Biotemas, 32 (2): 1-11, junho de 2019
ISSNe 2175-7925

http://dx.doi.org/10.5007/2175-7925.2019v32n2p1
Revisão

Cannabis sativa and pregnancy: a review

Iran A. Neves da Silva
Daiana Aparecida Souza Lima
Sarah Gomes de Menezes Benevenuto
Mariana Matera Veras *

Universidade de São Paulo, Faculdade de Medicina Veterinária e Zootecnia
Avenida Prof. Dr. Orlando Marques de Paiva, 87, CEP 05.508-270, São Paulo – SP, Brasil
* Autor para correspondência
verasine@gmail.com

Submetido em 10/09/2018
Aceito para publicação em 22/03/2019

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 tetrahidrocanabinol (Δ^9-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 (Δ^9-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

and late cognitive development in infants. Many controversies revolve around the topic of *C. sativa* and its effects on human health, making it necessary to include the discussion of public policies on the release of the drug taking into account scientific evidence.

Key words: Drugs of abuse; Fetal development; Marijuana; Placenta

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 woman 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 (Δ^9-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 is 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, cannabinol, 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) (MECHOULAM 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 aged 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.

Drug use during pregnancy is typically detected by maternal self-report, urine test or history report (LESTER et al., 2004), though approximately 32% of women who use illicit drugs also use licit drugs (such as cigarettes and alcohol) at the same time and that may underestimate the extent of prenatal exposure (WENZEL et al., 2001).

In the United States, the American College of Obstetricians and Gynecologists (ACOG) made several recommendations for the management of pregnant women who abuse drugs. Pregnant women who recognize the use of an illegal substance during pregnancy should be counseled and offered treatment. ACOG also recognized that some states consider intrauterine exposure to a drug as a form of child neglect or abuse according to the law (ACOG, 1993).

The prenatal consequences for both mother and fetus/child are described below.

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

transferred to the fetus resulting in levels of the drug that can be detected via umbilical cord blood (BROWN; GRAVES, 2013). That level in cord blood indicates that the fetus is exposed to a proportionally smaller dose than the mother (TENNES et al., 1985).

In recent users, breast milk also revealed the presence of THC (ALAPITI; HALE, 2012). Studies have determined exposure to the neonate to be 0.8% that of the mother's (DJULUS et al., 2005; BROWN; GRAVES, 2013). Also, there is evidence that inhibition of prolactin secretion may occur, and consequently, inhibition of milk production by using marijuana (MURPHY et al., 1998).

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 polyspermia 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; MENDELSON 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 prenatal 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

ACOG – AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS. Cocaine in pregnancy. Committee Opinion: Committee of Obstetrics: Maternal and Fetal Medicine Number 114. **International Journal of Gynecology & Obstetrics**, Legon, v. 41, p. 102-5, 1993.

ALAPITI, S.; HALE, T. W. **Effects of marijuana on the fetus and breast-feeding infants.** 2012. Lubbock: Infant Risk Center. Texas Tech University Health Sciences Center. Disponível em: <https://www.infantrisk.com/content/effects-marijuana-fetus-and-breastfeeding-infants>.

AMERI, A. The effects of cannabinoids on the brain. **Progress in Neurobiology**, Paris, v. 58, n. 4, p. 315-348, 1999.

ASCH, R. H., SMITH, C. G., SILER-KHODR, T. M., PAUERSTEIN, C. J. Effects of Δ9-tetrahydrocannabinol during the follicular phase of the rhesus monkey (*Macaca mulatto*). **The Journal of Clinical Endocrinology & Metabolism**, Stanford, v. 52, n. 1, p. 50-55, 1981.

ASHTON, C. H. Pharmacology, and effects of cannabis: a brief review. **The British Journal of Psychiatry**, Cambridge, v. 178, n. 2, p. 101-106, 2001.

ASHTON, J. C.; FRIBERG, D.; DARLINGTON, C. L.; SMITH, P. F. Expression of the cannabinoid CB2 receptor in the rat cerebellum: an immunohistochemical study. **Neuroscience Letters**, London, v. 396, n. 2, p. 113-116, 2006.

