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LESSON 35

Cannabis Use and Reproductive Health

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to define the short- and long-term effects of cannabis use on general health, discuss the general risks of cannabis use relating to male fertility and the benefits of cessation of use when attempting to conceive, and counsel patients regarding the potential impacts of paternal or maternal cannabis use and offspring outcomes.

This AUA Update aligns with the American Board of Urology Module on Impotence, Infertility, and Andrology. Additional information on this topic can be found in the AUA Core Curriculum sections on Infertility, and Sexual Medicine and Andrology.



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Jasper C. Bash, MD,^{1,*} Kimberly S. Ryan, MD,^{2,3*} Jamie O. Lo, MD, MCR,^{1,2,3,4†}
and Jason C. Hedges, MD, PhD^{1,2,4†}

¹Department of Urology, Oregon Health & Science University, Portland, Oregon

²Department of Obstetrics and Gynecology, Oregon Health & Science University, Portland, Oregon

³Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Oregon Health & Science University, Portland, Oregon

⁴Division of Reproductive & Developmental Sciences, Oregon National Primate Research Center, Oregon Health & Science University, Portland, Oregon

*Co-first authors.

†Co-senior authors.



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KEY WORDS: fertility, cannabis, marijuana, reproductive health

INTRODUCTION

Cannabis has become increasingly popular, especially among individuals of reproductive age both in the United States and worldwide (Table 1),^{1,2} driven in part by its increased legalization.³ Although not approved by the Food and Drug Administration for these therapeutic uses, cannabis is often used for analgesia, muscle relaxation, anti-inflammation, sedation, mood improvement, appetite stimulation, and anti-nausea.⁴ **Approximately 10% of regular cannabis users, and up to 50% of chronic daily users, can develop cannabis use disorder, which is diagnosed by cannabis use, and signs and symptoms of functional impairment per the Diagnostic and Statistical Manual of Mental Disorders criteria.** These signs and symptoms can include persistent desires or unsuccessful efforts to cut down or control cannabis use; dedicating a large portion of time to activities necessary to obtain cannabis, use cannabis, or recover from its effects; failure to fulfill role obligations at work, school, or home; and cravings to use cannabis.

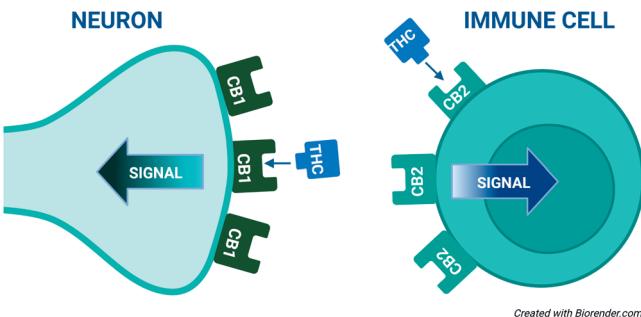
The prevalence of cannabis use has rapidly grown during the COVID-19 pandemic, in part due to heightened anxiety and stress,^{5,6} while in parallel, the potency of cannabis products has nearly doubled in the past decade.⁷ **This is concerning because the limited existing evidence suggests an adverse effect of cannabis use on male fertility, including changes in reproductive hormones, altered semen parameters, and decreased libido.⁸** In addition, the available evidence suggests that the impact of both paternal and maternal cannabis use preconception and/or during pregnancy is not limited only to fertility, but also to fetal outcomes, and longer-term offspring health and developmental trajectories.^{9,10} Thus, the American Society for Reproductive Medicine currently recommends abstaining from use of cannabis when intending to conceive.¹¹

Despite the growing prevalence of cannabis use among individuals of reproductive age, there is a paucity of safety information regarding its effects on fertility, reproductive health, and offspring outcomes. Existing human studies are conflicting due to small sample sizes, reliance on patient self-report, retrospective or observational study designs, and polysubstance use. Preclinical studies have predominantly studied the impact of acute cannabis exposure and administered cannabis intravenously or by oral gavage, which does not mimic typical human

