REVIEW PAPER

Pre-, Peri-, and Postnatal Trauma in Subjects With Attention-Deficit Hyperactivity Disorder

Michael Zappitelli, MD[1], Teresa Pinto[2], Natalie Grizenko, MD, FRCPC[3]

Objective: To review research on pre-, peri-, and postnatal stress and their potential relation to attention-deficit hyperactivity disorder (ADHD).

Method: We selected and critically reviewed 51 research reports from the medical and psychology literature, between January 1, 1976 and May 1, 2001, based on the subjects of pre-, peri-, or postnatal stress and ADHD.

Results: Children with ADHD show higher percentages of pre-, peri-, or postnatal insult, compared with unaffected children; however, the relative influence of various factors is still controversial.

Conclusions: The etiology of ADHD encompasses genetic and environmental factors. Pre-, peri-, and postnatal stressors are environmental factors that may play a role in its etiology. Future research should carefully examine interactions between genetic predisposition and environmental factors as etiologies of ADHD.

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Key Words: *prenatal, perinatal, postnatal, attention-deficit hyperactivity disorder, hypoxia, labour complications, delivery complications*

Attention-deficit hyperactivity disorder (ADHD) manifests itself in early childhood and is characterized by inattention, impulsiveness, and hyperactivity (1). It affects approximately 6% to 9% of children from diverse social and cultural backgrounds, with a higher representation of males to females (2,3).

Although the etiology of ADHD is not well understood, it is well established that ADHD has an important genetic component, as indicated by family (4–6), twin (7–10), and adoption (11) studies. Having a family history of ADHD increases the risk of developing the disorder (12). As this review paper discusses, environmental stressors such as pregnancy and delivery complications have been found to increase the risk of ADHD. It is believed that pre- and perinatal trauma may have a direct effect on the fetal brain during a crucial period of development. McGrath and others found that neonatal morbidity strongly influenced neurological outcome (13). With advancing medical technologies, it is worthwhile to study the different long-term effects of neonatal morbidity; ADHD, increasingly discussed in terms of its origins in neurochemical alterations, can be examined as a neurological outcome of insult sustained early in life. With regard to ADHD, it is important first to examine existing relations between pre- and perinatal stress and its development and ADHD, then, to identify the specific complications that most highly correlate with ADHD development.

In the search for ADHD's etiology, a huge number of factors that may predispose to neonatal brain insults have been studied. The literature, however, is very contradictory on this topic. Barkley and others, for example, found no greater pregnancy and birth complications among children with ADHD than among an unaffected control group (12). Study methods vary greatly, and there is a general tendency not to consider the role of genetics or family history when examining different risk factors. This review paper provides a critical overview of the literature describing a link between pre-, peri-, and postnatal events and ADHD development; synthesizes the findings; and interprets them according to what is currently known. We obtained references for this review from a Medline and PsycINFO search comprising the period January 1, 1976 to May 1, 2001. We reviewed 51 reports chosen for

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[1]Resident, Department of Pediatrics, University of Alberta, Edmonton, Alberta.
[2]Medical Student, McGill University, Montreal, Quebec.
[3]Associate Professor, Department of Psychiatry, McGill University, Montreal, Quebec; Director, Lyall Preadolescent Day Treatment Program, Douglas Hospital, Verdun, Quebec.
Address for correspondence: Dr N Grizenko, Lyall Pavilion, Douglas Hospital, 6875 Lasalle Blvd, Verdun, QC H4H 1R3

their research focus on obstetrical and delivery complications and ADHD.

Prenatal Stressors

In Utero Toxins

Research on the effect of in utero toxins on the developing fetus has focused mainly on cigarette smoking and alcohol exposure.

The accepted neurochemical hypothesis behind the pathophysiology of ADHD is a dysfunction of the dopamine systems in the prefrontal cortex (14–17). Animal studies have shown that pups prenatally exposed to nicotine showed decreased striatal dopaminergic receptor binding sites (18). Carboxyhemoglobin levels are elevated in pregnant mothers who smoke and in their fetuses, possibly leading to decreased oxygen-binding capacity and decreased oxygen delivery to fetal tissues (19). Hence, 2 main mechanisms are proposed for the effects of maternal cigarette smoking on the fetus: maternal smoking leads to fetal hypoxia, and nicotine causes disturbances to the dopaminergic system in the brain.

