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Pregnancy Outcomes Associated With Use of Tobacco and Marijuana

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Abstract: Tobacco and marijuana are the most common drugs of abuse among pregnant women. Cigarettes have been extensively studied and increase the risk of miscarriage, preterm birth, premature rupture of membranes, placental dysfunction, low birth rate, stillbirth, and infant mortality. There are sparse data on the specific effects of electronic cigarettes and smokeless tobacco in pregnancy. Literature on marijuana in pregnancy is limited by confounding, bias, and the retrospective nature of studies that do not capture contemporary trends in use. However, several studies suggest an association between marijuana and fetal growth restriction, low birth weight, and neurodevelopmental differences in offspring.
Key words: tobacco, marijuana, pregnancy outcomes

Introduction

In the United States, reported rates of tobacco smoking during pregnancy have decreased from 13.2% in 2006 to 7.2% in 2016, however, the actual prevalence of smoking varies greatly among demographic groups.[1] For example, rates of smoking are higher than the national average among women age 20 to 24, women of Native American or Alaska Native descent, and women with a high school education or less.[1] It has been known for several decades that maternal cigarette smoking is associated with a myriad of adverse pregnancy outcomes, although research on alternate forms of tobacco consumption, such as e-cigarettes, is more nascent.

Marijuana, also known as cannabis, is an illicit drug that has now been legalized in many states across the United States. Many use it for its medicinal properties, as cannabis has been found to have many potential therapeutic effects, including the treatment of nausea, anxiety, and pain.[2,3] There are many ways to consume marijuana, including smoking, eating, vaping,

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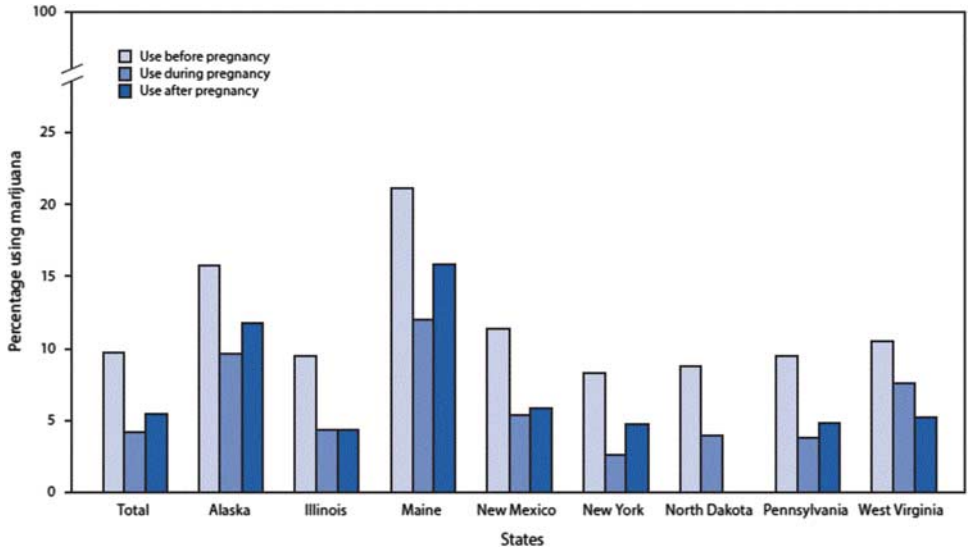

FIGURE 1. Prevalence of marijuana use before, during, and after pregnancy (N = 6236)—8 states. From Pregnancy Risk Assessment Monitoring System, from Ko et al.[4] full color online

or dabbing. It is the most commonly used drug in pregnancy, with a reported prevalence from 2% to 27%; this number varies based on age, socioeconomic status, and geographic location and is likely an underestimate given a high frequency of underreporting (Fig. 1).[5,6]

Given the ubiquity of maternal tobacco and marijuana use, the purpose of this chapter is to review the available evidence on pregnancy outcomes associated with the use of tobacco and marijuana products in pregnancy.

