Cannabis sativa and pregnancy: a review

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Resumo

Cannabis sativa e gravidez: uma revisão. Cannabis sativa, ou maconha, é a droga de abuso mais utilizada durante a gravidez. A gravidez é um período em que ocorrem mudanças fisiológicas consideráveis na mãe e, como resultado dessas mudanças, o feto pode ser diretamente afetado. A droga apresenta em sua composição uma gama de compostos químicos considerados medicinais ou psicoativos, os canabinoides. Um dos mais conhecidos é o tetrahydrocannabinol (Δ9-THC), componente psicoativo capaz de atravessar a barreira placentária, atingindo o feto em desenvolvimento. O uso crônico de C. sativa na gravidez pode resultar em diminuição da perfusão uteroplacentária, restrição do crescimento intra-uterino (RCIU) e distúrbios comportamentais nos fetos. Os canabinoides podem causar alguns distúrbios nos órgãos reprodutores dos usuários até atingir o feto. Em um estudo, 4,000 gestantes usuárias da droga apresentaram aumento na incidência de perdas gestacionais, conceptos com baixo peso e pequenos para a idade gestacional. Além do baixo peso nos neonatos, a droga aumenta o risco de complicações durante o parto e um desenvolvimento cognitivo tardio nos lactentes. Muitas controvérsias giram em torno do tema C. sativa e seus efeitos sobre a saúde, sendo necessário abranger a discussão de políticas públicas sobre a liberação do uso de drogas ilícitas levando em consideração evidências científicas.

Palavras-chave: Droga de abuso; Desenvolvimento fetal; Maconha; Placenta

Abstract

Cannabis sativa or marijuana is the most commonly used drug during pregnancy. Pregnancy is a period in which considerable physiological changes occur in the mother, and consequently, the fetus can be directly affected. Marijuana contains a range of medicinal or psychoactive components, the cannabinoids. The best known cannabinoid is tetrahydrocannabinol (Δ9-THC), a psychoactive drug capable of crossing the placental barrier and reaching the developing fetus. Chronic use of C. sativa in pregnancy may result in decreased uteroplacental perfusion, intrauterine growth restriction and behavioral disorders. Cannabinoids may cause some disorders in reproductive organs in users, which can harm the fetus. In one study, 4,000 pregnant women who used marijuana showed an increase in the incidence of pregnancy loss and low weight and small size for gestational age. In addition to low birth weight, the drug increases the risk of complications during childbirth
Marijuana (Cannabis sativa) is the most frequent drug used during pregnancy (BATALLA et al., 2013; BROWN et al., 2017). Studies report that in the United States, 4% of all pregnant women use marijuana (KO et al., 2015).

No other drug of abuse has instigated more controversy than C. sativa throughout history. During the last decade, some countries have legalized the medicinal and recreational use of the drug (GOVERNING, 2018). Therefore, the health effect of expanding legalization in vulnerable groups such as children and pregnant women is still unknown (WANG et al., 2018).

Tetrahydrocannabinol (Δ9-THC), the main psychoactive constituent in C. sativa, can cross the placental barrier and reach the developing fetus. Some studies suggest that chronic use of this drug may result in decreased uteroplacental perfusion, intrauterine growth restriction (IUGR) and behavioral disorders (ZUCKERMAN et al., 1989; NAVARRO; RUBIO, 1995; FERGUSSON et al., 2002).

Although there are different approaches to the implications of marijuana use during pregnancy, both from a biological point of view (BENEVENUTO et al., 2017) and a focus on social welfare policies and legal status (MARK; TERPLAN, 2017), drug use has increased among pregnant women and how it affects the growth and development of the offspring is an issue of great concern (ROCHA et al., 2016). The aim of this review was to summarize the results of recent studies related to this subject.

**Cannabis sativa overview**

This study was carried out on basis of a literature review about the association of marijuana use and pregnancy using the databases CAPES Portal, CAPE, PubMed, and relevant published literature. The keywords used in the search engines were: Cannabis sativa, endocannabinoids, drugs of abuse during pregnancy, fetal development and pregnancy.

