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Abstract

Marijuana use has become prevalent worldwide, especially amongst men and women of reproductive age. Marijuana acts on Cannabinoid receptors, which are a part of the Endocannabinoid system. CB1 and CB2 receptors are most found in humans. Activation of Cannabinoid receptors in males cause a reduction in healthy sperm parameters and inhibits the acrosomal reaction, and therefore minimizes fertility potential. Researchers have not yet discovered any significant interactions between marijuana and the female reproductive system. There has also been limited evidence displaying the effects that marijuana has on pregnancy and breastfeeding of infants. Nevertheless, physicians have recommended against marijuana use while trying to conceive and while pregnant. Researchers continue to search for evidence linking the adverse effects that marijuana has on the female reproductive system and on the offspring of chronic marijuana users.

Introduction

Approximately 1 in 6 couples globally have trouble conceiving. In recent years, researchers have discovered that unhealthy lifestyle factors can contribute to fertility issues. Alcohol and tobacco use have been widely studied and it has been proved that excessive consumption causes a moderate reduction in healthy sperm parameters (Joo et al, 2012). The recent legislative changes have brought a new focus on the role of marijuana and fertility potential. Marijuana is one of the most used drugs worldwide, due to its recent increased availability. Use is especially prevalent amongst men and women of reproductive age. Research shows that marijuana use adversely affects both male and female reproductive health. Additionally, there is limited evidence associating marijuana use during pregnancy and increased risk for preterm birth and small for gestational age infants. The purpose in this review is to analyze the effects that marijuana has on both male and female reproductive systems, as well as pregnancy outcomes amongst marijuana users.

Methods

Data was retrieved from PubMed and other sources, such as ProQuest and NIH, with access granted through Touro University Library. This comprehensive review and critical analysis on marijuana and how it affects reproductive health is based on the interpretation of various medical research papers. Key words used to retrieve data were "marijuana and reproductive health, "cannabis and reproductive health", "drug use", "male infertility" and "marijuana and pregnancy".

Discussion

Effects of Marijuana Use on Male Fertility

Marijuana is a product of the dried leaves and flowers of the plant Cannabis sativa. Marijuana contains several cannabinoids, such as cannabidiol and cannabinol, but the main psychoactive compound is called tetrahydrocannabinol (THC), with delta 9-tetrahydrocannabinol being the most active isomer. Upon consumption, it acts via release of cannabinoid compounds which bond to cannabinoid receptors, part of the endocannabinoid system (ECS). Numerous biological roles have been linked to the ECS, including inflammation reduction and post synaptic signaling. Studies have shown linkage to the ECS and functions of male reproduction. Cannabinoids are found in two categories, exogenous and endogenous. Endogenous cannabinoids are synthesized by various tissues in the human body, while exogenous cannabinoids, like THC, are plant based.

There are four endogenous substances characterized as endocannabinoids: N-arachidonoylethanolamine (AEA), 2-arachidonoylglycerol (2-AG), 2- arachidonoylglycerol ether, and virodhamine. AEA and 2-AG have been the most studied. They act on the cannabinoid receptors, CB1 and CB2, and perform biologically similar actions as THC (Du Plessis et al, 2015).

CB1 and CB2 are both G-coupled receptor proteins (GCPRs) (Howlett et al, 2002). CB1 is found mainly in the central nervous system (CNS) and have been found on the acrosomal region, midpiece and tail of spermatozoa (Cacciola et al, 2008). In the brain, they are found in the preoptic area of the hypothalamus, which stimulates the release of luteinizing hormone releasing hormone (LHRH). CB2 receptors are mainly linked to the immune system and cells within the peripheral nervous system but have also been found on Sertoli cells and in the post acrosomal region of spermatozoa (Agirregoita et al, 2010).

The Endocannabinoid System and the Hypothalamic-Pituitary-Gonadal-Axis

The hypothalamus-pituitary-gonadal axis is a major component in maintaining the reproductive functions in both males and females. In males, Gonadotropin-releasing hormone (GnRH) is released by the hypothalamus and stimulates the adenohypophysis to secrete two hormones, follicle stimulating hormone (FSH) and luteinizing hormone (LH). FSH stimulates Sertoli cells, which are involved in spermatogenesis, while LH stimulates Leydig cells to release testosterone.

The endocannabinoid system and hypothalamus-pituitary- gonadal axis are closely linked, due to the presence of CB1 and CB2 receptors found throughout the axis. Activation of these receptors, whether by endogenous endocannabinoids such as AEA or 2-AG, or exogenous

cannabis consumption, negatively affects the functioning of the hypothalamus-pituitary-gonadal axis. In the adenohypophysis, CB1 receptor activation leads to the inhibition of spontaneous release of gamma aminobutyric acid (GABA). Post synaptic GABA receptors, located on GnRH neurons are not activated, and consequently, GnRH is not released. Additionally, when the CB1 receptors located in the preoptic nucleus of the hypothalamus are activated, serum LH levels decrease. CB1 receptor expression is more prominent in males, making them more sensitive to cannabinoid induced changes.

