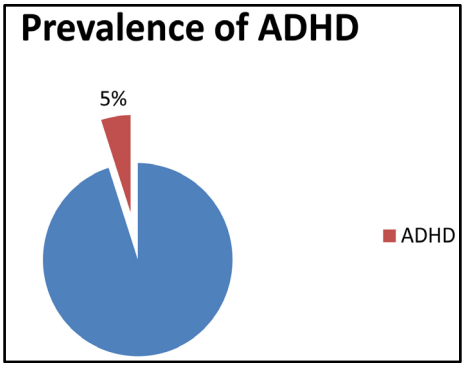

Figure 1. Global prevalence of ADHD in children and adolescents.

and learning problems, including autistic spectrum disorders (ASDs), speech and language difficulties, motor coordination and reading difficulties and a range of mental disorders, such as conduct and mood problems [11] [12] [13] [14] and IQ [15].

2. Causes of ADHD

ADHD, as other common medical and mental disorders, is affected by multiple genes, non-hereditary factors and their interaction [16]. The genetic factors can indirectly interact with environmental factors and modify the sensitivity to environmental risks (gene-environment interaction) [16]. Hereditary contribution also plays a big role in ADHD. Various studies have found steadily higher ADHD percentages (up to eight times) in parents and siblings of affected people compared to relatives of non-affected controls [17].

Various researchers have found that there is dopamine deficit in ADHD children and that its antagonist, methylphenidate, can therapeutically help. Brain stimulation and attention is controlled by two neurotransmitters, dopamine and noradrenalin, and it has been found that there is a correlation between the disorder and dopamine transfer (DAT 1) polymorphisms with dopamine receptors (DRD4, DRD5) and the serotonin transporter (5HTT) [18]. The interaction of dopamine and glutamic acid, released in the corpus striatum, has been blamed for the cognitive function of these people, while the serotonin/SNAP-25 protein disorder seems to result in the hyperactivity symptom in ADHD patients [19].

3. Gender Differences in ADHD

Boys and girls have both been shown to be affected by the attention deficit hyperactivity disorder (ADHD), although the literature supports a higher degree of prevalence in boys [20] [21]. Girls with ADHD are not usually hyperactive but tend to show an attention deficit as part of the disorder. The usual ADHD standard is expressed by a hyperactive boy. Girls with ADHD, though, who have not been diagnosed and treated, run the risk of low self-esteem and problems, such as depression and stress. They are more prone to become pregnant and start smoking before they become adults [22]. On the other hand, delinquent behaviors are more frequent in males who are more often imprisoned. The available data show, however, that treatments are more possible to be equally effective in boys and girls [20].

4. Perinatal Factors of ADHD

A total of 1.100 articles were identified, out of which 17 research studies were included in the study (**Figure 2**). The Embase, PsychINFO, PubMed and Google Scholar databases were used for this review. We conducted a review of different articles on perinatal causes of ADHD between the time period of 2002 to 2020 and the articles were all in English. Therefore, systematic reviews and meta-analyses were excluded from the study. The keywords used were: "ADHD and Perinatal