Finally, the articles were analyzed and organized according to the following topics: Cannabis sativa and its properties; Mechanisms of action of Cannabis sativa; Drugs of abuse and pregnancy; Cannabis sativa and pregnancy; Cannabinoids and reproductive effects; Cannabis sativa and prenatal and postnatal outcomes; and Transgenerational effects of cannabinoid exposure.

**Cannabis sativa and its properties**

C. sativa is one of the oldest plants cultivated by humans and it has been used for medicinal, religious and recreational purposes for thousands of years of recorded history and in modern times (ZUARDI, 2006; GREYDANUS et al., 2015). This drug may be inhaled or ingested, and, in the last decades, the use of marijuana has increased sharply around the world (MCLAREN et al., 2008).

C. sativa contains more than 101 substances known as cannabinoids already identified (NOTCUTT, 2016) and extracted from the plant. In the mid-1960s, Mechoulam and Gaoni (1965), isolated and characterized Δ-9-tetrahydrocannabinol (THC), the main psychoactive component of C. sativa. Cannabidiol (CBD) is also a compound present in C. sativa, and it is known for its non-psychoactive and medicinal properties (antianxiolytic, antinociceptive, antipsychotic-like and antiinflammatory effects) (MECHOULAM et al., 2007).

Marijuana does have a great number of well-documented therapeutic actions, showing antiemetic, analgesic and anticonvulsant properties (AMERI, 1999). Besides, the use of cannabis as an appetite stimulant has been indicated for patients with a terminal illness (AMERI, 1999). However, the existence of psychoactive properties, the development of tolerance and the
potential for abuse have discouraged the therapeutic use of that drug.

In addition, a relevant issue about *C. sativa* potency has been addressed. From the 1970s to 2000s, there has been a 6- to 7-fold increase in cannabis potency in the USA, as measured by the percentage of THC. Between 1993 and 2008, the average concentration of THC increased from 3.4 to 8.8% (MEHMEDIC et al., 2010). Cannabis potency monitoring is important to gauge negative effects on health and to better understand the characteristics and mechanisms of action of drug that users have used (ELSOHLY et al., 2016).

Despite the concerns about the potency of the drug, the amount of the drug being consumed has increased among young adults (SCHENKER; MINAYO, 2005). That increase can be related to the popularity of blunts (marijuana-filled cigarettes), which may contain 1.5 times more than joints and 2.5 times more than pipes (MARIANI et al., 2011).

Currently, many countries such as the United States, Canada, and Holland allowed regulating the use of medicinal cannabis. However, there is insufficient concern about its effects, and studies on the mechanism of action of cannabis remain scarce (ASHOTON, 2001).

**Mechanisms of action of Cannabis sativa**

Cannabinoid receptor 1 (CB1) has been found to be prevalent in many species, mainly expressed in the cerebrum (MATSUDA et al., 1990) and cerebellum (KISHIMOTO; KANO, 2006). In addition, this receptor was also evident in peripheral tissues such as the eye, placenta, fetal membranes and myometrium (DENNEDY et al., 2004). Also, cannabinoid receptor 2 (CB2) is expressed essentially by cells of the immune system (MUNRO et al., 1993), although some gene transcripts of this receptor have been demonstrated in placenta and trophoblastic cells (BUCKLEY et al., 1997). The distinction between these receptors is based on the heterogeneity of the amino acid sequence (MATSUDA et al., 1990; MUNRO et al., 1993), signaling mechanisms (FELDER et al., 1995) and tissue distribution (SHIRE et al., 1995).

Initially, THC affects the fetus as it crosses the placenta essentially during the early proliferative growth stage in relation to the hypertrophic growth stage of late gestation (VARDARIS et al., 1976). THC reaches the maternal circulatory system (HUTCHINGS et al., 1989). Moreover, the indirect exposure of the fetus and trophoblast to increased levels of carbon monoxide from burning marijuana is directly toxic (CLAPP et al., 1987). Finally, the elevation of maternal blood pressure and heart rate (SIDNEY, 2002) causes uterine vasoconstriction and limiting placental perfusion (ZUCKERMAN et al., 1989).