Table 1. Delta-9-tetrahydrocannabinol Use by Age Group in the United States in 2020

| Age, y | % Population |
|--------|--------------|
| <12 | 17.9 |
| 12-17 | 10.1 |
| 18-25 | 34.5 |
| ≥26 | 16.3 |

Data were derived from the Center for Behavioral Health Statistics and Quality.¹



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Figure 1. Main endocannabinoid receptors are CB1 (central nervous system) and CB2 (peripheral nervous system, especially immune cells). THC indicates delta-9-tetrahydrocannabinol.

use. This lack of evidence regarding the potential effects of cannabis has contributed to the limited ability of health care providers to counsel their patients, with only 9.4% of providers advising patients pursuing male fertility care to abstain from cannabis use.¹²

Thus, it is critical to review what is known to better identify and address the research gaps surrounding the effects of cannabis use on reproductive health and offspring outcomes. This information is necessary to guide health care providers and patients who are interested in conceiving or are pregnant, as well as inform future public health initiatives and policies.

MECHANISMS OF ACTION AND PHARMACOKINETICS OF CANNABIS

The endocannabinoid system is a molecular signaling pathway composed of endogenous endocannabinoids that bind to cannabinoid receptors, CB1 and CB2, to regulate homeostasis throughout the human body.¹³ The CB1 receptor is found primarily in the central nervous system, and the CB2 receptor is expressed largely on immune cells (Figure 1).¹⁴ Delta-9-tetrahydrocannabinol (THC), the main active component of cannabis, binds to CB1 and CB2 receptors located throughout the male and female reproductive tract, hypothalamus, pituitary, on sperm, and the placenta.^{10,15} Signal transduction through the cannabinoid receptors occurs via inhibition of adenylyl cyclase and MAP kinase activation.¹³ **The absorption of cannabis differs greatly depending on the mode of delivery; the most common mode of cannabis administration is smoking, followed by edibles.¹⁶** If cannabis is administered orally, THC absorption is often greater than 90%, but the bioavailability is approximately 4%-12% due to first-pass hepatic metabolism.¹⁶ In contrast, smoked cannabis avoids first-pass hepatic metabolism, but amounts of THC can be lost in sidestream smoke and from pyrolysis, heating the material, resulting in low THC absorption and greater variability in bioavailability, ranging from 2% to 56%, but on average approximately 30%.^{16,17}

SYNTHETIC CANNABINOID

Synthetic cannabinoids (eg, K2, spice, AK-47, Mr Happy, Scooby Snax, Kush, or Kronic) are human-made mind-altering chemicals that either are in liquid form to be vaporized and inhaled in e-cigarettes or are sprayed on dried plant material

ABBREVIATIONS: luteinizing hormone (LH), delta-9-tetrahydrocannabinol (THC)

to be smoked. They are called cannabinoids as they are similar to chemicals found in the cannabis plant and are often marketed as “safe, legal alternatives” to cannabis, but in reality can have more intense mind-altering effects that are unpredictable, dangerous, and potentially life-threatening.

ADVERSE GENERAL EFFECTS OF CANNABIS USE

Short-term use. Short-term cannabis use can result in impaired short-term memory, difficulties in learning or retention of information, poor motor coordination, altered judgment, and increased risk of sexual behaviors that can heighten exposure to sexually transmitted diseases (Table 2). With high THC doses, individuals can also experience paranoia and psychosis.¹⁸

Long-term use. Long-term cannabis use can result in addiction, lower IQ scores, cognitive impairment, diminished life satisfaction and achievement, symptoms of chronic bronchitis, and an increased risk of chronic psychosis (eg, schizophrenia) and mental health disorders.¹⁸ In addition, chronic cannabis use, especially when initiated during adolescent and teenage years, is associated with an increased likelihood of dropping out of school, unemployment, and altered brain development.¹⁸