CIGARETTE SMOKING AND PREGNANCY OUTCOMES

Miscarriage

Miscarriage is one of the most common pregnancy complications, and although several studies have examined the association between smoking and miscarriage, data have been mixed due to limitations in ascertaining cigarette use at various times during pregnancy, variations in study design, and the multifactorial nature of miscarriage and potential for confounding. In the largest, most recent systematic review and meta-analysis on this matter, Pineles et al[7] examined 98 studies on the association between tobacco smoke exposure and miscarriage. Active smoking was associated with a significantly greater risk of miscarriage [summary relative risk (RR): 1.23, 95% confidence interval: 1.16-1.30]. Furthermore, the authors observed a dose-response effect, with a 1% increase in RR per cigarette smoked per day.[7]

Congenital Anomalies

Although overall rates of congenital anomalies appear to be equal between smokers and nonsmokers, cigarette use in pregnancy has been associated with increased risks of specific malformations.[8] For example, the association between cigarette smoking and cleft lip and palate has been reported since the 1970s. In the largest study using US natality data, any amount of cigarette use during pregnancy conferred significantly greater odds of having a child with an orofacial cleft [odds ratio (OR) = 1.34, 95% CI: 1.16-1.54].[9] A dose-response

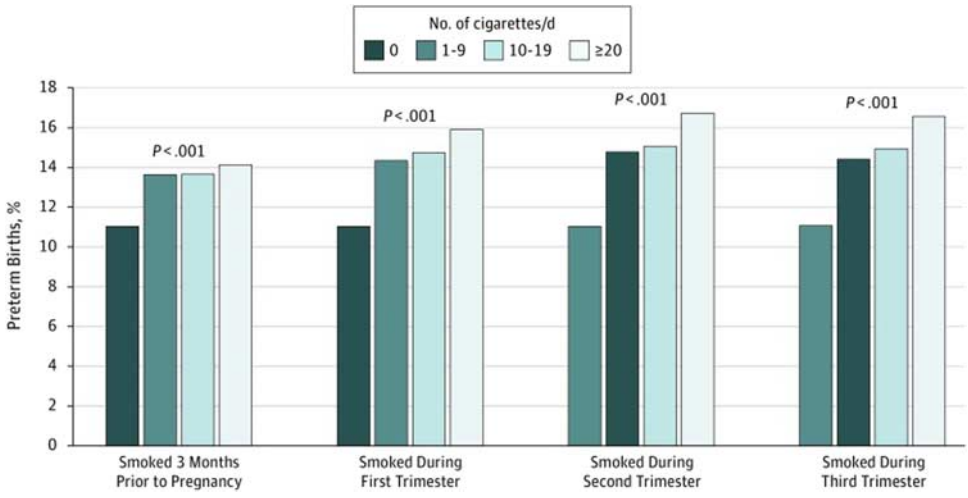

FIGURE 2. Rates of preterm birth <37 weeks' gestation by cigarette smoking status and quantity of cigarettes consumed preconception and during pregnancy trimesters 1, 2, and 3. Reproduced from Soneji and Beltrán-Sánchez.[14] full color online

effect was also found, with increasing odds of cleft lip and palate with increasing daily cigarette consumption.[9] Studies have also linked cigarette use and congenital heart defects. In a retrospective case-control study of state birth certificate data, maternal cigarette use in the first trimester of pregnancy was associated with higher odds of congenital heart disease [adjusted odds ratio (aOR) = 1.16, 95% CI: 1.08-1.24].[10] The association was stronger with older maternal age and heavier cigarette use, and the most commonly involved lesions included pulmonary valve abnormalities, pulmonary artery abnormalities, and atrial septal defects.[10]