In 1975, Denson and others found that mothers of hyperkinetic children smoked significantly more than did mothers of a control group (20). Later, in a study of 2256 children, Weitzman and others found that maternal smoking was independently associated with many childhood behaviour problems, including hyperactivity (21). All data were obtained from maternal reports, and maternal smoking during and after pregnancy was not distinguished. In response, Fergusson and others conducted a 15-year prospective study of 1265 children, examining the relation between maternal smoking and several childhood behaviours, including attention deficit disorder (ADD) (22). Their study was novel because they evaluated children and questioned mothers and teachers serially, from birth to a maximum age of 15 years. Several important confounding variables were included in the analyses (for example, sex, maternal age, socioeconomic status [SES], and parental discord). Smoking during, but not after, pregnancy was independently associated with higher teacher and maternal ADD ratings of children. These findings support a specific relation between pregnancy smoking and later development of attention deficit. Unfortunately, the effect of family history was not included.

In several studies, Milberger and others have specifically examined the effect of maternal smoking on the development of ADHD. In 1996, they compared 140 boys with ADHD with their first-degree biological relatives and with 120 control subjects (23). Twenty-two percent of the children with ADHD, compared with 8% of the control subjects, had a maternal history of smoking. Results remained significant when controlled for parental ADHD, children's IQ levels, and SES. These results were replicated in 1997 and 1998, supporting the hypothesis that nicotine or hypoxia from maternal cigarette smoking causes damage to the developing brain (24,25).

In a longitudinal study, Hill and others studied 150 adolescents who were either high or low risk for developing alcoholism, together with their families (26). Various psychiatric disorders were examined, and the 3 main risk factors tested were familial risk status for alcoholism, the child's exposure to prenatal alcohol, and the child's exposure to prenatal cigarettes. Analyses controlled for each of the risk factors, SES, and family history of antisocial personality disorder (APD), when calculating the risk of developing psychiatric disorders. The researchers found a relation only between ADHD and familial risk status for alcoholism; no relation was found with exposure to prenatal cigarettes or alcohol. Although findings pertaining to ADHD were fairly inconclusive, this study's strength was its detailed family history information. Unfortunately, the sample size was small, and pregnancy smoking history was retrospective, sometimes spanning several years.

The maternal use of alcohol while pregnant has been an area of interest, especially since children with fetal alcohol exposure (FAE) show signs of attention or memory deficits (27).

Streissguth and others examined the effects of prenatal alcohol exposure on 462 children, at birth and at age 14 years (28). Prenatal ethanol exposure was significantly related to attention and memory deficits in a dose-dependent fashion, even when controlled for maternal smoking. Aronson and others found that 10 of the 24 children whose mothers consumed alcohol while pregnant had ADHD, suggesting at most a link between fetal ethanol exposure and ADHD development (29). Unfortunately, the children were not all examined uniformly; some information was obtained from schools, while other information was obtained from clinical examination.

By contrast, Coles and others studied 149 African-American children of low SES (30). Of these, 87 had FAE, 27 had ADHD without FAE, and 35 were unaffected control subjects. Although both the alcohol-exposed and ADHD groups performed more poorly on tests of intellectual abilities, the sample with ADHD demonstrated more attention problems and conduct disorder (CD). This study suggests that alcohol may not play an important role in the development of ADHD per se but that attention problems associated with FAE may be related to cognitive deficits. The study by Hill and others mentioned above also does not support the role of maternal alcohol ingestion in ADHD development, although it does suggest that a family history of alcoholism increases the risk of having ADHD (26). This finding, however, is not strongly supported by Bennet and others' study, which specifically compared children from alcoholic families with children from nonalcoholic families (31). The controversy on this subject may exist because there is no clear pathophysiologic event directly relating maternal alcohol consumption to specific abnormalities found in ADHD.

