

Review

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Association between gestational cannabis exposure and maternal, perinatal, placental, and childhood outcomes

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Abstract

Globally, the availability and formulations for the administration of cannabis are changing with decriminalization or legalization of recreational use in some jurisdictions, and the prescription of cannabis also occurring. These changes are likely to affect the prevalence of use, including by women of childbearing age. The effects of in utero and infant alcohol and tobacco exposure are well-documented, but the outcomes of cannabis exposure are less certain. The content of delta-9-tetrahydrocannabinol (THC), the psychoactive component of cannabis has progressively increased over several decades. This review explores the limited knowledge surrounding the epidemiology of gestational and postnatal cannabis exposure and implications for the mother–placenta–fetus/neonate triad. We examine cannabis' effects from antenatal and lactation exposure on (a) pregnancy and perinatal outcomes, (b) placental health, and (c) longer term cardiometabolic and neurodevelopmental risks and outcomes. Though definitive outcomes are lacking, gestational cannabis has been associated with increased risk of other substance use during pregnancy; impaired placental blood flow; increased risk of small for gestational age births; and associated complications. Childhood and adolescent outcomes are sparsely assessed, with suggested outcomes including increased risk of depression and attention-deficit hyperactivity disorder. Cardiometabolic implications of gestational cannabis use may include maternal fatty liver, obesity, insulin resistance, and increased risk of gestational diabetes mellitus (GDM), with potential consequences for the fetus. Clinical implications for pediatric practice were explored in a bid to understand any potential risk or impact on child health and development.

Background

Cannabis is a substance that has been consumed in various formulations and for different purposes over many centuries.¹ There is a changing legislative landscape from decriminalization to the legalization of cannabis, primarily for medical purposes, and in some jurisdictions for recreational use. Despite the rising enthusiasm for cannabis use as a panacea for varied conditions, there are conflicting views and relatively few high-quality studies regarding the health benefits and harms of more liberal cannabis consumption.^{2,3} Unlike tobacco and alcohol, which have known dose-related adverse health outcomes,^{4,5} there is inadequate knowledge regarding the varied properties of different cannabis products. Recreational cannabis users claim to use it for relaxation, for stress release, during social activities, and to improve concentration.⁶ Quantification of cannabis usage is typically obtained through self-reporting or from mandated testing due to clinical presentation or risk of toxicity. In youth, cannabis use has been associated with an increased risk of psychosis, but associations with physical health are less clear.⁷ The legalization of recreational cannabis in Canada, several states of the USA, and the Australian Capital Territory, and increased availability of medicinal cannabis in various countries, emphasizes the importance of understanding the properties and adverse effects of cannabis use. Therefore, this review aims to summarize data regarding the epidemiology and clinical significance of gestational cannabis consumption for the mother, her developing fetus, neonate, and placenta.

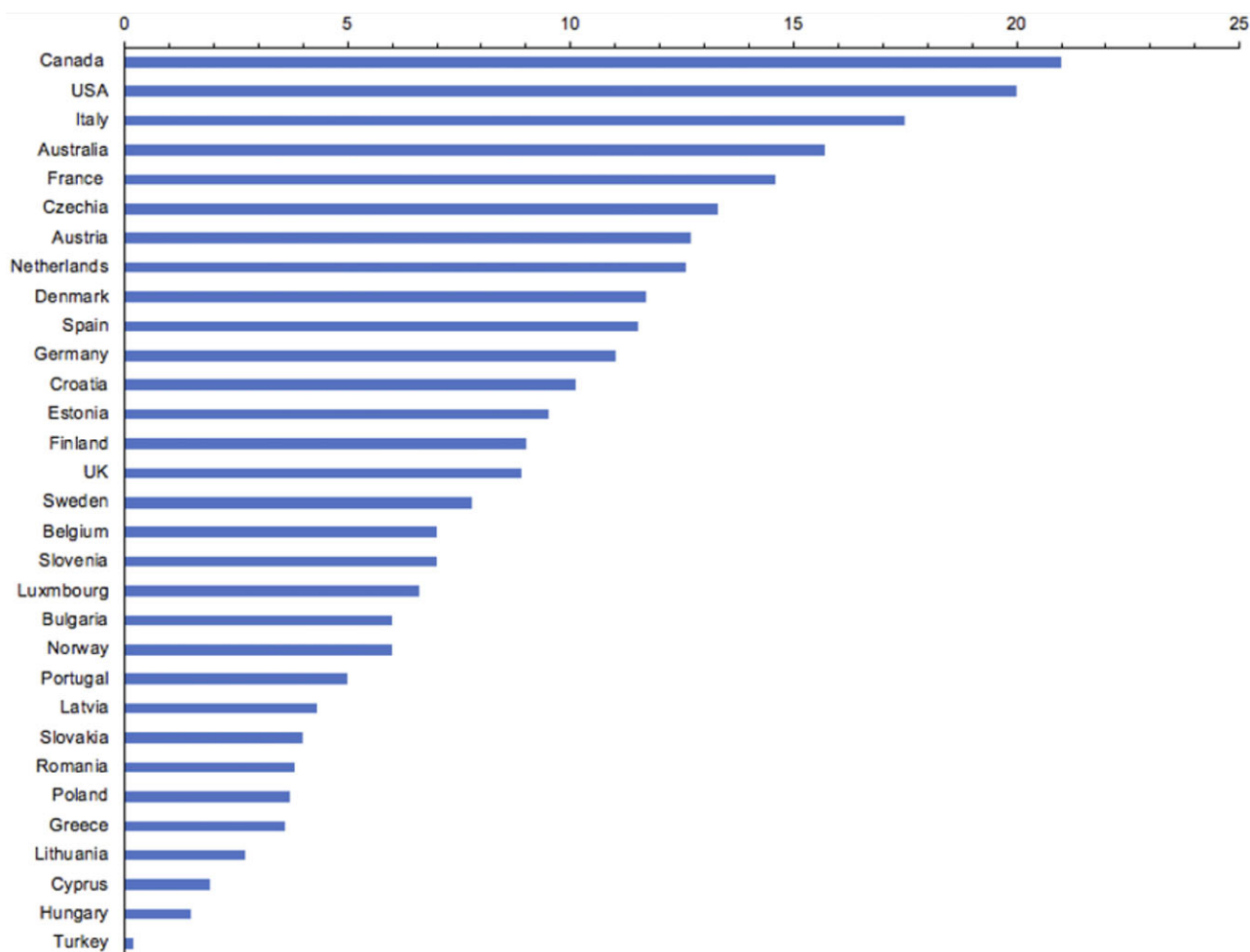


Fig. 1. Prevalence (%) of cannabis use among female adolescents and young adults in Canada, USA, Europe, and Australia.^{9,10,13,14}

