It’s Not Your Mother’s Marijuana
Effects on Maternal-Fetal Health and the Developing Child

Tamara D. Warner, PhD, Dikea Roussos-Ross, MD, Marylou Behnke, MD

KEYWORDS
- Pregnancy • Marijuana • Cannabis • Prenatal exposure • Substance use
- Perinatal outcomes • Fetal effects • Developmental effects

KEY POINTS
- Pro-marijuana advocacy may result in an increase in the prevalence of marijuana use during pregnancy, particularly among young adolescents who already report the highest use among all pregnant women.
- Today’s marijuana is 6 to 7 times more potent than in the 1970s; average marijuana consumption may be higher owing to growing popularity of blunts compared with joints.
- Adverse fetal outcomes related to marijuana use during pregnancy remain unclear. However, prenatal use has been associated with infertility, placental complications, and fetal growth restriction.
- Long-term effects of prenatal marijuana use on exposed offspring include poorer executive functioning skills and attention, increased conduct and behavior problems, and poorer school achievement.
- Intersecting political forces and medical issues mandate that physicians be knowledgeable marijuana use by their patients and be prepared to counsel their patients about the effects of prenatal marijuana use on fertility, pregnancy, and the exposed offspring.

INTRODUCTION
Societal attitudes toward marijuana use in the United States are undergoing an historical shift. In the 1960s, a generation of young people embraced marijuana for personal...
recreational use. Today, “medical” marijuana (*cannabis sativa*) has been approved for use in 22 states and the District of Columbia either by legislation or by popular vote in statewide referenda or ballot initiatives; 15 of the 22 legal actions were passed in the last decade (since 2004). As of May, 2014, another 7 states have pending legislation or ballot measures to legalize medical marijuana. In addition, 2 states—Colorado and Washington state—have legalized marijuana for recreational use. The attitudinal shift is apparent not just among adults but among teens as well. The most recent annual survey of adolescent drug use indicates that the annual prevalence of marijuana use has been trending upward since 2008 for 8th, 10th, and 12th graders; perhaps more important, the perceived risk of regular marijuana use has declined sharply in recent years, a trend that started in 2005.

**Epidemiology of Marijuana Use Among Pregnant Women**

Marijuana is the most commonly used illicit drug during pregnancy. Table 1 shows the 2011 through 2012 combined annual prevalence rates based on past-month use for illicit drugs, alcohol, and cigarettes by pregnant women in the United States. The rate for marijuana and hashish was 5.2%, which translates to 115,000 pregnant women using marijuana annually. Still, the prevalence rates for marijuana are significantly lower than the rates for alcohol (8.5%) and cigarette (15.9%) use during pregnancy. Table 1 also shows the prevalence rates by age and trimester for marijuana, cigarette, and alcohol use by pregnant women. Young adolescents (ages 15–17) have the highest rate of marijuana use during pregnancy (16.5%), which is more than double the rate for 18- to 25-year-olds (7.5%). Marijuana use during pregnancy is highest during the first trimester (10.7%), then declines significantly during the second trimester (2.8%) and third trimester (2.3%). After childbirth, marijuana use rebounds quickly. Box 1 outlines some of the sociodemographic characteristics that are common among women who use illicit drugs during pregnancy and some that may be unique to women who use marijuana during pregnancy.

**Potential Impact of Medical Marijuana**

The legal status of medical marijuana is under debate. Marijuana is a Schedule I drug under the Controlled Substance Act, a federal law that preempts actions taken by individual states to legalize its use, cultivation, and distribution. Legal scholars have argued that when used for medicinal purposes, marijuana should be considered a pharmaceutical agent governed by the Food, Drug and Cosmetic Act with regulatory oversight, including evaluation of its safety and efficacy, provided by the Food and Drug Administration.

There is emerging evidence that states with legalized medical marijuana have higher rates of marijuana use, depending on specific aspects of laws and policies. In states that allow home cultivation and legal dispensaries, higher levels of recreational use and higher levels of heavy use are found. By contrast, states that restrict broad access to medical marijuana by requiring annual registration of patients have lower prevalence rates and treatment admissions compared with those that do not.

