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Impact of cannabinoids on pregnancy, reproductive health and offspring outcomes

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Abstract

Cannabis is the most commonly used federally illegal drug in the United States and world, especially among people of reproductive age. In addition, the potency of cannabis products has increased significantly in the past decade. This is concerning because the available evidence suggests an adverse effect from cannabis exposure on male and female reproductive health. Exposure to cannabinoids may have differential impacts on female reproductive health across a woman's lifespan, from preconception to pregnancy, throughout lactation, and during menopause. Even more, cannabis use has been associated an adverse effect on fetal outcomes, and longer-term offspring health and developmental trajectories. Despite the prevalence of cannabis use, there is limited available evidence regarding its safety, especially in regard to reproductive health, pregnancy and lactation. The biological effects of cannabis are mediated by the endocannabinoid system and studies have reported the presence of cannabinoid receptors in the male and female reproductive tract, on sperm and the placenta, suggesting the endocannabinoid system plays a role in regulating reproduction. Cannabis use can impact male and female fertility and has been associated with altered reproductive hormones, menstrual cyclicity and semen parameters. Use of cannabis in males has also been associated with erectile dysfunction, abnormal spermatogenesis, and testicular atrophy. In females, cannabis use has been associated with infertility and abnormal embryo implantation and development. The main psychoactive component of cannabis, delta-9-

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tetrahydrocannabinol (THC), can also cross the placenta and has been detected in breastmilk. Maternal cannabis use during pregnancy and lactation has been associated with adverse effects including small for gestational age infants, preterm birth, fetal neurodevelopmental consequences, and impaired offspring sociobehavioral and cognitive development. The prevalence of cannabis use to alleviate menopausal symptoms has also increased despite the limited information on its benefits and safety. As cannabis use is on the rise, it is critical to understand its impact on reproductive health and offspring developmental outcomes. This is an understudied, but timely subject, with much needed information to guide healthcare providers and those interested in conceiving, or that are pregnant and lactating, as well as those at the end of their reproductive time span.

CONDENSATION:

The use of cannabis and its impact on reproductive health and offspring outcomes.

Keywords

cannabis; marijuana; menopause; maternal cannabis use; THC; cannabinoids; delta-9-tetrahydrocannabinol; reproductive health; substance use; fertility; cannabis use disorder; preterm birth; small for gestational age; low birth weight

INTRODUCTION

Cannabis is the most commonly used federally illegal drug in the United States (US) and world, in part due to widespread legalization and increasing social acceptability and accessibility.[1] Prevalence of cannabis use is on the rise, especially among people of reproductive age, including during the COVID-19 pandemic in part due to heightened anxiety and stress (Figure 1).[2,3] In addition, the potency of cannabis products has increased by almost two-fold in the past decade.[4] This is concerning because the available evidence suggests an adverse effect from cannabis exposure on male and female reproductive health, pregnancy and fetal outcomes, and longer-term offspring health and developmental trajectories.

The biological effects of cannabis are mediated by the endocannabinoid system. Expression of endocannabinoid receptors has been demonstrated in the fetus as early as 5 weeks gestation[5] and the endocannabinoid system has been detected at early stages of development (Figure 2).[6] Published studies have reported the presence of cannabinoid receptors in the male and female reproductive tract, on sperm and the placenta,[7,8] suggesting the endocannabinoid system plays a role in regulating reproduction.[9,10] Cannabis use can impact male and female fertility and has been associated with altered reproductive hormones, menstrual cyclicity and semen parameters.[11–13] The main psychoactive component of cannabis, delta-9-tetrahydrocannabinol (THC), can also cross the placenta and has been detected in breastmilk. Maternal cannabis use during pregnancy and lactation has been associated with adverse effects including small for gestational age (SGA) infants, preterm birth (PTB), fetal neurodevelopmental consequences, and impaired offspring sociobehavioral and cognitive development.[14–23]

Despite the prevalence of cannabis use, there is limited available evidence regarding its safety, especially in regard to reproductive health, pregnancy and lactation. This lack of information has resulted in approximately 70% of females in the US believing that consumption of cannabis once or twice per week is harmless[24] and cannabis retailers promoting cannabinoids as safe, natural and effective ways to manage common daily ailments, including in pregnancy, such as insomnia, pain, and morning sickness.[25] The heterogeneity in the existing human literature is due to methodologic issues, small sample sizes, lack of confirmatory testing, and difficulty controlling for confounders.[26] The available animal literature focuses largely on the effects of acute cannabis exposure, and often studied modes of cannabis delivery not representative of human use (e.g. intravenous or oral gavage), thus limiting the translation of those findings to humans. Taken together, these factors contribute to the paucity of safety information.

