

VIEWPOINT

Nora D. Volkow, MD
National Institute on
Drug Abuse, National
Institutes of Health,
Bethesda, Maryland.

**Wilson M. Compton,
MD, MPE**
National Institute on
Drug Abuse, National
Institutes of Health,
Bethesda, Maryland.

Eric M. Wargo, PhD
National Institute on
Drug Abuse, National
Institutes of Health,
Bethesda, Maryland.



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The Risks of Marijuana Use During Pregnancy

Currently, 29 states and Washington, DC, have passed laws to legalize medical marijuana. Although evidence for the effectiveness of marijuana or its extracts for most medical indications is limited and in many cases completely lacking, there are a handful of exceptions. For example, there is increasing evidence for the efficacy of marijuana in treating some forms of pain and spasticity, and 2 cannabinoid medications (dronabinol and nabilone) are approved by the US Food and Drug Administration for alleviating nausea induced by cancer chemotherapy. A systematic review and meta-analysis by Whiting et al¹ found evidence, although of low quality, for the effectiveness of cannabinoid drugs in the latter indication. The anti-nausea effects of tetrahydrocannabinol (THC), the main psychoactive ingredient in marijuana, are mediated by the interactions of THC with type 1 cannabinoid (CB1) receptors in the dorsal vagal complex. Cannabidiol, another cannabinoid in marijuana, exerts antiemetic properties through other mechanisms. Nausea is a medically approved indication for marijuana in all states where medical use of this drug has been legalized.

However, some sources on the internet are touting marijuana as a solution for the nausea that commonly accompanies pregnancy, including the severe condition hyperemesis gravidarum. Although research on the prevalence of marijuana use by pregnant women is

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limited, some data suggest that this population is turning to marijuana for its antiemetic properties, particularly during the first trimester of pregnancy, which is the period of greatest risk for the deleterious effects of drug exposure to the fetus. Marijuana is the most widely used illicit drug during pregnancy, and its use is increasing. Using data from the National Survey of Drug Use and Health, Brown et al² report in this issue of *JAMA* that 3.85% of pregnant women between the ages of 18 and 44 years reported past-month marijuana use in 2014, compared with 2.37% in 2002. In addition, an analysis of pregnancy data from Hawaii reported that women with severe nausea during pregnancy, compared with other pregnant women, were significantly more likely to use marijuana (3.7% vs 2.3%, respectively).³

Although the evidence for the effects of marijuana on human prenatal development is limited at this point, research does suggest that there is cause for concern. A recent review and meta-analysis found that infants of

women who used marijuana during pregnancy were more likely to be anemic, have lower birth weight, and require placement in neonatal intensive care than infants of mothers who did not use marijuana.⁴ Studies have also shown links between prenatal marijuana exposure and impaired higher-order executive functions such as impulse control, visual memory, and attention during the school years.⁵

The potential for marijuana to interfere with neurodevelopment has substantial theoretical justification. The endocannabinoid system is present from the beginning of central nervous system development, around day 16 of human gestation, and is increasingly thought to play a significant role in the proper formation of neural circuitry early in brain development, including the genesis and migration of neurons, the outgrowth of their axons and dendrites, and axonal pathfinding. Substances that interfere with this system could affect fetal brain growth and structural and functional neurodevelopment. An ongoing prospective study, for example, found an association between prenatal cannabis exposure and fetal growth restriction during pregnancy and increased frontal cortical thickness among school-aged children.⁶

Some synthetic cannabinoids, such as those found in "K2/Spice" products, interact with cannabinoid receptors even more strongly than THC and have been shown to be teratogenic in animals. A recent study in mice found brain abnormalities, eye deformations, and facial disfigurement (cleft palate) in mouse fetuses exposed at day 8 of gestation to a potent full cannabinoid agonist, CP-55,940.⁷ The percentage of mouse fetuses with birth defects increased in a linear fashion with dose.

(The eighth day of mouse gestation is roughly equivalent to the third or fourth week of embryonic development in humans, which is before many mothers know they are pregnant.) It is unknown whether these kinds of effects translate to humans; thus far, use of synthetic cannabinoids has not been linked to human birth defects, although use of these substances is still relatively new.

THC is only a partial agonist at the CB1 receptor, but the marijuana being used both medicinally and recreationally today has much higher THC content than in previous generations (12% in 2014 vs 4% in 1995), when many of the existing studies of the teratogenicity of marijuana were performed. Marijuana is also being used in new ways that have the potential to expose the user to much higher THC concentrations—such as the practice of using concentrated extracts (eg, hash oil).

More research is needed to clarify the neurodevelopmental effects of prenatal exposure to marijuana,

**Corresponding
Author:** Eric M. Wargo,
PhD, Science Policy
Branch, Office of
Science Policy and
Communications,
National Institute on
Drug Abuse, 6001
Executive Blvd, Room
5235, Bethesda, MD
20892-9591 (wargoem@nida.nih.gov).

especially high-potency formulations, and synthetic cannabinoids. One challenge is separating these effects from those of alcohol, tobacco, and other drugs, because many users of marijuana or K2/Spice also use other substances. In women who use drugs during pregnancy, there are often other confounding variables related to nutrition, prenatal care, and failure to disclose substance use because of concerns about adverse legal consequences.

Even with the current level of uncertainty about the influence of marijuana on human neurodevelopment, physicians and other health care providers in a position to recommend medical marijuana must be mindful of the possible risks and err on the side of caution by not recommending this drug for patients who are pregnant. Although no states specifically list pregnancy-related conditions among

the allowed recommendations for medical marijuana, neither do any states currently prohibit or include warnings about the possible harms of marijuana to the fetus when the drug is used during pregnancy.⁸ (Only 1 state, Connecticut, currently includes an exception to the medical marijuana exemption in cases in which medical marijuana use could harm another individual, although potential harm to a fetus is not specifically listed.)

In 2015, the American College of Obstetricians and Gynecologists issued a committee opinion discouraging physicians from suggesting use of marijuana during preconception, pregnancy, and lactation.⁹ Pregnant women and those considering becoming pregnant should be advised to avoid using marijuana or other cannabinoids either recreationally or to treat their nausea.

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