ASTLEY, S. J.; LITTLE, R. E. Maternal marijuana use during lactation and infant development at one year. **Neurotoxicology and Teratology**, Oxford, v. 12, n. 2, p. 161-168, 1990.

BANERJEE, A.; SINGH, A.; SRIVASTAVA, P.; TURNER, H.; KRISHNA, A. Effects of chronic bhang (cannabis) administration on the reproductive system of male mice. **Birth Defects Research Part B: Developmental and Reproductive Toxicology**, Reston, v. 92, n. 3, p. 195-205, 2011.

BARI, M.; BATTISTA, N.; PIRAZZI, V.; MACCARRONE, M. The manifold actions of endocannabinoids on female and male reproductive events. **Frontiers in Bioscience**, Irvine, v. 16, n. 498, p. e516, 2011.

BARKER, D. J. P. In utero programming of chronic disease. **Clinical Science**, London, v. 95, n. 2, p. 115-128, 1998.

BATALLA, A.; BHATTACHARYYA, S.; YÜCEL, M.; FUSAR-POLI, P.; CRIPPA, J. A.; NOGUE, S.; TORRENS, M.; PUJOL, J.; FARRÉ, M.; MARTIN-SANTOS, R. Structural and functional imaging studies in chronic cannabis users: a systematic review of adolescent and adult findings. **Plos One**, Cambridge, v. 8, n. 2, p. e55821, 2013.

BATTISTA, N.; PASQUARIELLO, N.; DI TOMMASO, M.; MACCARRONE, M. Interplay between endocannabinoids, steroids and cytokines in the control of human reproduction. **Journal of Neuroendocrinology**, Brighton, v. 20, p. 82-89, 2008.

BENEVENUTO, S. G.; DOMENICO, M. D.; MARTINS, M. A. G.; COSTA, N. S.; DE SOUZA, A. R. L.; COSTA, J. L.; TAVARES, M. F. M.; DOLHNIKOFF, M.; VERAS, M. M. Recreational use of marijuana during pregnancy and negative gestational and fetal outcomes: an experimental study in mice. **Toxicology**, Amsterdam, v. 376, p. 94-101, 2017.

BLOCH, E.; THYSEN, B.; MORRILL, G. A.; GARDNER, E.; FUJIMOTO, G. Effects of cannabinoids on reproduction and development. In: MUNSON, P. L.; DICZFALUSY, E.; GLOVER, J.; OLSON, R. E. (Ed.). **Vitamins & Hormones.** New York: Academic Press, 1979. p. 203-258.

BRENTS, L. K. Focus: sex and gender health: Marijuana, the Endocannabinoid System and the female reproductive system. **The Yale Journal of Biology and Medicine**, New Haven, v. 89, n. 2, p. 175, 2016.

BROWN, H. L.; GRAVES, C. R. Smoking and marijuana use in pregnancy. **Clinical Obstetrics and Gynecology**, Salt Lake City, v. 56, n. 1, p. 107-113, 2013.

BROWN, Q. L.; SARVET, A. L.; SHMULEWITZ, D.; MARTINS, S. S.; WALL, M. M.; HASIN, D. S. Trends in marijuana use among pregnant and nonpregnant reproductive-aged women, 2002-

2014. **Journal of the American Medical Association**, Chicago, v. 317, n. 2, p. 207-209, 2017.

BUCKLEY, N. E.; HANSSON, S.; HARTA, G.; MEZEY, E. Expression of the CB1 and CB2 receptor messenger RNAs during embryonic development in the rat. **Neuroscience**, Elmsford, v. 82, n. 4, p. 1131-1149, 1997.

CALVIGIONI, D.; HURD, Y. L.; HARKANY, T.; KEIMPEMA, E. Neuronal substrates and functional consequences of prenatal cannabis exposure. **European Child & Adolescent Psychiatry**, Berlin, v. 23, n. 10, p. 931-941, 2014.