EFFECTS OF CANNABIS ON MALE SEXUAL AND REPRODUCTIVE HEALTH

The most recent 2020 National Survey on Drug Use and Health reported an estimated prevalence of 34.5% (~11.6 million) for past-year use among 18- to 25-year-old men in the United States.¹ The available published studies on the

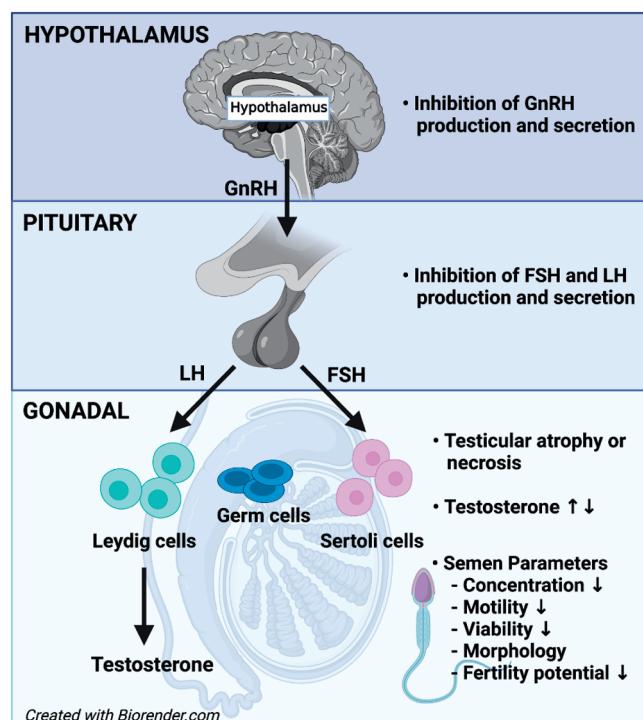


Figure 2. Impact of cannabis use on male reproductive health and fertility. FSH indicates follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

impact of paternal cannabis use on male reproductive health and offspring outcomes are mixed, but suggest that cannabis use is associated with changes in libido, erectile dysfunction, orgasmic dysfunction, altered reproductive hormones, deleterious changes in semen parameters, and premature or delayed ejaculation (Figure 2).¹⁵

Libido. Cannabis has been used as an aphrodisiac. A survey of 325 male customers at a dispensary reported that cannabis use was associated with increased orgasmic function, erectile function, and sexual satisfaction, although there was no correlation with the type or route of cannabis exposure.¹⁹ Using cannabis has also been shown to be independently associated with increased coital frequency (8.8 events/mo vs 7.8 events/mo, $P < .05$).²⁰ Additionally, daily use has been associated with having 2 or more sexual partners in the previous year (OR 2.08 for men, 2.58 for women).^{21,22}

Erectile function. Cannabis use has been associated with erectile dysfunction.¹⁵ Although the underlying mechanism is unclear, it may be secondary to penile endothelial damage and poor orgasmic function.²³ The prevalence of erectile dysfunction was doubled in cannabis users compared to controls in a meta-analysis of 5 case-controlled studies.²⁴ A 2010 Australian survey found that of the 8,656 men surveyed, daily use vs no use was associated with orgasmic disorders: reaching orgasm too quickly (OR 2.68), too slowly (OR 2.05), or the inability to reach orgasm (OR 3.94).²²

Testicular volume. Preclinical data in rodent, canine, and nonhuman primate models have demonstrated a strong dose-dependent association between cannabis use and testicular atrophy, as well as reduced prostate and seminal vesical weight.¹⁵ Rhesus macaques maintained on weight-based daily THC edibles experienced a 58% reduction in their total testicular volume after 7 months of exposure.²⁵ Similarly, histologic studies in rodents injected with THC have

Table 2. Potential Adverse Effects of Cannabis Use

| Effects of short-term use |
|------------------------------------------------------------------------------------------|
| Impaired short-term memory |
| Impaired motor coordination |
| Altered judgment |
| Difficulty problem-solving |
| Altered perception of time |
| Changes in mood |
| Psychosis or paranoia ^a |
| Effects of long-term or heavy use |
| Addiction |
| Altered neurodevelopment and increased likelihood of dropping out of school ^b |
| Lower IQ scores, and cognitive impairment |
| Respiratory issues |
| Lowered motivation |
| Difficulty with attention |
| Increased risk of mental health and psychosis disorders (eg, schizophrenia) |

Data were derived from Volkow et al.¹⁸

^aAssociated with high delta-9-tetrahydrocannabinol doses.

