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The effects of cannabis on female and male reproduction

More high-quality evidence is needed before physicians can reassure patients that marijuana use will not affect their fertility or their offspring.

ABSTRACT: Products of the *Cannabis sativa* plant, including marijuana and hashish, are the most popular recreational drugs in North America. In October 2018, smoking recreational cannabis became legal in Canada. At that time British Columbia had the second-highest per capita cannabis consumption level in the country. With legalization, consumption levels in Canada and BC are expected to rise. This is concerning because both female and male reproductive function may be affected by the ability of cannabis to interfere with the body's natural endocannabinoid system. Cannabinoid receptors have been isolated in the hypothalamus, pituitary, ovary, endometrium, testes, and spermatozoa. Research to date suggests marijuana affects some of the central processes of reproduction, including the release of follicle-stimulating hormone and luteinizing hormone, ovulation, sperm motility, fertilization, and placentation. Although large-scale population surveys have yet to demonstrate a delayed time to pregnancy or a consistent increase in perinatal complications, it seems reasonable to avoid cannabis when attempting to conceive. The Society of Obstetricians and Gynaecologists of Canada believes there is sufficient evidence of harm to advise women to avoid cannabis when preg-

nant or breastfeeding. Until we have high-quality evidence that cannabis is safe, physicians cannot reassure users that consumption will not affect their fertility or their offspring. With the legalization of cannabis, patients may be more forthcoming about their consumption and researchers may be able to generate more accurate data on reproductive outcomes.

On 17 October 2018, it became legal in Canada for adults age 19 and older to smoke products of the *Cannabis sativa* plant for recreational purposes.¹ Before legalization, according to Statistics Canada, 27% of people age 15 to 24 and 13% of people 25 and older were using cannabis.² This amounted to 4.6 million Canadians who reported consuming products of the cannabis plant, which include marijuana and hashish.² In 2017 British Columbia had the second-highest per capita cannabis consumption level in Canada at 24.6 grams per person per year.³

In the United States marijuana is the most popular recreational drug (excluding alcohol and tobacco) and the drug rising fastest in popularity.⁴ As of November 2018, 33 states permitted the use of marijuana for medical purposes and 10 of these had also decriminalized recreational use.⁵ Between 2001 and 2013, marijuana use among US adults more than doubled. This jump was attributed to legalization of the drug in many states and the increasingly permissive attitudes that followed.⁶ The National Survey on Drug Use and Health found a 62% increase in marijuana use by pregnant women between 2002 and 2014, with the prevalence

of past-month marijuana use highest in those age 18 to 25.⁶

Canada can learn some important lessons from the United States. First, cannabis products will continue to rise in popularity with legalization. Second, the fertility of men and women in their reproductive prime may be affected by marijuana use. As physicians it is imperative that we understand the research, or lack thereof, regarding cannabis and reproduction to guide our patients in this new era.

Consumption and effects

Over 500 different compounds are found in *C. sativa*, and at least 100 of these are cannabinoids.⁵ Tetrahydrocannabinol (THC) is the high-inducing component of marijuana.

Cannabis is consumed as raw plant materials and extracts that are smoked or converted into edibles for ingestion.⁵ Smoking is currently the most popular form of consumption but ingestion may eventually surpass smoking in popularity. According to *Current Opinion in Food Science*, ingestion of cannabis creates a slower, longer-lasting experience than smoking because a more psychoactive form of THC (11-hydroxy- Δ^9 -tetrahydrocannabinol) is created in the liver by cytochrome P-450.^{5,7}

Beyond the detrimental respiratory effects of inhaling burning plant material, excess consumption of cannabis products can lead to nausea, vomiting, and disorientation.^{5,8} Contaminants such as pesticides, metals, and microbial toxins are also potential sources of harm.⁵

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This article has been peer reviewed.

The endocannabinoid system

The endocannabinoid system is composed of endogenous cannabinoids found throughout the human body. These naturally occurring neurotransmitters bind to cannabinoid receptors. The two most commonly studied molecules are N-arachidonylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG), which target two main cannabinoid receptors: CB1 (found largely in the central nervous system) and CB2 (found largely in the immune system).⁹ These receptors have also been found in reproductive organs such as the endometrium (CB1 only) and the ovaries and testes (both CB1 and CB2).^{9,10}

THC acts as an exogenous ligand of the cannabinoid receptors. Compared with endogenous cannabinoids, however, THC has a much more pronounced effect that some experts have described as “clinically concerning.”⁹

Cannabis and female fertility

The first requirement for normal female reproduction is a functioning hypothalamic-pituitary-ovarian (HPO) axis. Pulses of gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulate the pituitary to release follicle-stimulating hormone (FSH), predominantly in the follicular phase, and luteinizing hormone (LH), predominantly in the luteal phase. Sex steroids are subsequently produced at the level of the ovary. FSH stimulation makes estrogens, and LH stimulation makes androgens and progesterone. It is only when these three structures are operating in a normal, cyclic pattern that an ovarian follicle can be induced to mature and ovulate. After ovulation, the newly formed corpus luteum needs LH stimulation to produce the progesterone that supports the endometrium for embryo implantation.