CAMACHO, I. A.; NAGARKATTI, M.; NAGARKATTI, P. S. Effect of 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD) on maternal immune response during pregnancy. **Archives of Toxicology**, Berlin, v. 78, n. 5, p. 290-300, 2004.

CLAPP, J. F. 3rd; WESLEY, M.; COOKE, R.; PEKALA, R.; HOLSTEIN, C. The effects of marijuana smoke on gas exchange in ovine pregnancy. **Alcohol and Drug Research**, Honnelles, v. 7, n. 2, p. 85-92, 1987.

COMPTON, W. M.; THOMAS, Y. F.; STINSON, F. S.; GRANT, B. F. Prevalence, correlates, disability, and comorbidity of DSM-IV drug abuse and dependence in the United States: results from the national epidemiologic survey on alcohol and related conditions. **Archives of General Psychiatry**, Chicago, v. 64, n. 5, p. 566-576, 2007.

CROCI, T.; MANARA, L.; AUREGGI, G.; GUAGNINI, F.; RINALDI-CARMONA, M.; MAFFRAND, J. P.; LE FUR, G.; MUKENGE, S.; FERLA, G. In vitro functional evidence of neuronal cannabinoid CB1 receptors in human ileum. **British Journal of Pharmacology**, London, v. 125, n. 7, p. 1393-1395, 1998.

DE FONSECA, F. R.; CEBEIRA, M.; FERNANDEZ-RUIZ, J. J.; NAVARRO, M.; RAMOS, J. A. Effects of pre-and perinatal exposure to hashish extracts on the ontogeny of brain dopaminergic neurons. **Neuroscience**, Elmsford, v. 43, n. 2-3, p. 713-723, 1991.

DENNEDY, M. C.; FRIEL, A. M.; HOULIHAN, D. D.; BRODERICK, V. M.; SMITH, T.; MORRISON, J. J. Cannabinoids and the human uterus during pregnancy. **American Journal of Obstetrics and Gynecology**, Saint Louis v. 190, n. 1, p. 2-9, 2004.

DEVANE, W. A.; DYSARZ, F. 3; JOHNSON, M. R.; MELVIN, L. S.; HOWLETT, A. C. Determination and characterization of a cannabinoid receptor in rat brain. **Molecular Pharmacology**, Bethesda, v. 34, n. 5, p. 605-613, 1988.

DEVANE, W. A.; HANUS, L.; BREUER, A.; PERTWEE, R. G.; STEVENSON, L. A.; GRIFFIN, G.; GIBSON, G.; MANDELBAUM, A.; ETINGER, A.; MECHOULAM, R. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. **Science**, New York, v. 258, n. 5090, p. 1946-1949, 1992.

DJULUS, J.; MORETTI, M.; KOREN, G. Marijuana use and breastfeeding. **Canadian Family Physician**, Mississauga, v. 51, n. 3, p. 349-350, 2005.

EL MARROUN, H.; TIEMEIER, H.; STEEGERS, E. A. P.; JADDOE, V. W. V.; HOFMAN, A.; VERHULST, F. C.; VAN DEN BRINK, W.; HUIZINK, A. C. Intrauterine cannabis exposure affects fetal growth trajectories: the Generation R Study. **Journal of the American Academy of Child & Adolescent Psychiatry**, Washington, v. 48, n. 12, p. 1173-1181, 2009.

ELSOHLY, M. A.; MEHMEDIC, Z.; FOSTER, S.; GON, C.; CHANDRA, S.; CHURCH, J. C. Changes in cannabis potency over the last 2 decades (1995-2014): analysis of current data in the United States. **Biological Psychiatry**, Dallas, v. 79, n. 7, p. 613-619, 2016.

FELDER, C. C.; JOYCE, K. E.; BRILEY, E. M.; MANSOURI, J.; MACKIE, K.; BLOND, O.; LAI, Y.; MA, A. L.; MITCHELL, R. L. Comparison of the pharmacology and signal transduction of the human cannabinoid CB1 and CB2 receptors. **Molecular Pharmacology**, Bethesda, v. 48, n. 3, p. 443-450, 1995.

