Protection Versus Progress: The Challenge of Research on Cannabis Use During Pregnancy

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abstract

A central tension in pediatric research ethics arises from our desire to protect children from harm while also allowing progress toward discoveries that could improve child health. A prime example of this tension is research on a controversial yet increasingly common practice: the use of cannabis by women to treat nausea and vomiting of pregnancy. Studies of cannabis use in pregnancy face a combination of ethical hurdles because of the inclusion of pregnant women and involvement of a schedule I controlled substance. Given the growing need for research on the safety and efficacy of cannabis for nausea and vomiting of pregnancy, we reflect on the multiple historical contexts that have contributed to the challenge of studying cannabis use during pregnancy and make a case for the ethical rationale for such research.
A common trope at the conclusion of empirical articles is “further studies are warranted.” In practice, however, practical, ethical, and historical barriers can pose considerable challenges for researchers attempting to advance knowledge in maternal and child health. Constraints on research with pregnant women, for example, are designed to protect the fetus from unknown harms but have left knowledge gaps on how to treat even the most common illnesses of pregnancy. “Morning sickness,” or nausea and vomiting of pregnancy, is experienced by an estimated 70% to 80% of women and can profoundly impact a woman’s professional, physical, and emotional functioning. Although symptoms range in severity, 50% of women with nausea and vomiting of pregnancy reported negative impacts on their work effectiveness and relationships with partners, and >55% reported feeling depressed. Severe cases can result in weight loss, high blood pressure, and increased risk of preeclampsia and hospitalization, with potential impacts on fetal health. Long-term effects of severe nausea and vomiting have been reported even after pregnancy, including increased posttraumatic stress in mothers and reduced insulin sensitivity in children. Despite the prevalence and impact of these symptoms on maternal and child health, there remain limited safety and efficacy data on currently used antiemetics during pregnancy.

THE TROUBLED HISTORY OF TREATMENTS FOR NAUSEA AND VOMITING OF PREGNANCY

A prime contributor to our lack of knowledge about antinausea medications in pregnancy is the lingering legacy of thalidomide. Thalidomide began to be sold as sedative in Germany in the late 1950s. When its antiemetic effects were noted, it was marketed as a “safe and effective” treatment of nausea and vomiting of pregnancy. Within 2 years of its widespread use in pregnancy, the first reports emerged of severe birth defects ranging from deformed limbs and organs to premature death. An estimated 10 000 children were impacted before distribution of thalidomide was banned worldwide in 1962. Thalidomide was never sold in the United States, in large part because of the work of Frances Kelsey, a US Food and Drug Administration (FDA) officer who refused to approve thalidomide because of insufficient safety evidence (she was subsequently awarded a Presidential Award for Distinguished Service). The narrowly missed thalidomide disaster in the United States led to major reform in the drug approval process in 1962, which tightened regulations for how drugs are approved and marketed, including the requirement to prove both safety and efficacy through controlled clinical trials.

Public awareness of the teratogenic effects of thalidomide led to generalized fears about the use of antiemetics during pregnancy. Bendectin (doxylamine and pyridoxine) was taken by ~25% of pregnant women from the mid 1950s to 1980. However, reports in the medical literature and popular media began to suggest that Bendectin was also associated with birth defects. After lawsuits were brought against the manufacturer, the drug was voluntarily taken off the market 1983, not because of evidence of teratogenesis but rather because of its lack of profitability with the manufacturer’s increasing insurance costs. A 30-year period followed in which no new antiemetics drugs were approved for use in pregnancy, and the number of hospitalizations of pregnant women for nausea and vomiting more than doubled.

In 2013 the FDA approved a “new” drug, Diclegis, which contains the same combination of pyridoxine and doxylamine as Bendectin. This approval followed numerous epidemiological studies and clinical trials in which researchers showed no evidence of teratogenic effects of this combination treatment. Diclegis is currently the first-line treatment of nausea and vomiting in women who do not respond to dietary and lifestyle changes. However, Diclegis is expensive, often not covered by insurance, and tends to be less effective for severe symptoms than alternatives. The more commonly used alternative is ondansetron, which is currently used by 1 in 4 pregnant women despite lacking FDA approval for use in pregnancy. In utero exposure to ondansetron has been associated with cleft lip and palate and heart defects in some trials but not others. According to the American College of Obstetricians and Gynecologists, “there are insufficient data on fetal safety with ondansetron use and further studies are warranted.”