Preterm Birth

While the pathophysiology of spontaneous preterm birth is still poorly understood, it is well-known that cigarette smoking is one of the few modifiable risk factors associated with preterm birth. The RR of preterm birth among cigarette smokers, compared with nonsmokers, ranges from 1.3 to 2.5 in the largest studies on the subject.[11,12] Several studies have investigated the dose-response relationship between cigarette use and preterm birth. The most recent study demonstrated that even low levels of cigarette smoking confers increased risks of preterm birth: even smoking 1 to 2 cigarettes/day was associated with significantly increased odds of preterm birth before 37 weeks' gestation compared with nonsmokers (OR = 1.31, 95% CI: 1.29-1.33).[13] Smoking cessation, particularly early in pregnancy, is associated with a reduced risk of preterm birth by up to 20% (Fig. 2).[14] Although further research is needed to ascertain the biologic mechanisms underlying this association, proposed pathways include nicotine-induced vasocontriction, altered steroid hormone production, carbon monoxide-induced fetal hypoxia, disruption of prostaglandin synthesis, and disruption of calcium signaling.[15]

Preterm Premature Rupture of Membranes (PPROM)

Smoking during pregnancy is an established risk factor for PPROM, with the largest retrospective studies reporting a 2- to 4-fold increased risk of PPROM with cigarette use.[16,17] The association persists after controlling for other known risk

factors, such as an intrauterine or genitourinary infection. The risk of PPROM appears to be concentrated primarily among heavy smokers: in a retrospective cohort study among births in Canada that stratified by level of cigarette use, England et al[18] demonstrated that smoking >10 cigarettes/day was associated with an increased risk of PPROM at <28, <32, and <37 weeks, however, smoking 1 to 10 cigarettes/day was not associated with a significantly increased risk of PPROM at any gestational age.

Fetal Growth Restriction and Low Birth Weight (LBW)

LBW, specifically birth weight <2500 g, is the most robustly studied complication of cigarette smoking during pregnancy, and the preponderance of epidemiological evidence is such that the relationship between smoking and LBW is now regarded as causal. The Centers for Disease Control and Prevention have estimated that at least 20% of LBW infants are attributable to tobacco use during pregnancy, and women who smoke are 1.5 to 3.5 times more likely to have a LBW infant.[19] As previously discussed, smoking does modestly increase the risk of preterm birth; however, the effect of smoking on birth weight is independent of gestational age at delivery, and even at term infants born to mothers who used cigarettes weigh 200 to 300 g less than infants born to nonsmokers.[19,20] In addition, several observational studies have demonstrated that smoking cessation, particularly in early pregnancy, can reduce the rate of LBW to that of nonsmokers. In the most recent retrospective study using state birth certificate data, Blatt et al[21] found that smoking only in the preconception period did not significantly increase the risk of fetal growth restriction but smoking in any trimester did. Women who smoked throughout the entire pregnancy had highest risks of growth restriction, compared with those who smoked in first or second trimesters.[21]

Gestational Diabetes

Several observational studies have suggested a modestly increased risk of gestational diabetes among women who smoke during pregnancy. In a secondary analysis of Pregnancy Risk Assessment Monitoring System (PRAMS) data, Bar-Zeev et al[22] reported that the odds of gestational diabetes were higher among women who smoked throughout pregnancy, compared with those who quit smoking or never smoked. This association persisted after adjusting for key confounders including race and ethnicity, age, and body mass index.[22] Similar findings were reported in observational cohort studies in international populations as well.[23,24] However, a recent meta-analysis did not support these findings, showing no significant association between cigarette smoking and gestational diabetes (pooled OR = 0.98, 95% CI: 0.88-1.10).[25] Additional studies are needed to further explore this association.

Preeclampsia

Paradoxically, cigarette smoking has been consistently associated with a lower risk of preeclampsia in pregnancy. Two separate meta-analyses of cohort and case-control studies demonstrated an inverse relationship between any cigarette smoking and preeclampsia, with pooled ORs ranging from 0.51 to 0.68.[26,27] The biologic mechanism underlying this association is unclear, but in vitro studies have postulated that cigarette smoking may prevent preeclampsia through nicotine-induced inhibition of thromboxane A2 production, stimulation of nitric oxide release, or inhibition of cytokine and free radial release in cytotrophoblast cells.[26] However, this observed risk reduction does not outweigh the multiple obstetric risks associated with cigarette smoking in pregnancy, especially as cigarette

smoking has been implicated in other mechanisms of placental dysfunction such as placental abruption and placenta previa.