As cannabis use is on the rise, especially among those of reproductive age, it is critical to understand its impact on reproductive health and offspring developmental outcomes. This is an understudied, but timely subject, with much needed information to guide healthcare providers and those interested in conceiving, or that are pregnant and lactating.

PHARMACOLOGY OF CANNABINOIDS

Cannabis, a plant of the *Cannabaceae* family, contains more than eighty biologically active chemical compounds. The most commonly known compounds are THC and cannabidiol. Cannabinoid receptors, CB1 and CB2, are distributed in the central nervous system and many peripheral tissues including reproductive, urinary and gastrointestinal tracts.[8,27] THC is an agonist to CB1 and the CB2 subtype of cannabinoid receptors. Properties of cannabinoids that might be of therapeutic use include analgesia, muscle relaxation, immunosuppression, anti-inflammation, anti-allergic effects, sedation, improvement of mood, stimulation of appetite, anti-emesis, and antineoplastic effects.[28] However, there is no Food and Drug Administration (FDA) approval for these therapeutic uses.

The most common mode of cannabis administration in both non-pregnant and pregnant populations is smoking followed by edibles.[29,30] Smoking is the quickest method for THC to enter systematically and provides rapid onset and a short duration of symptoms (Table 1), which results in a lesser chance of overconsumption.[31] Edibles are gaining popularity because they are palatable, discreet, and effects can last for hours (Table 1). Because edibles require gastrointestinal absorption, it takes longer before symptom onset and thus, can lend to a higher likelihood of overconsumption.[31–35]

CANNABIS USE DISORDER

Cannabis use disorder (CUD) can develop in approximately 10 percent of regular cannabis users and 50 percent of chronic daily users.[36] It is a problematic pattern of cannabis use associated with cognitive impairment and psychiatric comorbidity, with at least two manifestations in twelve months.[36] Screening is generally by brief questionnaires at yearly preventative visits, or if prompted by signs or symptoms from the patient's history and exam.[36] In high-risk patient populations, drug testing can be considered. The diagnosis

of CUD is guided by the patient's cannabis use, signs and symptoms and functional impairment per the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria.[36]

There are limited treatment options for CUD, but the goal is to achieve sustained abstinence from cannabis use, or reduced use that mitigates the patient's cannabis-related symptoms. In half of patients with CUD, cessation of cannabis after heavy and prolonged use results in withdrawal symptoms.[37] Options for treatment include brief intervention, psychosocial intervention, cognitive-behavioral therapy, and motivational enhancement therapy, or a combination. If these interventions fail, then adjunctive medications such as N-acetylcysteine, gabapentin, nabiximols, varenicline, and anti-depressants, can be considered, but are not FDA approved and some have limited safety information in pregnancy.[38]

LEGALIZATION OF CANNABIS AND DISPARITIES

Cannabis has been decriminalized in several regions of North America, Africa, Australia, Europe and South America. Use of cannabis has significantly increased due to widespread recreational cannabis legalization and increasing social acceptability and accessibility[1]. In 2021, cannabis was legalized for recreational use in eighteen US states.

Among adolescents, CUD has been associated with long-term adverse health, economic, and social implications. Individuals who have earlier initiation of cannabis are at an increased risk of lower levels of educational attainment, welfare dependence and unemployment, polysubstance use, including other illicit drugs, and psychotic symptomatology, suggesting that cannabis might contribute to racial and health inequity.[39] Research suggests that early (12–14 years old) to late (15–17 years old) adolescence is a critical risk period for the initiation of substance use and may exacerbate racial and health inequities.[40] While the legalization of cannabis may help reduce inequities in criminal justice, dysregulated cannabis use could widen gaps in health and social equity. Relative to the rates for whites, the odds of CUD are higher in American Natives and blacks but lower in Asians/Pacific Islanders and Hispanics.[41] By CUD severity, the odds are also higher in blacks than whites at moderate and severe levels.[41]

A recent study showed that the prevalence of prenatal cannabis use increased after legalization in the state of Colorado.[42] This was associated with an increase in fetal growth restriction (FGR) suggesting a population impact of legalization on obstetrical outcomes[42] and the need to develop well-evaluated policies to mitigate the potential adverse maternal and fetal consequences of prenatal cannabis use.