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* As used herein, *marijuana* refers to the crude drug derived from *Cannabis sativa*, specifically dried preparations of the floral and foliar material from outdoor-grown pollinated female plants commonly called *herbal cannabis* in Europe. *Sinsemilla* is used to refer to indoor-grown unfertilized female plants (known as *skunk* in the United Kingdom). Our use of the term *marijuana* excludes *hashish* preparations (*resin* in Europe) and hash oil. *Cannabis* is used as the umbrella term to refer to 2 or more preparations of the plant.
Table 1
Percentage substance use in the past month among women ages 15 to 44 by pregnancy status, age group and trimester

<table>
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<tr>
<th>Drug</th>
<th>Total Sample</th>
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<td>15–17</td>
<td>18–25</td>
<td>26–44</td>
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<tr>
<td>Illicit drugs(^a)</td>
<td>10.5</td>
<td>10.7</td>
<td>5.9</td>
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<td>16.5</td>
<td>7.5</td>
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<tr>
<td>Cigarettes</td>
<td>24.2</td>
<td>24.6</td>
<td>15.9</td>
<td>b</td>
<td>20.9</td>
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<tr>
<td>Alcohol</td>
<td>53.8</td>
<td>55.5</td>
<td>8.5</td>
<td>13.4</td>
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</table>

\(^a\) Illicit drugs include marijuana/hashish, cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used nonmedically.

\(^b\) Low precision; no estimate reported.

Growing pro-marijuana advocacy efforts may increase marijuana use among pregnant women. In the absence of public health messages about the potential risks, marijuana may be perceived as “safe” to use during pregnancy compared with other illicit drugs and in comparison with alcohol and cigarettes. Medical marijuana laws that involve the use of dispensaries have been shown to drive down prices, which will likely increase use among certain groups. In a recent study, urban, low-income, primarily African-American postpartum women reported perceptions of relatively lower risk of marijuana compared with licit drugs as well as roughly equivalent costs of marijuana and cigarettes.

Increasing Potency and Consumption of Marijuana

The potency of marijuana has increased markedly during the past 40 years in the United States, and elsewhere (review by McLaren and colleagues). From the 1970s to the 2000s, there has been an estimated 6- to 7-fold increase in the potency of cannabis seized in the United States as measured by the percentage of Δ⁹-tetrahydrocannabinol (THC), the most psychoactive of the 70 cannabinoids found in cannabis. Between 1993 and 2008, the mean concentration of THC rose from 3.4% to 8.8%. In addition to concerns about potency, the amount of marijuana consumed, on average, seems to be increasing among younger adults, particularly minorities owing to the growing popularity of blunts (marijuana-filled cigars) compared with joints and pipes. One study found that blunts contain significantly greater amounts of marijuana—up to 1.5 times more than joints and 2.5 times more than pipes.

ISSUES RELATED TO MARIJUANA USE DURING PREGNANCY

Screening Pregnant Women for Marijuana Use

Box 1 summarizes some of the recommendations made by the American College of Obstetrics and Gynecology and the American Society of Addiction Medicine.
related to drug use during pregnancy. The American College of Obstetrics and Gynecology recommends that screening for substance abuse be part of complete obstetric care and be performed routinely throughout pregnancy because women may be more willing to disclose substance abuse as they develop rapport with their provider. Additionally, it is recommended that providers become knowledgeable on brief intervention techniques and referral services for treatment. The American Society of Addiction Medicine also advocates universal screening for drug use among pregnant women and appropriate referral for substance treatment when patients who require services are identified.

Screening should be performed with the consent of the pregnant woman and can be conducted with standardized questionnaires such as the 4 Ps or the CRAFFT Interview (CRAFFT is available for download in 13 languages at http://www.ceasar-boston.org/CRAFFT/screenCRAFFT.php). Another evidence-based and readily available screening tool is the 5 Ps, an adaptation of the 4 Ps that includes a question about peers (friends); an “integrated” version also asks about intimate partner violence, emotional health (worry, anxiety, depression, or sadness), and cigarette use. Drug testing can be performed with the woman’s permission. The 3 most commonly used specimens to establish drug use during the prenatal and perinatal periods are urine, meconium, and hair. Of these, urine is used most frequently owing to the ease of collection. In regular marijuana users, urine testing can be positive up to 10 days after use; for chronic or heavy users, urine can be positive for up to 30 days after last use. Meconium is easily collected in the newborn nursery. It reveals exposure to marijuana in the second and third trimesters because this is when meconium is formed in the fetus. Hair sampling has not been found to be as useful for detection of marijuana.