FERGUSSON, D. M.; HORWOOD, L. J.; NORTHSTONE, K.; ALSPAC STUDY TEAM. Maternal use of cannabis and pregnancy outcome. **BJOG: An International Journal of Obstetrics & Gynaecology**, London, v. 109, n. 1, p. 21-27, 2002.

GLASS, M.; FAULL, R. L. M.; DRAGUNOW, M. Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. **Neuroscience**, Elmsford, v. 77, n. 2, p. 299-318, 1997.

GÓMEZ, M.; HERNÁNDEZ, M.; JOHANSSON, B.; de MIGUEL, R.; RAMOS, J. A.; FERNÁNDEZ-RUIZ, J. Prenatal cannabinoid exposure and gene expression for neural adhesion molecule L1 in the fetal rat brain. **Developmental Brain Research**, Amsterdam, v. 147, n. 1-2, p. 201-207, 2003.

GOVERNING – THE STATES AND LOCALITIES. **State Marijuana Laws in 2018.** 2018. Disponível em: <http://www.governing.com/gov-data/state-marijuana-laws-map-medical-recreational.html>. Acesso em: January 2018.

GRANT, K. S.; PETROFF, R.; ISOHERRANEN, N.; STELLA, N.; BURBACHER, T. M. Cannabis use during pregnancy: pharmacokinetics and effects on child development. **Pharmacology & Therapeutics**, Kansas City, v. 182, p. 133-151, 2018.

GREYDANUS, E. D.; KAPLAN, D.; BAXTER, E. L.; PATEL, R. D.; FEUCHT, L. C. *Cannabis*: the never-ending, nefarious, nepenthe of the 21st century: what should the clinician know?. **Disease-a-Month**, Glenview, v. 61, n. 4, p. 118-175, 2015.

HANUŠ, L.; ABU-LAFI, S.; FRIDE, E.; BREUER, A.; VOGEL, Z.; SHALEV, D. E.; KUSTANOVICH, I.; MECHOULAM, R. 2-Arachidonyl glyceryl ether, an endogenous agonist of the cannabinoid CB1 receptor. **Proceedings of the National Academy of Sciences of the United States of America**, Washington, v. 98, n. 7, p. 3662-3665, 2001.

HARBISON, R. D.; MANTILLA-PLATA, B. Prenatal toxicity, maternal distribution and placental transfer of tetrahydrocannabinol. **Journal of Pharmacology and Experimental Therapeutics**, Bethesda, v. 180, n. 2, p. 446-453, 1972.

HATCH, E. E.; BRACKEN, M. B. Effect of marijuana use in pregnancy on fetal growth. **American Journal of Epidemiology**, Oxford, v. 124, n. 6, p. 986-993, 1986.

HAYATBAKHSH, M. R.; FLENADY, V. J.; GIBBONS, K. S.; KINGSBURY, A. M.; HURRION, E.; MAMUN, A. A.; NAJMAN, J. M. Birth outcomes associated with cannabis use before and during pregnancy. **Pediatric Research**, Baltimore, v. 71, n. 2, p. 215, 2012.

HIGGINS, P. G.; CLOUGH, D. H.; FRANK, B.; WALLERSTEDT, C. Changes in health behaviors made by pregnant substance

users. **International Journal of the Addictions**, Salt Lake City, v. 30, n. 10, p. 1323-1333, 1995.

HOWLETT, A. C. The cannabinoid receptors. **Prostaglandins & Other Lipid Mediators**, New York, v. 68, p. 619-631, 2002.

HUTCHINGS, D. E.; BRAKE, S. C.; MORGAN, B. Plasma concentrations of delta-9-tetrahydrocannabinol in dams and fetuses following acute or multiple prenatal dosing in rats. **Life Sciences**, Elmsford, v. 44, n. 11, p. 697-701, 1989.

JAQUES, S. C.; KINGSBURY, A.; HENSHCKE, P.; CHOMCHAI, C.; CLEWS, S.; FALCONER, J.; ABDEL-LATIF, M. E.; FELLER, J. M.; OEI, J. L. Cannabis, the pregnant woman and her child: weeding out the myths. **Journal of Perinatology**, London, v. 34, n. 6, p. 417, 2014.