Placental Abruption

Cigarette use has been widely shown to increase the risk of placental abruption, with ORs reported from 1.4 to 4.0.[28] A dose-response relationship also has been consistently observed.[28–30] This relationship has been demonstrated independent of PPROM, which is a known risk factor for abruption and associated with maternal smoking. In a study examining the histologic effects of smoking on placental pathology in cases of placental abruption, the prevalence of intervillous thrombi was significantly higher among smokers but placental infarcts were seen less frequently than in nonsmokers.[31] These findings suggest there may be different pathologic mechanisms of placental abruption in smokers versus nonsmokers.

Abnormal Placentation

Several small studies have examined the relationship between cigarette use and placenta previa, with varying results. A 2015 meta-analysis of 21 studies demonstrated that compared with nonsmokers, cigarette use was associated with a significantly increased risk of placenta previa (RR = 1.42, 95% CI: 1.30-1.54).[32] One proposed explanatory mechanism for this association is that due to hypoxia-induced vasoconstriction in the uteroplacental circulation in the setting of cigarette smoking, placental surface area increases to facilitate gas exchange and is thus more likely to extend across the cervical os.[33] Data on tobacco use and the risk of placenta accreta are mixed, with one recent retrospective cohort study of the Nationwide Inpatient Sample demonstrating tobacco use was a significant risk factor for placenta accreta spectrum, but another large multicenter prospective cohort study demonstrating no significant relationship.[34,35] Further studies are warranted to better define this potential association.

Perinatal Mortality

In a meta-analysis of 142 studies, Pineles et al[36] demonstrated that any active maternal smoking was associated with a nearly 50% greater risk of stillbirth (RR = 1.46, 95% CI: 1.38-1.54) and an over 20% increased risk of neonatal death (RR = 1.22, 95% CI: 1.14-1.30). The RRs increased with the amount smoked, again suggesting a dose-response effect between cigarette smoking and adverse perinatal outcomes.[36] Another meta-analysis of 34 studies performed a subgroup analysis of studies defining stillbirth at various gestational age points.[37] Studies defining stillbirth at ≥ 20 weeks reported an OR of 1.43, whereas studies defining stillbirth at ≥ 24 and ≥ 28 weeks showed ORs of 1.58 and 1.33, respectively.[37] These data suggest that smoking through the second and third trimesters continues to increase the risk for perinatal mortality. Importantly, population-level studies have demonstrated that women who quit smoking at the beginning of pregnancy have similar stillbirth risks compared with nonsmokers, highlighting the importance of counseling patients on tobacco cessation preconception and in early pregnancy.[38]

Infant Mortality

Cigarette use in pregnancy has been associated with several postnatal morbidities. It has been established for several decades that smoking increases the risk of sudden unexplained infant death (SUID). In a recent large birth cohort study in the United States, maternal smoking increased the risk of SUID by >2-fold.[39] There also appears to be a dose-response curve between increased cigarette use and SUID, as well as a risk reduction following tobacco cessation, as women in this cohort who reduced or quit smoking during pregnancy decreased their odds of SUID compared with women who

continued smoking (reduced, aOR = 0.88, 95% CI: 0.79-0.98; quit, aOR = 0.77, 95% CI: 0.67-0.87).[39]

ELECTRONIC CIGARETTES AND PREGNANCY OUTCOMES

Electronic nicotine delivery systems (ENDS), also known as e-cigarettes or vape pens, are relatively new tobacco products that vaporize a solution containing nicotine, flavorings, and solvent to produce aerosols similar to cigarette smoke. ENDS have become increasingly popular, with the prevalence of ENDS consumption among those who have ever used tobacco increasing from 1.8% in 2010 to 13% in 2013.[40] Because ENDS did not go through the Food and Drug Administration approval process before their release in the market, packaging was not required to display warning messages on potential health hazards. In addition, many flavoring combinations and marketing campaigns in ENDS products have been directed at younger consumers, as well as the population of current smokers to use ENDS as a smoking cessation aid. As a result, there is a perception among current and former smokers that ENDS are less harmful than traditional cigarettes.[40]

