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AUTISM AND DEVELOPMENTAL ISSUES IN CHILDREN WITH PERINATAL EXPOSURE OF CANNABINOIDS

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ABSTRACT

Aim

The purpose of the present research was to study the effects of perinatal exposure of cannabinoids on children suffering from autism and developmental disorders.

Methodology

A retrospective analysis was done of 689,071births, between 1 April 2007 and 31 March 2012 where pregnancy and birth data was linked to provincial health administrative databases so as to ascertain child neurodevelopmental outcomes. We used matching techniques to control for confounding and Cox proportional hazards regression models to examine associations between prenatal cannabis use and child neurodevelopment.

Results

An association was found between maternal cannabis use in pregnancy and the incidence of autism spectrum disorder in the offspring. The incidence of autism spectrum disorder diagnosis was 4.00 per 1,000 person-years among children with exposure compared to 2.42 among unexposed children, and the fully adjusted hazard ratio was 1.51 (95% confidence interval: 1.17–1.96) in the matched cohort.

Conclusion

The incidence of intellectual disability and learning disorders was higher among offspring of mothers who use cannabis in pregnancy, although less statistically robust.

Keywords: Autism, cannabinoids, developmental disorders.

INTRODUCTION

The use of marijuana by healthy adults is commonly viewed as having limited adverse health effects; however, its potential risks for foetal developmental abnormalities when used during pregnancy have not been thoroughly evaluated. Further, the use of marijuana among pregnant women is rising and is predicted to continue to increase.[1]This may be in part to elevate symptoms of pregnancy such as nausea. It is, therefore, important that the effects of prenatal marijuana on the developing foetus be fully assessed in order to create a proper set of guidelines for use before, during and after pregnancy as is standard with other drugs such as alcohol and nicotine. The endocannabinoid system is heavily involved in both neural development, especially cell migration, neuronal growth and synaptic plasticity, as well as lifelong processes such as motivation, motor control, emotional responses, cognition, and homeostasis.[2-5] This system is altered in many neuropsychiatric conditions, including autism, schizophrenia and epilepsy, but it may also be altered upon foetal exposure to drugs and alcohol.[5-7] Autism Spectrum Disorder is known for its severe cognitive, social and behavioural impairments.[8] Since the endocannabinoid system is involved in cognition, behavioural, emotional and social regulations, it seems possible that alterations in the endocannabinoid system, particularly during critical developmental stages, could cause or put one at risk for an autism spectrum disorder. Marijuana is known to bind to endogenous cannabinoid receptors and induce the same effects in the body as endogenous cannabinoids.[9]It is, therefore, possible that the over-excitation of the endocannabinoid system during development causes changes in the endocannabinoid system which makes one at risk for development of autism spectrum disorder. Leveraging the scenario of a natural experiment whereby some individuals are exposed to potentially developmentally disruptive agents, epidemiological studies have been instrumental in uncovering associations between maternal use of antidepressants and anticonvulsants and adverse outcomes in offspring.[10] These findings have supported the notions that early interference with serotonergic, γ-aminobutyric acid GABAergic, or glutaminergic systems could underlie some neurodevelopmental disorders.[11] However, pregnant women are exposed to a much wider range of drugs than those considered to date, including medications with potentially protective effects on the

foetus. Furthermore, although those earlier studies tried to mitigate against the confounding effects of maternal indication, their designs inherently involved a tight link between offspring exposure and maternal disorder (eg, maternal diagnosis of bipolar disorder and/or epilepsy in studies on the prenatal effects of valproic acid).[12] Cannabis use is also linked to other negative pregnancy outcomes that could be contributing to ASD risk. For example, cannabis use is associated with a higher risk of foetal low birth weight, which in turn has been identified as a risk factor for ASD.[13] However, low birth weight as an intermediate step in the association between prenatal cannabis exposure and the risk of ASD was not assessed. In perinatal research, adjusting for intermediate variables is essential in determining if these variables are underlying drivers of the associations of interest.[14]

AIM OF THE PRESENT STUDY

The purpose of the present research was to study the effects of perinatal exposure of cannabinoids on children suffering from autism and developmental disorders.

METHODOLOGY

A total of 689,071births who born between 1April 2007 and 31March 2012. Following exclusions, the final cohort was based on 508,025births. Children who died before 18months (n=4,960) or 4years (n=10,204) of age were excluded from the primary analyses of autism spectrum disorder (ASD) and secondary analyses of neurodevelopmental outcomes, yielding analytical cohorts of 503,065 and 497,821, respectively. The mean age of mothers was 30.1years (s.d.=5.6), the mean gestational age at delivery was 38.9weeks (s.d.=1.7) and 51.4% of children were male. The rate of reported cannabis use in pregnancy was 0.6%. An analysis comparing excluded records to the analytical cohort indicated some modest differences by maternal age, area-level income, parity, maternal health conditions, rural residence and drug and medication use in pregnancy. The first prenatal consultation, where cannabis use information is collected, occurred at a median of the 79th gestational day (11weeks and 2d) overall, and the 94th day (13weeks and 3d) among women with reported cannabis use.

