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Evaluating the Effects of Cannabis Use on Fertility and Artificial Reproductive Technology

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Abstract: Background: Cannabis is widely used among males and females of reproductive age. A growing body of research suggests the endocannabinoid system is negatively impacted by the use of cannabis affecting many factors required for fertility. Objective: This article aims to evaluate existing literature on trends seen in patients undergoing artificial reproductive therapy (ART) and the effects cannabis has on fertility outcomes, including conception. Methods: This is a systematic review searching PubMed, MEDLINE, and Academic Search Premier databases through August 2022 using keywords derived from three defined concepts. Articles were then evaluated for relevance and included if meeting criteria. Results: Three studies meeting criteria were included in this article review. All three studies were retrospective or prospective studies

conducted on human populations of single clinics. Conclusion: Present studies aiming to evaluate any demonstrable detrimental effects of cannabis consumption on ART outcomes have been universally limited by small sample size, narrow geographical reach, self-reporting, and other confounding variables. Further studies are needed with larger sample sizes to more meaningfully assess the effects of cannabis on fertility and ART outcomes.

Keywords: marijuana, cannabis, cannabinoids, male fertility, female fertility, IVF, artificial reproductive therapy.

Introduction

Cannabis, often referred to as marijuana, is the most widely used federally illegal drug in the United States.[1] The recreational use of cannabis has become increasingly popular among men and women of reproductive age.[2] The 2020 National Survey on Drug Use and Health reported that 50 percent of Americans 12 years or older have used cannabis at least once in their lifetime and 21 percent have used it in the previous year.[3] The expressed reasons for its use, whether recreational, medicinal, or spiritual, are as varied as the manner in which this substance is consumed. There is no doubt that this widely used substance is well known around the globe, especially in the United States as recent legal changes and public perception have made recreational use readily accessible. While the effects of cannabis on neurocognitive and mental health outcomes have been broadly studied, knowledge of the impact of cannabis use on fertility and endocrine health is limited and often contradicting.

The well-studied and chemically-rich *Cannabis sativa L.* plant consists of cannabinoid compounds. Much of the research surrounding this plant focuses on the cannabinoids tetrahydrocannabinol (THC) and cannabidiol (CBD). These cannabinoids have been associated with the hypothalamic-pituitary-gonadal axis affecting the reproductive system.[4,5] The implications for cannabis consumption are better understood with the understanding of the endocannabinoid system (ECS). Upon consumption, this psychoactive substance acts by releasing compounds that bind to cannabinoid receptors found throughout the body.[4] CB1 receptors are mainly expressed in the central nervous system particularly concentrated in regions regulating cognition, memory, reward, anxiety, pain sensory perception, motor coordination, and endocrine function.[4] CB2 are chiefly found in the periphery and has a regulatory role in energy balance, immune function, and reproductive physiology.[4,6] Both of these receptors are found in

the reproductive tissues.[4,5,6] Together, CB1 and CB2 receptors form the basis of the endocannabinoid system with activation and overexpression of cannabinoid receptors, especially CB1, may be involved in the pathophysiology of reproductive disorders.[6]

While the neuropsychiatric effects of cannabis have been studied broadly, there is limited research to evaluate for consequences, if any, affecting the endocrine system. However, there is a growing body of evidence suggesting cannabinoids found in cannabis provoke potential negative effects on the reproductive system. In males, THC crosses the blood-testis barrier and its penetration is correlated with serum THC.[7] Chronic exposure to THC at medical and recreational doses resulted in significant dose-response testicular atrophy and decreased serum testosterone, suggestive of primary testicular failure in nonhuman primate models.[8] Recent studies have demonstrated that cannabis use can lead to delayed sexual maturation and growth spurts in pubertal animal models.[9,10,11,12] In females, THC has been seen to decrease levels of prolactin, luteinizing hormone (LH), and follicule-stimulating hormone (FSH).[13,14] Female cannabis users are also more likely to suffer menstrual cycle disruption.[15] As cannabis is such a widely used substance, the potential effects on fertility should be a topic of great concern and continued research. While there is much research to indicate that cannabis can impact various reproductive features, there are few studies that have seen a direct impact on the ability to conceive.