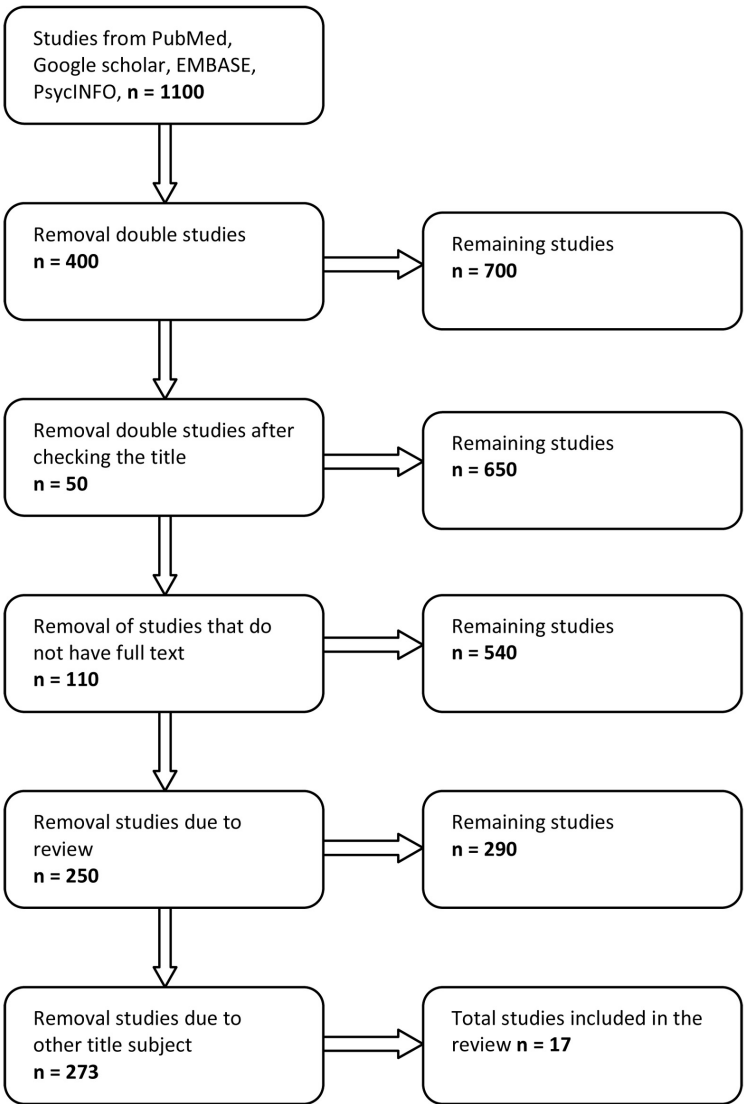

Figure 2. Flow chart.

factors", "ADHD and alcohol during pregnancy", "ADHD and Drugs during pregnancy", "ADHD and smoking during pregnancy", "ADHD and maternal stress during pregnancy", "ADHD and preterm birth", "ADHD and low Apgar score", "ADHD and cesarean section", "ADHD and low birth weight".

4.1. Maternal Smoking, Drug and Alcohol Use and Stress in Pregnancy

There is strong evidence supporting hereditary contribution to ADHD, although non-hereditary factors, including environmental causes (mother smoking, alcohol, drug abuse and stress in pregnancy, low weight at birth, low Apgar score, abnormal presentation, cesarean section), are implicated in its etiology. The results of this study show that apart from the gene phenotype and the hereditary psychopathological background [23], the contribution of environmental variables to ADHD must not be ignored (Table 1).

Table 1. Studies included in the review.