^bAssociated with cannabis use initiated in adolescence.

also shown decreased testicular volume secondary to reduced seminiferous tubule diameters.¹⁵

Male reproductive hormones. The current literature is inconsistent regarding the effects of cannabis use on the male hypothalamic-pituitary-gonadal axis. Some studies have reported decreased testosterone and luteinizing hormone (LH) levels, but these findings have not been confirmed by others.¹⁵ Overall, follicle-stimulating hormone is not *significantly* affected by cannabis use, nor is its rise in response to exogenous gonadotropin-releasing hormone.¹⁵ In contrast, LH is altered by cannabis exposure; serum LH levels have been reported to be significantly lower in men after acute THC exposure, but elevated LH levels were observed with chronic exposure in nonhuman primates.^{15,25} There also appears to be an upper limit to the effect of cannabis exposure as a prior study observed no difference in degree of LH suppression when comparing men who consumed 5-9 cannabis cigarettes per week to those who consumed greater than 10 cannabis cigarettes weekly.¹⁵ The impact of cannabis use on testosterone is variable, as noted by a recent systematic review of 91 studies.¹⁵ A previous large-population study of Danish men aged 18-26 years old found 7% higher serum testosterone levels in those using cannabis compared to nonusers, while a former study of Italian men presenting for infertility demonstrated that users had lower serum testosterone than never-users.¹⁵ Analysis of the National Health and Nutrition Examination Survey data found an inverse association between THC abstinence duration and serum testosterone,²⁶ which suggests that the effects may be both acute and transient.

Effects on semen parameters. The preclinical and clinical literature most strongly supports the association between THC exposure and worsened semen parameters. THC activates the CB1 receptor present on sperm, which inhibits the acrosomal reaction and decreases motility by limiting the sperm mitochondrial transmembrane potential.¹⁵ Multiple studies have found that chronic exposure to recreational doses of THC is associated with decreased spermatogenesis.¹⁵ Two prior human studies^{27,28} have reported lower sperm counts in weekly THC users compared to never-users. Moderate THC use is associated with an OR of 3.4 for teratospermia,²⁹ and exposure in the prior 3 months is associated with OR of 1.94 for poor morphology in infertile men.¹⁵ Preclinical studies in rodents and canines also demonstrated that chronic THC exposure is associated with decreased spermatogenesis and spermatogenic arrest.^{10,15} However, the results of many of these studies were from a single semen collection, and there is a high degree of variation between semen samples from the same individual.

Time to conception. There is scant literature assessing whether regular cannabis use impacts the time to conception. A prior retrospective review used cross-sectional survey data of past-year use from 758 male respondents aged 15-44 years participating in the National Survey of Family Growth, which used population-based sampling from 121 geographic areas in the United States.³⁰ This study noted the time ratio to pregnancy for never-smokers vs daily users of cannabis in men was 1.08 (95% CI: 0.79-1.47), demonstrating no statistically significant impact of cannabis use or frequency of use on time to conception. Similarly, another study evaluating the association between male cannabis use and fecundability, the probability

of conception in a month or in a menstrual cycle, in Pregnancy Study Online, a prospective cohort of North American couples, reported little overall association.³¹ Wise et al showed that fecundability ratios for male cannabis use less than 1 and greater than or equal to 1 time per week relative to nonuse were 0.87 (95% CI 0.66 to 1.15) and 1.24 (95% CI 0.90 to 1.70), respectively.³¹ An increased frequency of cannabis use was observed in men reporting intercourse at least 4 times per week (fecundity ratio = 1.35, 95% CI 0.72 to 2.53).

