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Effects of marijuana on reproductive health: preconception and gestational effects

Kimberly S. Ryan[a,*], **Jasper C. Bash**[b,*], **Carol B. Hanna**[c], **Jason C. Hedges**[b], **Jamie O. Lo**[a,c]

[a]Department of Obstetrics and Gynecology, Oregon Health & Science University, Portland

[b]Department of Urology, Oregon Health & Science University, Portland

[c]Division of Reproductive & Developmental Sciences, Oregon National Primate Research Center, Oregon Health & Science University, Beaverton, Oregon, USA

Abstract

Purpose of review—Recent widespread legalization changes have promoted the availability of marijuana and its increased potency and perceived safety. The limited evidence on reproductive and perinatal outcomes from marijuana exposure is enough to warrant concern and action. The objective of this review is to provide a current and relevant summary of the recent literature surrounding this topic.

Recent findings—The available published studies on the effect of marijuana exposure on reproductive health and pregnancy outcomes are conflicting. Human studies are often observational or retrospective and confounded by self-report and polysubstance use. However, the current, limited evidence suggests that marijuana use adversely affects male and female reproductive health. Additionally, prenatal marijuana exposure has been reported to be associated with an increased risk of preterm birth and small for gestational age infants.

Summary—With the increasing prevalence of marijuana use, there is an urgent need for evidence-driven recommendations and guidelines for couples interested in conception, affected by infertility or who are expecting. At this time, no amount of marijuana use during conception or pregnancy is known to be well tolerated and the limited available evidence suggests that the safest choice is to abstain.

Keywords

cannabis; fertility; marijuana; maternal substance use; pregnancy; reproductive function; reproductive health

Correspondence to Jamie O. Lo, MD, Department of Obstetrics and Gynecology, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Mail Code L458, Portland, OR 97239, USA. Tel: +1 503 494 2101/503 679 2025; fax: +1 503 494 5296; loj@ohsu.edu.

*Kimberly S. Ryan and Jasper C. Bash contributed equally to the work.

Conflicts of interest

There are no conflicts of interest.

INTRODUCTION

Marijuana is the most commonly used drug worldwide [1], especially among men and women of reproductive age. This is concerning as marijuana use may affect both male and female reproductive health by interfering with the body's innate endocannabinoid system. Cannabinoid receptors are present throughout the body, including the hypothalamus, pituitary, ovary, uterus, testes, and sperm [2].

Research to date suggests that marijuana use may affect the processes involved with reproduction including the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), testosterone, menstrual cyclicity, ovulation, and sperm parameters [2]. Additionally, as its main active ingredient, delta-9-tetrahydrocannabinol (THC), can cross the placenta, there is concern for potential harmful effects to the developing fetus and offspring from maternal use during pregnancy and lactation.

Most of the marijuana research that exists surrounding its effects on reproductive health and pregnancy are limited and conflicting. The majority of the available human studies are observational or retrospective, confounded by polysubstance use, and rely on self-report thus contributing to the heterogeneity in reported results [3]. Prior animal studies primarily studied the effects following acute marijuana exposure, often intravenous, which is not representative of human use. Contemporary marijuana products and edibles also have higher quantities of THC than when much of the existing marijuana research was performed [4–6].

This review aims to summarize the literature and provide an update on our current understanding of marijuana use exposure for an understudied but timely aspect of reproductive health and pregnancy that will open an important area of inquiry into better understanding how marijuana exposure can impact a couples' fertility and pregnancy outcomes.

EFFECTS OF DELTA-9-TETRAHYDROCANNABINOL ON FEMALE REPRODUCTIVE HEALTH PRECONCEPTION

The available human literature on the effects of marijuana use on female reproductive health is limited and largely derived from women undergoing assisted reproductive technology.