CANNABIS USE AND IMPACT ON PUBERTY

The recent changes in cannabis legalization will also likely influence the prevalence of cannabis use by children and adolescents.[43] This can result from increased availability, greater exposure to second-hand cannabis smoke, messaging that minimizes the health and behavioral risks, and the potential impact of role-modeling by adults who use cannabis on child and adolescent behavior. Studies have suggested that cannabis exposure can impact pediatric endocrine and metabolic health, and puberty.[44] Prior animal studies have

demonstrated that THC can delay puberty, interrupt sexual maturation, and impair growth and gonadal function.[45,46] The limited human literature regarding the effect of cannabis use on puberty[28] focuses largely on male subjects, consists of one abstract and a case report, and observed delayed puberty and reduced growth spurt in boys who smoked cannabis compared with non-smokers[47].

CANNABIS USE AND MALE REPRODUCTIVE HEALTH

In 2020, the estimated prevalence of past year use was 34.5% amongst adult males ages 18 to 25 year-old and 16.3% in ages 26 years or older in the United States.[48] Overall, the literature supports an adverse impact of paternal cannabis use on male reproductive health and offspring outcomes, but there is significant heterogeneity in the available published studies. It has been associated with erectile dysfunction, orgasmic dysfunction, and may cause premature or delayed ejaculation,[49,50] but the contrary has also been reported.[51] The effect of chronic cannabis use in men is inconsistent with some studies reporting minimal or no effect on follicle stimulating hormone (FSH) levels,[52] an association with lower testosterone and luteinizing hormone (LH) levels,[53,54] and poorer semen parameters,[11,55–57] while other studies have not confirmed these findings.[58–61] Previous animal studies suggest that acute exposure to THC can adversely impact spermatogenesis,[62] including inhibition of Leydig cell function[63], reduction in gonadotropins,[64–66] testicular atrophy,[67–72] and abnormal sperm morphology.[73–76]

IMPACT OF PATERNAL CANNABIS USE

In addition to affecting sperm function, cannabis may impact epigenetic regulators that can then influence the health and developmental trajectory of future offspring. A recent study reported that cannabis exposure in humans and rats is associated with altered widespread DNA methylation in sperm[77]. Affected genes identified are involved in early development, including neurodevelopment, while others are implicated in cancer. Additionally, paternal cannabis use during conception, pregnancy and the postnatal period has been significantly associated with sudden infant death syndrome, after adjusting for tobacco and alcohol co-use, but the underlying mechanism is unknown[78].

CANNABIS USE AND FEMALE REPRODUCTIVE HEALTH

The concern for adverse effects from cannabis use on female reproductive health is because cannabis use is commonly used by reproductive age females and both CB1 and CB2 receptors are present in the hypothalamus, pituitary, ovary, and uterus.[7,8] Currently, the existing literature suggests that cannabis can affect the processes involved with female reproductive health including the secretion of FSH and LH, ovulation and menstrual cyclicity. Although the exact underlying mechanism for these findings is unclear, the likely site of action is central[79–85] but, can also be a direct THC effect at the gonadal level.[86]

Pre-clinical rat models have demonstrated that acute THC administration resulted in suppressed LH, FSH, and prolactin levels,[85–87] and a 24-hour delay in ovulation.[86] Non-human primates (NHP) have a similar THC plasma disposition, menstrual cycle length,

and endocrine properties to humans.[88] Prior NHP studies of chronic THC exposure have reported ovulatory dysfunction, increased menstrual cycle length, anovulation, and altered female reproductive hormone levels.[12,82,89,90]

The existing human literature is conflicting and has likely contributed to the increased perception of cannabis users seeking infertility treatment that cannabis is safe and will not adversely impact fertility[61,91,92]. Similar to prior NHP studies, Jukic et al. found that cannabis users had more anovulatory cycles compared with nonusers (43% vs. 15%).[93] Some studies have found no significant association between cannabis use and spontaneous conception rate,[94,95] while other studies have found that women that smoked cannabis within a year of trying to conceive were twice as likely to experience infertility secondary to ovulatory dysfunction.[96] A recent study in women with a history of a prior first trimester pregnancy loss using cannabis preconception noted decreased fecundability despite increased intercourse frequency.[97] In women that smoked cannabis 1 year prior to undergoing *in vitro* fertilization, after adjusting for cigarette smoking and other relevant confounders, one study noted 25% fewer oocytes retrieved and 28% fewer oocytes fertilized[78] and another reported more than double the adjusted probability of pregnancy loss compared to non-smokers.[98]

