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Epigenetics: The Effects of Prenatal Drug Usage On The Development of Attention-Deficit/Hyperactivity Disorder in Offspring

ABSTRACT

Background Information

Attention-deficit/hyperactivity disorder, or ADHD, is a neurodevelopmental disorder known for hyperactivity, inattention, and impulsiveness. In recent years, there has been an increase in the diagnosis of ADHD in children.

Objectives

This paper aims to identify how different pharmaceutical and illicit drugs taken during pregnancy impact the risk of developing ADHD in offspring.

Methodology

PubMed was searched with the following keywords: ADHD, tobacco, methylphenidate, acetaminophen, medication, and illicit drugs.

Results

The studies used in this paper assessed various pharmaceutical and illicit drugs, including acetaminophen, cannabis, tobacco, amphetamine/dextroamphetamine, and methylphenidate. Acetaminophen, methylphenidate, and tobacco usage result in a heightened risk for ADHD. Cannabis use resulted in a slight increase in the risk of ADHD while amphetamine/dextroamphetamine did not affect susceptibility to the neurodevelopmental disorder.

Conclusion

These studies revealed that some, but not all, illicit and pharmaceutical products resulted in a heightened risk for ADHD.

INTRODUCTION

In the past decade, there has been a significant increase in the diagnosis of neurodevelopmental disorders. Neurodevelopmental disorders are disorders that take shape during childhood [1]. The umbrella term encompasses attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder, down syndrome, and various other conditions [1]. Recently, researchers have started to explore the DNA methylation mechanisms related to ADHD. While a number of genes have been identified in relation to ADHD development, it is important to understand why these methylation patterns exist. One of the factors contributing to the rise in ADHD diagnosis could be the increase in the use of medication/drug use during pregnancy in the past decade. To analyze this connection, this paper will explore the epigenetic effects associated with the use of different drugs in pregnancy, and the association between these epigenetic changes and the development of ADHD in offspring. Through analysis of both pharmaceutical and illicit drugs, a connection can be formed between prenatal drug use and ADHD risk. The drugs evaluated in this paper include acetaminophen, cannabis, tobacco, amphetamine/dextroamphetamine, and methylphenidate.

To allow for a greater scope of comparison, different types of drugs, including pharmaceutical and recreational, were chosen in this review. Acetaminophen was selected for its common use as a pain reliever, tobacco and cannabis for their use as illicit drugs, and methylphenidate and amphetamine/dextroamphetamine for their roles as prescription medications. Acetaminophen is a pain relieving and fever reducing medication commonly used during pregnancy [2]. Cannabis, for recreational use, is composed of high levels of THC and is known for resulting in cardiovascular, gastrointestinal, and mental complications [3]. Tobacco is an illicit drug that is considered the number one cause of preventable disease in the United States [4]. As for prescription medication, amphetamine/dextroamphetamine is a type of central nervous system stimulant that is used to treat ADHD and narcolepsy by increasing the release of dopamine and norepinephrine in the body [5]. Another drug used to treat ADHD and narcolepsy, methylphenidate is also a central nervous system stimulant. While amphetamine/dextroamphetamine increases dopamine and norepinephrine, methylphenidate acts as an inhibitor, preventing the reuptake of these neurotransmitters [6]. By comparing the effects of these drugs on the development of ADHD in childhood, newer guidelines may be designed to advise patients during pregnancy.

METHODS

This paper is a narrative review conducted using PubMed. Keywords searched on PubMed included ADHD, tobacco, methylphenidate, acetaminophen, medication, and illicit drugs, with boolean operators used as needed. Papers from various clinical trials and cohort studies were included. Review papers, case studies, and articles not in English were excluded.

RESULTS

Table 1. Summary and key takeaway of each study included in this review. The studies all looked at the effects of different drugs and substances on ADHD.