CANNABIS AS AN ALTERNATIVE

Into this frequently changing (and potentially confusing) treatment landscape for nausea and vomiting of pregnancy now enters cannabis, which was initially approved for medical uses, including treatment of nausea for patients undergoing chemotherapy, in 1996. Cannabis appears to be an effective antiemetic during pregnancy, and its use during pregnancy is rising. Researchers in a recent Canadian study found that 92% of respondents reported that cannabis was effective for treating their nausea and vomiting of pregnancy, and women with more severe nausea and vomiting symptoms report higher rates of cannabis use. Whether taken for antiemetic, stress-relieving, or recreational purposes, cannabis use during pregnancy has doubled over the past 2 decades, outpacing the trend in nonpregnant women; studies have reported an estimated 12% to...
34% of pregnant women tested positive or reported taking cannabis during their first trimester.\textsuperscript{22,23} Prenatal cannabis exposure may be increasing even faster in states where recreational use is legalized; in a study from Colorado, researchers reported a 69% increase in tetrahydrocannabinol concentration in meconium specimens since legalization.\textsuperscript{24} Similar to the case with prescription antiemetics, there is uncertainty about the safety of cannabis use during pregnancy. There have been few epidemiological studies to date, with the most consistent finding an association with preterm birth and/or low birth weight.\textsuperscript{25,26} However, existing studies are confounded by concurrent use of other known teratogenic substances during pregnancy, such as tobacco and alcohol.\textsuperscript{27} Despite these limited data, official medical guidance is unambiguous: the Centers for Disease Control and Prevention,\textsuperscript{28} American Academy of Pediatrics,\textsuperscript{29} and American College of Obstetricians and Gynecologists\textsuperscript{30} have all recommended against any cannabis use while pregnant or breastfeeding. Despite these official recommendations, women continue to use cannabis during pregnancy, and many perceive it as safe.\textsuperscript{31} Compared with the known risks of alcohol and tobacco during pregnancy, women report less awareness about the risks of cannabis, and some perceive cannabis to be safer than prescription medications.\textsuperscript{32} Use of cannabis may be recommended to pregnant women by dispensary employees,\textsuperscript{33} and studies have revealed that health care providers tend not to discuss potential clinical risks of cannabis when counseling their pregnant patients.\textsuperscript{32,34,35} Providers are hesitant to discuss clinical risks because of inadequate data,\textsuperscript{34} and some women have interpreted this reticence as evidence that cannabis during pregnancy is safe.\textsuperscript{31} The absence of data is felt by both pregnant women and their providers; both groups have expressed a desire for more information to guide decision-making about cannabis use during pregnancy.\textsuperscript{32,34,35} As they say, further studies are warranted.

A barrier, however, to conducting research on cannabis is its legal status. Although medical cannabis is currently legal in 33 states (and recreational use is legal in 11), the US government still classifies cannabis as a schedule I controlled substance. Researchers seeking to understand the mechanisms of action of schedule I drugs face multiple regulatory and financial hurdles that have significantly impacted research progress.\textsuperscript{36} In addition, research involving pregnant women is subject to an increased degree of legal, ethical, and regulatory scrutiny dating back to the days of thalidomide.\textsuperscript{37} Together, these two factors can make conducting even observational research on prenatal cannabis exposure difficult (as discussed below) and randomized trials impossible.\textsuperscript{27} The legal status of cannabis also has real consequences for pregnant women. Women who test positive for cannabis during pregnancy or at time of delivery risk involvement of child protective services and even law enforcement.\textsuperscript{32,35} Depending on the state, evidence of substance use during pregnancy can be reported as child abuse and result in loss of custody, jail time, or forced substance treatment.\textsuperscript{38} Structural inequities in how testing and reporting laws are applied (ie, only to women on Medicaid) and systematic bias in rates of reporting to child protective services mean that in many states the impact of punitive policies is felt most strongly by pregnant women of color and those from disadvantaged backgrounds.\textsuperscript{38} The fear of punitive consequences is assumed to result in significant underreporting to providers. For example, one study found that only 36% of pregnant patients who tested positive for cannabis disclosed use to providers.\textsuperscript{39} Fear of consequences may lead women who are using substances during pregnancy to avoid prenatal care entirely.\textsuperscript{40} Indeed, at the state level, more punitive responses to prenatal substance use are associated with an increase in low birth weight and preterm births, suggesting that such policies have the unintended effect of worsening birth outcomes.\textsuperscript{41}