Box 2
Professional organizations’ recommendations related to drug use during pregnancy

<table>
<thead>
<tr>
<th>Professional organization</th>
<th>Recommendations</th>
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<td>American College of Obstetrics and Gynecology</td>
<td>• Universal screening for drug use in females of reproductive age&lt;br&gt;• Screening at the first prenatal or intake visit and at least once per trimester thereafter&lt;br&gt;• Consider drug testing (with patient consent) when screening tests are positive&lt;br&gt;• Refer for substance abuse treatment for all pregnant women who have evidence of drug use in pregnancy&lt;br&gt;• Protect the physician–patient relationship</td>
</tr>
<tr>
<td>American Society of Addiction Medicine</td>
<td>• Prenatal education about all drugs for all pregnant women&lt;br&gt;• Universal screening to identify “at risk” women including repeated follow-up assessments&lt;br&gt;• Culturally competent public prevention programs to educate the public about realistic dangers of drug use in pregnancy&lt;br&gt;• Education of health care providers in the care and management of women with evidence of drug use before, during, and after pregnancy&lt;br&gt;• Women who are pregnant should receive priority admission to substance treatment facilities</td>
</tr>
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</table>

When considering drug testing in pregnancy, it is important for the clinician to be familiar with the reporting laws of the state in which he or she practices. States vary about whether evidence of drug exposure to a fetus or newborn mandates reporting the case to the child welfare system with possible removal of children and/or incarceration of the mother.\textsuperscript{18} As of May 2014, there are 17 states that consider substance abuse during pregnancy to be child abuse under civil child welfare statutes; 3 states consider it grounds for involuntary commitment to a mental health or substance abuse treatment facility (\textit{Table 2}).\textsuperscript{24} These laws have been found to hinder the physician–patient relationship, decrease compliance with prenatal care, and increase the risk of perinatal mortality.\textsuperscript{17,18,25} Owing to fears of incarceration or the loss of one’s children, pregnant women may not be willing to disclose their use. For this reason, it is imperative to preserve the physician–patient relationship, which will allow women to feel safer discussing drug use with their provider. Pregnant women who are identified as using drugs should be counseled and referred for substance abuse treatment. Early detection of drug use allows for timely implementation of harm reduction strategies during pregnancy.\textsuperscript{26}

Aside from the legal implications, there are additional barriers that obstetricians face when deciding whether to screen and/or test patients for substance use. Two such barriers are concerns about having the time to screen patients appropriately and a lack of local substance use treatment resources, particularly for pregnant women. The time barrier could be reduced if reimbursement was provided to physicians for screening pregnant patients for substance use, similar to the reimbursement for tobacco use screening. Local substance abuse treatment facilities can be located through the online Behavioral Health Treatment Services Locator, available from the Substance Abuse and Mental Health Services Administration at http://findtreatment.samhsa.gov/locator/home.

\textbf{Effects of Prenatal Marijuana Use}

A list of the possible pregnancy-related effects of prenatal marijuana use can be found in \textit{Box 3}. Marijuana easily passes through the maternal circulation, into the placenta, and then fetus. It is also found in breast milk. Marijuana can be detected in umbilical cord blood, neonatal urine, and meconium.

Preclinical studies are important because they can (1) provide a level of control for confounding variables not achievable in clinical studies, (2) offer a framework for developing hypotheses for further study in human populations, and (3) help to identify the pathologic changes that underlie the medical and behavioral changes observed in clinical studies. A full discussion of the preclinical literature is beyond the scope of this review and the reader is referred to pertinent studies and reviews available in the extant literature.\textsuperscript{27–30}

Research into the effects of THC in humans began in the late 1800s with 2 major advances occurring when the main psychoactive compound in marijuana, THC, was identified by Gaoni and Mechoulam in 1964\textsuperscript{31} and when the existence of cannabinoid receptors, called the endocannabinoid system, was confirmed by Devane and colleagues\textsuperscript{32} in 1988.