CANNABIS USE IN PREGNANCY

Cannabis is now the most commonly used federally illegal drug in pregnancy,[2,99–101] with prevalence of use nearly doubling in the past decade in the US.[102] A recent report noted that the prevalence of last month cannabis use was over 4.9% among pregnant women aged 15–44 years old and rose to 8.5% in those aged 18–25 years-old.[103] Characteristics associated with prenatal cannabis use include being single or unmarried, young, lower socioeconomic status, less education, or residing with a partner who also uses cannabis.[104] Women that use cannabis in pregnancy often engage in polysubstance use with alcohol, tobacco, or other illicit drugs, that can result in an additive or synergistic effect.[105] First trimester use of cannabis to treat nausea is common, and marks a developmental window when the fetus is most vulnerable to adversity; and half of female individuals who use cannabis continue to use throughout pregnancy.[106,107] The most frequent methods of cannabis use during pregnancy are smoking, edibles, vaping, and topicals.[108]

The US Surgeon General, American College of Obstetricians and Gynecologists (ACOG), and the American Academy of Pediatrics (AAP) recommend that pregnant women should be counseled regarding the potential risks of prenatal cannabis use and encouraged to abstain from use in pregnancy and while breastfeeding.[99,109,110] However, the continued high prevalence of use is partly because patients are unsure about the level of safety regarding prenatal cannabis use due to the heterogeneity in the available literature,[111] healthcare providers are not appropriately counselling or educating patients,[112–114] and cannabis retailers are promoting cannabis as a safe, natural and effective method for mitigating pregnancy symptoms.[25,115] Patients most commonly report using cannabis during pregnancy to help with nausea, stress, sleep, and appetite changes.[115,116]

There is concern for adverse fetal and neonatal outcomes given THC can access and bind to cannabinoid receptors in the placenta and fetal brain (Figure 3).[117–120] The limited, available evidence suggests that prenatal cannabis exposure is associated with a negative impact to the developing fetus and offspring.[17,18,22,23,121] There is a possible increase in risk of miscarriage and stillbirth, but the results are inconsistent among studies, and many studies do not control for important confounders such as tobacco use.[122,123] Some studies suggest an increased risk of neonatal intensive care unit (NICU) admission, SGA, placental abruption, 5-minute Apgar less than 4, and infant death.[22,120,122,124,125] There is evidence prenatal cannabis exposure is associated with low birth weight (LBW)[22] and PTB.[120,126] The most recent systematic review and meta-analysis reported that cannabis use in pregnancy is associated with an increased risk of LBW (RR, 2.06 [95% CI, 1.25 to 3.42]; $P = .005$), SGA (RR, 1.61 [95% CI, 1.44 to 1.79]; $P < .001$), PTB (RR, 1.28 [95% CI, 1.16 to 1.42]; $P < .001$), and NICU admission (RR, 1.38 [95% CI, 1.18 to 1.62]; $P < .001$).[120] The limited literature on teratogenicity is conflicting and inconsistent, but include reports of congenital anomalies with maternal cannabis use such as acrania, gastroschisis, esophageal atresia, and congenital diaphragmatic hernia.[127,128]

Amongst pregnant females that used cannabis in the past-year, it has been reported that 18.1% meet criteria for CUD.[24] The rate of CUD increased from 1.8 to 9.4 per 1000 deliveries from 1993 to 2014 respectively.[129] Recently, Shi et al. reported that infants born to mothers with CUD were more likely to experience adverse health outcomes, including SGA, PTB, low birth weight, and death within 1 year of birth, than those born to women without CUD.[124,130] This adds to the growing body of evidence that prenatal cannabis exposure may be associated with poor birth outcomes.