CB1 receptor activation on spermatozoa causes a decrease in motility and viability. Additionally, it inhibits the acrosomal reaction. CB2 receptor activation has also been linked to decreased motility. A decrease in sperm concentrations have been found in both humans and animals who are regularly exposed to cannabis (Du Plessis et al, 2015).

A cross-sectional study analyzed semen samples of 229 men ages 23-72. Forty seven percent of the group admitted to chronic marijuana use, and 21% reported recent use. Regression analysis showed that frequent and recent users were 2.6-4.3 times more likely to have sperm with abnormal morphology and motility parameters (Carrol et al, 2019). A second study assessed both urine and semen from 62 participants. The study found 25% of the urine samples contained THC, the active compound found in marijuana. Semen analysis performed on the THC positive samples showed a large percentage of sperm with abnormal morphology. A third study performed a laboratory analysis on morphology and spontaneous acrosomal reactions after exposing 78 healthy sperm samples to THC. The researchers conducting the study separated the sperm into subgroups by the sperm fertilizing potential, 90% potential and 45% potential. The samples were incubated with recreational doses of THC for 3 hours. The acrosome reaction was artificially induced in vitro by incubating the sperm with a Ca2+/ H+ ionophore. A moderate decrease of normal morphology and spontaneous acrosomal reaction was found in the 90% potential group. In the 45% group, THC caused a significant decline in normal morphology and spontaneous acrosomal reaction (Whan et al, 2004).

Implications for Further Research

The studies performed highlight the effects that marijuana consumption has on sperm parameters. THC directly affects sperm parameters, likely by activating CB1 and CB2 receptors which negatively affect the function of the hypothalamic- pituitary-gonadal- axis and the function of the sperm itself. However, some of the studies were performed on small groups and were not controlled trials. More extensive research, such as expanded, controlled trials would be stronger evidence.

The Female Reproductive System

In contrast to males, where spermatogenesis only begins at puberty, formation of gametes in the ovaries begins in females before they are born. During early fetal development, primordial germ cells migrate from the yolk sac to the ovaries where they differentiate into oogonia. Oogonia are diploid stem cells which divide mitotically to produce millions of germ cells. Even before birth, many oogonia degenerate, while the remaining oogonia develop into primary oocytes which complete prophase of meiosis I. During the reproductive years, some will complete meiosis to form a haploid oocyte. In the interim, the primary oocyte is surrounded by follicular cells in a primordial follicle. Beginning at puberty, the menstrual cycle occurs each month, in which one oocyte completes meiosis, matures within its follicle, and gets released into the fallopian tubes. The menstrual cycle has two aspects, the ovarian cycle, and the uterine cycle (Tortora and Derrickson, 2017)

The Ovarian Cycle

At the beginning of the month, the hypothalamus releases GnRH. GnRH stimulates the release of FSH by the adenohypophysis. FSH stimulates follicular growth in the ovary. As the follicle reaches maturation, it releases estrogen. When maturation is reached, estrogen reaches peak levels, initiating a feedback response inhibiting the release of FSH. Peak levels also trigger a surge in LH to be released from the adenohypophysis. The LH surge causes the mature follicle to release an oocyte into the fallopian tubes. The remaining follicular tissue becomes a corpus luteum, which secretes estrogens and progesterone (Tortora and Derrickson, 2017).

The Uterine Cycle

The uterus closely parallels the events occurring in the ovaries.

The inner lining of the uterus, the endometrium, also undergoes cyclic events every month. Menses marks the beginning of the cycle, when levels of progesterone become insufficient, and the endometrial tissue sloughs off. As estrogen levels increase due to follicular activity, the proliferative phase begins, and the uterine epithelium is restored. Around the time of ovulation, the secretory phase begins. Endometrial glands increase secretions, and the endometrium reaches maximum thickness and maturity. If fertilization occurs and the embryo successfully implants in

the uterine wall, Human Chorionic Gonadotropin (hCG) hormone is released. HCG signals the corpus luteum to continuously release progesterone, which maintains the endometrial lining and the pregnancy, until the placenta forms and takes over progesterone secretion. If fertilization does not occur, the corpus luteum aborts progesterone secretion about 14 days post ovulation. Progesterone withdrawal stimulates menses, and the cycle restarts (Tortora and Derrickson, 2017)