Although these studies suggest a relation between maternal smoking and ADHD, it is difficult to draw any conclusions about the specific correlation between alcohol exposure and ADHD development. Certain study strengths and limitations must be examined. For example, samples were often drawn from pediatrician or psychiatrist referrals, making it difficult to generalize findings. Similiarly, several studies acquired information from retrospective maternal reports; prospective information gathering from more than 1 domain (such as parent, teacher, or medical records) is more reliable. It is also important to compare children whose mothers smoked during pregnancy with children whose mothers only smoked before or after pregnancy. Confounding variables must also be addressed. As pointed out by Barkley, the relation of maternal smoking and alcohol use to ADHD development cannot be studied without controlling for variables such as SES, family history, learning disabilities, and social or family environment (32). Moreover, maternal alcohol consumption and cigarette smoking in themselves are collinear and must be controlled for (26). For these reasons, large sample sizes, examined prospectively in a serial fashion, using standardized questionnaires from several domains, and diligently controlling for confounding variables, are of utmost importance.

Maternal Characteristics During Pregnancy

Studies have suggested numerous maternal factors during pregnancy that correlate with ADHD. Hartsough and Lambert studied 301 children with hyperactivity and 191 unaffected children (33). They found that young maternal age, poor maternal pregnancy health, eclampsia, and pregnancy parity were factors predicting subsequent ADHD diagnosis. Unique to their study, subjects were obtained through parents, schools, and physicians. All obstetrical information, however, was obtained from maternal interviews.

Chandola and others compared the birth records of 129 referred children with hyperactivity with the remaining 24 656 members of a geographical birth cohort (34). Factors associated with increased referral were mothers younger than 25 years at the time of their child's birth and mothers not in a first marriage. Use of birth records uniquely supported the results' reliability.

In the Milberger and others study, family problems, maternal bleeding, and complications of maternal accidents during pregnancy were positively associated with the development of ADHD (24).

These studies suggest that a myriad of maternal events during pregnancy may contribute to future childhood ADHD symptoms. More in-depth studies are needed, however, to classify the type of insult that would most harm the developing brain. Important study strengths would be prospective information gathering (for example, following women throughout their pregnancies), together with use of medical records and data gatherers and analysts with sufficient medical knowledge to record and interpret data accurately. In retrospective analyses, data collectors should be blind to the ADHD status of subjects.

Perinatal

Hypoxia

Studies have suggested dysfunction in dopamine transmission in the right prefrontal cortex and striatum in patients with ADHD (2). It is possible, then, that perinatal events resulting in hypoxia may adversely affect the developing brain acutely, leading to brain ischemia and abnormalities in the dopaminergic system.

Vaillancourt and Boksa found that rats born by cesarean section under general anesthesia showed increases in dopamine-mediated behaviours (35). Brake and others, demonstrated that rats born by cesarean section and exposed to intra uterine anoxia were hyperactive and had mesocortical dopamine activation impairments in the left prefrontal cortex (unpublished). These studies simply support the hypothesis of a defective dopaminergic system, resulting from neonatal hypoxic events, leading to symptoms of ADHD.

Hypoxic-ischemic brain damage and intraventricular hemorrhage, secondary to perinatal asphyxia, can result in neurologic and intellectual dysfunction and, possibly, psychiatric disorders (36,37). Numerous factors may lead to perinatal asphyxia: prenatal risk factors like eclampsia and diabetes mellitus; obstetrical abnormalities like prolapsed umbilical cord, placenta previa, or multiple pregnancies; intrapartum risk factors, including abnormal fetal position or prolonged labour; and neonatal factors, such as prematurity, respiratory distress, or cardiopulmonary abnormalities (36).

Examining the relation between perinatal hypoxia and ADHD, Hartsough and Lambert demonstrated that fetal distress during birth or delivery (nonspecific distress, head, or other birth injuries) was reported by 17% of mothers of children with hyperactivity, compared with 8% of control-group mothers (33).