Placental development, function and pregnancy outcomes

Animal studies have demonstrated that the endocannabinoid system is present in midgestational placentas, where it is suggested to play a critical role in placentation, trophoblast differentiation, as well as fetal outcomes.[131] In the human term placenta, CB1 receptor expression has been demonstrated in the amniotic epithelium, reticular and decidual cells suggesting that the placenta is a likely target for cannabinoid action.[132] Studies demonstrate that THC inhibits the migration of the epithelial layer of human placental amnion tissue through the regulation of metalloproteinases, affecting the development of the amnion during the gestation and contributing to preterm labor and other adverse pregnancy outcomes.[133] *In vitro* studies have shown that THC impairs cytotrophoblasts fusion and biochemical differentiation, inhibits trophoblast cell turnover and, consequently, can impair placental development[134]. This is consistent with histological studies demonstrating increased syncytiotrophoblastic knots and fibrin deposition in the villous stroma of human placentas from cannabis users.[135] In rodents, prenatal THC exposure induces FGR and increased placental weight resulting in increased fetal/placental weight ratio.[135–137] Abnormal placental steroidogenesis and estrogen signaling induced by THC might also explain placental dysfunction and adverse pregnancy outcomes in women that use cannabis during pregnancy.[138]

Pharmacodynamics of Prenatal Cannabis Use

Prior animal studies have shown that fetal blood and tissue THC concentrations are approximately 10% lower than maternal blood levels,[139] but can be higher with chronic heavy exposure.[140] In humans, THC levels in umbilical cord blood samples were 3 to 6 times lower than simultaneously collected maternal blood.[141]

OFFSPRING OUTCOMES WITH MATERNAL CANNABIS USE

The recent rise in prevalence of prenatal cannabis use has been associated with increasing evidence of associated adverse effects for fetal and neonatal developmental outcomes.[142] In THC-exposed rat offspring, deleterious effects on fetal ovarian development and long-term reproductive health have been demonstrated such as accelerated folliculogenesis and follicular development arrest, transient effects on circulating steroid hormones level, and reduced ovarian vasculatures.[143] It has also been demonstrated that exposure to THC *in utero* affects fetal brain development increasing the risk for neurocognitive and neuropsychiatric disorders, suggesting that maternal use has interfered with the proper maturation of the brain.[5,144,145] *In utero* exposure to THC has also been linked to a "withdrawal"-like syndrome in newborns[146] and increased aggressive behavior and attention deficits were observed in offspring as early as at 18 months of age.[146,147] Abnormal verbal and visual reasoning, hyperactivity, attention deficit, and impulsivity have also been noted in preschool children born to mothers that used THC in pregnancy.[21,146] A negative association of short-term memory with first and/or second trimester cannabis usage has also been described[148]. These changes in neurocognitive and behavioral function persisted throughout the school years and at age 10, depression and anxiety was observed in these children.[21,149,150] Most recently, maternal cannabis use has been associated with an increased incidence of neurobehavioral changes, mental health issues, autism spectrum disorder, attention problems, attention scores, intellectual disability, and learning disorders.[122,151–155] However, other studies have not demonstrated an association with childhood cognitive impairments.[154,156]

Maternal cannabis use has been associated with increased psychotic-like experiences in pre-adolescent offspring. Genetic susceptibilities in parents and their offspring, including epigenetic transgenerational changes of substance use and psychiatric disorders may play a role.[157] A recent study also identified prenatal cannabis exposure as a risk factor for psychopathology during middle childhood.[153] Prenatal cannabis exposure before and after maternal knowledge of pregnancy were associated with higher psychotic life experiences and internalizing, externalizing, attention, thought, social, and sleep problems, as well as reduced cognitive function and gray matter volume in children aged 9 to 11 years.[153] Only the observed associations with cannabis exposure before maternal knowledge of pregnancy showed to be dependent on potential confounders such as socioeconomic status and familial history of psychopathology.[153]

Offspring Epigenetic Regulation

Altered epigenetic regulation can impact gene transcription in response to different environmental stimuli, including the intrauterine environment.[158] Epigenetic mechanisms

are increasingly recognized as a critical factor in the relationship between early life experience and risk of psychopathology.[159] Pre-gestational and gestational cannabis exposure has been shown to alter epigenetic processes, such as DNA methylation and histone modifications, with functional consequences for gene expression. *In utero* exposure to cannabis has been associated with fetal epigenetic programming of genes and some molecular pathways in brain regions involved in the development of autism spectrum disorder, attention deficit hyperactivity disorder, schizophrenia, addiction, and other psychiatric diseases.[160] A former study aimed to identifying the neurobiology underlying the risk of addiction vulnerability in humans detected diminished dopamine receptor D2 mRNA expression in fetal brain specimens of the nucleus accumbens, from mothers using cannabis who underwent elective abortions between 18 and 22 weeks of gestation compared to controls.[161] The nucleus accumbens core is an important component of motor and reward circuits, respectively[162] and disruptions in the dopamine signaling pathways could lead to adverse psychiatric outcomes.[163]