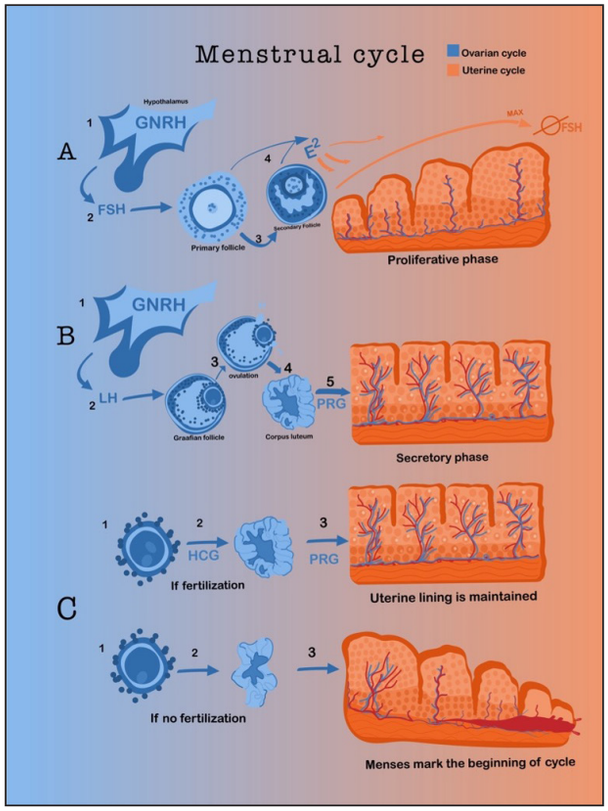

Figure 1: Correlation of the ovarian and uterine cycles

Marijuana's effect on the Menstrual Cycle

Endocannabinoid receptors are found throughout the female reproductive tract, including the ovaries, fallopian tubes, myometrium, and endometrium, and throughout the hypothalamus. Activation of these receptors may cause disruption of the menstrual cycle and implantation. One of the mechanisms in which marijuana disrupts the menstrual cycle is by suppressing GnRH from the hypothalamus. GnRH suppression prevents the secretion of cyclical female hormones which regulate the menstrual cycle. Several animal studies have suggested that marijuana use causes prolonged and anovulatory menstrual cycles which decrease fertility potential (Brents, 2016).

Studies were conducted on rhesus monkeys since their reproductive cycle closely mimics the human female reproductive cycle. Rhesus monkeys' menstrual cycles are also 28 days long and are regulated by mechanisms similar to humans. Two studies analyzed the effects of daily THC exposure on menstrual cycle length and ovulation. Daily THC injections during the follicular phase caused lengthy and anovulatory cycles. THC injections during the luteal phase did not have any profound effects on the menstrual cycle. (Asch et al., 1981). A study performed on ovariectomized female rhesus monkeys found decreases in serum LH and FSH levels shortly after marijuana administration. A final study analyzed female rhesus monkeys who were given marijuana 3 times per week beginning on cycle day 1 for about 230 days or until at least two anovulatory cycles occurred. Results showed decreased serum LH, estrogen, and prolactin levels for greater than 100 days since treatment began (Smith et al., 1979). However, two studies from the 1980s examined a small group of self-reported human marijuana smokers during the follicular phase of the menstrual cycle and found no significant changes to their hormones (Mendelson et al., 1985) Another human study performed on marijuana users during the luteal phase resulted in a decrease in serum LH and prolactin hormones within the first 1-2 hours after the dose. (Mendelson, et al., 1986). LH is involved in maintaining progesterone secretion during the luteal phase, and a decrease in LH serum concentrations can disrupt the endometrial lining and shorten cycle length.

Implications for Further Research

Although several animal studies showed findings indicating the effect of marijuana on reproductive hormones, most of the human studies did not show any clinically significant results. More research is necessary to determine the effects that marijuana has on the menstrual cycle. The studies were performed several years ago, before marijuana was popular and use was prevalent amongst reproductive age women. Additionally, sample sizes were small and largely relied on self-report. Larger and more robust trials would need to be performed in order to yield significant evidence.

Cannabis Impact on Pregnancy

Maternal cannabis use during pregnancy has been associated with small for gestational age infants, preterm birth, and impaired behavioral and cognitive development. Women who use cannabis often use other substances such as alcohol or tobacco, which cause a synergistic affect and increases the danger for the fetus. Cannabis is often used by pregnant women to minimize nausea during the first trimester. The first trimester is the most

vulnerable time for a fetus since most of the organ development occurs during that time. Fetal exposure to harmful substances during the first trimester can cause serious birth defects or developmental delays.

In the 1950s, a drug called Thalidomide became popular in many countries in Europe. It was used to treat morning sickness and nausea in early pregnancy. However, it soon became apparent that the children born to mothers who used Thalidomide during their first trimester were born with Phocomelia, a congenital deformity in which the child's hands and feet are connected to their trunk instead of their limbs. Researchers later discovered that the clinical trials of the drug were performed using only the R- enantiomer of the molecule. They marketed the drug, however, as a racemic mixture, not realizing the harmful effects that the other enantiomer would have on the fetus. This incident further proves the vulnerability of the fetus during early pregnancy.