KENNEDY, J. S.; WADDELL, W. J. Whole-body autoradiography of the pregnant mouse after administration of 14C-Δ9-THC. **Toxicology and Applied Pharmacology**, Orlando, v. 22, n. 2, p. 252-258, 1972.

KISHIMOTO, Y.; KANO, M. Endogenous cannabinoid signaling through the CB1 receptor is essential for cerebellum-dependent discrete motor learning. **Journal of Neuroscience**, Washington, v. 26, n. 34, p. 8829-8837, 2006.

KO, J. Y.; FARR, S. L.; TONG, V. T.; CREANGA, A. A.; CALLAGHAN, W. M. Prevalence and patterns of marijuana use among pregnant and nonpregnant women of reproductive age. **American Journal of Obstetrics and Gynecology**, Saint Louis, v. 213, n. 2, p. 201. e1-201. e10, 2015.

LAZZARIN, N.; VALENSISE, H.; BARI, M.; UBALDI, F.; BATTISTA, N.; FINAZZI-AGRO, A.; MACCARRONE, M. Fluctuations of fatty acid amide hydrolase and anandamide levels during the human ovulatory cycle. **Gynecological Endocrinology**, Pisa, v. 18, n. 4, p. 212-218, 2004.

LESTER, B. M.; ANDREOZZI, L.; APPIAH, L. Substance use during pregnancy: time for policy to catch up with research. **Harm Reduction Journal**, London, v. 1, n. 1, p. 5, 2004.

MACCARRONE, M. CB2 receptors in reproduction. **British Journal of Pharmacology**, London, v. 153, n. 2, p. 189-198, 2008.

MACCARRONE, M.; FRIDE, E.; BISOGNO, T.; BARI, M.; CASCIO, M. G.; BATTISTA, N.; FINAZZI AGRÒ, A.; SURIS, R.; MECHOULAM, R.; DI MARZO, V. Up-regulation of the endocannabinoid system in the uterus of leptin knockout (ob/ob) mice and implications for fertility. **Molecular Human Reproduction**, Oxford, v. 11, n. 1, p. 21-28, 2005.

MANIKKAM, M.; TRACEY, R.; GUERRERO-BOSAGNA, C.; SKINNER, M. K. Dioxin (TCDD) induces epigenetic transgenerational inheritance of adult onset disease and sperm epimutations. **Plos One**, Cambridge v. 7, n. 9, p. e46249, 2012.

MARIANI, J. J.; BROOKS, D.; HANEY, M.; LEVIN, F. R. Quantification and comparison of marijuana smoking practices: blunts, joints, and pipes. **Drug and Alcohol Dependence**, Baltimore, v. 113, n. 2-3, p. 249-251, 2011.

MARK, K.; DESAI, A.; TERPLAN, M. Marijuana use and pregnancy: prevalence, associated characteristics, and birth outcomes. **Archives of Women's Mental Health**, Heidelberg, v. 19, n. 1, p. 105-111, 2016.

MARK, K.; TERPLAN, M. Cannabis and pregnancy: maternal child health implications during a period of drug policy liberalization. **Preventive Medicine**, Montreal, v. 104, p. 46-49, 2017.

MATSUDA, L. A.; LOLAIT, S. J.; BROWNSTEIN, M. J.; YOUNG, A. C.; BONNER, T. I. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. **Nature**, London, v. 346, n. 6284, p. 561, 1990.

MAYKUT, M. O. Health consequences of acute and chronic marihuana use. **Progress in Neuro-Psychopharmacology & Biological Psychiatry**, Quebec, v. 9, n. 3, p. 209-238, 1985.

MCLAREN, J.; SWIFT, W.; DILLON, P.; ALLSOP, S. Cannabis potency and contamination: a review of the literature. **Addiction**, London, v. 103, n. 7, p. 1100-1109, 2008.