BREASTFEEDING AND CANNABIS USE

Overall, there is very little known about cannabis use and lactation. With recent legalization, the prevalence of cannabis use while breastfeeding has increased and is approximately 5%[164] with up to 18% reported in certain populations.[165] Lactating mothers tend to increase cannabis use within the first two months after childbirth.[166] This is concerning because THC is lipid soluble and transferred through breastmilk where it is stored in lipid-filled tissue and slowly release over time in the offspring. This includes the offspring brain where it can impact sensitive neurodevelopmental processes. Thus, the Center for Disease Control and Prevention (CDC), ACOG and AAP all recommend against using cannabis in any form while lactating.[99,109]

The passage of THC into breastmilk has not been extensively studied, but the literature suggests that with chronic use, THC can concentrate in human breastmilk, up to 7.5 times, relative to plasma.[166,167] When cannabis is smoked, it has been shown that THC levels peak in breastmilk 1 hour post inhalation and remain detectable for 6 days after use.[164,168] Infants that are exclusively breastfed have been found to ingest a mean of 2.5% of the maternal THC dose used.[164,168] A prior study found that offspring exposed to THC in breastmilk within the first month of life can have decreased motor development compared with those not exposed.[169] However, the literature is limited on the effects of THC exposure through breastfeeding on long-term offspring neurodevelopment. Other studies have suggested that infants exposed to THC through breast milk experience more lethargy, less frequent feeding, growth delay, poor sucking, and shorter feeding times.[169–173]

CANNABIS AND MENOPAUSE

An increasing number of women are using cannabis to manage their menopausal symptoms[174,175] with the frequency of cannabis use significantly correlating to the number and severity of menopausal symptoms.[174] While cannabis use appears to mitigate musculoskeletal discomfort, irritability, insomnia, depression, anxiety, and hot flashes, other symptoms such as heart discomfort, exhaustion, vaginal dryness, and bladder problems were

not alleviated by cannabis use.[174] There is a significant gap between the marketed benefits of cannabis and the supporting evidence in the medical literature.[176] Prior studies, published in the 1970s, have reported the pro- and anti-estrogenic properties of THC.[177 178]

However, the underlying mechanism for which THC provides symptom relief is unclear and the data on the efficacy and safety of cannabis use for menopausal symptom relief is limited and further evidence is needed to guide informed decision making.[179]

CONCLUSION

In summary, despite the increase in cannabis use, there is limited available evidence regarding its safety, especially in regard to reproductive health, pregnancy and lactation. Considering the existing literature suggests that cannabis use has health implications for women, men, and subsequent offspring, it is concerning almost 70% of females in the US believe that consumption of cannabis is safe in pregnancy and only approximately half of US healthcare providers discouraged the perinatal use of cannabis.[180] While the literature regarding the safety of cannabis use is limited, women and their health care providers should be informed of the potential adverse effects of cannabis use, especially when planning to conceive, during pregnancy and the postpartum period.

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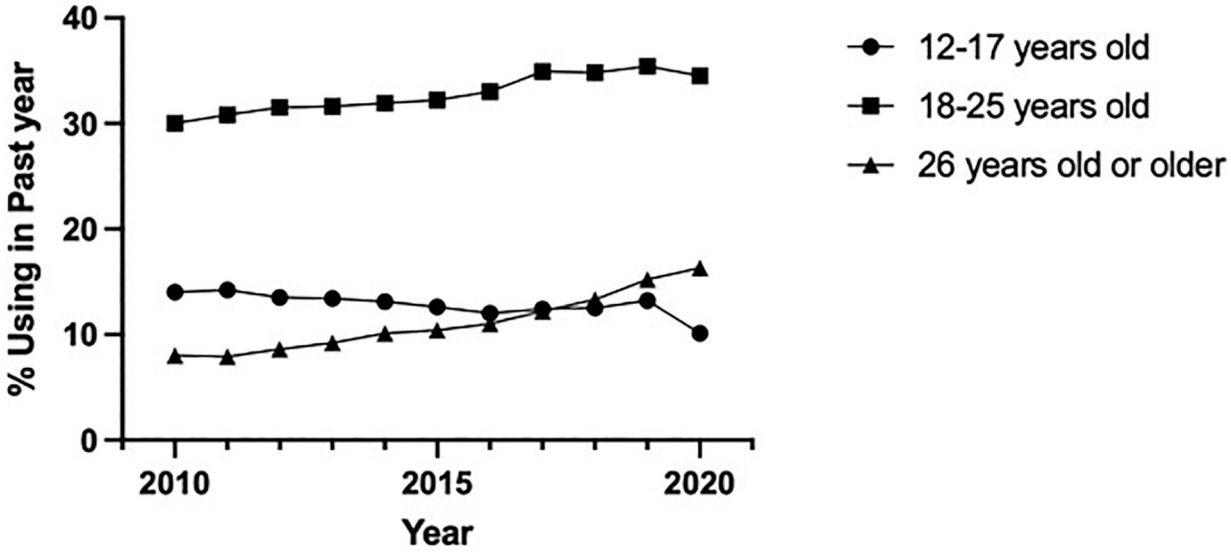