Pregnancy Outcomes

Given the relative novelty of ENDS, there are very few longitudinal data on their use in pregnancy. In the largest study to date examining the association between electronic cigarette use and adverse perinatal outcomes, Regan et al[41] used PRAMS survey data from 79,176 pregnancies. After adjusting for key confounders, ENDS use was associated with an increased prevalence of LBW infants.[41] Stratified analyses by concurrent cigarette use demonstrated that among those who did not also use cigarettes during pregnancy, ENDS use was associated with higher prevalence of both preterm birth and LBW, particularly with daily ENDS use.[41]

Dual Use

Dual usage of cigarettes and ENDS is of particular concern, due to increased exposure to nicotine and the fairly commonplace use of both products during pregnancy. An online national survey of nicotine use during pregnancy reported that 5% used only cigarettes, 6.5% used only ENDS, and 8.5% used both products.[40] Studies specifically examining pregnancy outcomes in the setting of dual usage are sparse. A recent study found that among dual users, women who continued ENDS but stopped smoking cigarettes still had an increased risk of small-for-gestational-age infants compared with nonusers (RR = 3.2, 95% CI: 1.5-6.6).[42] This suggests that while cigarette cessation has been previously shown to clearly reduce the risks of adverse pregnancy outcomes, continued use of ENDS in pregnancy should not be considered an acceptable nicotine substitution strategy given the residual risks of poor perinatal outcomes.

SMOKELESS TOBACCO AND PREGNANCY OUTCOMES

Although combustible cigarettes and ENDS are the most common forms of tobacco consumption worldwide, there are several other forms of nicotine used by reproductive-age women. For example, smokeless tobacco consumed orally (chew) or nasally (snuff) is prevalent in several Scandinavian countries, nicotine combination with additional ingredients (betel nut or betel leaf) is found in South Asia and hookah or waterpipe smoking is a common practice in the Middle East. Data on these alternative tobacco products and pregnancy outcomes are lacking. In a systematic review of smokeless tobacco use and adverse pregnancy outcomes, Inamdar et al[43] found that smokeless tobacco exposure was associated with LBW in 5/7 studies, preterm birth in 3/6 studies, and 4/4 studies that examined stillbirth. However, this review found the available studies

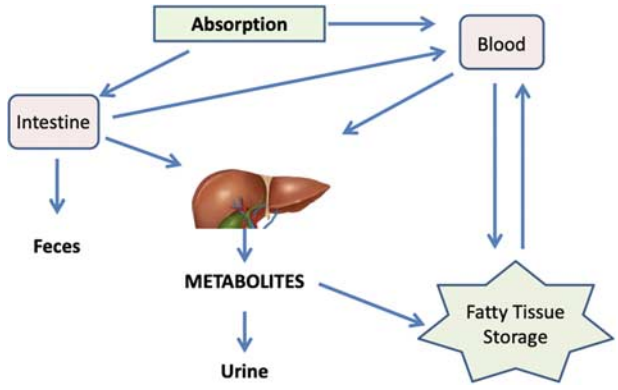

FIGURE 3. After consumption, the primary psychoactive component of marijuana, delta-9-tetrahydrocannabinol, is metabolized by the liver, and metabolites are stored in fat and other tissues until excretion by the kidney. Reproduced with permission from Metz et al.[3] full color online

limited by confounding and bias due to their small, observational, and retrospective nature. Thus, examining the effects of all forms of nicotine exposure in pregnancy should remain an active area of study, especially given the worldwide prevalence of nicotine use and the global effort to reduce maternal and childhood morbidity and mortality.