One area of limited study is the effects of cannabis use on those attempting to conceive using artificial reproductive technology. Recent decades have been marked by an increase in employing IVF methods for reproduction with continued efforts to make this technology accessible, affordable, and reducing the burden of care.[16] Currently, there are inadequate evidence-based guidelines for clinical practice regarding cannabis and its effects on fertility and early embryonic development. In order to contribute to a growing body of evidence, this review

highlights the latest evidence regarding the effect of marijuana use on fertility in persons attempting to conceive in the setting of ART.

Materials and Methods

The search engine EBSCOhost was used to retrieve data from the Medline and Academic Search Premier databases. PubMED was additionally used to retrieve relevant articles. The search was conducted through August 2022. When considering the aims for this article, three main concepts were decided upon and keyword searched: cannabis, reproductive system, and artificial reproductive technologies. Next these concepts were further broken down to include relevant and more specific terms. Colloquial terms for cannabis such as “weed”, “pot”, or “grass” were not included as they are not typically used in scientific, academic, or research settings. Additionally, these terms tend to include articles that are not in the context of cannabis use but rather the literal meaning of these words. The keywords used when searching in all databases are summarized in Table 1.

There were no geographical limitations placed on this search, though all articles were based in the United States and Canada. Due to the recent emergence of studies addressing cannabis use in the context of IVF, the range of dates for the articles produced was from 2002 to 2022 and there was no further need to narrow this any further. Resulting articles were screened for relevance and limited to include human trials in the setting of artificial reproductive technology only. As discussed in the introduction of this article, there is compounding evidence regarding the consequences of cannabis use on the reproductive system primarily in the context of animal models. For this reason, this review aims to evaluate the evidence found in humans.

Table 1. Search terms for PubMED, Medline, and Academic Search Premier databases	
Cannabis	Cannabis or marijuana or THC or cannabinoids or cannabidiol
Reproductive	Female fertility or male fertility or endocrine or conception or infertility
Artificial Reproductive Technology	In vitro fertilization (IVF) or artificial reproductive therapy or artificial reproductive technology or assisted reproductive technologies or gamete intrafallopian transfer or infertility treatment

Results

PubMed yielded thirteen articles after duplicates were omitted. Of the thirteen articles, three addressed the aims of this article review. Relevance criteria included the use or discussion of artificial reproductive technologies in the context of cannabis use or exposure to cannabinoids in human models. One of the three articles was conducted on an animal model and therefore did not meet inclusion criteria and was omitted from official review. The remaining two articles were published in 2006 and 2018. They were both conducted in single clinics and included males and females in their study.

EBSCOhost yielded nine articles after duplicates were excluded. Five articles were not relevant using the same criteria previously mentioned. Two articles were already included from previously mentioned PubMED searches. Two of the remaining articles were looking at humans undergoing IVF. However, one article was looking at sperm morphology and motility specifically and did not include parameters to measure success of artificial reproductive technology and or fertility such as pregnancy or live birth in their partners. For this reason, it was not included. The remaining article was a prospective study on couples undergoing IVF and met criteria for inclusion. This resulted in a total of three articles meeting criteria for relevance.

Of the three articles, there were two prospective studies and one retrospective study observed in human participants undergoing IVF. The three articles were published within the

prior twenty years: 2006, 2019, 2021. All three studies were done with population samples from one clinic respectively.

Discussion

As aforementioned, the resultant articles meeting criteria for relevance to the topic at hand have been recently published. This is a reflection of the emerging interest in the topic of cannabis use effects on fertility - particularly in vitro fertilization. It is to be expected that this will continue to be the case as trends for IVF use continue to rise.[16] In vivo controlled human studies would be highly unethical and for this reason limited data is available. Presently, only three studies were found to use human participants and were evaluated retrospectively or prospectively.

Har-Gil et al. conducted a retrospective study seeking to analyze non-donor IVF outcomes among cannabis users and nonusers.[17] This single clinic-based study included 722 non-donor patients that completed oocyte retrieval and embryo transfer within a three-year span.[17] The parameters evaluated included ovarian response, sperm quality, efficiency of fertilization, early embryonic development, and implantation.[17] The use of cannabis was categorized as light(up to 3 times a week) and heavy (more than 3 times a week) and researchers did not include information on other lifestyle confounders such as tobacco use.[17] Overall, the study included only 68 cannabis users, most defined as light users.[17] Based off the sampled data, Har-Gil et al. found that reproductive outcomes of cannabis users and non-users were comparable, suggesting that the use of cannabis is not associated with a compromised outcome for couples undergoing IVF.[17] However, a notable limitation of this study includes a grossly underrepresented population sample of cannabis users – 68 users versus 654 non-users and vague categorization to define use.[17] Researchers did not evaluate for clinical pregnancy loss or live birth. It was noted that

female participants in the user group were younger than the non-user counterparts and therefore could not meaningfully attribute the higher trending pregnancy rate per IVF cycle to cannabis use.[17] Ultimately, this study should be validated by a larger prospective study with clearly defined use of cannabis consumption including amount, frequency, and method of ingestion.