The effects of acute delta-9-tetrahydrocannabinol exposure in preclinical models

Early studies mostly used small animal models to study the effects of THC and the impact of acute exposure on the hormonal axis, including the hypothalamus and anterior pituitary. An older study in proestrus rats demonstrated that the administration of THC (2 mg per rat) suppressed plasma levels of LH, FSH, and prolactin and delayed ovulation by 24 h [7]. Chakravarty *et al.* [8] also revealed that intraperitoneal administration of high, acute doses of THC in rats significantly decreased serum LH and prolactin. Proestrus rats exposed to THC had a significant dose–response decrease in hypothalamic LH-releasing hormone content, suggesting a possible hypothalamic impact from THC use [8]. Additionally, serum prolactin levels were decreased while LH and FSH serum levels were similar to that of dioestrous rats [8]. Another former study noted that THC exposure in dioestrous female rats significantly

decreased plasma concentrations of LH and FSH, whereas those post ovariectomy had varying responses [9].

The effects of chronic delta-9-tetrahydrocannabinol exposure in preclinical models

The nonhuman primate (NHP) is a strong translational model because of its similar plasma disposition of THC [10] and menstrual cycle lengths to that of humans [11–13]. Several reports have used this model to study the implications of chronic THC use. In a study by Asch *et al.* [14], daily THC was administered by intramuscular injection to regular cycling NHPs the first 18 days of the menstrual cycle and anovulation was subsequently observed in a majority of the female individuals, supporting the prior findings described in rats [7]. Another study injected regular cycling NHPS ($n = 5$) with THC (2.5mg/kg/day) three times a week on varying days over 230 days total or two consecutive ovulatory cycles [15]. Initially, the animals became anovulatory with abnormal serum hormones, however, with tolerance to THC, they eventually restored normal menstrual cyclicity, ovulation and hormone levels [15]. Similarly, in ovariectomized NHPs, regular intramuscular injections of THC resulted in a reversible reduction in LH levels [16]. A more recent study ($n = 8$) of chronic THC, edible consumption reported that increasing doses of THC (0.625, 1.25, 2.5, or 5mg/kg) resulted in a dose–response relationship of significantly increased menstrual cycle length and FSH levels suggestive of ovulatory dysfunction [17■■].

Overall, the research reports concerning the effects of THC on reproductive health have indicated that the major pharmacologic site of action is central in both NHPs [18–20] and other animal models [8,21,22], whereas other studies have indicated a direct THC effect at the gonadal level [7].

The effect of marijuana use on female reproductive health in humans

Many human studies have reviewed women's perception of marijuana use in relation to fertility. Within a cross-sectional study, 270 infertility patients were surveyed regarding marijuana usage, perception of the effect on infertility and pregnancy, and cessation because of infertility [23■]. Of those surveyed, 13% reported marijuana use and those who used more recently were less likely to think that marijuana can negatively impact fertility. Additionally, the perception of harm from marijuana varied with form of use. Particularly, edibles have gained popularity and are perceived to be safe despite evidence of increased danger from over intoxication [24].

Effects of delta-9-tetrahydrocannabinol on fertility outcomes

A study from 1990 found that women who had smoked marijuana within 1 year of trying to conceive were twice as likely to have infertility because of ovulatory dysfunction than their counterparts who did not use marijuana [relative risk (RR) = 2.1; 95% confidence interval (CI) 1.1–4.0] [25]. However, a recent observational study ($n = 4200$) found little association between female marijuana use and spontaneous conception rates after controlling for confounders [26]. Similarly, retrospective review of cross-sectional survey data from female respondents noted no significant impact of marijuana use on time to conception [27]. Most recently, a secondary analysis of women with a history of prior first trimester pregnancy loss

found preconception marijuana use to be associated with reduced fecundability despite an increased frequency of intercourse [28■■].

Effects of delta-9-tetrahydrocannabinol on assisted reproductive technology outcomes

Research studying the effects of THC on ART outcomes have noted that the amount of lifetime heavy marijuana use adversely affects in-vitro fertilization and gamete intra-fallopian transfer (IVF/GIFT) [29]. In a prospective study of 221 couples, women who smoked marijuana within lyear prior to IVF/GIFT had 25% fewer oocytes retrieved and these couples also had 28% fewer oocytes fertilized [29]. A more recent prospective study found that among women undergoing ART with a positive beta-human chorionic gonadotropin (bHCG), those who were marijuana smokers at enrollment had more than double the adjusted probability of pregnancy loss than past marijuana smokers or nonmarijuana smokers (54 vs. 26%; $P = 0.0003$) [30].