Cannabis consumption in reproductive age adolescents and adults

In Australia, cannabis use or misuse frequently begins during adolescence.⁸ Approximately 35% of Australians aged 14 years and over have used cannabis during their lifetime. In adolescents and young adults aged 14–24 years, the average age for first cannabis use was 17 years. Among young adults aged in their 20s, 21% had used cannabis, making it the most commonly used recreational drug.⁹ Adolescents with early trajectories of cannabis consumption are more vulnerable to problematic substance use in early adulthood, plus lower educational and employment achievements.^{4,5} In Canada, about 49% of males aged 15 years and above and 41% of females of the same age have used cannabis in their lifetime, while 44% of 15–19-year olds and 51% of 20–24-year olds report cannabis use in the past 12 months.¹⁰ In females, cannabis use beginning prior to or during early reproductive life could be associated with an unplanned pregnancy or inadvertent fetal exposure to cannabis during unrecognized pregnancy. Ceasing or reducing cannabis use after discovering unplanned pregnancy could be challenging for women who are dependent on cannabis. Consequently, at least one-third of cannabis users continue consuming it as a cheaper or “safer” option than tobacco during pregnancy.¹¹ Though males consume larger quantities of cannabis than females and tend to initiate use at younger ages, females

increase their rate of cannabis use more rapidly than males.¹² International population surveys have described varied prevalence data for cannabis consumption in female adolescents and young adults, including 21% in Canada,¹⁰ 20% in the USA,¹³ 16% in Australia,⁹ and a wide range in Europe; from 0.2% in Turkey to 17.5% in Italy.¹⁴ Comparative data from these geographical jurisdictions are summarized in Fig. 1.

Perinatal cannabis consumption and maternal and perinatal outcomes

Cannabis is the most common recreational drug used during pregnancy, often in combination with alcohol or tobacco. The American College of Obstetricians and Gynecologists (ACOG) guidance reports a 2%–5% self-reported prevalence of gestational cannabis use that increased to up to 15%–28% in young, urban, socioeconomically disadvantaged women with an increased likelihood of concomitant tobacco and alcohol consumption.¹¹ Other studies from various countries have identified indigenous ethnicity, young maternal age, and lower socioeconomic status to be risk factors for gestational cannabis use.^{15–17} In a study of Australian women from an Aboriginal birth cohort, 21% used cannabis during pregnancy.¹⁸ This associates with increasing cannabis consumption by unemployed or Indigenous Australians.⁹ Another study found gestational cannabis users, when compared with

nonusers, had a lower level of education, lower household income, and lower likelihood of perinatal folic acid use.¹⁹ Contrasting with the perception of sociodemographic disadvantage in women who consume cannabis during pregnancy, a large British study from nearly two decades ago described a 5% prevalence of perinatal cannabis smoking, predominantly in women who were younger, of lower parity, and better educated but more likely to smoke, use alcohol, and other substances.²⁰ In that study, gestational cannabis was not associated with adverse maternal or perinatal outcomes. In the USA, gestational cannabis use doubled between the first and second decades of the twenty-first century, though reported to reduce as the pregnancy progressed from the first to the third trimester.^{21,22} The ACOG report, however, described higher rates of cannabis consumption at the time of delivery compared to reports at prenatal visits, and up to 60% of gestational cannabis consumption continuing through pregnancy, suggesting earlier underreporting.¹¹ Therefore, accurate and objective statistics on cannabis use in pregnant women, though important, are often elusive.

A proportion of women use cannabis for relief of severe pregnancy-associated nausea, pain, or mental health problems such as anxiety or depression^{23,24} and not necessarily addiction or dependence. With the legalization of cannabis in various jurisdictions, a corresponding rise in the reported rates of prenatal cannabis consumption has been observed.²⁵ This may reflect either increased gestational cannabis consumption, or alternatively increased honesty about cannabis use in a decriminalized and more accepting environment. In some instances, cannabis use may explain or worsen nausea during pregnancy. A reduction in cannabis use as the pregnancy progresses is not surprising if hyperemesis improves with the duration of pregnancy and women are repeatedly counseled about potential harms of cannabis for their fetus.

There are conflicting reports regarding associations of gestational cannabis use with adverse perinatal outcomes such as fetal growth restriction, small for gestational age, preterm birth, and admission to the neonatal intensive care unit.^{16–18,26–28} These are all risk factors for subsequent obesity and cardiometabolic disorders,²⁹ nonalcoholic fatty liver disease (NAFLD),³⁰ and neurodevelopmental problems.^{31,32} Consequently, unlike the recognized adverse health consequences of heavy gestational alcohol consumption on fetal and child outcomes,³³ the longer term effects of gestational cannabis use are relatively unknown. A Canadian cohort study found prenatal cannabis exposure was associated with increased risk of small for gestational age neonates, placental abruption, transfer to neonatal intensive care, and lower 5-minute Apgar score.³⁴ Another large study linked gestational cannabis use with a higher prevalence of neonatal neurological morbidity, infection, and mortality.³⁵

There is a paucity of high-quality longitudinal studies examining associations between consumption of varied quantities and formulations of cannabis during different pregnancy trimesters, and postnatal physical and mental health outcomes in offspring. Existing data frequently fail to account for confounding effects of maternal gestational smoking, alcohol intake, obesity, gestational diabetes, and pregnancy-associated hypertension. Furthermore, cannabinoids are secreted in breast milk with potential for additional adverse consequences for the neonate or infant resulting from exposure from breastmilk.^{36–38} Therefore, some mothers may choose not to breastfeed their infant in order to avoid lactational cannabis exposure, following the guidance of authorities such as the ACOG. This may be relevant to intergenerational health, since reduced breastfeeding rates and durations are

associated with subsequent adverse cardiometabolic sequelae such as obesity and NAFLD in offspring.³⁹ Thus, there is a need for a better understanding of the influence of perinatal cannabis use on pregnancy outcomes for the mother, fetus, and placenta, as this may provide insights into early developmental health and intergenerational health.