IMPACT OF PATERNAL CANNABIS USE ON OFFSPRING OUTCOMES

There is growing evidence suggesting that paternal cannabis use during spermatogenesis can alter epigenetic regulation during spermatogenesis and impact offspring health, including brain and neurobehavioral development.^{10,32} Schrott et al reported that some methylation changes across the sperm methylome associated with cannabis exposure persisted despite discontinuation of cannabis³³ and were also detectable in offspring DNA methylation that was functionally related to changes in gene expression and cardiomegaly.³⁴ However, because THC abstinence for even 70 days (approximately 1 spermatogenic cycle) has been shown to diminish epigenetic alterations associated with cannabis use,^{33,35} providers should consider counseling patients to abstain from THC for at least 70 days prior to attempting to conceive. In addition, paternal cannabis use during pregnancy is associated with sudden infant death syndrome and poorer offspring mental health, in particular hyperactivity and attention deficit/hyperactivity disorder.³⁶

CANNABIS USE AND FEMALE REPRODUCTIVE HEALTH

Cannabinoid receptors, CB1 and CB2, are present in the hypothalamus, pituitary, ovary, and uterus, therefore, raising concern for the potential influence on the hormonal reproductive axis and female reproductive health.³⁷ Specifically, studies have suggested that cannabinoids may impact the secretion of gonadotropin-releasing hormone, follicle-stimulating hormone, and LH; ovulation; fecundability; in vitro fertilization success (eg, fewer oocytes retrieved and fertilized); and menstrual cyclicity (Figure 3).^{10,15,38} Alternatively, other studies have found no significant association between cannabis use and spontaneous conception rate.^{30,31}

GESTATIONAL EFFECTS OF MATERNAL CANNABIS USE

The prevalence of prenatal cannabis use in the United States has almost doubled in the past decade, and it is commonly used for nausea, pain, sleep, anxiety, stress, mood, and appetite in pregnancy.¹⁰ Currently, self-reported prenatal cannabis use in the United States is 2%-5% with some studies reporting up to 14%-28% in younger, urban-dwelling, single, and socioeconomically disadvantaged pregnant populations.¹⁰ Often pregnant individuals using cannabis engage in other substances including alcohol, tobacco, or other illicit drugs that can result in a synergistic and/or additive effect. The most

common modes of cannabis delivery in pregnancy are smoking, edibles, and vaping.

Half of female cannabis users continue to use throughout pregnancy in part because of the limited safety information; often women who continue to use cannabis in pregnancy perceive no general or pregnancy-specific risk compared to nonusers.¹⁰ The lack of safety data has also impacted the ability of health care providers to appropriately counsel or educate patients on the effects of prenatal cannabis use in pregnancy.¹⁰ As a result, patients have turned to the Internet and cannabis retailers as sources of information, where cannabis is often promoted as a safe, natural, and effective method for mitigating pregnancy symptoms.¹⁰

As THC can cross the placenta and CB1 and CB2 receptors are present in the placenta and major fetal organs, including the brain, there is concern for adverse fetal and neonatal outcomes with prenatal cannabis exposure.^{10,15} **The emerging literature suggests that prenatal cannabis exposure is associated with a negative impact to the developing fetus and offspring (Figure 4).** As a result, the United States Surgeon General, American College of Obstetricians and Gynecologists, and the American Academy of Pediatrics recommend that pregnant individuals be informed regarding the potential risks of prenatal cannabis use and advised to abstain from use in pregnancy and during lactation.