MECHOULAM, R.; GAONI, Y. Hashish. IV. The isolation and structure of cannabinolic cannabidiolic and cannabigerolic acids. **Tetrahedron**, Fort Collins, v. 21, n. 5, p. 1223-1229, 1965.

MECHOULAM, R.; BEN-SHABAT, S.; HANUS, L.; LIGUMSKY, M.; KAMINSKI, N. E.; SCHATZ, A. R.; GOPHER, A.; ALMOG, S.; MARTIN, B. R.; COMPTON, D. R.; PERTWEE, R. G.; GRIFFIN, G.; BAYEWITCH, M.; BARG, J.; VOGEL, Z. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. **Biochemical Pharmacology**, Oxford, v. 50, n. 1, p. 83-90, 1995.

MECHOULAM, R.; PETERS, M.; MURILLO-RODRIGUEZ, E.; HANUŠ, L. O. Cannabidiol-recent advances. **Chemistry & Biodiversity**, Saint Louis, v. 4, n. 8, p. 1678-1692, 2007.

MEHMEDIC, Z.; CHANDRA, S.; SLADE, D.; DENHAM, H.; FOSTER, S.; PATEL, A. S.; MENDELSON, J. H.; MELLO, N. K.; ELLINGBOE, J. Acute effects of marihuana smoking on prolactin levels in human females. **Journal of Pharmacology and Experimental Therapeutics**, Bethesda, v. 232, n. 1, p. 220-222, 1985.

MENDELSON, J. H.; MELLO, N. K.; ELLINGBOE, J.; SKUPNY, A. S.; LEX, B. W.; GRIFFIN, M. Marihuana smoking suppresses luteinizing hormone in women. **Journal of Pharmacology and Experimental Therapeutics**, Bethesda v. 237, n. 3, p. 862-866, 1986.

MUNRO, S.; THOMAS, K. L.; ABU-SHAAR, M. Molecular characterization of a peripheral receptor for cannabinoids. **Nature**, London, v. 365, n. 6441, p. 61, 1993.

MURPHY, L. L.; MUÑOZ, R. M.; ADRIAN, B. A.; VILLANÚA, M. A. Function of cannabinoid receptors in the neuroendocrine regulation of hormone secretion. **Neurobiology of Disease**, Pittsburgh, v. 5, n. 6, p. 432-446, 1998.

NAVARRO, M.; RUBIO, P. Behavioural consequences of maternal exposure to natural cannabinoids in rats. **Psychopharmacology**, Berlin, v. 122, n. 1, p. 1-14, 1995.

NOTCUTT, W. Cannabinoids. **British Journal of Hospital Medicine**, London, v. 77, n. 5, 2016.

PARK, B.; GIBBONS, H. M.; MITCHELL, M. D.; GLASSA, M. Identification of the CB1 cannabinoid receptor and fatty acid amide hydrolase (FAAH) in the human placenta. **Placenta**, Elizabeth Vale, v. 24, n. 5, p. 473-478, 2003.

PARK, B.; MCPARTLAND, J. M.; GLASS, M. Cannabis, cannabinoids and reproduction. **Prostaglandins, Leukotrienes and Essential Fatty Acids**, Shellfied, v. 70, n. 2, p. 189-197, 2004.

PERTWEE, R. G. Cannabinoid receptors and pain. **Progress in Neurobiology**, Paris, v. 63, n. 5, p. 569-611, 2001.

POPE, H. G.; YURGELUN-TODD, D. The residual cognitive effects of heavy marijuana use in college students. **Journal of the**

American Medical Association, Chicago, v. 275, n. 7, p. 521-527, 1996.

ROCHA, P. C.; CHAGAS, D. C. D.; SILVA, A. A. M. D.; BATISTA, R. F. L.; SILVA, R. A. D. Prevalência e fatores associados ao uso de drogas ilícitas em gestantes da coorte BRISA. **Cadernos de Saúde Pública**, São Paulo, v.32, e00192714, 2016.

ROSS, S. A.; KHAN, I. A.; ELSOHLY, M. A. Potency trends of Δ9-THC and other cannabinoids in confiscated cannabis preparations from 1993 to 2008. **Journal of Forensic Sciences**, Hoboken, v. 55, n. 5, p. 1209-1217, 2010.