Perinatal hypoxia may affect the brain, with resulting behavioural disorders; however, no conclusions can be made yet. Again, a longitudinal follow-up, beginning at birth, comparing high- and low-risk neonates with respect to hypoxic events, and taking into account confounding variables (for example, other pregnancy complications, maternal factors, SES, and family history) would be ideal.

Low Birth Weight

Low birth weight (LBW) has been examined in relation to cognitive and behavioural development (13,38,39). In the study by Milberger and others, LBW was associated only with lower IQ scores but not with ADHD (24). Hartsough and Lambert found no significant difference in their studied

groups in terms of prematurity or LBW (33). O'Callaghan and others examined the learning abilities and attention problems of 87 children who were born as extremely LBW (ELBW) infants (40). They found a significant difference between case and control subjects on all learning levels but not on teacher ADHD assessments. No other confounding variables were accounted for, however. These findings, which suggest no link between birth weight and later ADHD symptoms, have been contradicted by several studies.

Szatmari and others compared 82 five-year olds weighing between 500 and 1000 g at birth with an age-equivalent control group (41). Psychiatric diagnoses were based on information from mothers and teachers. Parent-questionnaire results showed that 7.3% of ELBW children displayed ADHD symptomatology, compared with 1.4% of control subjects. This association was specific to ADHD and not to other diagnoses. When teacher and parent ratings were combined, 15.9% of the ELBW children, compared with 6.9% of the control group, were rated as hyperactive.

Using 1 urban and 1 suburban sample, Breslau and others performed cognitive testing on 473 children, aged 6 years, who had been LBW babies (42). Birth weights and perinatal histories were obtained from medical records. Their results showed that the rate of ADHD was higher in LBW than in normal birth weight (NBW) children and that this association was stronger in the urban than in the suburban population, even when confounding variables (maternal smoking, alcohol use, SES, and maternal anxiety) were accounted for. They suggested that examining urban and suburban populations separately controlled for many confounding variables. Botting and others compared 136 LBW children, aged 12 years, with 148 full-term NBW children matched for age and sex (43). The results showed that LBW children were more likely to have ADHD, but not oppositional defiant disorder (ODD) or CD.

These results suggest a theory of an independent relation between LBW and ADHD. Findings are clearly contradictory, however, and study methodologies vary in controlling for confounding variables, sample sizes, and data gathering. Moreover, reporters were not always blind to subjects' birth weights. The fact that findings are so contradictory is not surprising because, although LBW has a clear relation to future intelligence level and learning abilities (13,39), it does not provide a clear etiology for some specific hypoxic brain-damaging event. LBW is also associated with many other different risk factors (13), making it a difficult causative factor to examine.

Postnatal Events

Hypoxia

Rat neonates exposed to anoxia within the first 24 hours of life demonstrated increased motor activity in ambulation, rearing, and sniffing at 10, 15, and 20 days of age, compared with controls (44). By day 25, the only difference remaining was increased sniffing in the anoxia-exposed rats. Though a correlation between postnatal anoxia and hyperactivity may be drawn from this experiment, it is somewhat difficult to make a direct correlation with humans, because rodents are less sensitive to anoxia (45).

In a retrospective analysis, Chandola and others found a relation between referral for ADHD and infants who received Cardiff Bag Resuscitation and had a 1-minute Apgar score of below 7 or a 5-minute Apgar score of below 9 (34). These factors, though, were strongly correlated with each other and not significant when controlled for confounding variables. This finding suggests either an interaction between these postnatal factors or a cumulative effect from all factors.

In a study of 11 children (aged 6 to 15 years) with ADD, Lou and others showed through use of xenon 133 inhalation and CT, that cerebral hypoperfusion of the frontal lobes was present in all (46). This, they believe, is linked to early hypoxic-ischemic damage. The sample chosen, however, lacked uniformity and demonstrated such confounding variables as differences in gestational conditions, birth weights, and use of medication.