In conjunction with the Environment and Reproductive Health Study (EARTH), an ongoing prospective study aimed at identifying environmental and lifestyle determinants to fertility, 421 women who underwent 730 ART cycles at facility centers between 2004 and 2017 were followed.[18] These women were monitored for serum estradiol (E_2), follicle size and counts, and endometrial thickness.[18] Clinical outcomes assessed included implantation as defined by serum B-hCG concentration, clinical pregnancy as defined by intrauterine gestational sac on transvaginal ultrasonography at 6 weeks gestation, and live birth with pregnancy loss considered as positive B-hCG test without a live birth.[18] Among participants were 200 male partners who also enrolled and evaluated for marijuana use and couple co-exposure.[18]

Nassan et al. found that women who were marijuana smokers at enrollment had a significantly higher adjusted probability of pregnancy loss during infertility treatment with ART.[18] Marijuana smokers at enrollment had more than double the adjusted proportion of pregnancy loss than women who were past users or never smoked cannabis.[18] Similar to Har-Gil et al., no statistically significant difference in the adjusted probabilities of implantation were seen.[17,18] Additionally, no difference was seen in clinical pregnancy or live births according to women's baseline marijuana smoking status.[18] This data suggests that smoking cannabis among women undergoing ART may be related to worse infertility treatment outcomes. In contrast to animal studies and the hypothesis of researchers, couples where the male partner was a marijuana smoker at enrollment had a higher adjusted probability of live birth.[18] It was noted that

men actively using cannabis at the time of enrollment had higher sperm concentration than those who never smoked cannabis.[18] This is in stark contrast to many animal models suggesting the opposite, most notably a recent study in primates in which chronic exposure to THC at medically and recreationally relevant doses resulted in significant testicular atrophy and decreased serum testosterone.[8] Given the preponderance of evidence, researchers acknowledge that findings in this study may be better interpreted as lack of evidence for a deleterious effect rather than as evidence of a positive effect of male partner marijuana smoking on outcomes of infertility treatment.[18] It should be noted that most animal studies count for total exposure to the cannabinoids in their animal subjects. This study only accounted for smoking and did not inquire about forms of cannabis use other than smoking.

Limitations of this study include confounding variables, self-reported cannabis use, and limited data on female cannabis use at the time of enrollment. Participants self-reported cannabis smoking at enrollment. When compared to Har Gil et al., Nassan et al. conducted a more thorough assessment of use by including reports on age at which they started to smoke marijuana, efforts for quitting, last time of use, lifetime duration of smoking as well as including parallel questions regarding other drugs, lifestyle factors, and medical history.[17,18] Notable limitations include reluctance to accurately self-report use given social stigma, fear of potential effects on care delivery, and legal status as recreational cannabis use was illegal during most of the study. There was no data on representing ongoing use while undergoing treatment. It is unclear whether women who were active cannabis users at the time of enrollment continued to use or were reluctant to report use while undergoing ART. Joint participation of male and female in a couple was encouraged, but it was not required. While co-exposure was not seen to

be a contributing factor to decreased fertility, not including all male partners of female participants is a limiting factor in this study.

Similarly, Klonoff-Cohen et al. conducted a prospective study of 221 IVF/gamete intrafallopian transfer (GIFT) couples.[19] Researchers found that the amount of marijuana smoked in a woman's lifetime had negative effects on the number of oocytes retrieved and number of embryos transferred.[19] Women who had smoked more than 90 times in their lifetime demonstrated 27% fewer oocytes retrieved.[19] Participants that had smoked 1 year prior to the procedure had 25% fewer oocytes retrieved.[19] Calculations showed that for each year the woman smoked closer to the time of the procedure, there was a 1% decrease in the number of oocytes retrieved.[19] Among couples in which either partner smoked marijuana the year before the procedure, there were 28% fewer oocytes fertilized when compared to couples who did not smoked the year before.[19]