Study	**Subject**	**Findings**	**Relevance**
Gervin et al. [7]	Effects of prolonged use of acetaminophen in pregnancy on DNA methylation differences associated with ADHD	If an individual is susceptible to ADHD, then long term exposure to acetaminophen may account for differences in DNA methylation	Links ADHD diagnosis to long term exposure to acetaminophen during pregnancy
Andrade [8]	Effects of maternal cannabis use on the development of ADHD in offspring	Maternal cannabis use has minimal effect on the risk of offspring developing ADHD	Not all illicit drugs result in a substantial risk for ADHD development in offspring
Rovira et al. [9]	Epigenetic alterations as a result of maternal smoking and their link to ADHD in offspring	In adulthood, smoking status doesn't substantially change DNA methylation variation for ADHD	Performs epigenome-wide association studies for a clinical sample of adults with ADHD, offering a comparison between methylation patterns of patients and controls
Liew et al. [10]	DNA methylation differences as a result of exposure to acetaminophen over varying time periods	Utero exposure to acetaminophen increases the likelihood of ADHD diagnosis in early childhood	Uses an NCE analysis to evaluate data from 8,856 children with ADHD born in the period between 1993 and 2005, displaying acetaminophen's role in ADHD development
Miyake et al. [11]	Effects of prenatal smoking exposure on offspring over different time periods	Maternal smoking is associated with the diagnosis of ADHD in children, with	Provides an example of how smoking can change epigenetics and result in ADHD

		DNA methylation of GFI1 causing this effect	symptoms of offspring
Suarez et al. [12]	Effects of prenatal amphetamine/dextroamphetamine or methylphenidate use on ADHD development in offspring	Amphetamine/dextroamphetamine did not increase the risk of neurodevelopmental disorders. However, methylphenidate increased the risk of ADHD development.	Different types of stimulants have different effects on child development

The studies in this review suggest a link between the use of pharmaceutical or street drugs in pregnancy and the development of ADHD in children.

Gervin et al. demonstrates the effects of prolonged use of acetaminophen in pregnancy on DNA methylation and its association with the development of ADHD [7]. The study was conducted through an epigenome-wide association study with samples selected from the Norwegian Mother and Child Cohort. Through an analysis of changes in DNA methylation using umbilical cord blood, the study found that if an individual is susceptible to ADHD, then long term exposure to acetaminophen will account for differences in DNA methylation. Similarly, Liew et al. evaluates the relationship between ADHD development in offspring and maternal use of acetaminophen during pregnancy[10]. Pulling data from 8,856 children with ADHD born in the period between 1993 and 2005 to women enrolled in the Nurses' Health Study II cohort, an NCE analysis was performed to evaluate ADHD development after different time periods of exposure to the drug. The study concluded that utero exposure to acetaminophen increases the likelihood of ADHD diagnosis in early childhood.

Suarez et al. studied a possible correlation between prenatal prescription medication use and neurodevelopmental disorders in children [12]. By using a study consisting of Medicaid data from 2000 to 2018 and MarketScan from 2003 to 2020, offspring development was monitored. Amphetamine/dextroamphetamine or methylphenidate use in the second half of pregnancy was studied [12]. Suarez et al. concluded that amphetamine/dextroamphetamine did not increase the risk of neurodevelopmental disorders while methylphenidate increased the risk of ADHD development [12]. This paper demonstrates that not all types of prescription drugs result in a higher risk of ADHD.

Regarding illicit and recreational drugs, Rovira et al. evaluates methylation profiles of ADHD, focusing on the co-occurrence between epigenetic signatures and their relation to stress and other environmental triggers [9]. Through epigenome-wide association studies (EWASs) on a clinical

sample of adults with ADHD, the paper uses quantitative methodology to find that smoking status in adulthood doesn't change DNA methylation patterns related to ADHD. On the other hand, Miyake et al. analyzes the effects of prenatal smoking exposure on offspring development over several time periods, assessing whether DNA methylation differences in children are a result of the mother's prenatal smoking habits [11]. This study selected mother-infant pairs from the Hokkaido Study on Environment and Children's Health to allow for quantitative analysis. Miyake et al. found that maternal smoking is associated with the diagnosis of ADHD in children, with DNA methylation of GFI1 causing this effect [11].

Andrade analyzed the effects of maternal cannabis use on the development of ADHD in offspring [8]. The paper used 13 observational studies to assess the impact of cannabis use before pregnancy and during pregnancy to observe the risk of ADHD development. It was observed that the risk for ADHD during a child's developmental years barely increased as a result of the parent's prenatal cannabis use [8]. Andrade demonstrates that not all illicit drugs result in a substantial risk for ADHD development in offspring.

These studies relay the association between DNA methylation differences and the use of various drugs. Not only are different genes suppressed and altered, but a link between some pharmaceutical and illicit drugs and the development of ADHD can be established.