Exogenous cannabinoids can interfere with the intricate balance of HPO signaling at every level. For example, high levels of endocannabinoids and exogenous cannabinoids have been shown to suppress the release of GnRH, FSH, and LH.⁹ Studies in rats have found that large quantities of THC inhibit ovulation.^{9,11} Studies in humans have been largely observational, but moderate/heavy users of marijuana seem more likely to present with infertility related to ovulatory disorders.^{9,12-14} Disturbances to the

endocannabinoid system may also contribute to polycystic ovary syndrome through dysregulation of appetite and glucose metabolism.^{9,15}

Despite evidence that marijuana can disrupt ovulation, large-scale cohort studies have failed to demonstrate a prolonged time to pregnancy in women who use the drug. The Pregnancy Study Online followed 1125 couples prospectively from 2013 to 2017, tracking their fertility rates and self-reported marijuana use.¹⁶ The study authors concluded that there was little association between female or male marijuana use and fecundability.¹⁶ Another large observational study, the American National Survey for Family Growth, reported that 16.5% of men and 11.5% of women used marijuana while trying to conceive.⁴

Of the 758 male and 1076 female respondents, the time ratio to pregnancy for never users versus daily users was 1.08 in men (95% CI, 0.79-1.47) and 0.92 in women (95% CI, 0.43-1.95).⁴ The authors concluded that marijuana use in any frequency does not prolong the time to pregnancy.

Cannabis and pregnancy

After the legalization of cannabis, the Society of Obstetricians and Gynaecologists of Canada launched a campaign urging pregnant and breastfeeding women to avoid using the drug.¹⁷ No clinical practice guideline has been developed yet, but the *Journal of Obstetrics and Gynaecology Canada* recently published a review article on the subject.¹⁸ In it, the authors highlight the potential for cannabis to cause harm. However, they also state that the effects of cannabis use in pregnancy remain “largely unknown.”¹⁸ Those who research marijuana’s effects face the formidable challenge of controlling for confounding factors such as concomitant use of other drugs and socioeconomic influences.¹⁸

THC and its metabolites can cross the placenta.¹⁹ THC has been isolated in cord blood

samples and maternal blood samples taken simultaneously, with the cord blood containing levels three to six times lower than the maternal blood.^{19,20} Cannabis products can also be found in breast milk during lactation and are metabolized by the infant.²¹

There is evidence that prenatal exposure to cannabis may stunt fetal growth and lead to enduring neurobehavioral effects.^{18,22} A review from the Canadian Centre on Substance Use and Addiction states that prenatal exposure to cannabis can “alter neurodevelopment, leading to adverse effects on cognition and academic achievement.”²¹ Hyperactivity, impulsivity, attention deficits, and increased likelihood of substance abuse are listed as risks.²¹

CB1 receptors are also believed to play a significant role in regulating mitochondria and cellular adenylyl cyclase.⁹ THC has the potential to induce mitochondrial dysfunction, leading to oxidative stress and vascular dysregulation in the placenta.⁹

A recent study of British Columbia’s Perinatal Data Registry reviewed records for 243 140 women to measure drug consumption as documented on antenatal history forms completed from 2008 to 2016.²³ Over the 8-year study period, the proportion of pregnant women who used cannabis rose from 2.2% to 3.3%. Cannabis use during pregnancy was associated with an increased risk of poor perinatal outcomes, including small for gestational age (adjusted OR 1.47; 95% CI, 1.33-1.61), preterm birth (adjusted OR 1.27; 95% CI, 1.14-1.42), and intrapartum stillbirth (adjusted HR 2.84; 95% CI, 1.18-6.82). Women were also more likely to have used other illicit substances during pregnancy and to have a history of mental illness.²³ Like many studies on this subject, the authors relied on self-reported data, which means that actual cannabis use may have been underestimated.

A systematic review of 31 studies published by the American College of Obstetricians and Gynecologists included 7851 patients who used

The use of cannabis products will almost certainly increase in British Columbia. Furthermore, population studies have consistently shown that men and women of reproductive age are the highest users of marijuana.

marijuana during pregnancy and 124 867 who did not.²⁴ The initial, unadjusted analysis of the two groups showed an increased risk for low birth weight (15.4% vs 10.4%; RR 1.43, 95% CI, 1.27-1.62) and preterm delivery (15.3% vs 9.6%; RR 1.32, 95% CI, 1.14-1.54). However, when the authors controlled for confounding factors, primarily tobacco use, these risks were no longer statistically significant. They concluded that “the association between maternal marijuana use and adverse outcomes appears attributable to concomitant tobacco use and other confounding factors.”²⁴

Some women use marijuana in pregnancy because they believe it is safe. A qualitative study of pregnant women found that while they reported trying to reduce marijuana consumption because of potential risks, women believed it was “more natural and safer than other substances, including prescribed medicines.”²⁵ Women frequently justified their marijuana use because it treated pregnancy-related nausea and allowed them to provide nourishment to the fetus by eating. Many women in the study expressed concern that smoking marijuana might affect their babies; the list of perceived harms included asthma, memory function, and eczema. Interestingly, the authors note, “the one perceived risk of prenatal marijuana use about which there was universal agreement was the risk of being reported to child protective services if found using marijuana at the time of delivery. . . . They perceived this involvement as negative, as it was felt to be stigmatizing.”²⁵

A randomized controlled trial of marijuana use in pregnancy is obviously not feasible. However, the medical community recognizes the urgent need for better research in this area and studies that look at the implications of cannabis consumption for pregnancy and prenatal development are reportedly being prioritized by the Canadian Institutes of Health Research.¹⁸

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Cannabis and sperm function

Not surprisingly, more studies have considered the effects of cannabis on male reproduction than on female reproduction and offspring, probably in part because sperm is more accessible than oocytes and embryos.