In the USA, a comprehensive research agenda was proposed to address research gaps related to cannabis,⁴⁰ incorporating: (a) “basic science studies to help inform efforts to minimize harms and maximize benefits of acute and chronic use of cannabis and cannabinoids”; (b) “health policy and public health research to examine health effects of broader social and behavioral changes associated with the legalization of recreational and/or medical cannabis and other changes in cannabis policy”; (c) “research that identifies plausible mechanisms by which cannabis affects specific health endpoints”; and (d) translational research “to ensure that research findings will be of practical use to help inform health care practices, public health priorities, national and state policy, and public safety standards”. Similar research priorities have been made in Canada.⁴¹ From the evidence documented in these reviews, a critical component should be the effects of gestational cannabis exposure.

A systematic review and meta-analysis of maternal and perinatal outcomes associated with prenatal exposure to cannabis concluded that “use of cannabis during pregnancy may increase adverse outcomes for women and their neonates. As use of cannabis gains social acceptance, pregnant women and their medical providers could benefit from health education on potential adverse effects of use of cannabis during pregnancy”.⁴² Consistent with this, in 2020, the UK Food and Safety Authority recently advised pregnant and breastfeeding women not to consume foods containing chemicals from the cannabis plant.⁴³

Cannabinoids and receptor signaling

To date over 100 different cannabinoids have been isolated, with these molecules broadly classified according to their source (Fig. 2). Endogenously produced endocannabinoids (ECs) are further separated into two distinct types of fatty acid members, the first being anandamide (also known as N-arachidonylethanolamine; AEA) (Fig. 2), a product formed from arachidonic acid and ethanolamine conjugation. The second EC member, 2-arachidonyl glycerol (2-AG) is formed from glycerol esterification of arachidonic acid. Both of these ECs act as ligands for two separate G protein-coupled (GPCRs) cannabinoid receptors, CB1 and CB2 (Fig. 3a, b). Under physiological conditions, CB1 is expressed predominantly in the central nervous system (CNS) and to a lesser degree the peripheral nervous system and several peripheral organs. CNS CB1 receptors are expressed from early in the first trimester of gestation,⁴⁴ and are concentrated within the striatum, basal nuclei, hippocampus, cingulate gyrus, cortex, and cerebellum structures, and their embryonic precursors. On an ultrastructural level, CB1 localizes to the plasma membranes of presynaptic neurons where it modulates neurotransmitter release, thereby regulating synaptic signaling and protecting against glutamate excitotoxicity^{45,46} (Fig. 3a). In contrast, CB2 shows limited neuronal expression but strong localization to various cells of the immune system, including monocytes/macrophages, dendritic cells, B- and T cells^{47,48} (Fig. 3b). CB2 expression is also identified within the spleen, thymus, and gastrointestinal system.⁴⁹ Cannabinoid binding to CB2 causes potassium and calcium channel gating changes and altered gene expression through inhibition of adenylyl cyclase (AC) and activation of the

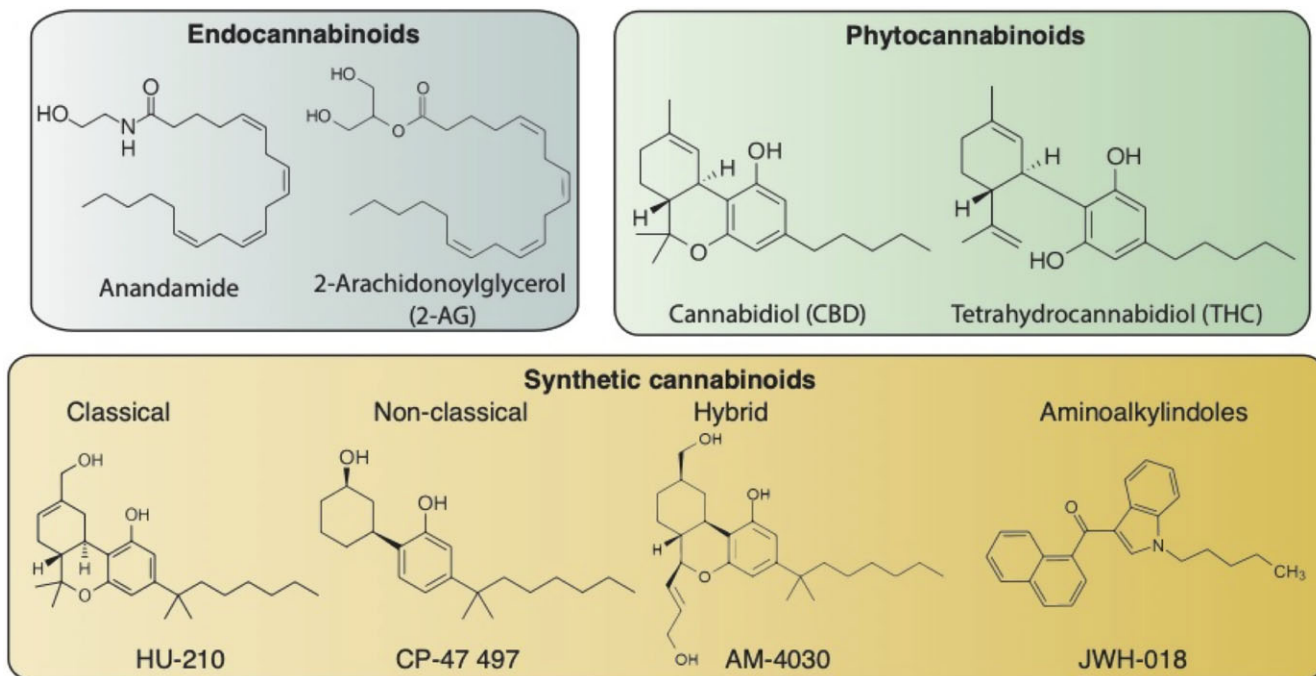
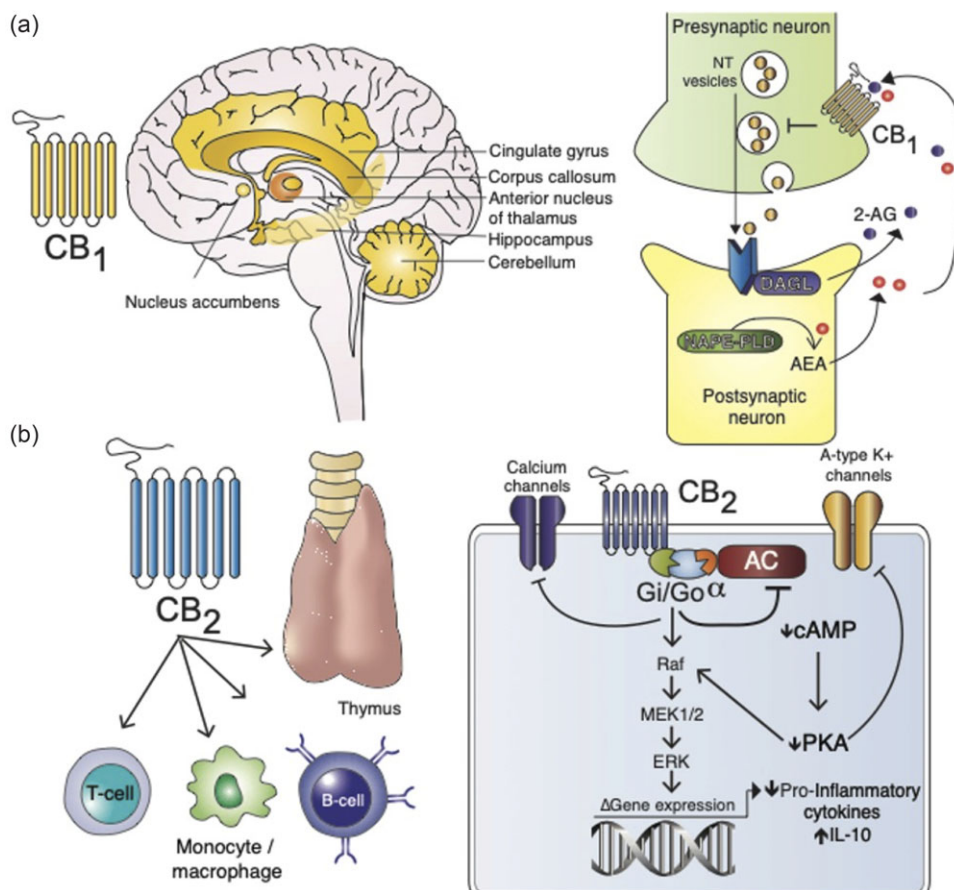