DISCUSSION

This review aimed to identify the different pharmaceutical and illicit drugs that are associated with an increase in the risk of developing ADHD. By analyzing a collection of different observational studies evaluating the effect of maternal usage of various types of drugs on the neurodevelopment of offspring, common themes were identified. The drugs analyzed included acetaminophen, cannabis, tobacco, amphetamine/dextroamphetamine, and methylphenidate. Gervin et al., Liew et al., and Suarez et al. looked at the effects of prescription drugs on ADHD development in early childhood [7,10,12]. Andrade, Rovira et al., and Miyake et al. analyzed the impact of prenatal illicit drug usage [8,9,11].

Prescription Drugs

Gervin et al. associated the prolonged usage of acetaminophen with DNA methylation differences that result in ADHD [7]. Specifically, prenatal exposure for more than 20 days resulted in a higher chance of ADHD diagnosis compared to offspring whose mothers did not use acetaminophen during pregnancy. While this prolonged exposure did not cause the development of ADHD, it heightened the risk of it for individuals who were already susceptible to the neurodevelopmental disorder. Liew et al. corroborates, finding that acetaminophen usage only during the time of pregnancy is associated with childhood ADHD [10]. Together, these studies support the theory that prenatal acetaminophen exposure can be linked to ADHD diagnosis. A study conducted by Suarez et al. looks at the effects of amphetamine/dextroamphetamine and methylphenidate during pregnancy to establish a connection between methylphenidate and ADHD but debunks the theory that amphetamine/dextroamphetamine use leads to an increase in the risk of ADHD [12]. Amphetamine/dextroamphetamine are both central nervous system stimulants that are used to treat ADHD and narcolepsy [5]. Similarly, methylphenidate is a prescription drug used to treat the same disorders [6]. Some, but not all, prescription drugs are associated with a heightened risk of ADHD. The composition and mechanism of these drugs may play a role in these varying results. For instance, acetaminophen disrupts the endocrine system, can lead to oxidative stress, and has been associated with brain connectivity changes [13]. On the other hand, amphetamine/dextroamphetamine impacts neurotransmitters and the placenta [14]. These differences in the systems affected could account for how different drugs influence ADHD development.

Illicit Drugs

In an analysis of illicit drugs like cannabis, Andrade found that prenatal cannabis use had little to no effect on the risk of ADHD development during childhood [8]. Of the 10 observational studies focused on ADHD, an average risk ratio of 1.13 was observed. While there was an increase in the risk of development of ADHD between the age of 1.5 years and 12 years, the risk was lower than anticipated. However, it is also important to note that there may have been some publication bias, accounting for this disparity. Instead of cannabis use, Rovira et al. explored the

impact of maternal smoking on neurodevelopmental disorders [9]. For individuals who had ADHD in adulthood, maternal smoking was reported as the number one prenatal stressful life event associated with increased risk of ADHD. A possible mechanism for the association between maternal smoking and childhood ADHD is suggested by Miyake et al., who revealed that DNA methylation of GFI1 was directly correlated to prenatal smoking exposure [11]. GFI1 is a transcriptional repressor that is crucial to the development of different tissues and cell types [11]. As relayed by Miyake et al., DNA methylation of this transcription factor may result in neurodevelopmental disorders such as ADHD due to abnormal development of neural cells [11].

Conclusion

These findings suggest that prenatal acetaminophen, methylphenidate, and tobacco usage result in a heightened risk for ADHD. Cannabis is also associated with a small increase in the risk of this neurodevelopmental disorder. Although amphetamine/dextroamphetamine has been hypothesized to affect ADHD risk, this review finds that amphetamine/dextroamphetamine has no association with ADHD in childhood. These findings show that while not all medications and drugs are correlated with ADHD development, some are. Identifying drugs with increased risk for ADHD is particularly important when prescribing medication for pain and pre-existing health conditions during pregnancy. Similarly, patients should be counseled on the various risks of illicit drug use during pregnancy, including the risk of ADHD. While this paper explored some illicit and prescription drugs, many have yet to be explored in regard to their effect on the risk of ADHD development. Additionally, future research needs to be targeted towards identifying similarities in the chemical composition between drugs associated with a higher risk of ADHD.

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