Author/Year	Design	N	Population	Country	Outcome (ADHD)
1) Roigé-Castellví, J. (2020) [23]	Cross-sectional study	6720	Children from General population	Spain	Association of prenatal and perinatal factors, such as metabolic disorder in the pregnancy, difficulties in childbirth and specific family phenotype (expression of the genetic risk) with childhood ADHD
2) Markussen Linnet, K. (2006) [25]	Follow-up study	1355	Singletons born from mothers who smoking during pregnancy	Denmark	60% increased risk of hyperactivity in children born from mothers who smoke
3) Gustavson, K. (2017) [29]	Cohort study	N > 100,000	Children born from mothers who smoking during pregnancy	Norway	Smoking during pregnancy is an unmeasured confounding
4) Parvaresh, N. (2016) [31]	Case-control study	200	Parents of 7 to 12 year-old children who referred to child and adolescent psychiatric clinics	Iran	A higher frequency of substance abuse, smoking, and anxiety disorders was observed among parents of children suffering from ADHD
5) Rodriguez, A. (2005) [33]	Cohort study	414	Children born from mothers who smoking and who had stress during pregnancy	Sweden	Prenatal exposure to stress was independently associated with later symptoms of ADHD. Results are less clear for smoking
6) Ronald, A. (2011) [34]	Cohort study	2900	Children born from mothers who had stress during pregnancy	UK	Stressful life events are associated with autistic traits as well as ADHD behaviors independently
7) Pagnin, D. (2019) [40]	Cohort study	449	Children born from mothers who used alcohol during pregnancy	Brazil	Binge drinking at any time during pregnancy or low-moderate alcohol consumption in all trimesters of pregnancy was associated with fivefold increased odds of child ADHD
8) Mick, E. (2002) [43]	Case-control study	522	Children born from mothers who used alcohol, drugs and smoking during pregnancy	USA	ADHD may be an additional deleterious outcome associated with prenatal exposure to alcohol independently of the association between prenatal exposure to nicotine and smoke products and other familial risk factors for the disorder
9) Sagiv, S. (2013) [44]	Cohort study	604	Children who exposed to perinatal risk factors	USA	Low paternal education, prenatal smoking, prenatal illicit drug use, maternal depression, were associated with greater risk for ADHD
10) Eilertsen, E. (2017) [46]	Cohort study	114,247	Children born from mothers who measured from using alcohol during pregnancy	Norway	Possibly causal association with maternal alcohol use during pregnancy, but no such effect was observed for clinical ADHD diagnosis
11) Soltanifar, A. (2009) [48]	Cohort study	50	Mothers of children who have ADHD	Iran	The Intensity of depression and trait anxiety in mothers of ADHD children are more than the control group

The research of Langley K. *et al.*, determines the double increase of ADHD risk for people whose mothers smoke in pregnancy, although the mechanisms for the operation of such risks are unknown [24]. Similar conclusions were drawn in the Markussen K. *et al.*, cohort that studied the relationship of intrauterine exposure to smoke and behaviour disorders in school-age children [25] [26]. A number of biological reasonable mechanisms from correlative findings in studies in people have been experimentally tested in animals. Animal studies based on multiple methods and use of multiple species demonstrate that the prenatal exposure to nicotine results in hyperactivity of their descendants [27] [28]. Other studies have not found a causal link between the mother smoking and ADHD; this is a confusing factor, as women under stress are extremely possible to smoke and, as a result of smoking, they give birth to a low-weight baby. Furthermore, a percentage of women may have been smoking at a different level in their pregnancy [29] [30] or may have at the same time abused substances [31]. Furthermore, young women of low social and educational level may be smokers, which may decrease the value of generalizing the findings [32].

In general lines, the results for smoking are less clear, but the results correlating perinatal stress with ADHD are more specific [33]. Many studies have shown that high stress levels in pregnancy are a risk factor both for autism and ADHD [34]. Stress is also a risk factor for the development of other mental childhood disorders, such as cognitive and language problems, even schizophrenia [35]. Family problems [36], stressful life events [37] and natural disasters [38] in pregnancy have been proven to be related to an increased risk of mental disorders in childhood.

On the other hand, alcohol is a known teratogenic substance, strengthening the migration of nerve cells, and is suspected to be involved in behavioral disorders in childhood. Furthermore, it intervenes in the production of neuroendocrine hormones, which can disturb brain development [39]. More specifically, the mothers of ADHD children are more possible to have consumed alcohol in their pregnancy trimesters [40] [41]. Prenatal exposure to heavy alcohol consumption by the mother can cause the fetal alcohol syndrome, including hyperactivity symptoms, and is a risk factor for the development of psychopathology in childhood [26] [42] [43]. The study of Biederman, M., *et al.* mentions that prenatal alcohol exposure can be a significant risk factor, if there is excessive consumption in pregnancy [43], while the study of Sagiv, K. *et al.*, did not show strong correlation between alcohol consumption in pregnancy and ADHD in childhood [44]. Of course, in some studies, the correlation between alcohol consumption in pregnancy and ADHD symptoms in childhood seems to get confused by family factors and heredity [45] [46]. Generally, however, the harmful consequences of the alcohol in a developing fetus are related to many cases of neurodevelopmental disorders and, consequently, alcohol consumption in pregnancy must be recognized as a global public health problem [40].