Fig. 2. Cannabinoid classes. Cannabinoids are categorized into physiologically available endocannabinoids (ECs), which include anandamide and 2-arachidonoylglycerol (2-AG), plant-derived phytocannabinoids, and fully synthetic cannabinoids. The most common phytocannabinoids are CBD and THC. The synthetic cannabinoid class includes over 100 separate molecules that possess increased affinity for CB1 compared with EC and phytocannabinoids. This class is substratified into several major groups according to their chemical structure. Classical synthetics, such as HU-210, retain the core THC structure, while the THC pyran ring is absent in nonclassical cannabinoids as seen in CP-47497. Hybrid cannabinoids, which include AM-4030 share structure features of both classical and non-classical. Conversely, aminoalkylindoles are chemically distinct molecules, which in addition to CB1 and CB2 receptor activity also inhibit cyclooxygenase activity.¹⁰⁸

Fig. 3. Physiological localization and function of CB1 and CB2. (a) CB1 is the most abundant transmembrane Gi/Go-protein-coupled receptor (GPCR) expressed in the brain and is highly concentrated in the basal nuclei, cingulate gyrus, nucleus accumbens, hippocampus, cerebellum, cortex, and striatum. Here, CB1 is localized to the presynaptic neurons and is essential in modulating neurotransmitter (NT) signaling.¹⁰⁹ Following NT release from presynaptic neurons, signal activation occurs at the postsynaptic neuron leading to N-acetylphosphatidylethanolamine-hydrolyzing phospholipase D (NAPE-PLD) synthesis of anandamide (AEA). Similarly, diacylglycerol lipase generates nascent 2-AG. 2-AG and AEA then diffuse into the synaptic space and activate CB1 at the presynaptic neuron which, in turn, inhibits further NT vesicle release. Non-EC cannabinoids potentiate this pathway to induce psychotropic effects. (b) CB2 is selectively expressed on monocytes, B- and T cells, within the thymus, spleen, and gastrointestinal system. Cannabinoid activation of CB2 results in adenylyl cyclase (AC) inhibition and downstream reductions in cyclic adenosine monophosphate (cAMP), which negatively regulates cAMP-dependent protein kinase (PKA). A-type potassium channels are closed as a consequence. CB2 is also capable of directly inhibiting calcium channels, as well as activating the Raf/MEK/ERK pathway leading to suppression of pro-inflammatory and augmentation of anti-inflammatory genes.