Maternal cannabis consumption is harmful for the fetus since expression of Endocannabinoid receptors has been found in the fetus as early as 5 weeks of gestation. The main psychoactive compound in Marijuana, THC, can cross the placenta and activate receptors in the fetal brain and placenta, and cause adverse effects. Researchers have suggested that cannabinoid receptor activation in the placenta may cause stillbirth and miscarriages.

A study analyzed 12,000 women with singleton pregnancies between 18 to 20 weeks of gestation. Five precent self- reported marijuana use before or during pregnancy. Results showed that women who had chronically used marijuana before and throughout pregnancy had offspring with smaller head circumference and shorter birth length than offspring of non- users. (Fergusson et al., 2003)
Another study analyzed 5588 participants. The proportion of women who used marijuana during or before pregnancy was 5.6%, while tobacco use was 24%. Small for Gestational Age infants were born to the marijuana and tobacco users. There were also minimal findings of Spontaneous Preterm Birth and Preeclampsia amongst marijuana users. (Leemaqz, et al., 2016)

A third study involved 3164 participants. Participants self- reported marijuana, alcohol, cocaine, and tobacco use before or during pregnancy. Heavy use of all four substances decreased birth weight by 26%. (Janisse, et al., 2014)

Several studies suggested that marijuana use is associated with stillbirth and early miscarriage. However, no statistically significant findings were reported with marijuana use alone. The largest study performed was conducted by Stillbirth Collaborative Research Network, which studied the impact of drug use and smoking on stillbirth. The study included 663 stillbirth deliveries from 5 different clinical locations over 2 years. The researchers performed cord homogenate toxicology and maternal cotinine assays at the time of delivery. Marijuana use was detected through tetrahydrocannabinolic acid (THC-COOH). There were significant findings of concurrent marijuana and tobacco use associated with stillbirth, but no significant findings with marijuana alone (Varner, et al., 2014).

Implications for Further Research

Although there is a correlation seen between marijuana and negative effects on birth weight and on time delivery, most of the existing research regarding pregnancy and marijuana dates to an era when marijuana use was far less prevalent than it is currently. Additionally, most of the studies relied on self-report and contained relatively small sample sizes. Women may have inaccurately reported their use and there is no biological validation for self-report. Thirdly, many of the studies analyzed the effects of marijuana as well as other substances. The effects cannot be sourced to marijuana alone. More up to date trials with better methodology would be needed to yield significant results.

Marijuana and Lactation

Tetrahydrocannabinol (THC) is 99% protein bound, highly lipid soluble and has low molecular weight. Therefore, it easily travels into human breastmilk. The THC can then activate receptors in the breastfeeding infant's brain or reproductive tract and cause adverse effects. A Non-human primate study recorded that .2% of THC ingested by the mother was found in breastmilk. If a mother uses marijuana 1-2 times per day, the breastfeeding infant may ingest several milligrams of THC daily. However, there is not much significant research that proves the direct effects of marijuana on a breastfeeding infant's development. Several studies were conducted without proper long term follow up. Since there is little evidence, the American College of Obstetricians and Gynecologists (ACOG) recommended Ob/Gyn providers to counsel breastfeeding women against marijuana consumption until future studies can delineate proper clinical guidance. ACOG also recommended that women trying to conceive, and pregnant women should refrain from marijuana consumption.

Conclusion

In conclusion, cannabis disrupts the reproductive system by activating CB1 and CB2 which are present throughout the hypothalamic-pituitary-gonadal axis. In males, significant evidence has proved that Tetrahydrocannabinol, the main psychoactive component in cannabis negatively

affects semen parameters. THC affects sperm production and thereby reduces sperm concentration and quality. It also activates receptors on the sperm, which causes a reduction in motility and normal morphology. CB1 receptor activation on spermatozoa can also inhibit the acrosome reaction and disables fertilization of an oocyte. THC has not been proven to interfere with the functioning of the female menstrual cycle. Although evidence has shown that THC may impact some animal serum hormone concentrations, the human studies did not yield positive results. Weak evidence has been found regarding the effects of marijuana on pregnancy and lactation. Studies show that THC can cross the placenta and breastmilk and can therefore harm the fetus or breastfeeding infant. However, the direct effects in either case have not been researched enough. Despite the inconclusive results, ACOG has recommended against the use of maternal marijuana consumption until studies prove that marijuana is deemed safe enough to use while breastfeeding. Similarly, the American Academy of Pediatrics has also recommended against marijuana use during pregnancy and lactation. Additionally, the American Society for Reproductive Medicine (ASRM) states that a prospective gestational carrier and their partner may not be marijuana users. Emphasis should be placed on educating patients and their partners in the preconception and early pregnancy period about the risks associated with fertility and fetal development when consuming marijuana.

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