




COMMENT

The impact of antenatal cannabis use on the neonate: Time for open engagement?

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Cannabis is a potent psychoactive agent that continues to be used routinely during pregnancy.¹ The overall prevalence of cannabis use has consistently increased from 2002 to 2014, primarily in women who had completed high school.^{2,3} The 2019 National Survey on Drug Use and Health (NSDUH) reported any cannabis use among pregnant women at 5.4% compared to 4.7% in 2018.⁴ Studies have consistently reported that the majority of cannabis use is recreational and probably under-reported due to recall bias with the NSDUH survey.^{5,6} Of particular concern is the increased potency of currently available cannabis products. Chandra et al. reported that mean Δ^9 -tetrahydrocannabinol (Δ^9 -THC) concentrations have increased dramatically over the past 10 years from 8.9% in 2008 to 17.1% in 2017, and the mean Δ^9 -THC:cannabidiol (CBD) ratios also increased substantially from 23 in 2008 to 104 in 2017.⁷ These trends are worrisome since the greatest reported use occurs in the first trimester, often before the woman is aware of her pregnancy.

A lot still remains unknown with regard to the impact of cannabis use in pregnancy since most of the current information relies on self-reporting and retrospective analyses. A report on prenatal, perinatal, and neonatal exposure to cannabis by the National Academies of Sciences, Engineering, and Medicine (NASEM) summarized that, apart from substantial evidence linking cannabis smoking and lower birth weight, there was limited evidence of a statistical association between cannabis smoking and neonatal intensive care unit admission and insufficient evidence to support or refute an association with cognitive/academic achievement in exposed offspring.⁸ Despite the paucity of high-level clinical evidence, data suggest that cannabis use (1) during pregnancy results in significant fetal exposure through the placenta and (2) during the postpartum period results in significant neonatal exposure through breastmilk and second-hand exposure (with abundant THC receptors in the brain and other organs).^{9–11} THC may remain in breast milk for up to 6 weeks after marijuana use and can reach up to eight times the maternal serum level.^{12,13} Since the publication of the NASEM report, more recent studies have suggested that cannabis use during pregnancy may be associated with adverse perinatal outcomes such as placental abruption, preterm birth, fetal growth restriction, admission to a neonatal intensive care unit, and lower 5-min Apgar scores.^{14–17} Statements from the American Academy of Pediatrics, American College of Obstetrics and Gynecology, and Academy of Breastfeeding Medicine (ABM) highlight the

importance of eliciting a history of cannabis use during prenatal care visits and recommend counseling the mother to avoid the drug during pregnancy and breastfeeding.^{18–20} While all three organizations recommend counseling pregnant women on the potential dangers of marijuana use during pregnancy and lactation, there are subtle differences within each of the recommendations (especially in the context of breastfeeding), which highlights the lack of robust evidence regarding longer-term neurodevelopmental outcomes.

In this issue of *Pediatric Research*, Lee and colleagues evaluated the cardiovascular structure and function in rat pups born to pregnant dams exposed to Δ^9 -THC, the active component of the endocannabinoid system. The dams were randomly selected, acclimated to their new environment, and then randomized either to the administration of intraperitoneal Δ^9 -THC or saline throughout gestation. Some pups were culled at birth to assess cardiac volume relative to body weight and others had an echocardiogram performed on the day of life 1 and 21, after which their heart tissue was harvested for molecular analysis of cardiac structure.²¹ At birth, Δ^9 -THC-exposed pups were noted to have more fetal growth restriction, lower heart/body weight ratios, higher heart rate, and lower stroke volume compared to controls. Although by 3 weeks of age the Δ^9 -THC male pups did demonstrate significant catch-up growth, they had increased left ventricular wall thickness (possibly due to hypertension) and decreased stroke volume and cardiac output. Lastly, these pups also had evidence of cardiac remodeling with significant increases in cardiac collagen content. The authors suggest that in utero exposure to Δ^9 -THC not only leads to fetal growth restriction (notable at birth) but also cardiac remodeling with resultant cardiac dysfunction. Although the study contained a relatively small number of animals in each experimental group, the data are quite compelling and raise new concerns in the fetus and neonate with in utero exposure to Δ^9 -THC.