Conclusions

Cigarette smoking in pregnancy has been extensively studied for decades and is associated with increased risks of several adverse pregnancy outcomes. It remains one of the few modifiable risk factors that can significantly improve maternal and child health. While the prevalence of cigarette use in pregnancy is slowly decreasing in the United States, the increasing popularity of ENDS and other smokeless tobacco products among women of reproductive age demonstrate that addressing tobacco use in pregnancy should remain a public health priority. Future studies should continue to characterize the relationship between ENDS and smokeless tobacco and perinatal outcomes, to better counsel pregnant patients and inform cessation initiatives.

MARIJUANA AND PREGNANCY OUTCOMES

Marijuana Mechanism of Action

Cannabinoid is the active compound in marijuana that is absorbed into the body after smoking or ingesting the drug. Tetrahydrocannabinol (THC), also known as THC, is a small molecule within cannabinoid that is deposited primarily in fat and brain tissue and is metabolized by the liver (Fig. 3). THC is small enough to cross the placenta and enter into breastmilk.[4]

The endocannabinoid system is a neuromodulatory system that affects central nervous system development. It also plays a part in normal implantation and early pregnancy maintenance (Fig. 4). A specific lipase within this system, N-acylphosphatidylethanolamine-specific phospholipase D, is highly expressed within the epithelium of the uterus before implantation occurs.[5] Blastocyst implantation depends on these levels. Adverse outcomes occur in the setting of imbalance within the endocannabinoid system. These include poor blastocyst implantation, inhibition of decidualization, abnormal embryonic development, miscarriage, and compromised placentation. There

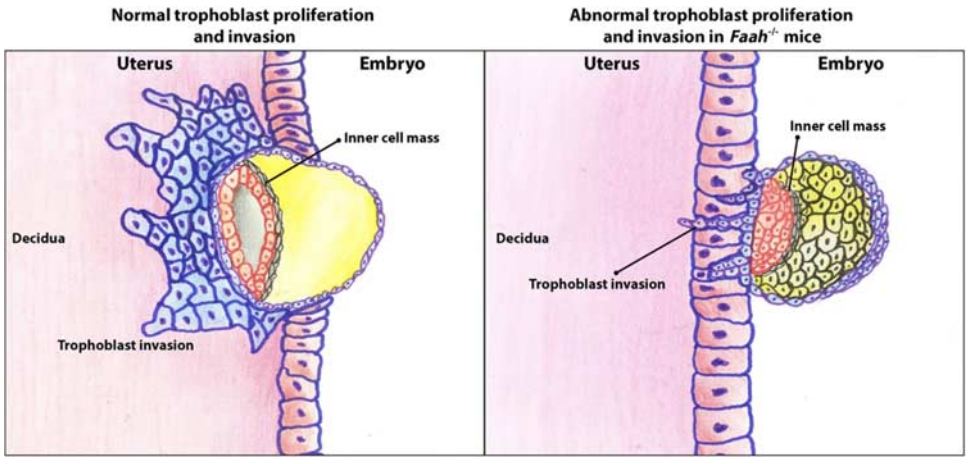

FIGURE 4. Feto-maternal interface and the role of the endocannabinoid signaling during trophoblast proliferation and invasion. Trophoblast proliferation and invasion are compromised in Faah$^{-/-}$ mice suggesting an important role of the endocannabinoid system in these processes. Placentae from Faah$^{-/-}$ mice show an abnormal differentiation of trophoblast precursor cells, which are more prone to differentiate into trophoblast giant cells. This biased trophoblast differentiation compromises the invasive capacity of these cells to reshape and redirect the maternal blood vessel to support embryo growth, representing a risk for the pregnancy outcome. Reproduced with permission from Correa et al.[5] full color online

are certain levels of endocannabinoids throughout the course of implantation and placentation that naturally occur in our bodies, and using marijuana can cause an imbalance within the system.[5] Miscarriage and other adverse outcomes are associated with an imbalance of the endocannabinoid system.