RESULTS

Significant imbalance in covariates was identified between cannabis users and nonusers. The L1 statistic, a global measure of imbalance, was 0.77 in the unmatched cohort, but this was reduced to 0.02 following coarsened exact matching (CEM). Imbalance in the distribution of baseline covariates was reduced in the matched cohort (standardized mean difference (SMD).In the 18-month cohort, 7,125 (1.4%) children were diagnosed with ASD by the end of follow-up (median length of follow-up, 7.4 years). The rate of ASD diagnosis was 2.2% among children with in utero cannabis exposure. The incidence of ASD diagnosis was 4.00 per 1,000person-years (95% confidence interval (CI): 3.65–4.38) among children exposed to cannabis compared to 2.42 (95% CI: 2.39–2.44) among unexposed children, and the crude hazard ratio (HR) was 1.63 (95% CI: 1.29–2.06). (Table 1)

Table 1- Hazard ratios and 95% CIs for the association between prenatal cannabis exposure and study outcomes

Outcome	Crude HR (95% CI)	Adjusted HR (95% CI)	Additionally adjusted HR (95% CI)
Primary outcome ASD	1.63 (1.29–2.06)	1.53 (1.18–1.98)	1.51 (1.17–1.96)
Secondary outcomes Intellectual disability and learning disorders	2.04 (1.68–2.49)	1.23 (0.97–1.55)	1.22 (0.97–1.54)
ADHD	2.60 (2.35–2.86)	1.11 (0.99–1.25)	1.11 (0.98–1.25)

Table 2- Hazard ratios and 95% CIs for the association between prenatal cannabis exposure and outcomes in subgroups

Subgroup/outcome	Crude HR (95% CI)	Adjusted HR (95% CI)	Additionally adjusted HR (95% CI)
Prenatal cannabis only			
ASD	1.83 (1.41–2.39)	1.57 (1.19–2.07)	1.54 (1.17–2.03)
Intellectual disability and learning disorders	2.01 (1.58–2.55)	1.38 (1.07–1.77)	1.35 (1.05–1.73)
ADHD	2.32 (2.05–2.63)	1.11 (0.98–1.26)	1.11 (0.97–1.26)
Preterm birth			
ASD Preterm birth (<37 weeks gestation)	1.42 (0.78-2.57)	1.98 (1.05-3.71)	1.97 (1.05-3.71)

Full-term birth (≥37 weeks gestation completed)	1.61 (1.25–2.09)	1.45 (1.09–1.93)	1.44 (1.08–1.91)
P value for interaction between cannabis use and preterm birth	0.69	0.37	0.36

In the 4-year cohort, the rates of secondary outcomes were 1.7% for intellectual and learning disorders and 5.7% for attention deficit, hyperactivity and conduct disorders (ADHD). Rates were higher among children with prenatal cannabis exposure. The unadjusted incidence of intellectual disability and learning disorders was 10.3 (95% CI: 9.4–11.2) per 1,000person-years among children with prenatal exposure compared to 4.9 (95% CI: 4.80– 4.93) among unexposed children. The incidence of ADHD was 45.0 (95% CI: 42.2–48.1) per 1,000person-years among children born to women who reported cannabis use in pregnancy and 17.1 (95% CI: 16.90–17.2) among unexposed children. To account for preterm birth, we analyzed the primary outcome stratified by deliveries occurring before 37weeks' and ≥37weeks' gestation. Among women with preterm deliveries (6% of the cohort, n=30,744), the CEM-adjusted HR was 1.97 (95% CI: 1.05–3.71) compared to 1.44 (95% CI: 1.08–1.91) in full-term deliveries (P interaction=0.36). For secondary outcomes, the associations were attenuated in the preterm sample. (Table 2)

DISCUSSION

Autism spectrum disorder is a neurodevelopmental disorder with an early life onset that is characterized by social and communication deficits, and unusual restricted repetitive behaviors resulting in significant social and occupational impairments. A subset of these patients also experiences seizures, anxiety, intellectual disabilities, motor dysfunctions, altered sleep, disrupted response to sensory stimuli and metabolic disturbances. These symptoms are caused by widespread neural impairments/alternations. One of the neural systems affected by the disease is the endocannabinoid system. The endocannabinoid system also plays a role in social behavior and emotionality, which are two aspects of human behavior that are altered in individuals with autism.[15]Prenatal exposure to drugs may impact fetal central nervous system development and subsequent behavior. Animal data support that prenatal insults to the developing central nervous system continue to affect fetal, neonatal, infant and childhood development. Neuroimaging studies have demonstrated region- and gene-specific neural changes associated with prenatal exposure to cannabis. Fetal brain development occurs throughout pregnancy, including in the first trimester. Prenatal insults during this period show an association with anomalies of the central nervous system and neurodevelopmental disorders. Furthermore, animal data indicate that the fetalendocannabinoid type 1 receptor, through which cannabis primarily affects the brain, is expressed at the equivalent of 5–6weeks of gestation in humans. Associations between prenatal cannabis exposure and potential neurodevelopmental outcomes in children may be complex and subject to confounding or mediation. Factors including individual genetic profile, prematurity, fetal and postnatal environment, dose and type of substance of exposure and environmental factors may be involved, thus limiting our ability to ascertain causality between in utero cannabis exposure and later childhood outcomes.[16] In this large retrospective cohort, we found that children with mothers who reported cannabis use in pregnancy were at higher risk for ASD diagnosis. Children with prenatal cannabis exposure had an increase of 50% in the risk of an autism diagnosis over the study period, and these associations were robust after controlling for confounding. Also, children with prenatal cannabis exposure appeared to have some increased risk for developing intellectual disabilities, learning disorders and ADHD compared to unexposed children. However, these associations were smaller in magnitude (11–22% increase) and did not attain statistical significance at conventional levels after matching and covariate adjustment. The primary association between maternal cannabis use and ASD persisted in sensitivity analyses by other substance use, income and preterm birth.

CONCLUSION

Cannabis use was associated with an increased risk of neurodevelopmental disorders by age 10. Further study is needed on the amount and timing of cannabis use in pregnancy and childhood health outcomes and following the legalization of cannabis in many jurisdictions. Moreover, novel analytical approaches to addressing potential residual confounding bias in this area are required.

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