Further studies on the effect of hypoxemia and hypotension on the developing brain were done by Low and others, who prospectively studied 130 preterm neonates (47). The infants were evaluated for echosonographically demonstrable cerebral lesions (EDCL) during the neonatal period, at either 3 or 6 months. Among the preterm neonates who experienced hypotension or hypoxemia in the early hours of life, 34% showed EDCL (namely, intraventricular hemorrhage, 21%; ventriculomegaly, 18%; and hyperechoic parenchymal lesions, 8%), compared with preterm neonates who had not experienced hypotension or hypoxemia, where the rate of EDCL was 13%. When hypotension and hypoxemia were both present, the chance of having EDCL surpassed 50%. In 1997, Whitaker and others examined the relation between neonatal cranial ultrasound abnormalities (reflecting perinatal brain injury) and psychiatric disorders in 685 LBW children aged 6 years (37). Compared with normal cranial ultrasounds, cranial ultrasound abnormalities near birth independently increased the risk of having a future diagnosis of ADHD even when neonatal complications, prenatal factors, and social disadvantage were accounted for.

These studies are based on the hypothesis that brain injury may lead to ADHD. All previously mentioned risk factors in this article refer to events and physical or mental states affecting the pregnant mother, fetus, or newborn that might place a child at increased risk of developing a brain abnormality that could lead to ADHD. Imaging, however, potentially provides a way to quantify the damage done and, theoretically, predict

the contribution of the physical aspect of ADHD etiology in a given individual.

Conclusion

Research generally supports the hypothesis that pre-, peri-, and postnatal stressors may play an important role in the development of ADHD. A wide spectrum of prenatal events associated with eventual symptoms of ADHD has emerged. These range from chronic insults throughout pregnancy, such as maternal smoking, high blood pressure, age, and the mother's emotional state to more acute events like maternal bleeding, eclampsia, or abruption. It is unclear which events —those leading to chronic fetal hypoxia during gestation or the acute events—have the major role in abnormal development of neural dopaminergic systems; this is a research area worth exploring. The literature shows that the role of maternal ethanol ingestion is still unclear; it is a difficult risk factor to study due to the presence of several confounding variables (for example, SES, maternal smoking, presence of maternal psychiatric illness, or symptoms of FAE). Among perinatal events, acute hypoxic damage resulting from long labour, cesarean deliveries with hypoxia, and hypoxic-ischemic damage to the brain may also contribute to a future presentation with ADHD. All these factors need more detailed study to achieve more definite conclusions. The role of LBW, which may simply be an indicator of prematurity or intrauterine problems, also remains unclear.

Finally, it has recently been discovered that early brain imaging abnormalities may indicate increased risk for ADHD development. This finding is particularly interesting because presumably these abnormalities result from all previously mentioned risk factors. This leads to the question whether further research should focus on this method of assessing risk, rather than looking at specific events that lead to the same end.

The purpose of all this research is to contribute to our understanding of what causes ADHD. There is still much uncertainty, which partly explains many of the limitations existing in the studies reviewed—limitations that must be examined to propose future directions. As mentioned, a major limitation of many studies is the lack of accounting for confounding variables: with a disorder so obviously multifactorial, one must account for variables that might affect the causative role of specific factors. Variables that should always be included are SES, family history, and the presence of learning disorders. Moreover, studies should control for other possible causative factors when assessing a specific one. For example, if one is to assess the role of LBW in ADHD development, it is imperative to control for maternal smoking and other intrauterine risk factors because they may be collinear with the factor studied (LBW), which could unpredictably alter results. The strongest studies are those with large, representative sample sizes (identified from school, physician or psychologist, and parent referrals) and with sound diagnostic methods. Child behaviour information should include parent and teacher reports, and any medical data should ideally include data from patient charts. Prospective studies are ideal, eliminating recall bias and allowing for serial assessment of child biopsychosocial status. More specifically, studies that examine maternal smoking should compare the effects of smoking during pregnancy and smoking only after pregnancy to truly test the theory that nicotine causes intrauterine hypoxia or damage to the brain's dopaminergic system.