Findings from this study in conjunction with reports of potential epigenetic and biochemical alterations in the placenta and fetal brain highlight the potential negative impact on short- and long-term health and development of the offspring.^{22–24} The concept of fetal origins of adulthood disease is no longer new and robust data exist about adult cardio-metabolic disorders secondary to fetal and/or early childhood exposures (biochemical, nutritional, psychosocial, environmental, etc.).^{25–27} Recent studies examining chronic cannabis use in adults also demonstrate negative

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cardiovascular and neurological outcomes.^{28,29} Through biologically plausible mechanisms, Lee and colleagues have demonstrated that alterations secondary to in utero organ growth and development persist into childhood equivalent in human years, with significant functional impairments. The authors suggest that this cardiac dysfunction could persist throughout the lifespan and contribute to long-term cardiovascular morbidity and mortality.²¹ Additional studies focusing on genetics and epigenetics associated with cannabis use in pregnancy are urgently needed.

As noted in the NASEM report, there is a critical need to address the research gaps relevant to cannabis use during pregnancy and prenatal, perinatal, and neonatal outcomes.⁸ Over the past few years, the legalization of cannabis and cannabinoids for both medicinal and recreational purposes has gained momentum; only six states in the United States now consider the use as illegal.³⁰ In some ways, this is a welcome move, as criminalization and legal issues faced by women using cannabis during pregnancy puts the mother–infant dyad at significant risk. In contrast, dissemination of proper education, counseling, and discussion of potential risks to fetal health has not occurred in a similar manner to nicotine and alcohol use. This may have partly contributed to the perception that cannabis use in pregnancy is safe. While the Food and Drug Administration strongly advises against the use of CBD in any form during pregnancy or while breastfeeding, there appears to be a lack of understanding from the users of these products.³¹ An elegant review tracing the path of cannabis legalization with the unintended effects on fetal and neonatal outcomes was recently published and highlights the need for additional research in this field.³²

A healthcare provider's personal beliefs, choices, experiences, and perceptions (if robust evidence does not exist) consistently influences the guidance and counseling provided to pregnant women. The continuing misinformation and/or misconception about cannabis use in pregnancy needs to be addressed in order for pregnant women to make more informed choices. In their study, Ko et al. noted that ~70% of pregnant and non-pregnant women believe that there is slight or no risk of harm from using cannabis once or twice a week.³³ While some women using cannabis decrease use once a pregnancy is identified due to concerns for risk to the fetus, others report continued use to alleviate nausea and vomiting.³⁴ Ironically some consider it more natural and safer than over the counter and/or prescribed medications. Others report not considering cannabis to be addictive and not sure of the potential risks for themselves or their infants.³⁴ Since healthcare providers lack Grade 1 evidence for the detrimental effects of cannabis on the fetus and neonate, it makes it more difficult to consistently counsel them to avoid the drug. A lack of communication and education with healthcare providers regarding the health aspects of cannabis was evident in the study by Bayrampour et al. and was perceived by women as an indication that adverse outcomes associated with cannabis use are not significant.³⁵ This lack of education and understanding of potential risks along with continued increases in use across the general population is contributing towards the increased use of cannabis during pregnancy as well as with breastfeeding.⁶

It is time to better educate healthcare providers, develop evidence-based guidelines supported by national organizations and adopt a harm reduction approach to decrease cannabis use in pregnant women. It is very clear that clinicians and policymakers have the capacity to provide this counseling and support in a respectful manner. It is essential that we avoid stigmatization and utilize trauma-informed practices, particularly in the care of marginalized populations, similar to family-centered care developed for pregnant women with Opioid Use Disorder.³⁶ Finally, while adopting these programs and guidelines, there is still an urgent need to continue research in the field, improve the quality of available evidence, and issue recommendations based on facts and not perceptions. There are substantial advocacy efforts to

support this approach, primarily directed to ensuring that a portion of the revenue states generates (or hope to generate) from marijuana taxes directly fund more research via state-based grants while promoting more informative public health campaigns. These are achievable goals, especially with further industry, regulatory, and legislative support such as the Cannabidiol and Marijuana Research Expansion Act, a bill to encourage scientific and medical research on marijuana and its associated compounds.³⁷

AUTHOR CONTRIBUTIONS

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ADDITIONAL INFORMATION

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