The central nervous system effect of marijuana relies on a cannabinoid receptor, which was found to be present as early as 14 weeks of gestation on the fetus. As the fetus advances in gestation, the receptors increase. This suggests that fetal brain development relies in part on the endocannabinoid system.[4]

Prevalence and Perception

As marijuana becomes legal in more states, there has been a greater acceptance of its use, which has steadily increased since the early 2000s. A study showed that marijuana use among pregnant women (age 18 to 25) has gone from 5% in 2002 to 9% in 2014.[44] This linear increase over the years has created a new field of research within the obstetric field. However, the body of evidence on pregnancy outcomes is still emerging, and there is a lack of agreement among professional society guidelines on marijuana use in pregnancy.

As legalization and medical approval for the general population increases around the country, so do pregnant consumers, who cite various reasons for using marijuana use during pregnancy (Fig. 5). Despite many studies that show marijuana may negatively impact pregnancy, no unanimous guidelines have been drawn, therefore making it difficult for providers to educate their patients. The American College of Obstetricians and Gynecologists (ACOG) recommends against any marijuana use in pregnancy. A common perception of pregnant women is that marijuana has no risk to their pregnancy and to their fetus.[4] A study asked pregnant women if they believe that there is

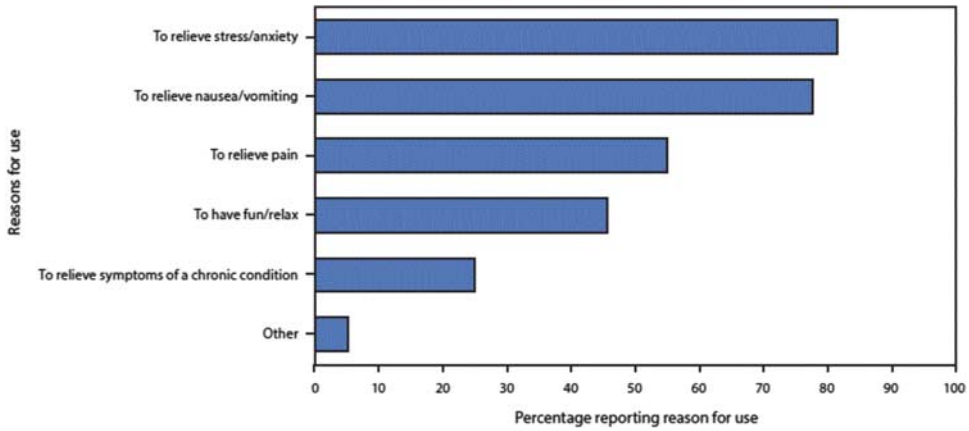

FIGURE 5. Reasons for marijuana use during pregnancy (N = 413)—8 states, Pregnancy Risk Assessment Monitoring System, from Ko et al.[4] full color online

any risk to consuming marijuana. The number of women who believed that there was no risk increased from 25.8% in 2005 to 65.4% in 2015.[45] Reproductive-aged women who were not pregnant had similar increases in perceived safety, with 62.6% believing there were no risks to pregnancy in 2015.[45] These data suggest that even before considering childbearing, women believe marijuana confers minimal or no risks in pregnancy.

In a 2017 survey of former marijuana users, over 300 pregnant women were surveyed on their reasons for cessation. 74% quit because they did not want to be a bad example, and the others quit due to their providers' recommendation.[46] Only a quarter of women in this study quit because of medical recommendation.[46] This reinforces the need for clear guidelines to inform counseling on marijuana use and cessation during pregnancy.

Confounding Factors

Data are limited on marijuana use in pregnancy and neonatal outcomes. Reasons for this include the fact that many women are not willing to report their use due to its illegal nature in many states and fear of legal repercussions. Another major issue in identifying marijuana's impact on pregnancy is confounding with polysubstance use, as many women use other drugs in combination with marijuana. This makes it difficult to ascertain which complications are due to the marijuana itself. In addition, these studies often rely on recall from the participants, which results in bias. A study showed that women who use marijuana in pregnancy are less likely to use folic acid.[4] Another study showed that those who use marijuana are at higher risk for intimate partner violence.[4] This would be another confounding factor in assessing neonatal outcomes. In addition, there are other forms of marijuana consumption, such as oral ingestion of edible products, which have yet to be studied.