An avenue that has not been explored very much is the role of pre- and perinatal risk factors in affecting the variable expression of ADHD. Children with ADHD may be inattentive, hyperactive and impulsive, or both, and many have comorbid disorders such as ODD and CD (48–50). Despite this variable phenotypic expression, most children benefit from methylphenidate therapy. Approximately one-third of children do not, however (51). Hence, the theory exists that ADHD may not be a single syndrome but, rather, several different subtypes that may dictate treatment response. Moreover, it is not known whether these different expressions of ADHD are actual subtypes or simply differences in severity. Pre- or perinatal complications may be involved in modulating the phenotypic expression of ADHD. It is also not known whether methylphenidate responders and nonresponders differ in their pre- and perinatal histories.

ADHD consists of a spectrum, so that although a child may not fulfill criteria for diagnosis, certain symptoms may be present, and children diagnosed with ADHD can have different levels of symptom severity. It is possible that the severity of ADHD presentation may be linked to interactions between genetic susceptibility and environmental stressors. Are these factors additive in producing phenotypic expression of ADHD, or are they independent, producing different types of the disorder? These are other questions that well-designed studies on pre- and perinatal risk factors may help to elucidate.

Future research should explore the importance of genetic and environmental factors, such as perinatal events, in different subgroups of ADHD (for example, inattentive vs hyperactive). The involvement of these possible etiologic factors should also be studied both in children with "pure," non comorbid ADHD and in those with comorbid ADHD. In addition, it is important to research the relevance of genetic and environmental factors in the expression of ADHD severity by exploring whether these factors correlate with increasing symptomatology. An ideal way of doing this would be to compare children with ADHD with their siblings, who presumably have similar genetic backgrounds and home environments but may have different perinatal histories.

Clarifying the genetic and environmental interactions in ADHD will lead to a better understanding of the disorder's

biological aspect and may lead to improved therapeutic approaches. Understanding what early events play a role in ADHD development may eventually help clinicians to design preventative measures for at-risk families.

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Clinical Implications

- Research suggests that certain common pre-, peri-, and postnatal stresses may have a significant role in the etiology of attention-deficit hyperactivity disorder (ADHD).
- Identifying specific early-life events that predispose children to ADHD may lead to its earlier detection or prevent certain behaviours in at-risk families.
- The role of maternal alcohol ingestion during pregnancy in the etiology of ADHD is still unclear; however, many effects of fetal alcohol exposure include attention and behaviour problems.

Limitations

- This review only examines pregnancy and delivery complications with relation to ADHD and not to other childhood behaviour disorders.
- Reviewed studies are of mixed quality without standardized formats, and many lack objective data collection for pregnancy, delivery, and neonatal complications.
- There is no original research material presented here, and more research is needed to validate many findings.

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Résumé — Traumatisme prénatal, périnatal et postnatal chez les sujets souffrant du trouble d'hyperactivité avec déficit de l'attention

Objectif : *Passer en revue la recherche sur le stress prénatal, périnatal et postnatal et sur sa relation possible avec le trouble d'hyperactivité avec déficit de l'attention (THADA).*

Méthode : *Nous avons choisi 51 rapports de recherche dans la documentation médicale et psychologique, entre le 1er janvier 1976 et le 1er mai 2001, portant sur le stress prénatal, périnatal ou postnatal et le THADA, puis nous en avons fait l'analyse critique.*

Résultats : *Les enfants souffrant du THADA affichent des pourcentages plus élevés de traumatismes prénataux, périnataux ou postnataux que les enfants qui n'en souffrent pas. Cependant, l'influence relative de divers facteurs est encore controversée.*

Conclusions : *L'étiologie du THADA englobe des facteurs génétiques et environnementaux. Les facteurs de stress prénataux, périnataux et postnataux sont des facteurs environnementaux qui peuvent jouer un rôle dans l'étiologie du trouble d'hyperactivité. Les futures études doivent examiner attentivement les interactions entre la prédisposition génétique et les facteurs environnementaux comme étiologies du THADA.*