An equally important factor for ADHD seems to be drug abuse by the mother

in pregnancy. The study of Farokhzadi *et al.*, showed that the drug abuse frequency by parents of ADHD children compared to parents of normal children was 21.0% higher, with poorer levels of skills and significant psychopathology [47].

It is worth noting that stress, depression, and substance abuse (alcohol, smoking, drugs) affect the relationship of parents-ADHD children and harmfully impact their upbringing standards. For example, stressed parents are more concerned about accidents and, therefore, show higher degree of vigilance and less persistence in their children's education. In these cases, the repercussions in the upbringing of ADHD children are negative. Furthermore, depressed parents are more possible to be obsessive about the inabilities and mistakes made by children with ADHD. Stability and monitoring of behaviour are the principles of parental care and in cases of parental addiction, depression or other mental disorders, the parents are not able to comply with these principles and, thus, either generate or deteriorate behaviour problems [48].

4.2. Cesarean Section, Low Birth Weight, Preterm Birth and Apgar Score

Delivery complications have also been implicated for ADHD (**Table 2**). There are studies correlating the low Apgar score at birth with the development of ADHD in these children [49]. The Apgar score is widely used to assess the physical status of a baby immediately after birth and can be considered a perinatal complication indicator; it is based on a 5-point check (skin color, heart rate, reflexes, muscle tone and breathing effort) [50]. Apgar scores are usually checked at minute 1, minutes 5 and 10 and when ranging from 7 to 10 are considered normal [49]. Low Apgar scores at minutes 1 and 5, have been related to an increased risk for neurological and psychiatric disorders, such as autism spectrum disorder [51] and ADHD [52] [53]. Furthermore, the results of the study of Grizenko N., *et al.*, showed that low Apgar scores in minute 1 are related to an increased severity of ADHD symptoms [50].

Breech presentation and perinatal conditions that can cause neonatal hypoxia were found to be a risk factor for ADHD. According to Zhu, T., *et al.*, this was explained by the possible decreased movement of the fetus due to neurological anomalies or by the delivery procedure that may be extremely difficult resulting in neonatal hypoxia [54]. Neonatal hypoxia that may be due to normal childbirth complications but also due to complications in the first two months of the baby's life (hospitalization, oxygen administration) [55] seem to contribute more to ADHD in childhood. Therefore, the prevention of hypoxia in pregnancy and delivery are of major importance to prevent ADHD in childhood. The findings also show that particularly stressful conditions at the beginning of a person's life can be a cause of ADHD and these children must be followed up and be rechecked in childhood.

The delivery method and, specifically, scheduled CS is interesting for the development of ADHD in childhood and experts still try to explain this relationship

Table 2. Studies included in the review.

Author/Year	Design	N	Population	Country	Outcome (ADHD)
1) Grizenko, N. (2016) [49]	Cohort study	452	2 groups of children with and without ADHD	Canada	Low 1-minute Apgar scores are associated with a significant increase in ADHD symptom severity
2) Gustafsson, P. (2011) [52]	Retrospective study	237	Children with ADHD	Sweden	ADHD was significantly associated with preterm birth < 32 weeks and Apgar scores at 5 minutes below 7 were significantly associated with ADHD
3) Sucksdorff, M. (2018) [53]	Population-based study	10,409	Children who had diagnosed with ADHD and a control group	Finland	Cesarean sections and perinatal adversities leading to lower Apgar scores increased the risk of ADHD
4) Ben Amor (2005) [55]	Retrospective study	70	Children with ADHD	France	The children with ADHD had significantly higher rates of neonatal complications compared with their unaffected siblings
5) Hatch, B. (2014) [61]	Longitudinal study	197	Children. The sample was a part from a larger longitudinal study	USA	lower birth weight was associated with ADHD symptoms
6) van Mil (2015) [62]	Cohort study	6015	Children. Sample from a population based birth cohort	Holland	Higher birth weight was related to less attention problems
7) Perapoch, J. (2019) [66]	Cohort study	3744	Children who born premature	Spain	Prevalence of ADHD increases as gestational age decreases, 12.7% for those born ≤28 gw, compared to 3.2% for those born after the 37 gw