Cannabinoid receptors are found in various tissues throughout the human body, including the brain and uterine decidua. Thus, the physiologic functions of the endocannabinoid system are important to both early embryonic development and synaptic brain plasticity. However, exposure to exogenous cannabinoids could result in pathophysiologic changes secondary to the longer binding of THC to the receptors compared with naturally occurring endocannabinoids.
With regard to early embryonic development, it is possible that exogenous cannabinoi
d could significantly disrupt regulation of blastocyst maturation, oviductal trans-
port, implantation, and pregnancy maintenance. In addition, THC acts as an in vivo
weak competitor of the estrogen receptor, producing a primary estrogen effect in
male and female rats, stifles trophoblast cell proliferation, and inhibits successful
placentation, possibly producing other pregnancy-related complications.

In the brain, cannabinoids alter executive functions in the prefrontal cortex,
including working memory, attention, and cognitive flexibility. Additionally, the release
of neurotransmitters such as dopamine, serotonin, and acetylcholine, each of which
affects cognitive functions in the prefrontal cortex, as well as behavior and mood,
has been shown to be altered in the face of cannabinoid exposure.

**Marijuana and Infertility**

Human studies on male subjects have shown disruptions in the hypothalamic–pitui-
tary–testicular axis with decreased luteinizing hormone, decreased testosterone, oli-
gospermia, and decreased sperm motility, thus possibly affecting male infertility.

Likewise, in women, chronic marijuana exposure has been associated with sup-
pressed ovulation, altered prolactin, follicle-stimulating hormone, luteinizing hormone,
and estrogen.

**Pregnancy-Related Complications**

The endocannabinoid system is present in the uterine decidua, thus suggesting
possible involvement in pregnancy complications such as miscarriage, preeclampsia,
growth restriction and preterm labor. Additionally, first trimester placentas express
cannabinoid receptors, further implicating the role that alterations in the endocanna-
binoid system may play in pregnancy complications. Marijuana use during pregnancy
has been shown to be associated with an increased fetal pulsatility index and resis-
tance index of the uterine artery, suggestive of increased placental resistance.

These findings may provide a partial explanation for intrauterine growth restriction.

**Fetal Growth and Birth Outcomes**

Available data to this point do not reveal marijuana-associated fetal teratogenicity.
Studies on the effects of prenatal maternal marijuana use on fetal growth and birth out-
comes have yielded inconsistent results. A 2013 review of studies on prenatal mari-
juana exposure by Huizink specifically examined fetal growth, birth outcomes and
early infant development using data from several sources including 3 prospective lon-
titudinal studies: (1) The Ottawa Prenatal Prospective Study (OPPS), which began in
1978 and enrolled a predominantly middle-class, low-risk, Caucasian sample from
Canada, (2) the Maternal Health Practice and Child Development Study
(MHPCD), which started in 1982 and enrolled a high-risk, low socioeconomic status
mixed Caucasian and African-American sample from Pittsburgh, Pennsylvania,

and (3) the Generation R study, which started in 2010 and recruited a multi-ethnic pop-
ulation-based cohort in Rotterdam, The Netherlands. Of the 3 cohorts, only the Gen-
eration R study has examined fetal growth through ultrasound assessments several
times during pregnancy.

**Fetal growth**

A study using elective mid-gestation aborted fetuses (17–22 weeks) who were
exposed to marijuana, tobacco, and alcohol demonstrated decreased weight and
decreased foot length that was associated with marijuana exposure after controlling
for other drug exposures. No association was found between prenatal marijuana
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**TOTAL**: 17 3 15 4 18 10 4

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a Priority applies to pregnant women referred for treatment.
b Applies only to women and newborns eligible for Medicaid.
c Establishes requirements for health care providers to encourage and facilitate drug counseling.
d The South Carolina Supreme Court held that a viable fetus is a “person” under the state’s criminal child endangerment statute and that “maternal acts endangering or likely to endanger the life, comfort, or health of a viable fetus” constitute criminal child abuse.