Figure 1. Past year cannabis use among females aged 12 or older: 2010–2020.[48,185]

Prevalence of past year cannabis use has increased most rapidly in females aged 26 years or older.

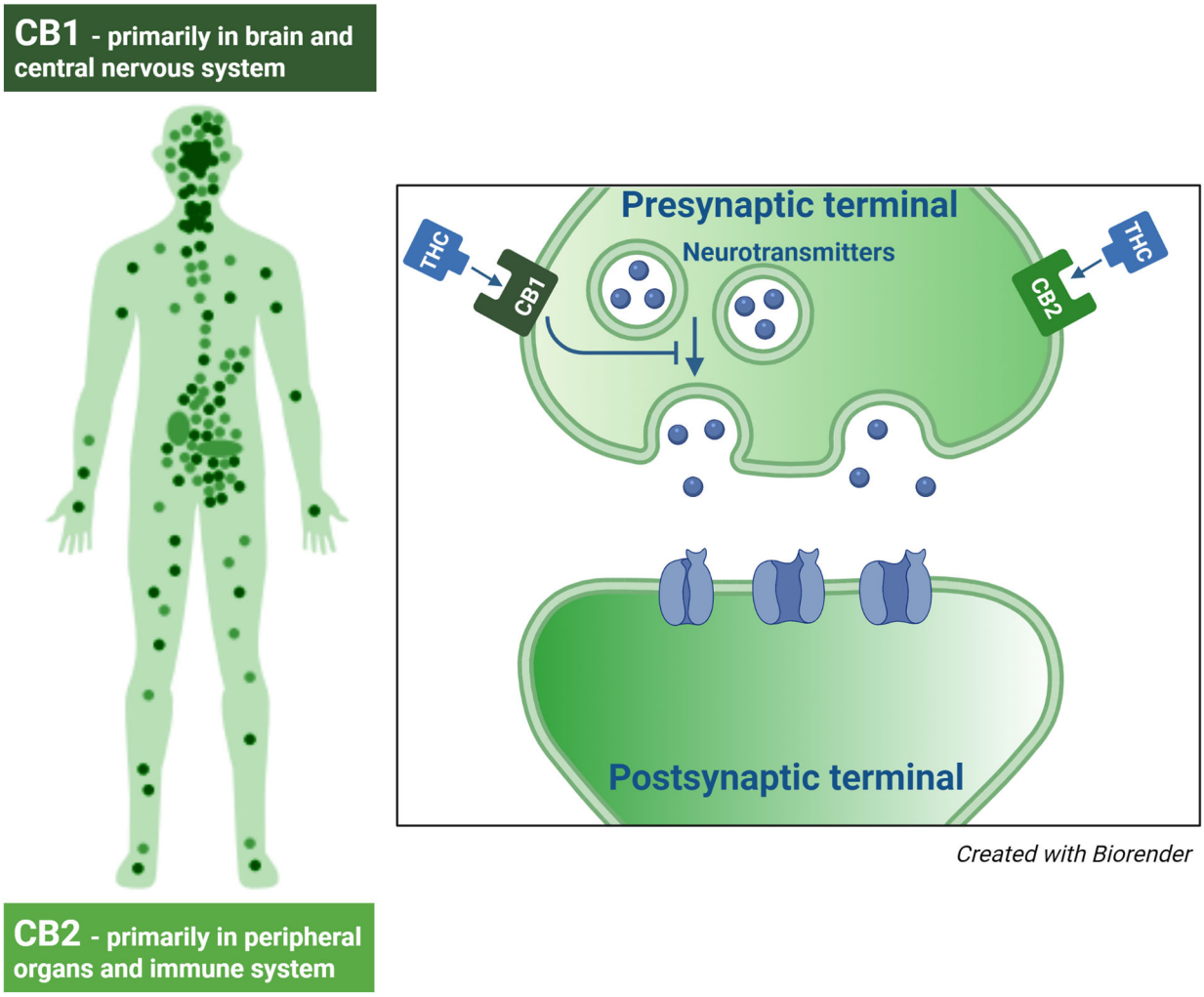

Figure 2. Human endocannabinoid system.