[56]. Many reasons seem to exist leading to a scheduled operation, such as the mother's desire, disproportion, pathology of pregnancy or the mother's mental disorders [53] [57]. Scheduled cesarean delivery affect early childhood as it changes the microbial colonization of the neonatal [58], and is related to many illnesses, including autism [59]. Scheduled cesarean section also decreases the possibility for successful breastfeeding [60]. The impact of anesthetic factors on the brain of the newborn baby is unknown to date to a big degree [53].

A correlation of low birth weight and ADHD has been found and some studies show that children with low birth weight run a higher risk of developing a series of neuropsychological deficits, many of which overlap with the ones found in ADHD children [61]. More specifically, low birth weight (≤2500 g) has been related to working memory, and cognitive flexibility tasks, which involve aspects of executive functioning as well as, visuo-spatial reasoning, and motor control [62]. Some studies, of course, correlated low birth weight with low IQ but not with ADHD [63] while according to van Mil, N. *et al.*, in 2015, the bigger the birth weight, the fewer the ADHD symptoms. However, in children from obese mothers (BMI > 30 kg/m^2), high birth weight can increase the risk of attention problems [64]. Furthermore, apart from low birth weight, prematurity has also

been implicated for ADHD in school age [65]. Indeed, a recent study of Perapoch, J., *et al.*, observed an increase in ADHD prevalence when the pregnancy age decreases and ranges from 3.2% for the neonates born after week 37 of gestation up to 12.7% for neonates born ≤28 weeks of gestation [66].

5. Discussion/Conclusions

According to the above results we come to the conclusion that the cesarean section seems to play a role in the manifestation of ADHD. Also, cesarean section is recommended when there are complications during delivery. Therefore, it is possible that the fetus may have already been affected by cerebral hypoxia or other causes and later in life and syndromes such as autism or ADHD may become clinically evident. Furthermore, maternal conditions such as smoking, drugs and alcohol use may affect fetal brain development intrauterine, as well as birth weight and week of delivery and often lead to cesarean section. During vaginal delivery, part of the mother's microbiome is transferred to the fetus and stimulates its immune system. This procedure is disrupted at the cesarean section with unknown consequences. Neonatal complications (included several events occurring during the first 2 months of life) may be a risk factor with a putative causal link to the development of ADHD. Although neonatal complications do not point to a single event that may lead to behavioral or cognitive problems, they support that children with ADHD have a higher rate of stressful events in early life. Therefore, except the specific family phenotype, the combination of these factors is interpreted by above results.

In conclusion, this study presents the correlation between prenatal factors, such as maternal stress, difficult family conditions, smoking, alcohol consumption and drug abuse, with ADHD. Furthermore, various factors that may occur during or after labor, relating to CS, fetal hypoxia, low Apgar score, low birth weight and prematurity, were correlated. Although the mother's habits in pregnancy could, on their own or in combination result in ADHD in childhood, the factors related to conditions during labor seem to have a strong correlation with ADHD. Therefore, although the early detection of the specific disorder by mental health experts plays a critical role in the progression of the disease, the timely detection of perinatal conditions and the prevention of complications during labor contribute to the prevention of the disorder. Furthermore, the decrease in the number of unnecessary cesarean sections and the provision of information for women about its complications, the frequent follow-up of children with low birth weight, prematurity and neonatal hypoxia shall contribute to the timely detection of the syndrome. Additionally, the thorough monitoring of women in pregnancy and the timely detection of risk factors that may contribute to the development of neuropsychiatric disorders in a child is of major importance for the special monitoring of the pregnant woman. ADHD concerns a person before birth, while prevention, diagnosis and treatment are related to a wide range of sciences.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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