Results from the Generation R study have shown reduced fetal growth from the second trimester onward, particularly for mothers who used early marijuana during pregnancy or throughout the entire pregnancy.46

Birth outcomes
Results have differed between the 3 longitudinal cohorts described, with the OPPS reporting reduced gestational age but no differences in birth weight,47 the MPHCD reporting reduced birth length after first trimester exposure and unexpectedly, increased birth weight after third trimester exposure,48 and Generation R reporting lower birth weight.46

Studies drawn from other sources yield conflicting results. A recent study by Hayatbakhsh and colleagues49 reported lower birth weight, by an average of 375 g, lower gestational age, shorter body length, and an increase in neonatal intensive care unit admissions owing to marijuana exposure after adjusting for tobacco, alcohol, and other illicit drug exposures. However, studies reporting no association between marijuana use and fetal growth include the Maternal Lifestyle Study,50 a multicenter, prospective study of 8600 women (which also included cocaine use)51 and the Avon Longitudinal Study of Pregnancy cohort of more than 12,000 pregnant women.52 A population-based study using data from the National Birth Defects Prevention Study also found no associations between marijuana use during pregnancy and mean birth weight, gestational age, low birth weight, or preterm delivery.6

Maternal Marijuana Use and Lactation
There is a paucity of data regarding the effects of maternal marijuana use on breastfeeding and infant outcomes. Small to moderate amounts of THC are secreted into breast milk after maternal use with significant absorption by the infant. However, identification of side effects in the lactation-exposed infant are inconsistent,53,54 and no long-term outcome studies are available. As noted in the previous section, studies of the endocannabinoid system from both the animal and human literature indicate there are neurobehavioral complications after marijuana exposure during pregnancy, raising the possibility of complications after exposure during lactation as well. More detailed information is available in recent reviews by Rowe and colleagues55 and Hill and Reed.25 At the present time, the American Academy of Pediatrics recommends that women who are using street drugs, including marijuana, not breastfeed their infants.56

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<th>Possible pregnancy-related effects of prenatal marijuana use</th>
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<td>Decreased male fertility</td>
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<td>Decreased ovulation</td>
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<td>Altered hormones (prolactin, follicle-stimulating hormone, luteinizing hormone, estrogen)</td>
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<td>Altered oviductal transport, embryo implantation, and maintenance of pregnancy</td>
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<td>Altered placental blood flow</td>
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<td>Decreased gestational age</td>
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DEVELOPMENTAL OUTCOMES OF PRENATAL MARIJUANA EXPOSURE: NEONATAL PERIOD TO EARLY ADULTHOOD

As outlined previously, several prospective, longitudinal cohort studies have evaluated the effects of prenatal marijuana exposure on offspring. However, the OPPS and the MHPCD are the only cohorts that have been followed into adolescence and early adulthood. Despite the demographic differences between these 2 cohorts, when the results overlap, they are remarkably consistent.

Neonatal Withdrawal and Neurobehavior

Withdrawal

Neonatal withdrawal from marijuana exposure has not been reported in any of the prospective, longitudinal studies.

Neurobehavior

Evidence of altered state regulation, manifested as increased startles and tremors, was identified in the OPPS sample during the first week of life using the Neonatal Behavioral Assessment Scale with similar results found again at 9 and 30 days using the Prechtl neurologic examination. Poorer visual habituation and responses were also noted during the first week of life, but these problems were not seen again at 9 or 30 days. No effects were reported from the MHPCD on newborn behavior using the Neonatal Behavioral Assessment Scale. However, exposed newborns demonstrated altered sleep patterns with a decrease in quiet sleep and increased sleep motility, suggesting increased activity in the noradrenergic system. Other newborn studies have demonstrated abnormal newborn cry, also suggestive of increased arousal. Other investigators have found no abnormalities in infant behavior.

Prenatal Marijuana Exposure and Outcomes from Late Infancy to Young Adulthood

This section focuses on the areas of development where prenatal marijuana exposure seems to have a significant impact: Executive function, attention, achievement, and behavior. Findings in other areas of development can be summarized as follows, with details found in Box 4.