EFFECTS ON MALE REPRODUCTIVE HEALTH PRECONCEPTION

Marijuana is the most commonly used drug in the United States [1] and is most prevalent among men of reproductive age, thus understanding its impact on male fertility is critical [31]. It is plausible that marijuana can disrupt sperm function as cannabinoid one receptors (CB1) are present on sperm and the endocannabinoid system has a role in regulating male reproduction [32–35]. The available human literature is variable partly as studies are often from assisted reproductive centers or have polysubstance abuse histories, limiting the generalizability of the findings and precluding determination of a causal effect specific to marijuana [26,20,36–38].

The effects of delta-9-tetrahydrocannabinol on male reproductive hormones

The hypothalamic–pituitary–gonadal (HPG) axis plays a critical role in both spermatogenesis and testosterone production. This axis regulates the release of two vital gonadotropin hormones for reproduction, FSH and LH, which act on cells in the testes including Leydig cells, which produce testosterone.

Follicle-stimulating hormone and luteinizing hormone

The few studies that have investigated the effect of acute or chronic marijuana exposure on FSH levels in male individuals have found minimal effect [39], nor did it alter their FSH response to exogenous gonadotropin-releasing hormone (GnRH) [40]. In contrast, there is robust evidence to support the inhibitory effect of marijuana on LH. A prior study noted that plasma LH levels are significantly reduced 60 min after administration of low dose THC in male rats (0.5 mg THC/kg body weight) [41]. Vescovi *et al.* [40] studied daily marijuana users ($n = 10$) and never-user controls ($n = 10$) aged 19–20 years old, and reported significantly lower serum LH levels in users, as well as a weaker LH response to exogenous GnRH. Similar findings were noted by Cone *et al.* [39] that plasma LH was significantly depressed after smoking marijuana cigarettes versus placebo cigarettes. In a study comparing two groups of chronic THC users, no difference in LH was noted between those who smoked five to nine cigarettes weekly versus more than ten cigarettes weekly, suggesting an upper limit on the dose-dependent effect of THC on LH [42].

Testosterone

A recent systematic review of 91 articles noted that existing literature regarding chronic THC consumption and testosterone changes are mixed [43]. In-vivo acute (10 mg/kg) and chronic (2 mg/kg) THC exposure in rats caused decreased testosterone bio-synthesis [44], whereas mice showed a dose-dependent decrease in testicular LH receptor expression in the testes when similarly exposed [45]. Long-term THC exposure in mice resulted in a blocked testosterone response to HCG in the testes whereas a single oral THC dose caused decreased LH and serum testosterone levels [46]. The above preclinical findings support multifactorial causes for hypogonadism in THC-exposed male individuals, which is less well studied in the human literature. A large group of young Danish men ages 18–28 years old reported 7% higher testosterone levels in THC users compared with nonusers [47]. A subsequent study using the National Health and Nutrition Examination Survey (NHANES) database found no difference in testosterone levels between marijuana ever-users ($n = 1055$) and never users ($n = 533$) [48]. They did report an inverse relationship between duration of THC abstinence and testosterone levels, suggesting that the effect of THC on testosterone may be more acute and transient [48].

Testicular size

Preclinical research suggest a dose-dependent association between chronic marijuana use and reduction in the prostate and seminal vesicle weight [45,49–51] of mice and rats as well as testicular atrophy in dogs [52]. The mechanism for these findings is unclear but may be secondary to oxidative stress secondary to the significant decrease in antioxidant enzymes noted in affected testicles [53,54].

The effects of delta-9-tetrahydrocannabinol on semen parameters and sperm

A number of animal and human studies have reported that the most deleterious effects of marijuana on male reproductive capacity is its impact on semen parameters but this has not been adequately confirmed [36,42,46,47,55–57].

Sperm count and concentration

Studies in mice, rats, and dogs indicate that chronic use of recreational doses (3–12.5 mg/kg/day) of THC lead to decreased spermatogenesis and spermatogenic arrest [45,49,52,57]. Similarly, prior human studies, largely in men presenting for infertility evaluation, have also demonstrated reduction in sperm count and concentration after THC exposure [27,37,58]. In the Danish cohort described previously, weekly THC users had dramatically lower sperm counts than never users [47]. A case–control study of chronic weekly users ($n = 12$) and never users ($n = 12$) also found significantly lower sperm concentrations in the users but no change to their volume, motility, or morphology [59].