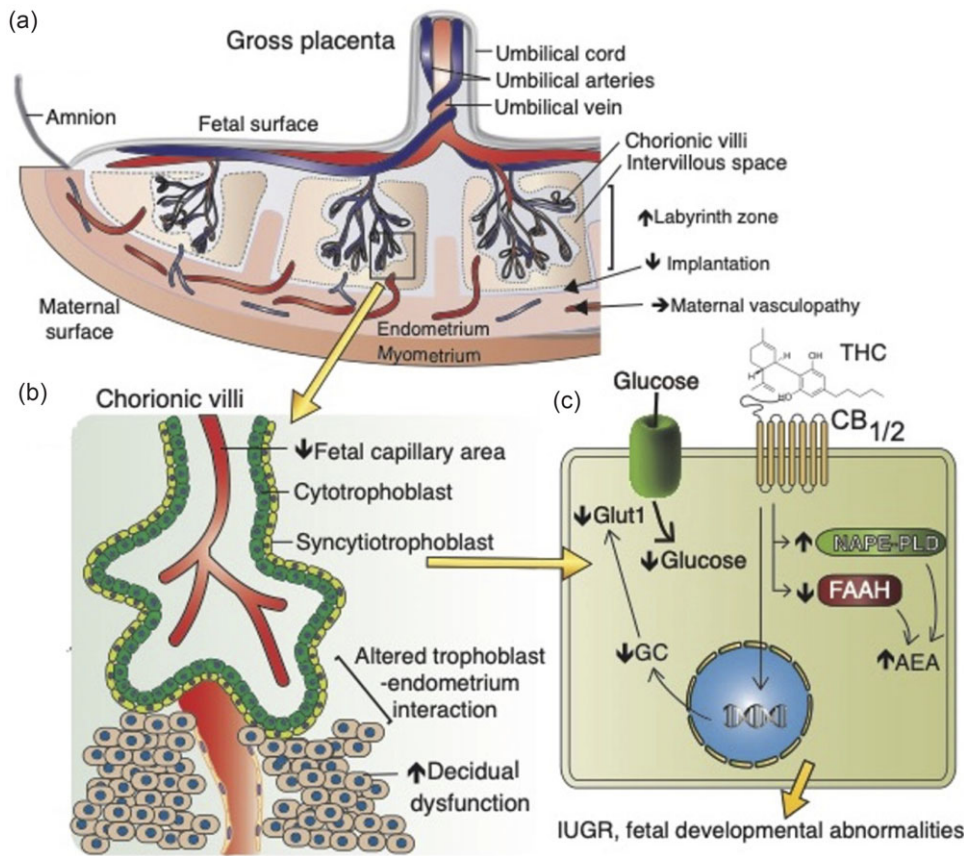


Fig. 4. Summary of cannabinoid-induced changes within the placenta. (a) Following THC exposure, labyrinth zone expansion occurs within the placenta, which contributes to increased placental weight. Maternal vasculopathy is also observed in post-THC use. (b) Chorionic villi changes include reduced fetal capillary area, trophoblast, and decidual dysfunction leading to impaired implantation during the early stages of fetal development. (c) Trophoblasts undergo several phenotypic changes in post-THC exposure. These include increased endogenous EC synthesis downstream from cannabinoid induced CB1/CB2 stimulation. Here, NAPE-PLD activity is increased with simultaneous reductions in FAAH enzyme expression. This leads to AEA synthesis and accumulation of ECs within the placenta, which negatively affects placenta viability and fetal development. THC also results in reduced GC expression that, in turn, reduces GLUT1 expression. This results in lower glucose transport across to the fetal surface contributing to IUGR.

mitogen-activated protein kinase (MAPK) pathways. This, in turn, increases anti-inflammatory cytokine IL-10 expression and modulation of pro-inflammatory genes⁵⁰ (Fig. 3b).

Cannabis metabolism

Cannabis is a heterogeneous substance containing numerous different phytocannabinoids. These phytocannabinoids are metabolized by the liver, with the half-life considered to be 1–5 days, depending on the frequency of consumption and exact phytocannabinoid composition.¹¹ Complete excretion may, however, take weeks. The composition of cannabis has changed in recent decades, with a considerable increase of up to 10-fold in the concentration of delta-9-tetrahydrocannabinol (THC), the psychoactive ingredient, compared with 1980.^{2,51} This creates challenges in comparison of different effects of cannabis through the life course.

Gestational cannabis consumption and the placenta

Physiologically, the EC system is involved in all stages of ovary and uterus function, embryo development, embryo placentation, as well as maintenance of pregnancy.⁵² These EC pathways are carefully regulated by controlled synthesis and degradation of AEA and 2-AG. Cannabis, however, contains multiple phytocannabinoid molecules with nonphysiological CB1 and CB2 affinities and activities. These phytocannabinoids, along with their respective metabolites, readily cross the placenta and disrupt these physiological EC pathways,⁵³ thereby contributing to several pathological changes within the placenta and developing fetus (Fig. 4a). In a mouse model, fetuses exposed to cannabis in utero had increased placental

weight and reduced fetal-to-placental weight ratio, mostly in male pups.⁵⁴ In humans, maternal cannabis consumption also alters placenta to neonate weight ratios. Following chronic gestational cannabis consumption, placentas are disproportionately larger unless coexistent pathologies develop, such as fetal and maternal vasculopathy.⁵⁵ Furthermore, gestational cannabis consumption is associated with impaired placental blood flow and increased placental vascular resistance^{56,57}. Uteroplacental vascular lesions, in turn, can lead to complications such as trophoblastic necrosis, thereby exacerbating fetal growth restriction^{58,59} (Fig. 4b). Fetal growth restriction has also been demonstrated in a rat model, in which pregnant dams were exposed to THC. Again, in this model, fetuses displayed symmetrical intrauterine growth restriction, small birth weights, and lower brain to body weight parameters. While the placentas from these cannabis-exposed dams were significantly larger with a marked expansion of the labyrinth zone, there was an overall reduction in fetal blood surface area. Moreover, placental trophoblast expression of glucose transporter (GLUT)1 and glucocorticoid receptor (GR) were significantly reduced post-THC exposure; these results were replicated by the authors in the established human BeWo trophoblast cell line (Fig. 4c). It should be noted that placental GLUT expression is regulated by GR.⁶⁰ These data suggest THC use may decrease the availability of glucose, the primary energy substrate of the fetus, during fetal development.

Interestingly, THC use does not significantly alter CB1 or CB2 expression within placental tissues.⁵² However, it does significantly augment N-arachidonoylphosphatidylethanolamine-specific phospholipase D (NAPE-PLD) activity and suppress fatty acid amide hydrolase (FAAH). An imbalance between these two enzyme

profiles results in higher concentrations of ECs within the placenta milieu (Fig. 4) leading to reduced fetal survival, altered development, and neurophysiological abnormalities¹⁷ (Fig. 4c).