Klonoff-Cohen et al. discerned the study sample to be representative of the age, race, and education level of couples enrolling in IVF/GIFT programs in the United States.[19] Lifetime exposure was calculated for these participants, with these scores being weighted according to how recent the exposure was to time of undergoing IVF – a unique parameter to this study.[19] However, similar to other studies mentioned in this review, there exists a possibility for misreporting true cannabis intake. These results in combination with blood and urine marijuana samples, would have provided strong evidence. Like Har-Gil et al., this study does not report on nor set parameters that define pregnancy loss.[17,19] The results from this study were in parallel with observations made in bovine models where it was suggested that cannabis may hold a disruptive effect on oocyte maturation in addition to early embryonic development.[20]

Table 2. Summary of key findings and article conclusions.

Authors	*Sample size*	*Parameters Considered*	*Main Results*	*Conclusions*
Har-Gil et al.	722 (single clinic) - 68 users - 654 nonusers	ovarian response sperm quality efficiency of fertilization early embryonic development implantation	Implantation rate - Users 40.74% - Nonusers 41.13% Ongoing pregnancy rate - Users 35.2% - Nonusers 29.15%	Reproductive outcomes of users and non-users were comparable
Nassan et al.	421 - 44% of women users - 61% of men users	estradiol (E2) follicle size and counts endometrial thickness implantation clinical pregnancy live birth	Pregnancy loss rate - Users 54% - Nonusers 26% Live Birth (men) - Users 48% - Nonusers 29%	For women, active users had more than double the adjusted proportion of pregnancy loss than women who were past users or never smoked cannabis For men, active users had higher sperm concentration than those who never smoked cannabis Treatment outcomes for both men and women who were past marijuana smokers did not differ significantly from those who had never smoked.
Klonoff-Cohen et al.	221 couples	Oocytes retrieved Embryos transferred Fertilization Infant birth weight	Oocyte retrieval - > 90 lifetime use with 27% fewer oocytes retrieved Embryo transfer - Male use 1 year prior was associated with 1 fewer embryo transferred Fertilization - Smoking within 1 year had 28% decrease Infant Birth weight - >10 lifetime use with 15% decrease - >90 lifetime use with 23% decrease - Women and men with use within 15 years had 12% and 16% smaller infants, respectively	For women, lifetime amount of cannabis, timing, and composite score (timing and amount) negatively affected the number of oocytes retrieved, the number of embryos transferred, and birth weight For men, cannabis use in year prior negatively impacted embryo transfer

Conclusion

In conclusion, one study found no difference in reproductive outcomes of cannabis users and non-users and two studies found damaging effects to fertility in women undergoing artificial reproductive therapy.[17,18,19] It was seen that women who were actively using cannabis at time of treatment enrollment had more than double the adjusted proportion of pregnancy loss than

women who were past users or never smoked cannabis.[18] In addition, researchers found that the amount of marijuana smoked in a woman's lifetime had negative effects on the number of oocytes retrieved and number of embryos transferred.[19] In stark contrast to many animal and human studies, one study found higher sperm concentration in actively using cannabis users at the time of enrollment; however, it was concluded that this finding was more suggestive of a lack of deleterious effects than a benefit to fertility.

All three studies have been limited by self-reporting of cannabis, unaccounted confounding variables in lifestyle, limited geographical reach, and varied parameters to define and measure fertility outcomes. The ethical implications of in vivo human studies makes exploring the effects of cannabis use virtually impossible in conventional blind controlled trials. As more people turn to assisted reproductive technology to conceive, it is important to continue building upon current knowledge.

When considering the vast use of cannabis in communities around the globe, there are surprisingly few studies exploring the effects of its use on the reproductive system and fertility. Even fewer studies exist regarding the impact of marijuana use in couples attempting to achieve fertility, particularly in the setting of artificial reproductive treatment. Despite the increased use and legalization of cannabis, the scarcity of data on the effects of cannabis on reproductive efforts persists. Additional research to clarify the role of cannabis use on human reproduction is urgently needed. Future research may benefit from greater geographical reach, day-specific data, and including couples of reproductive age not limited to those undergoing artificial reproductive therapy.