Pregnancy loss and still birth. Previous studies have not demonstrated a significant association between maternal cannabis use and miscarriage or stillbirth, but many of these studies are limited by confounders such as tobacco use that are also associated with adverse perinatal outcomes.¹⁰ Mumford et al studied 1,228 women with a history of pregnancy loss in a prospective cohort study assessing whether cannabis use via urinary metabolites and self-report preconception is associated with fecundability, live birth, and preg-

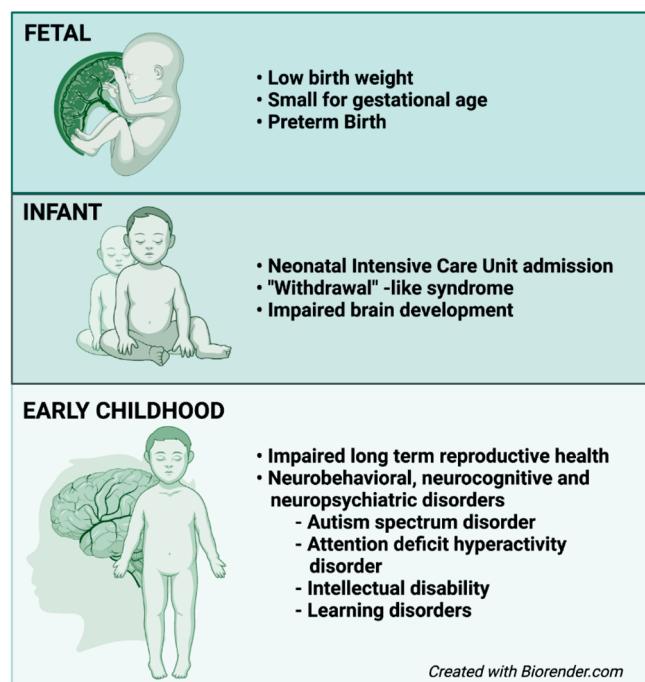


Figure 4. Impact of prenatal cannabis exposure.

nancy loss.³⁹ They reported that women with preconception cannabis use had reduced fecundability (fecundability ratio 0.59; 95% CI 0.38 to 0.92) and suggestive associations with anovulation (RR 1.92, 95% CI 0.88 to 4.18) and live birth (42%, 19/45) vs nonusers (55%, 578/1,043; RR 0.8, 95% CI 0.57 to 1.12).³⁹ No associations were observed between preconception cannabis use and pregnancy loss (RR 0.81, 95% CI 0.46 to 1.42).³⁹

Preterm birth. The existing data suggest an increased risk of preterm birth (delivery prior to 37 weeks' gestation) with prenatal cannabis exposure.^{9,10,15} Several prior systematic reviews and meta-analyses, including those adjusted for concomitant tobacco use, found that maternal cannabis use significantly increased risk for preterm delivery.^{9,10,15}

Birth weight. Overall, multiple studies suggest there is an association with low birth weight, with the association ranging from 84 to 256 g.^{9,10,15} However, studies do not consistently adjust for cofounders such as nicotine use.

Neonatal intensive care unit admissions. The most recent systematic review and meta-analysis reported that cannabis use in pregnancy is associated with an increased risk of neonatal intensive care unit admission (RR 1.38, 95% CI 1.18 to 1.62, $P < .001$).⁹ Within these same studies there were no significant differences found in the outcomes of mean gestational age (in weeks), risk of 5-minute Apgar scores less than 7, mean Apgar score at 5 minutes, or mean infant length (in centimeters).

Teratogenicity. The limited studies focused on teratogenicity and prenatal cannabis use are conflicting and inconsistent. However, there are reports of congenital anomalies associated with maternal cannabis use including acrania, gastroschisis, esophageal atresia, and congenital diaphragmatic hernia.¹⁰

Infant and childhood outcomes. In utero cannabis exposure has been associated with newborn withdrawal-like symptoms and increased aggression in addition to attention deficits in offspring as early as 18 months of age.¹⁰ Preschool-age children exposed