Exogenous cannabinoids (i.e., THC, cannabiol, cannabidiol) exert their effects by binding to specific cannabinoid receptors. The first receptor was identified by Devane et al. (1988), and it was designated CB1. This receptor has been found in the brain and peripheral nerves of humans, rats, monkeys and pigs. A second cannabinoid receptor (CB2) was identified by Munro et al. (1993) in immune cells.

Endogenous cannabinoids derived from arachidonic acid with potent effects on cannabinoid receptors were also discovered: anandamide (N-arachidonoyl-ethanolamine) (DEVANE et al., 1992), 2-AG (2-arachidonylglycerol2-AG) (MECHOU LAM et al., 1995) and 2-arachidonylglyceryl ether (HANUŠ et al., 2001).

The endocannabinoid system (ECS) consists of cannabinoid receptors, their endogenous ligands, and enzymes (SALZET, 2000), and they act as retrograde synaptic signaling molecules that may be involved in the inhibition of neurotransmitter release (SVÍŽENSKÁ et al., 2008).

CB1 is distributed in many different brain regions, mainly cerebral cortex, hippocampus, amygdala, cerebellum and basal ganglia, cardiovascular and reproductive systems and gastrointestinal tract as well (CROCI et al., 1998; AMERI, 1999; PERTWEE, 2001; SZABO et al., 2001). On the other hand, CB2 is localized in peripheral nerve cells and tissues derived from the immune system (AMERI, 1999). Most recently, CB2...
was detected in the microglial cells (ASHTON et al., 2006).

Both cannabinoid receptors are members of the class of G protein coupled receptors inhibiting adenylyl cyclase and activating mitogen-activated protein kinase (MAPK) cascades. CB1 activation attenuating the production of cAMP and consequently cAMP-dependent protein kinase (PKA) is inhibited (HOWLETT, 2002).

For embryo survival, it is crucial that the expression of CB1 receptor and its antagonists be synchronized. However, it is essential to determine the potential of exogenous cannabinoids to affect the functioning of endogenous cannabinoids and their corresponding receptors during gestation (CAMACHO et al., 2004, SINGH et al., 2012). In addition, a study showed that endocannabinoids exhibit the ability to cause transgenerational effects (MANIKKAM et al., 2012).

**Drugs of abuse and pregnancy**

The extensive use of psychoactive drugs such as tobacco, alcohol, cocaine and marijuana during pregnancy has led to several medical and social challenges, especially regarding mother-child health (ZILBERMAN et al., 2003).

The prevalence of recreational drug abuse among young adults, including women, has increased over the past two decades (TAYLOR et al., 2010). In the United States, it is estimated that 40% of the people who have a drug use problem are women and 26% (STINSON et al., 2006) of them are most likely to potentiate substance use disorder during reproductive age (COMPTON et al., 2007).

Among the illicit drugs, cannabis has been increasingly used in the last decade among pregnant and non-pregnant women (BROWN et al., 2017). According to the United States Department of Health and Human Services (2013), among pregnant women ages 15 to 44, 5.9% use illicit drugs, 8.5% drink alcohol and 15.9% smoke cigarettes. Moreover, the spectrum of illicit drug use among pregnant women in these combined 2011-2012 American data was 18.3% for ages 15 to 17, 9% for 18 to 25, and 3.4% for 26 to 44.

**Cannabis sativa and pregnancy**

Although cannabis is the most commonly used illegal drug among pregnant women, this vulnerable group reports less use of this substance (4.5% overall) compared to non-pregnant women who markedly reduce the use of this drug during this period (SAMHSA, 2015; MARK et al., 2016).

Moreover, pregnant cannabis users are more likely than non-pregnant users to report daily use (16.2 versus 12.8%). Also, they are more likely to meet the criteria for a cannabis use disorder (18.1 versus 11.4%) (KO et al., 2015). In addition, the concern about negative effects of drugs on fetal development can motivate some women to curb their substance abuse during pregnancy (HIGGINS et al., 1995). On the other hand, the societal acceptance of cannabis as a harmless drug, compared with cocaine and heroin, may contribute to continuing use during pregnancy (TAYLOR et al., 2010).