The increased availability of illicit synthetic cannabis products, and their rapidly changing chemical composition means that there are limited data on their associated harms in humans.^{61,62} In vitro studies involving synthetic cannabinoid, for example, impair the cellular communication between trophoblasts and maternal decidua, in turn, potentially affecting placental implantation.⁶³ Additionally, phytocannabinoids signal through CB1 and CB2 to induce trophoblast mitochondrial and endoplasmic reticulum stress pathways culminating in the generation of reactive oxygen species (ROS) and an overall reduction in trophoblast viability.^{64–66} Using the BeWo trophoblast tissue culture model, Almada and colleagues⁶⁷ observed mitochondrial stress, ROS, and caspase nine activation following synthetic cannabinoid exposure. This pathogenic pathway is dependent on CB1 and CB2 receptor signaling. Accordingly, cannabis use during pregnancy may have significant adverse effects on offspring health.^{17,36} The major placental changes seen with cannabis use are summarized in Fig. 4a–c.

Antenatal cannabis use and subsequent child and adolescent outcomes

Despite the rising number of observational studies describing inconsistent, but predominantly adverse, short-term neonatal outcomes in cannabis-exposed fetuses, there remains a paucity of longitudinal studies examining longer term associations of fetal cannabis exposure on subsequent behavioral, academic, and health outcomes during childhood, adolescence, and adulthood. In a systematic review, a possible relationship between gestational cannabis use, and mood disorders, and ADHD, but not psychosis in offspring was described.⁵⁹ Gestational cannabis use has been associated with the severity of depressive symptoms and academic deficits in children^{68,69} and subsequently increased rates of cannabis use during adolescence.⁷⁰ The pediatric literature is relatively sparse in expanding the knowledge on the impact of maternal cannabis consumption on children. Perinatal studies suggest a possible significant mild reduction in birth weight.^{16,17} However, Fergusson and colleagues²⁰ did not find significant effects on neonatal head size using postnatal MRI brain scans, nor any significant adjusted effects on length and head circumference of the newborn. Similarly, Gunn *et al.*⁴² did not identify a significant difference in the usual birth anthropometric measurements including head circumference. A review of neuroimaging in children following cannabis exposure highlighted changes to the frontal cortex and basal ganglia of the fetal brain, as well as cortical gray matter and parenchymal volume loss in children aged 10–14 years with intrauterine cannabis exposure.⁷¹ While an association between early life cannabis exposure and subsequent neurodevelopmental impairments may exist, inability to exclude confounding effects of other substances limits the interpretation of any conclusions. There, thus, remains a paucity of studies examining associations between perinatal cannabis consumption and brain growth and development, behavior, and cognition. Warshak *et al.*,⁷² Conner *et al.*⁷³ and Varner *et al.*⁷⁴ described an increase in small babies, neonatal intensive care unit admission, and stillbirth rate, though tobacco smoking and other substance use may be cofactors in some cases. Preterm birth had a cannabis dose–frequency relationship.⁷³ Some studies suggest a negative effect on language, memory, executive function, and attention, but do also acknowledge the impact of multiple substance misuse concurrently in some pregnant women.^{75,76} Pediatricians may not necessarily enquire about cannabis specifically in child development clinics. Furthermore,

other environmental and lifestyle factors may partly contribute to any neurobehavioral observations.

Cannabis exposure and birth abnormalities

Early human and animal studies suggested that cannabis use could cause genetic damage and chromosomal abnormalities. However, more recent systematic reviews and a position statement have not found an association between maternal cannabis use and birth abnormalities.^{40,42,73} The relationship is considered more likely due to tobacco use or other confounding factors. Nevertheless, questions are still raised from studies that use less extensive controls. An analysis of a state birth defect register found that for people who reported cannabis use, 19 of the 54 assessed conditions were significantly increased among those who used cannabis.⁷⁷ A recent spatial–temporal analysis of increasing cannabis use and the incidence of gastroschisis also postulated a causal link⁷⁸ although this is in contrast to a previous study of recreational drug use as assessed by hair analysis and fetal anomalies, which showed no significant association after adjusting for confounding variables.⁷⁹ While these observations raise questions regarding rising rates of congenital anomalies in parallel with the timing of legalization of marijuana in parts of the USA, causality has not been established.⁸⁰

Cannabis use and breastfeeding

THC is transferred into breast milk at low concentrations, with infants ingesting a mean of 2.5% of the maternal dose⁸¹ and a concentration of 9.5 ng/ml.⁸⁰ THC can be detected in breast milk up to 6 days after last maternal use.⁸² Studies looking at the long-term outcomes of offspring after cannabis use during breastfeeding are limited.^{83,84} Breastfeeding from chronic THC users has been reported to be associated with delayed motor development at 1 year of age.⁸⁴ However, it is difficult to isolate the impact of marijuana intake via breast milk from in utero exposure. The use of other illicit substances by these mothers remains a confounding factor, and the heterogeneity of the small sample sizes limits the interpretation of the results.³⁷ Due to concerns regarding the rebound of cannabis use rates in the postpartum period compared with use during pregnancy, the World Health Organization (WHO) highlights a focus on psychosocial interventions during pregnancy. The WHO also recommends that mothers with substance use disorders should be encouraged to breastfeed unless the risks clearly outweigh the benefits.⁸⁵

Cannabis and adiposity, the liver, and gastrointestinal system

Cannabis is associated with adiposity distribution, serum leptin, appetite, and gastrointestinal symptoms. THC is highly lipophilic, rapidly absorbed and stored in adipose tissue from where it passively diffuses back into the bloodstream, but may still be detectable in fat biopsies after 4 weeks and in urine up to 11 weeks after the last consumption.⁸⁶ Enhanced levels of THC and its metabolites thus become evident on lipolysis after food deprivation. Cannabinoid receptor 1 (CB1)-activating ECs, via CNS effects, regulate appetite and are associated with the development of metabolic syndrome and ameliorated obesity, type II diabetes, fatty liver, and insulin resistance in animal models.⁸⁷ This appetite-stimulating property of CB1 has resulted in its use for improving food intake in patients with reduced appetite associated with cancer chemotherapy, HIV,