Several aspects of the endocannabinoid system have been shown to play a role in male reproductive function. Like females, males also need a functional HPO axis to produce spermatozoa and sex steroids. Hypothalamic GnRH leads to FSH and LH production in the testes. This maintains spermatogenesis in the Sertoli cells and testosterone production in the Leydig cells. CB1 receptors are present in the anterior pituitary, Sertoli cells, and Leydig cells, while CB2 receptors are present in Sertoli cells.²⁶ Several studies have shown that disruption of the endocannabinoid system alters secretion of anterior pituitary hormones and decreases testosterone production.²⁶⁻²⁹

Spermatozoa contain both CB1 and CB2 receptors and are exposed to endocannabinoids in the epididymis.^{26,30} Alteration in the delicate balance of endocannabinoids within the seminal plasma has the potential to lower sperm count and motility.³¹

Sperm also appears to be susceptible to damage from THC exposure.^{32,33} In one study, sperm samples from 78 men were exposed in vitro to concentrations of THC equivalent to a therapeutic-use plasma level (0.032 μ M) and recreational-use plasma levels (0.32 μ M and 4.8 μ M).³² In the sperm initially classified as the highest quality, motility was decreased dose-dependently by 2% to 21% ($P < .05$, $P < .001$). In the sperm initially classified as poorer quality, the motility decrease was even more dramatic. Motility was 28% lower in the 0.32 μ M recreational-use plasma level ($P = .004$) and 56% lower in the 4.8 μ M recreational-use plasma level ($P = .01$).³² Spontaneous acrosome reactions (changes to the spermatozoon as it approaches and prepares to bind to and

penetrate an oocyte) were also reduced in all sperm samples. There was a 35% decrease in both the high and poorer quality samples at the highest dose exposure.³²

Other evidence suggests that marijuana does not harm men’s reproductive health. For instance, one older study (1974) measured plasma testosterone in 27 men before and after a 21-day period of marijuana use.³⁴ The 12 “casual users” smoked an average of 54 marijuana cigarettes in that time, while the “heavy users” smoked an average of 119. No statistically significant changes in testosterone levels were observed.³⁴

Another study (2019) made headlines when researchers reported on their analysis of 1143 semen samples along with 317 blood samples from men attending a fertility clinic.³⁵ The study authors state, “Men who had ever smoked marijuana (N = 365) had significantly higher sperm concentrations. . . than men who had never smoked marijuana (N = 297).” It is important to note that the sperm concentrations of *both* the “ever” and “never” marijuana users were within the normal reference range (> 15 million/mL).³⁶ There were also no significant differences in sperm concentration between current and past marijuana smokers. Additionally, marijuana smoking was not associated with alterations in sperm DNA integrity.³⁵

As mentioned above, the cross-sectional survey data from the American National Survey for Family Growth included 758 male respondents. No difference was found when the time ratio to pregnancy was compared for men who were never users and men who were daily marijuana users (1.08, 95% CI, 0.79-1.47).⁴

Overall, the research on marijuana use and male reproduction has produced mixed results. High-quality data from in vitro and animal studies suggest that HPO function, sperm motility, and sperm fertilization are impaired by THC. However, cohort studies have not consistently found that marijuana harms male fertility, although these findings may be due to confounders and the self-reported nature of the studies.

Looking ahead

The use of cannabis products will almost certainly increase in British Columbia.

Furthermore, population studies have consistently shown that men and women of reproductive age are the highest users of marijuana. There is an urgent need for more data so that physicians can counsel their patients using solid evidence. Without this, women may continue to think that smoking marijuana is safe because it is “natural.”

The Society of Obstetricians and Gynaecologists of Canada believes there is sufficient evidence of harm to advise women to avoid cannabis when pregnant or breastfeeding. Advising men is more challenging. Men's testosterone production, sperm motility, and fertility potential has been unaffected by marijuana in some clinical studies, but we cannot ignore the benchtop research that has demonstrated harm. As we wait for unambiguous evidence, it seems reasonable to recommend patients avoid cannabis when trying to conceive.

Until high-quality evidence shows that cannabis is safe, physicians cannot reassure users that consuming the drug will not affect their fertility or their offspring. Hopefully the legalization of cannabis will make patients more forthcoming about their use of the drug, and this in turn will allow researchers to generate more accurate data on reproductive outcomes. ■

Competing interests

Dr Dunne is now a member of the *BCMJ* Editorial Board, but was not when this article was accepted.

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