Research on cannabis use during pregnancy is still in its early stages and has the potential to follow a path similar to that taken by prenatal cocaine exposure research. In the 1980s, a small amount of initial data suggesting possible teratogenic effects of cocaine became amplified and publicized, and the resultant fear of “crack babies” was used to enforce racially-biased criminalization of substance use among pregnant women.\textsuperscript{27} A recent suggestion to define a “fetal cannabis spectrum disorder”\textsuperscript{42} suggests a similar inclination among present-day scholars to prematurely label and segment a cohort of children born to primarily low-income, minority mothers. Particular care is warranted to avoid the same stigmatization from cannabis that resulted from early research on prenatal cocaine exposure.

\textbf{THE SOCIAL CONSEQUENCES OF PRENATAL CANNABIS EXPOSURE RESEARCH}

Research on illicit substances and research with pregnant women each face their own regulatory hurdles and, together, create an area of research that is not only more challenging to conduct but also more likely to raise ideological hackles.\textsuperscript{43} Many research topics in pediatrics fit into this category, given the strong reactions that perceived harm or mistreatment of children can engender. Parents do not always act...
in their child’s best interest; therefore, a key tenant in pediatric ethics is to restrict parents from making decisions that could cause unnecessary harm.44,45 However, the premise that children should be protected from research that poses any risk would preclude discovery of new treatments for pediatric illness. As Laventhal and colleagues stated, “The tension between these two goals—protection and progress—is inevitable.”45 Pediatric research that stirs up public controversy (for example, a public health study of children exposed to lead-based paint in low-rent housing in Baltimore) can shift the priority of courts and other regulatory bodies toward protection and away from progress.46

The personal experience of one of us (N.M.K.) illustrates this tension in the context of prenatal marijuana exposure research. Our study is designed to evaluate the impact of cannabis and other antiemetics used during pregnancy on infant brain development. It is the first neuroimaging study of infants exposed to prenatal cannabis and is funded through the National Institute on Drug Abuse (NIDA) and approved by the local institutional review board (IRB). The study is recruiting pregnant women who experienced nausea and vomiting and took either prescription antiemetics or cannabis during the first trimester to manage symptoms. Participants are followed through pregnancy, and their infants receive MRI scans at 6 months of age to compare structural and functional indices of brain development across the two groups.

A press release announcing the launch of the study was met with criticism on social media condemning the study as “unethical,” incorrectly describing the design as “paying women to use marijuana in pregnancy,” and comparing the study to the thalidomide tragedy and the Tuskegee syphilis experiment. Complaints by the public filed with NIDA and the IRB led to an in-depth re-review of the study that involved soliciting input on protocol and design from external experts in teratology and obstetrics and gynecology. Two minor changes to the protocol were requested: clarifying that continued cannabis use was not required and providing a fact sheet on cannabis and pregnancy. Both NIDA and the IRB also confirmed the social value of this research. However, the research continues to be targeted by activists who have explored numerous avenues in their attempt to disrupt or halt the study, including threatening to expose participants and make reports to child protective services.

As this experience makes clear, research on cannabis use in pregnancy is impacted by the same complex social and historical factors that affect individual pregnant women and their providers. Researchers must contend with increased regulatory scrutiny and potential public criticism. Women who choose to enroll must weigh the potential social consequences of participating against the potential to contribute new knowledge. However, we believe that persevering in such research, despite its challenges, is critical for 3 reasons. The first is pragmatic: avoiding research on controversial practices will not make those practices disappear; rather, they will persist unguided by evidence. The lack of research to date has not stopped pregnant women from taking cannabis but has denied them the opportunity to make an informed choice. The second reason is historical: the lessons of thalidomide and Bendectin and Diclegis are that unregulated use of a drug during pregnancy can cause serious harms but also that acceding to public fears and social contagion can lead to the provision of inadequate care. The final reason is ethical. It is necessary to conduct research on potentially controversial topics like cannabis use during pregnancy to permit the creation of social policies and informed health care decisions for women and children that are based on evidence rather than opinion.

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ABBREVIATIONS
FDA: US Food and Drug Administration
IRB: institutional review board
NIDA: National Institute on Drug Abuse

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