Consists of cannabinoid receptors and endocannbinoids. The two most common cannabinoid receptors are CB1 and CB2. CB1 receptors are predominantly located in the brain and central nervous system, but can also be found in other tissues. CB2 receptors are largely found in peripheral organs, especially cells associated with the immune system.

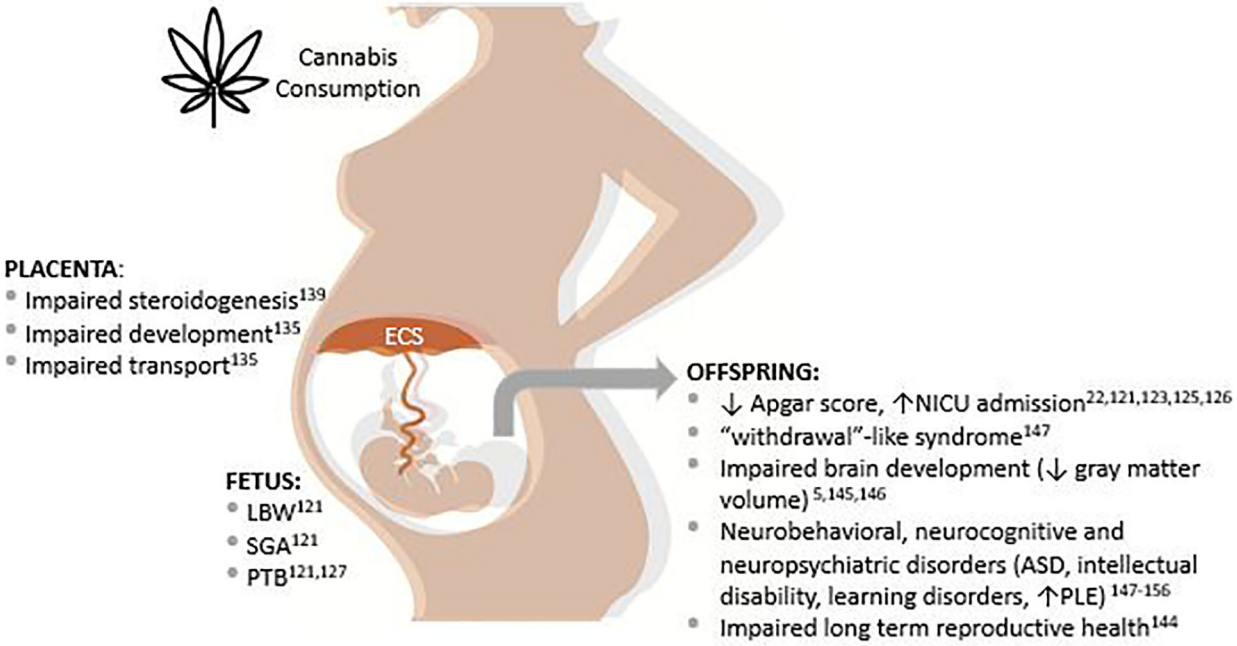

Figure 3. Adverse effects of cannabis consumption on the placenta, fetus and offspring.

FGR: fetal growth restriction, SGA: small for gestational age, PTB: preterm birth, ASD: autism spectrum disorder, PLE: psychotic-like experience.

Table 1.

Summary of different modes of cannabis delivery

Method	Peak	Duration
Inhaled (vapor or smoke)[181]	9 minutes	1–2 hours
Oral (drops, lozenge, spray)[182]	10–25 minutes	≤10 hours
Ingested (capsules, edibles, powder, tablets)[31–35]	60 minutes – 5hours	≤25hours
Transdermal (patch, gels)[183]	120 minutes	≤48 hours
Rectal suppository[184]	60–120 minutes	≤8 hours