Neonatal Outcomes

Several studies have reported an increased risk of fetal growth restriction with marijuana use. In a retrospective cohort study of 6468 pregnant women, there was a 16.3% rate of fetal growth restriction within women who consumed marijuana, compared with 9.6% for those who did not.[4] Further research into this topic has shown that this was pertinent only for women who were heavier users of the drug, with at least weekly use. Though some studies find

fetal growth restriction to be prevalent with marijuana use, other studies have found that when separating those who use tobacco from those who use marijuana, there is no link between the 2.

A systematic review and meta-analysis looked at neonatal outcomes associated with marijuana use alone versus marijuana use with tobacco. They found that marijuana use alone was not related with any adverse outcomes, whereas marijuana use with tobacco resulted in higher rates of LBW, preterm delivery, and placental abruption.[6] However, they were only able to find pregnant women who smoke marijuana alone, less than once per week. Thus, leaving uncertainty about the association between heavier marijuana use and pregnancy outcomes.

A meta-analysis found that pregnant women who smoke marijuana are more likely to be anemic throughout their pregnancy (using hemoglobin under 11 g/dL as a cutoff), have a fetus with growth restriction, or require neonatal intensive care unit admission after birth. However, the included studies did not exclude individuals with polysubstance use, making it difficult to evaluate an independent association with marijuana use.[47]

Stillbirths are excluded from the majority of studies examining the association between marijuana use and adverse pregnancy outcomes. However, in a secondary analysis of NICHD Stillbirth Collaborative Research Network data, marijuana use as ascertained by drug assays of umbilical cord segments demonstrated an association between detectable marijuana metabolite and stillbirth. These data have not yet been replicated in other studies.[48]

Another factor to consider is that many people who consume marijuana do so via smoking. This leads to a 5-fold higher serum carbon monoxide level when compared with tobacco.[6] As a result, mothers experience an imbalance of gas exchange, and as we previously know, a mother's oxygenation is important for fetal oxygenation and well-being.[49]

Overall, research has not shown a consistent association between marijuana use and stillbirth, spontaneous abortion, fetal distress, congenital malformation, abnormal birth length, or head circumference. The only complication that has more substantial and consistent evidence is the LBW of the neonate.[4]

Some studies evaluate the association between marijuana use and neurodevelopment of children after exposure to marijuana in utero. They have found impaired brain development and cognition. We know that cannabinoid receptors are present in the brain during fetal development.[4] Maternal marijuana use has been associated with decreased attention span and behavioral problems in the offspring. Studies have noted diminished academic performance and cognitive function, quantified by lower IQ scores in young children. These findings were among mothers who were exposed to marijuana during the first and third trimester.[3] Data related to child neurodevelopmental outcomes are limited by confounding, as it is difficult to adjust for other differences in home environment and ongoing exposure during childhood and adolescence.

Conclusions

The impact of marijuana use in pregnancy has become an active area of study, especially as legalization increases the prevalence of recreational use among pregnant people. However, despite the burgeoning research in this field, more data are needed to provide strong evidence-based clinical recommendations on marijuana and pregnancy outcomes. This lack of robust, prospective evidence seems to be highly correlated with the fact that prior studies have combined tobacco and marijuana use, thus confounding many findings on marijuana use alone and obstetric outcomes. In addition, very few

studies have looked at the timing of marijuana use within the course of the pregnancy, and most existing studies do not consider the amount of marijuana consumed. If patients report marijuana use, they should be counseled on the possible adverse effects this may have on the fetus, such as fetal growth restriction and attention problems in childhood. Overall, in the setting of insufficient data regarding marijuana use in pregnancy, the American College of Obstetricians and Gynecologists recommends against marijuana use during the preconception, pregnancy, and postpartum periods.[4]

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