Morphology

THC can also affect sperm morphology. In a study of 229 Jamaican men presenting to establish primary care, 47% reported marijuana use of which, 21% recently used [60]. Recent and high-dose use had odds ratios (OR) of 2.6 and 4.3, respectively for asthenospermia whereas moderate quantity users had an OR of 3.4 for teratospermia [60].

A larger study of over 1900 men from infertile couples reported an OR of 1.94 for poor morphology in those with THC exposure in the prior 3 months [58].

Motility

Motility and metabolism are also diminished in the sperm after THC exposure. Activation of the sperm CB1 receptor has been shown to reduce sperm mitochondrial transmembrane potential [61] as well as limit the acrosomal reaction [62]. Whenever applied to sperm *in vitro,* THC caused an immediate decline in sperm mitochondrial oxygen consumption, though whole semen did have a protective effect [63]. In addition, when challenged with both recreational and therapeutic levels of THC, sperm motility and acrosomal reaction were decreased in a dose-dependent manner, with more pronounced effects in sperm that were weaker at baseline [36].

Sperm epigenetics

There is evidence of associations between THC exposure and altered DNA methylation of sperm in humans and rats [59]. Another study using a rat model noted that exposure to THC and nicotine alters sperm DNA methylation of active neurodevelopmental genes [64■■]. These studies suggest possible preconception paternal reproductive risks associated with cannabis use.

Clinical effects

Marijuana's clinical effect on sexual function has been investigated in both preclinical models and humans, with general conclusion that THC increases sexual desire but may limit coital performance.

Erectile dysfunction

Marijuana use has been associated with erectile dysfunction; Elbendary *et al.* [65] demonstrated that chronic use can potentially induce early endothelial damage. In humans, a survey of 1203 men in 2006 found a significant association between marijuana use and inhibited orgasm (OR 1.76) but no increased risk of low sexual desire or excitement. Similar results were reported in a computer-assisted telephone survey of 8656 Australians where 8.7% used marijuana in the previous year: 1.5% reported daily use, 1.5% weekly use, and 5.8% less often than weekly use [66]. Daily use was associated with orgasmic disorders in men: inability to reach orgasm (OR 3.94), reaching orgasm too quickly (OR 2.68), or too slowly (OR 2.05) [66]. A prior systematic review and meta-analysis of five case–control studies found that erectile dysfunction was twice as high in marijuana users compared with controls [67].

Sexual function

The evidence supporting marijuana as an aphrodisiac is strong. Marijuana use is independently associated with increased sexual frequency, and daily use carries an increased likelihood of reporting two or more sexual partners in the previous year (OR 2.08 for men, 2.58 for women) [66,68]. When surveying 325 men visiting a marijuana dispensary, Bhambhvani *et al.* [69] found increased marijuana use was associated with increased erectile

function, orgasm function, and sexual satisfaction, but no correlation with the type of marijuana product or delivery method.

GESTATIONAL EFFECTS OF MATERNAL MARIJUANA USE

Marijuana is the most common illicit drug used during pregnancy [70,71]. At present, the United States Surgeon General [72] and American College of Obstetricians and Gynecologists [71] advise pregnant and lactating patients to abstain from using marijuana. However, as the current safety data is insufficient, approximately half of marijuana users continue to use throughout pregnancy, especially for its anti-emetic properties, particularly in the first trimester during a developmentally vulnerable period. A recent study found that cannabis use disorder (CUD) in pregnancy increased from 2.8 to 6.9 per 1000 deliveries from 2001 to 2012 [73■]. The available published studies on marijuana exposure in pregnancy are limited but support some degree of developmental disruption associated with maternal marijuana use. Prenatal marijuana exposure has been associated with stillbirth, intrauterine growth restriction (IUGR), fetal neurodevelopmental consequences [74–81], and impaired offspring cognitive development [77,79,82]. However, most of the prenatal marijuana research that exists, including animal studies, was performed in the 1980s, reflecting marijuana exposure largely through smoking, with few reports studying doses and routes of administration that are comparable or relevant to contemporary use [83–87].