or anorexia nervosa.⁸⁷ CB1 antagonists/inverse agonists, therefore, held appeal for reducing appetite, abdominal adiposity, and cardiometabolic risk factors, however, psychiatric side effects resulted in withdrawal from such use for obesity treatment.⁸⁸ This was the fate of Rimonabant that had demonstrated efficacy for ameliorating obesity, insulin resistance, and hepatic steatosis.⁸⁹ Hepatic stellate cells express CB1 and cannabinoid receptor 2 (CB2) that are up-regulated and associated with liver fibrosis,^{90,91} while CB1 has also been associated with hepatic steatosis.⁹² Any potential association of cannabis consumption with fatty liver may have consequences for the mother and fetus, as maternal gestational fatty liver signifies insulin resistance, increased risk of gestational diabetes mellitus (GDM), and associates with fetal macrosomia independent of maternal GDM.⁹³ Cannabis use can result in cannabis hyperemesis syndrome⁹⁴ and has also been linked with irritable bowel syndrome (IBS).^{95–97} Nevertheless, a putative role for exogenous cannabinoid has been proposed for treatment of pain syndromes, including migraine, fibromyalgia, and IBS⁹⁸ as well as a role in gastrointestinal symptoms, such as nausea and vomiting, cannabinoid hyperemesis syndrome, anorexia, weight loss, and chronic abdominal pain.⁹⁹

Sex differences in the effect of cannabis

Sex differences in the consumption and effects of cannabis have been observed. Males are more likely to initiate cannabis use or develop a cannabis use disorder (CUD) than females, but the trajectory from first use to CUD is higher in females.^{100,101} This may have implications for the antenatal and early postnatal periods. Male cannabis smokers exhibit higher circulating levels of THC and more cardiovascular effects than female cannabis users.¹⁰² By contrast, cannabis use to treat nausea or abdominal pain is more common in females than in males.¹⁰³ Sex differences in the effects of cannabis may relate in part to the amount and distribution of body fat, with females having more subcutaneous fat that may provide a depot. Men experience increased appetite and caloric intake, while women describe more anorexia after cannabis consumption but in withdrawal, men feel more insomnia and women more nausea, abdominal pain, and anxiety.^{104,105}

There is growing evidence of neurobiological differences involving the EC system and cannabinoid metabolism between male and female cannabis consumers.^{106–108} Cannabis use may perpetuate functional nausea and vomiting disorders (FNVDs) such as the cannabis hyperemesis syndrome.⁹⁵ It is plausible that some women will use cannabis to ameliorate pregnancy-associated nausea or that gestational cannabis use could result in hyperemesis mistakable for hyperemesis gravidarum.²³ Rodent models have provided additional insights into the mechanisms of neurobiological sex differences in offspring exposed to cannabinoids in utero. Bara *et al.* exposed pregnant Wistar rats to synthetic cannabinoid WIN55,212–2 and THC, with the effects studied in the litter pups.¹⁰⁷ Male pups demonstrated significantly lower levels of socialization compared with drug and sex controls. Further, increased excitability of prefrontal cortex pyramidal neurons was observed along with long-term suppression of synaptic plasticity within the medial prefrontal cortex.

Conclusions and future directions

“Cannabis” refers to a heterogeneous group of substances of varying properties, potencies, routes of consumption, speed of absorption, and effect. Studies have not consistently or conclusively quantified the level of risk to the fetus or offspring of the pregnant user independent of other substances. Gestational cannabis is not routinely

screened for in most countries beyond an antenatal interview. Consequently, there are inadequate data to suggest a fetal cannabis syndrome, cannabis-related neonatal abstinence syndromes, or a relationship with congenital abnormalities related to perinatal cannabis use. Given the current uncertainties regarding potential adverse effects on the fetus, current guidance that cannabis and cannabinoid products be avoided during pregnancy and lactation seem appropriate. However, this should be balanced against potential harms of alcohol, tobacco, and other substances that have more established adverse fetal effects, that may be used as alternative substances during pregnancy. Given the prevalence of cannabis usage during pregnancy relative to other substances, it is time that documentation of perinatal cannabis becomes a more prominent aspect of neonatal/pediatric care beyond concerns of domestic consumption in young people, and the cumulative concerns that result in child protection input. To what degree there could be a cumulative dose-dependent risk independent of, or associated with, other substances remains unclear. Future longitudinal studies with high-quality data regarding the routes of administration and more accurate quantification of gestational consumption of cannabis and other substances throughout pregnancy will improve knowledge about longer term cognitive, broader developmental, and cardiometabolic sequelae of perinatal cannabis exposure. Such data are required to strengthen the evidence for guiding women of reproductive age and clinicians involved in their care about potential intergenerational harms of perinatal cannabis use.

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References

1. Ayonrinde OA. Cannabis and psychosis: revisiting a nineteenth century study of ‘Indian Hemp and Insanity’ in Colonial British India. *Psychol Med.* 2020; 50, 1164–1172.
2. Hall W, Stjepanović D, Caulkins J, *et al.* Public health implications of legalising the production and sale of cannabis for medicinal and recreational use. *Lancet.* 2019; 394, 1580–1590.
3. Andrews CN, Devlin SM, Le Foll B, *et al.* Canadian association of gastroenterology position statement: use of cannabis in gastroenterological and hepatic disorders. *J Can Assoc Gastroenterol.* 2019; 2, 37–43.
4. Nelson SE, Van Ryzin MJ, Dishion TJ. Alcohol, marijuana, and tobacco use trajectories from age 12 to 24 years: demographic correlates and young adult substance use problems. *Dev Psychopathol.* 2015; 27, 253–277.
5. Silins E, Horwood LJ, Najman JM, *et al.* Adverse adult consequences of different alcohol use patterns in adolescence: an integrative analysis of data to age 30 years from four Australasian cohorts. *Addiction.* 2018; 113, 1811–1825.