Animal studies have shown that THC, the active compound of *C. sativa*, and its metabolites, are able to cross the placental barrier freely and, upon entering the fetal circulation, affecting fetal development (EL MARROUN et al., 2009). In the placenta, THC is
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The cannabinoids may cause some disturbances in reproductive organs in users and since it reaches the fetus, it also may exert some negative effects on fetal development that can be extended longer in life (BRENTS, 2016). Consistent with the Barker (1998) hypothesis, several studies have found that maternal exposure to substances and other environmental factors can affect fetal development, also causing long-term effects. These effects can be called “prenatal programming” since it is possible to associate fetal negative outcomes and disorders in postnatal development. This evidence has been identified in animal studies (BARKER, 1998).

Cannabinoids and reproductive effects

The endocannabinoid system (formed by cannabinoid receptors, CB1 and CB2) is present since as of conception and peri-implantation and during pregnancy and plays a fundamental role in maintaining these events (BATTISTA et al., 2008). CB1 has been identified in reproductive organs such as ovary, placenta, and uterus (PARK et al., 2003; MACCARRONE et al., 2005). In recent years, new lines of study have focused on the effects of exposure to noxious substances (such as alcohol, tobacco and marijuana) on the uterus of pregnant women.

During the cycle of human ovulation, fluctuations in endocannabinoid levels reinforce the principle that ECS contributes to the regulation of fertility (LAZZARIN et al., 2004). Moreover, CB1 plays an important role in the effect of endocannabinoids on reactive events (MACCARRONE, 2008).

Maccarrone (2008) also evaluated the distribution of CB2 mRNA and/or protein in reactive cells and tissues and found that this receptor subtype may be involved in placentation, maternal and fetal signaling, specific ICM cell lines and development in vivo in females, but also in the survival of Sertoli cells in spermatogenesis and in sperm interactions, including polyspermy blockade in males.

Exposure to low doses of marijuana smoke during pregnancy in mice resulted in reduced maternal net body weight gain and placental wet weight in the offspring and fetal to placental weight ratio was decreased in male fetuses, showing a sex-specific effect (BENEVENUTO et al., 2017).

In a study conducted by Mendelson et al. (1985), the prolactin level was determined in women before and after smoking marijuana and placebo cigarette, at both the follicular and luteal phase of the menstrual cycle. The results showed that prolactin decreased in women during the luteal phase when smoking marijuana compared to the placebo group. Similar effects were not seen during the follicular phase of the menstrual cycle. Ovulation suppression has been reported in the chronic use of cannabis (MAYKUT, 1985). The production of estrogen and progesterone by the human placenta may also be affected (PARK et al., 2004).

Overall, the mechanism by which cannabinoids disrupt female reproduction involves the hypothalamic-pituitary-ovarian (HPO) axis (TERRANOVA, 2003). Studies in humans and animals suggest that acute administration of THC suppresses the release of gonadotropin-releasing hormone (GnRH) and thyrotropin-releasing hormone (TRH) from the hypothalamus, consequently impairing the release of prolactin and the gonadotropins, follicle stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary. Alterations in gonadotropin levels can disrupt ovarian follicle maturation, stimulation of the production of the ovarian steroids estradiol and progesterone, and induction of ovulation (ASCH et al., 1981; MENDELSOHN et al., 1985; 1986).
In the implantation and pregnancy phase, the uterus undergoes changes in hormonal levels (WESTERLIND et al., 1997; WANG et al., 1999; 2004). In association with these findings, oocyte studies show that exposure to cannabis leads to early pregnancy failure and abortion, the repercussion of the imbalance in the endocannabinoid system during the gestational period and the impacts on the offspring (HARBISON; MANTILLA-PLATA, 1972; BLOCH et al., 1979; WALLACH et al., 1987).

**Cannabis sativa exposure and prenat al and postnatal outcomes**

The prenatal and early postnatal period plays a fundamental role in the proper development of the brain. Cannabis enters the blood stream within seconds and in the brain within minutes after inhalation (BROWN; GRAVES, 2013). In addition, there is evidence that THC can bioaccumulate in offspring tissues, including the brain (HARBISON; MANTILLA-PLATA, 1972; KENNEDY; WADDELL, 1972; HUTCHINGS et al., 1989).