References:

1. Data and statistics. Centers for Disease Control and Prevention. https://www.cdc.gov/marijuana/data-statistics.htm. Published June 8, 2021. Accessed July 17, 2022.
2. United Nations Office on Drugs and Crime. Market Analysis of plant-based drugs. 2017. https://www.unodc.org/wdr2017/field/Booklet_3_Plantbased_drugs.pdf
3. 2020 National Survey on Drug Use and Health. file:///Users/irihermenegildo/Downloads/2020NSDUHDetTabs01112022/NSDUHDetailedTabs2020.htm
4. Adams IB, Martin BR. Cannabis: pharmacology and toxicology in animals and humans. Addiction. 1996;91:1585–1614.
5. Reece AS. Chronic toxicology of cannabis. *Clinical Toxicology*. 2009;47(6):517-524. doi:10.1080/15563650903074507
6. Fonseca BM, Rebelo I. Cannabis and cannabinoids in reproduction and fertility: Where we stand. *Reproductive Sciences*. 2021. doi:10.1007/s43032-021-00588-1
7. Lee MS, Lanes A, Ginsburg ES, Fox JH. Delta-9 THC can be detected and quantified in the semen of men who are chronic users of inhaled cannabis. *Journal of Assisted Reproduction and Genetics*. 2020;37(6):1497-1504. doi:10.1007/s10815-020-01762-1
8. Hedges JC, Hanna CB, Bash JC, et al. Chronic exposure to delta-9-tetrahydrocannabinol impacts testicular volume and male reproductive health in rhesus macaques. Fertility and Sterility. 2022;117(4):698-707. doi:10.1016/j.fertnstert.2021.12.028

9. Sims ED, Anvari S, Lee Y, et al. The effect of cannabis exposure on pubertal outcomes: A systematic review. Adolescent Health, Medicine and Therapeutics. 2018;Volume 9:137-147. doi:10.2147/ahmt.s175864
10. Field E, Tyrey L. Delayed sexual maturation in the female rat during chronic exposure to delta-9-tetrahydrocannabinol. Life Sci. 1984;35(17):1725–1730.
11. Field E, Tyrey L. Delayed sexual maturation during prepubertal cannabinoid treatment: importance of the timing of treatment. Journal of Pharmacology and Experimental Therapeutics. 1990;254(1):171–175.
12. Gupta D, Elbracht C. Effect of tetrahydrocannabinols on pubertal body weight spurt and sex hormones in developing male rats. Res Exp Med. 1983;182(2):95–104.
13. Mendelson JH, Mello NK, Ellingboe J, Skimpy AS, Lex BW, Griffin M. Marihuana smoking suppresses luteinizing hormone in women. J Pharmcol Exp Ther. 1986;237:862-6.
14. Wenger T, Croix D, Tramu G. The effect of Chronic Prepubertal administration of Marihuana (delta-9-tetrahydrocannabinol) on the onset of puberty and the postpubertal reproductive functions in female rats. *Biology of Reproduction*. 1988;39(3):540-545. doi:10.1095/biolreprod39.3.540
15. Brents LK. Marijuana, the Endocannabinoid System and the Female Reproductive System. Yale J Biol Med. 2016;89(2):175-191. Published 2016 Jun 27.
16. Kushnir VA, Smith GD, Adashi EY. The future of IVF: The new normal in human reproduction. *Reproductive Sciences*. 2022;29(3):849-856. doi:10.1007/s43032-021-00829-3

17. Har-Gil E, Heled A, Dixon M, Ahamed AM, Bentov Y. The relationship between cannabis use and IVF outcome—a cohort study. *Journal of Cannabis Research*. 2021;3(1). doi:10.1186/s42238-021-00099-5

18. Nassan FL, Arvizu M, Mínguez-Alarcón L, et al. Marijuana smoking and outcomes of infertility treatment with assisted Reproductive Technologies. *Human Reproduction*. 2019;34(9):1818-1829. doi:10.1093/humrep/dez098

19. Klonoff-Cohen HS, Natarajan L, Victoria Chen R. A prospective study of the effects of female and male marijuana use on in vitro fertilization (IVF) and Gamete Intrafallopian Transfer (GIFT) outcomes. *American Journal of Obstetrics and Gynecology*. 2006;194(2):369-376. doi:10.1016/j.ajog.2005.08.020

20. Misner MJ, Taborek A, Dufour J, Sharifi L, Khokhar JY, Favetta LA. Effects of delta-9 tetrahydrocannabinol (THC) on oocyte competence and early embryonic development. *Frontiers in Toxicology*. 2021;3. doi:10.3389/ftox.2021.647918