Executive function and attention

Of importance, both cohorts have reported a negative effect of prenatal marijuana exposure on specific areas of cognition related to executive function at age 3 years, 4 years, and 6 years. Findings in both cohorts include poorer scores on memory and verbal measures. At 6 years, Fried and colleagues reported a negative effect of prenatal marijuana exposure on the attentiveness of subjects using a vigilance task. This finding is consistent with that from the MHPCD at 6 years, which showed increased impulsivity on a vigilance task. Children ages 9 to 12 in both the OPPS

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<th>Box 4</th>
<th>Finding in areas of development in prenatal marijuana exposure</th>
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<td>1.</td>
<td>Minimal, inconsistent effect on general cognition</td>
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<td>2.</td>
<td>Altered sleep patterns</td>
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<td>No effect on language</td>
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and the MHPCD showed poorer abstract/visual reasoning, impulse control, hypothesis testing, and visual problem solving. At age 10, marijuana-exposed youth in the MHPCD were more likely to exhibit hyperactivity, impulsivity, and inattention, according to maternal report. Finally, 2 studies from the OPPS when subjects were 13 to 16 years old documented continued problems with executive function and attention. Adolescents with prenatal marijuana exposure demonstrated decreased attentional stability as evidenced by a decreasing consistency in reaction time as the test progressed and by an increase in errors of omission. The exposed adolescents also had poorer scores on 2 measures indicative of problems with visual memory, analysis, and integration. Several additional studies from the Ottowa sample have used functional magnetic resonance imaging to evaluate the subjects between 18 and 22 years. While performing a response inhibition task, changes in neural activity were noted on functional magnetic resonance imaging when compared with nonexposed subjects.

Although the exposed subjects committed more errors of commission, all were able to finish the task with 85% accuracy or more. While performing a visuospatial working memory task, the exposed subjects showed changes in neural activity on functional magnetic resonance imaging when compared with the nonexposed subjects, although there were no group differences in performance.

**Academic achievement**

Using tests, studies from the OPPS at ages 6 to 9 years and 13 to 16 years showed no effect of prenatal marijuana exposure on standardized academic achievement test scores. This is in contrast to the findings from the MHPCD. Again, using standardized achievement tests, prenatally exposed children had lower reading, spelling, and reading comprehension scores at age 10. Similar results were found at age 14 with lower global achievement and reading scores in the prenatally exposed adolescents.

**Behavior problems**

Parental reports for subjects in the OPPS showed increased conduct disorders in children from 6 to 9 years old. Parental and teacher reports obtained at age 10 for subjects in the MHPCD revealed increased delinquency and externalizing behaviors. Also, an increase in self-reported depressive symptoms was identified at age 10 for exposed subjects in the MHPCD. At age 14, the age of onset and frequency of the youth’s marijuana use was predicted by their prenatal exposure. This finding was also seen in 16- to 21-year-olds from the OPPS. In this study, subjects who were prenatally exposed to marijuana were at greater risk for initiating cigarette smoking and daily use and for initiating marijuana use.

**SUMMARY**

Evidence about the effects of marijuana use during pregnancy- and fetal-related complications and child development is inconclusive. Data from preclinical studies is suggestive of negative outcomes based on disruptive effects on the endocannabinoid system. The results from longitudinal, prospective studies that started in the late 1970s and early 1980s indicate subtle effects on attention, executive functions, and behavior, particularly as marijuana-exposed youth develop into adolescence and early adulthood. Given that today’s marijuana is 6 to 7 times more potent and more likely to be consumed in greater average amounts by younger users, continued surveillance is warranted and may reveal more significant short-term and long-term harms. The practice of medicine for physicians who care for marijuana-using pregnant women is being shaped by shifting societal pressures. Increasingly, marijuana is being thought of as...
“medicine” by the general public as evidenced by “medical” marijuana laws. Pro-marijuana advocacy efforts may lead to perceptions about marijuana as being relatively “safe” and result in increased use by several groups, including pregnant women. At the same time, pregnant women who use illicit drugs and controlled substances such as prescription opioid analgesics are being criminalized and charged with child abuse and other felonies, despite efforts from scientists and medical professionals. Nationwide educational efforts are imperative to ensure women are not misled into believing that marijuana use in pregnancy is without possible danger to the developing fetus. Further research is critical to ascertain the specific risks to the developing fetus both in utero and beyond.

REFERENCES


42. Fried PA. The Ottawa Prenatal Prospective Study (OPPS): methodological issues and findings — it’s easy to throw the baby out with the bath water. Life Sci 1995;56(23–24):2159–68.