Pregnancy loss

Studies on preconception marijuana use and pregnancy loss are limited but largely do not support an association [28■■]. Overall, there does not appear to be any statistically significant association between prenatal marijuana use and stillbirth or miscarriage [77,88–90] but often studies that report an association are partially confounded by polysubstance use, especially co-use of tobacco and marijuana, or are under powered to detect such an association. A large case–control study by the Stillbirth Collaborative Research Network found that marijuana use was significantly associated with stillbirth (OR 2.34, 95% CI 1.13–4.81) but the effect was partly confounded by tobacco use [75].

Fetal and neonatal outcomes

In general, the literature is mixed but support an association between any prenatal marijuana used and an increased risk of preterm delivery [91–93], decreased birth weight ranging from an 84 to 256 g difference [88,91,94,95] and neonatal ICU (NICU) admissions [90,91]. There has not been strong evidence to support an increase of congenital anomalies from periconceptional marijuana use [9,90] but anomalies previously described involve the cardiac, genitourinary, gastrointestinal, and central nervous system [96–99].

Most recently, a large, population-based retrospective cohort ($n = 661617$) in Ontario, Canada found that any self-reported maternal marijuana use in pregnancy was significantly associated with an increased risk of preterm birth (RR 1.41, 95% CI 1.36–1.47), small for gestational age (RR 1.53, 95% CI, 1.45–1.61), placental abruption (RR 1.72, 95% CI, 1.54–1.92), transfer to neonatal intensive care (RR 1.40, 95% CI, 1.36–1.44), and 5 min Apgar score less than 4 (RR 1.28, 85% CI, 1.13–1.45) [100■]. Another recent, large

retrospective study found that prenatal CUD was associated with greater odds of being small for gestational age (OR = 1.13, 95% CI = 1.07–1.2), preterm birth (OR = 1.06, 95% CI = 1.01–1.12), low birth weight (OR = 1.13, 95% CI = 1.07–1.20), and death within 1 year of birth (OR = 1.35, 95% CI = 1.12–1.62) [73■]. In particular, infants whose mothers were Hispanic had a higher likelihood of hospitalization and death and infants born to non-Hispanic black mothers had greater odds of being small for gestational age [73■].

Childhood outcomes

Currently, there is insufficient evidence to establish a strong association between prenatal marijuana exposure and later offspring outcomes including sudden infant death syndrome, cognition, academic achievement, and later substance abuse [101]. The literature consists largely of three main large, longitudinal cohort studies from 1970 to 2001 when marijuana was largely smoked and the potency of THC was lower [77,82,102,103]. Prior human studies have suggested that prenatal marijuana exposure may affect neurological development in offspring. In babies, an increased incidence of altered responses to visual stimuli, trembling, and high-pitched cry [104] have been reported. School-aged children have been shown a greater likelihood for gaps in problem-solving skills and memory, symptoms of depression and anxiety, and decreased attention span [105,106]. Adolescents haver a higher tendency towards delinquency and marijuana use by age 15 years old [79,107]. Most recently, Corsi *et al.* found an association between prenatal marijuana use and the incidence of autism spectrum disorder in the offspring [108■■], 4 per 1000 person-years among children with prenatal marijuana exposure compared with 2.42 among unexposed children (OR 1.51, 95% CI 1.17–1.96) [108■■]. Overall, the incidence of intellectual disability and learning disorders was higher in offspring exposed to marijuana prenatally but not statistically significant [108■■].

CONCLUSION

Marijuana is becoming more prevalent, especially among those of reproductive age, because of increasing accessibility, secondary to the shifting legal landscape and in parallel, the perception of safety. At this time, there is sufficient evidence of harm to warrant avoiding marijuana when attempting to conceive or when pregnant or breastfeeding. However, more research on the safety of marijuana is needed for healthcare providers to better counsel users regarding its effects on fertility or offspring.

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KEY POINTS

- Chronic marijuana use can negatively affect female reproductive health and result in ovulatory dysfunction, menstrual cycle irregularity, and reproductive hormones.
- Long-term marijuana use adversely affects male reproductive function and has been associated with testicular atrophy, low libido, sexual dysfunction, semen parameters, and reproductive hormone levels.
- Prenatal marijuana use does not increase the risk of pregnancy loss but may be associated with preterm birth, decreased birth weight, and neonatal ICU admissions.