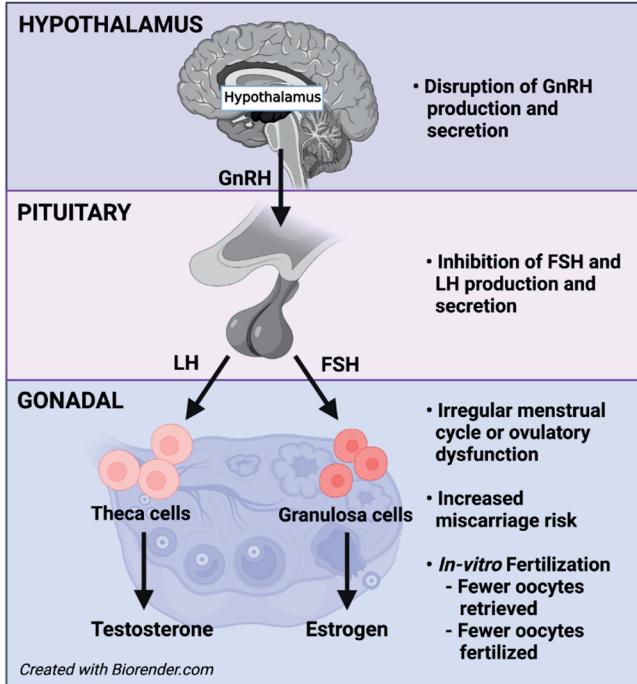


Figure 3. Effect of cannabis use on female reproductive health and fertility. FSH indicates follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

prenatally to cannabis have demonstrated increased abnormal verbal and visual reasoning, impulsivity, hyperactivity, and attention deficit. **Both animal and human studies have also shown that prenatal THC exposure has been associated with an increased risk for substance use, neurocognitive and neuropsychiatric disorders, delinquency of behavior, enhanced heroin-seeking profiles, and altered areas of the brain associated with behavioral responses to various environmental stimuli.**¹⁰ A large retrospective Canadian study noted an increased incidence of autism spectrum disorder, with an incidence of 4 per 1,000 person-years among those exposed to cannabis compared to 2.42 among the unexposed children.⁴⁰ Additionally, those exposed to cannabis prenatally had a higher incidence of intellectual disability and learning disorders; however, this was notable as residual confounding was not adjusted for.

CONCLUSIONS

In summary, cannabis use is rising in the United States and worldwide, especially among reproductive-age individuals, and of concern is the paucity of safety data regarding the impact on reproductive health, pregnancy, and offspring

outcomes. The limited existing literature suggests that paternal and maternal cannabis use has adverse health implications including for subsequent offspring. In the meantime, it is important to focus research efforts on bridging gaps in knowledge and to better educate health care providers, improve patient awareness, and increase public health initiatives regarding the potential adverse effects of cannabis use.

DID YOU KNOW?

- Cannabis use can negatively affect male fertility and reproductive health.
- Exposure to cannabis can alter the sperm methylome and potentially affect offspring health, including brain and neurobehavioral development.
- Chronic cannabis use can impact female reproductive health, including menstrual cyclicity and ovulation.
- Prenatal cannabis exposure is associated with adverse short- and long-term offspring outcomes.

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Study Questions Volume 42 Lesson 35

1. Which male fertility factor is most strongly associated with delta-9-tetrahydrocannabinol use?
 - a. Follicle-stimulating hormone
 - b. Luteinizing hormone
 - c. Testosterone
 - d. Sperm parameters
2. What are the current recommendation(s) regarding the use of cannabis when attempting to conceive or during pregnancy?
 - a. Edibles are safe, but avoid smoking cannabis
 - b. Low potency cannabis can be used
 - c. Cannabis should be avoided
 - d. Synthetic cannabinoids are a safe alternative
3. Long-term cannabis use can most likely result in
 - a. Cannabis use disorder and addiction
 - b. Impaired motor coordination
 - c. Paranoia
 - d. Altered judgment
4. Frequent prenatal cannabis use is associated with which of the following?
 - a. Low birth weight
 - b. Teratogenicity
 - c. Stillbirth
 - d. Aneuploidy
5. Exposure to cannabis prenatally most likely increases the risk to subsequent offspring of which condition(s)?
 - a. Short stature
 - b. Fetal alcohol spectrum disorder-like impairment
 - c. Substance use and addictive behaviors
 - d. Decreased motor coordination