SALZET, M. Invertebrate molecular neuroimmune processes. **Brain Research Reviews**, Amsterdam, v. 34, n. 1-2, p. 69-79, 2000.

SAMSHA – SUBSTANCE ABUSE AND MENTAL HEALTH SERVICES ADMINISTRATION. **Behavioral health trends in the United States:** Results from the 2014 National Survey on Drug Use and Health. 2015. Disponível em: <http://www.samhsa.gov/data/>.

SATO, K.; FUKATA, H.; KOGO, Y.; OHGANE, J.; SHIOTA, K.; MORI, C. Neonatal exposure to diethylstilbestrol alters expression of DNA methyltransferases and methylation of genomic DNA in the mouse uterus. **Endocrine Journal**, Kyoto, v. 56, n. 1, p. 131-139, 2009.

SCHENKER, M.; MINAYO, M. C. S. Fatores de risco e de proteção para o uso de drogas na adolescência. **Ciência & Saúde Coletiva**, Rio de Janeiro, v. 10, p. 707-717, 2005.

SHIRE, D.; CARILLON, C.; KAGHAD, M.; CALANDRA, B.; RINALDI-CARMONA, M.; LE FUR, G.; CAPUT, D.; FERRARA, P. An amino-terminal variant of the central cannabinoid receptor resulting from alternative splicing. **Journal of Biological Chemistry**, Bethesda, v. 270, n. 8, p. 3726-3731, 1995.

SIDNEY, S. Cardiovascular consequences of marijuana use. **The Journal of Clinical Pharmacology**, Winnipeg v. 42, n. S1, p. 64S-70S, 2002.

SINGH, N. P.; SINGH, U. P.; GUAN, H.; NAGARKATTI, P.; NAGARKATTI, M. Prenatal exposure to TCDD triggers significant modulation of microRNA expression profile in the thymus that affects consequent gene expression. **Plos One**, Cambridge, v. 7, n. 9, p. e45054, 2012.

SVÍŽENSKÁ, I.; DUBOVÝ, P.; ŠULCOVÁ, A. Cannabinoid receptors 1 and 2 (CB1 and CB2), their distribution, ligands and functional involvement in nervous system structures - a short review. **Pharmacology Biochemistry and Behavior**, Chilly-Mazarin, v. 90, n. 4, p. 501-511, 2008.

STINSON, F. S.; GRANT, B. F.; DAWSON, D. A.; RUAN, W. J.; HUANG, B.; SAHA, T. Comorbidity between DSM-IV alcohol and specific drug use disorders in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. **Drug and Alcohol Dependence**, Baltimore, v. 29, n. 2, p. 94, 2006.

SZABO, B.; NORDHEIM, U.; NIEDERHOFFER, N. Effects of cannabinoids on sympathetic and parasympathetic neuroeffector transmission in the rabbit heart. **Journal of Pharmacology and Experimental Therapeutics**, Bethesda, v. 297, n. 2, p. 819-826, 2001.

TAYLOR, A. H.; AMOAKO, A. A.; BAMBANG, K.; KARASU, T.; GEBEH, A.; LAM, P. M.; MARZCYLO, T. H.; KONJE, J. C. Endocannabinoids and pregnancy. **Clinica Chimica Acta**, Amsterdam, v. 411, n. 13-14, p. 921-930, 2010.

TENNES, K.; AVITABLE, N.; BLACKARD, C.; BOYLES, C.; HASSOUN, B.; HOLMES, L.; KREYE, M. Marijuana: prenatal and postnatal exposure in the human. **NIDA Research Monograph Index**, Bethesda, v. 59, p. 48-60, 1985.

TERRANOVA, P. F. The female reproductive system. In: RHOADES, R. A.; TANNER, G. A. (Ed.). **Medical Physiology.** 2 ed. Baltimore, New York: Lippincott William & Wilkins, 2003. p. 667-683.

UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES; SUBSTANCE ABUSE AND MENTAL HEALTH SERVICES ADMINISTRATION; CENTER FOR BEHAVIORAL HEALTH STATISTICS AND QUALITY. **National survey on drug use and health.** 2013. Ann Arbor: Inter-university Consortium for Political and Social Research, 2015-11-23. Disponível em <https://doi.org/10.3886/ICPSR35509.v3>.

VARDARIS, R. M.; WEISZ, D. J.; FAZEL, A.; RAWITCH, A. B. Chronic administration of delta-9-tetrahydrocannabinol to pregnant rats: studies of pup behavior and placental transfer. **Pharmacology Biochemistry and Behavior**, Chilly-Mazarin, v. 4, n. 3, p. 249-254, 1976.

VASSOLER, F. M.; JOHNSON, N. L.; BYRNES, E. M. Female adolescent exposure to cannabinoids causes transgenerational effects on morphine sensitization in female offspring in the absence of in utero exposure. **Journal of Psychopharmacology**, London, v. 27, n. 11, p. 1015-1022, 2013.

WALKER, B. E.; HAVEN, M. I. Intensity of multigenerational carcinogenesis from diethylstilbestrol in mice. **Carcinogenesis**, Oxford, v. 18, n. 4, p. 791-793, 1997.

WALLACH, E. E.; SMITH, C. G.; ASCH, R. H. Drug abuse and reproduction. **Fertility and Sterility**, New York, v. 48, n. 3, p. 355-373, 1987.

WANG, G. S.; DAVIES, S. D.; HALMO, L. S.; SASS, A.; MISTRY, R. D. Marijuana legalization and adolescent health. **Journal of Adolescent Health**, San Francisco, v. 63, n. 3, p. 367, 2018.

WANG, H., GUO, Y., WANG, D., KINGSLEY, P. J., MARNETT, L. J., DAS, S. K., DUBOIS, R. N., DEY, S. K. Aberrant cannabinoid signaling impairs oviductal transport of embryos. **Nature Medicine**, London, v. 10, n. 10, p. 1074, 2004.

WANG, J.; PARIA, B. C.; DEY, S. K.; ARMANT, D. R. Stage-specific excitation of cannabinoid receptor exhibits differential effects on mouse embryonic development. **Biology of Reproduction**, New York, v. 60, n. 4, p. 839-844, 1999.

WENZEL, S. L.; KOSOFSKY, B. E.; HARVEY, J. A.; IGUCHI, M. Y.; STEINBERG, P.; WATKINS, K. E.; SHAIKH, R. **Prenatal cocaine exposure scientific considerations and policy implications.** Santa Monica: RAND Drug Policy Research Center, 2001. 52 p.

WESTERLIND, K. C.; WRONSKI, T. J.; RITMAN, E. L.; LUO, Z. P.; AN, K. N.; BELL, N. H.; TURNER, R. T. Estrogen regulates the rate of bone turnover but bone balance in ovariectomized rats is modulated by prevailing mechanical strain. **Proceedings of the National Academy of Sciences of the United States of America**, Washington, v. 94, n. 8, p. 4199-4204, 1997.

ZILBERMAN, M. L.; HOCHGRAF, P. B.; ANDRADE, A. G. Gender differences in treatment-seeking Brazilian drug-dependent

individuals. **Substance Abuse**, Pittsburgh, v. 24, n. 1, p. 17-25, 2003.

ZUARDI, A. W. History of *Cannabis* as a medicine: a review. **Revista Brasileira de Psiquiatria**, São Paulo, v. 28, n. 2, p. 153-157, 2006.

ZUCKERMAN, B.; FRANK, D. A.; HINGSON, R.; AMARO, H.; LEVENSON, S. M.; KAYNE, H.; PARKER, S.; VINCI, R.; ABOAGYE, K.; FRIED, L. E.; CABRAL, H.; TIMPERI, R.; BAUGHNER, H. Effects of maternal marijuana and cocaine use on fetal growth. **New England Journal of Medicine**, Waltham, v. 320, n. 12, p. 762-768, 1989.