Cannabinoids are able to alter the expression of key neurotransmitter genes for neural development leading to behavioral disturbances (GÓMEZ et al., 2003). In addition, the early presence of cannabinoid receptors during fetal brain development provides a mechanism by which cannabinoids can produce some negative effects found in rat offspring, such as alterations in spontaneous locomotor and exploratory behavior (NAVARRO; RUBIO, 1995). Astley and Little (1990) evaluated the effects of prenatal exposure to marijuana during the first year of childhood development. Children exposed to marijuana had low scores on the psychomotor development index.

One of the major sites of cannabinoid receptors in the vertebrate’s brain is part of the forebrain that is associated with higher cognitive functions (GLASS et al., 1997), as well as in the cerebellum. There is evidence that chronic use of *C. sativa* may be associated with functional brain alterations and subtly impinging on cognitive function (POPE; YURGELUN-TODD, 1996). In addition, another study showed that prenatal exposure to cannabis altered the development of nigrostriatal and mesolimbic dopaminergic neurons (DE FONSECA et al., 1991).

In a prospective study conducted by Hatch and Bracken (1986), 4,000 pregnant women who used marijuana during pregnancy, reported an increase in the incidence of low birth weight babies (< 2500 g) and small size for gestational age. In the same study, cannabis was also related to preterm birth. They have concluded that frequent use of cannabis during pregnancy may be a risk factor for sudden infant death syndrome. In addition, the use of the drug by pregnant women raises the risk of complications during childbirth (HAYATBAKHSH et al., 2012) and late cognitive development in infants of cannabis-addicted mothers (GRANT et al., 2018).

Since most cannabis addicts also use other drugs such as tobacco, cocaine, and alcohol, it is difficult to identify the specific effects of cannabis on the fetus (ZUCKERMAN et al., 1989).

**Transgenerational effects of cannabinoid exposure**

The transgenerational effects triggered by epigenetic changes caused by intertemporal external factors act not only on somatic cells but also on germ cells (WALKER; HAVEN, 1997; SATO et al., 2009). There are few studies that address transgenerational impacts through exposure to cannabinoids, with no exploration of possible immunological implications. It is noteworthy that exposure to cannabinoids in the uterus in humans is linked to several neurological and behavioral impacts in young or adult individuals, leading to a greater predisposition to drug abuse (JAQUES et al., 2014).

Young female rats that were briefly exposed to the cannabinoid agonist WIN-55,212, showed transgenerational effects on morphine sensitization in offspring. The offspring demonstrated a total lack of uterine exposure to the cannabinoid agonist, yet the exposure of female adolescents to cannabinoids can affect endocrine, behavioral, and transcriptional events in future offspring (VASSOLER et al., 2013).
In addition, even if exposure to cannabis occurs before pregnancy, there is a likelihood of potential harm to the offspring. It is understood that female reproductive tissues, including the ovaries, contain CB1 and endocannabinoids (BARI et al., 2011). In this sense, CB1activation by endo- or exo- ligands, such as THC, can interfere with gonadal functions and may affect spermatogenesis in men (BANERJEE et al., 2011).

Taking into account cannabis use by young mothers, the high drug popularity among adolescents, and the possibility of mixtures of different drugs (e.g., alcohol, tobacco), drugs of abuse are especially relevant since they may affect fetal development. However, there is not enough data on the physiological effects and detail on the consequences of fetal exposure to marijuana and associated substances (CALVIGIONI et al., 2014).

In this review, we covered important pharmacological and epidemiological issues about *C. sativa* and pregnancy. In the literature evaluated, we found several pieces of evidence of how harmful drug use during pregnancy can be to both mother and fetal health. Pregnancy is a period in which many dynamic physiological changes occur in the mother, and we can clearly observe that as a result of these changes, the fetus can be directly affected.

Many controversies surround the topic of *C. sativa* and its effects on human health. In this review, the findings raise concern regarding the discussion of public policies on the release of the drug, showing the need for taking into account the scientific evidence.

References


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