6. Hyman SM, Sinha R. Stress-related factors in cannabis use and misuse: implications for prevention and treatment. *J Subst Abuse Treat.* 2009; 36, 400–413.
7. Bahji A, Stephenson C. International perspectives on the implications of cannabis legalization: a systematic review & thematic analysis. *Int J Environ Res Public Health.* 2019; 16(17), 3095.
8. Australian Institute of Health and Welfare. *Australia's health 2016. Australia's health series no. 15. Cat. no. AUS 199.* Canberra: AIHW, 2016. Available from <https://www.aihw.gov.au/getmedia/9844cefb-7745-4dd8-9ee2-f4d1c3d6a727/19787-AH16.pdf.aspx> (accessed on 25 February 2020).
9. Australian Institute of Health and Welfare. *National Drug Strategy Household Survey 2016: detailed findings.* Drug Statistics series no. 31. Cat. no. PHE 214. Canberra: AIHW, 2017. Available from <https://www.aihw.gov.au/getmedia/15db8c15-7062-4cde-bfa4-3c2079f30af3/21028a.pdf.aspx?inline=true> (accessed on 25 February 2020).
10. Canadian Cannabis Survey 2019 – Summary. <https://www.canada.ca/en/health-canada/services/publications/drugs-health-products/canadian-cannabis-survey-2019-summary.html> (accessed on 5 June 2020).
11. Committee on Obstetric Practice. Committee opinion no. 722: marijuana use during pregnancy and lactation. *Obstet Gynecol.* 2017; 130(4), e205–e209.
12. World Drug Report 2018 (United Nations publication, Sales No. E.18.XI.9). Women and Drugs. *Drug Use, Drug Supply and Their Consequences.* https://www.unodc.org/wdr2018/prelaunch/WDR18_Booklet_5_WOMEN.pdf (accessed 23 August 2020).
13. Substance Abuse and Mental Health Services Administration U.S. Department of Health and Human Services. 2018 National Survey on Drug Use and Health: Women. https://www.samhsa.gov/data/sites/default/files/reports/rpt23250/5_Women_2020_01_14_508.pdf (accessed 5 June 2020).
14. European Monitoring Centre for Drugs and Drug Addiction. *European Drug Report 2018: Trends and Developments,* Luxembourg, Publications Office of the European Union. 2018. https://www.emcdda.europa.eu/system/files/publications/8585/20181816_TDAT18001ENN_PDF.pdf (accessed 5 June 2020).
15. Passey ME, Sanson-Fisher RW, D'Este CA, Stirling JM. Tobacco, alcohol and cannabis use during pregnancy: clustering of risks. *Drug Alcohol Depend.* 2014; 134, 44–50.
16. Leemaqz SY, Dekker GA, McCowan LM, et al. Maternal marijuana use has independent effects on risk for spontaneous preterm birth but not other common late pregnancy complications. *Reprod Toxicol.* 2016; 62, 77–86.
17. Grant KS, Petroff R, Isoherranen N, Stella N, Burbacher TM. Cannabis use during pregnancy: Pharmacokinetics and effects on child development. *Pharmacol Ther.* 2018; 182, 133–151.
18. Brown SJ, Mensah FK, Ah Kit J, et al. Use of cannabis during pregnancy and birth outcomes in an Aboriginal birth cohort: a cross-sectional, population-based study. *BMJ Open.* 2016; 6, e010286.
19. van Gelder MM, Reefhuis J, Caton AR, et al. Characteristics of pregnant illicit drug users and associations between cannabis use and perinatal outcome in a population-based study. *Drug Alcohol Depend.* 2010; 109, 243–247.
20. Fergusson DM, Horwood LJ, Northstone K; ALSPAC Study Team. Avon longitudinal study of pregnancy and childhood. Maternal use of cannabis and pregnancy outcome. *BJOG.* 2002; 109, 21–27.
21. Volkow ND, Han B, Compton WM, McCance-Katz EF. Self-reported medical and nonmedical cannabis use among pregnant women in the United States. *JAMA.* 2019; 322, 167–169.
22. Young-Wolff KC, Sarovar V, Tucker LY, et al. Self-reported daily, weekly, and monthly cannabis use among women before and during pregnancy. *JAMA Netw Open.* 2019; 2(7), e196471.
23. Metz TD, Borgelt LM. Marijuana use in pregnancy and while breastfeeding. *Obstet Gynecol.* 2018; 132, 1198–1210.
24. Roberson EK, Patrick WK, Hurwitz EL. Marijuana use and maternal experiences of severe nausea during pregnancy in Hawai'i. *Hawaii J Med Public Health.* 2014; 73(9), 283–287.
25. Gnofam M, Allshouse AA, Stickrath EH, Metz TD. Impact of marijuana legalization on prevalence of maternal marijuana use and perinatal outcomes. *Am J Perinatol.* 2020; 37, 59–65.
26. Kharbanda EO, Vazquez-Benitez G, Kunin-Batson A, Nordin JD, Olsen A, Romitti PA. Birth and early developmental screening outcomes associated with cannabis exposure during pregnancy. *J Perinatol.* 2020; 40, 473–480.
27. Hayatbakhsh MR, Flenady VJ, Gibbons KS, et al. Birth outcomes associated with cannabis use before and during pregnancy. *Pediatr Res.* 2012; 71, 215–219.
28. Moster D, Lie RT, Markestad T. Long-term medical and social consequences of preterm birth. *N Engl J Med.* 2008; 359, 262–273.
29. Calkins K, Devaskar SU. Fetal origins of adult disease. *Curr Probl Pediatr Adolesc Health Care.* 2011; 41, 158–176.
30. Cianfarani S, Agostoni C, Bedogni G, et al. Effect of intrauterine growth retardation on liver and long-term metabolic risk. *Int J Obes (Lond).* 2012; 36, 1270–1277.
31. Saenger P, Czernichow P, Hughes I, Reiter EO. Small for gestational age: short stature and beyond. *Endocr Rev.* 2007; 28, 219–251.
32. Moster D, Lie RT, Markestad T. Long-term medical and social consequences of preterm birth. *N Engl J Med.* 2008; 359, 262–273.
33. Popova S, Lange S, Probst C, Gmel G, Rehm J. Estimation of national, regional, and global prevalence of alcohol use during pregnancy and fetal alcohol syndrome: a systematic review and meta-analysis. *Lancet Glob Health.* 2017; 5, e290–e299.
34. Corsi DJ, Walsh L, Weiss D, et al. Association between self-reported prenatal cannabis use and maternal, perinatal, and neonatal outcomes. *JAMA.* 2019; 322, 145–152.
35. Metz TD, Allshouse AA, Hogue CJ, et al. Maternal marijuana use, adverse pregnancy outcomes, and neonatal morbidity. *Am J Obstet Gynecol.* 2017; 217, 478.e1–478.e8.
36. Metz TD, Stickrath EH. Marijuana use in pregnancy and lactation: a review of the evidence. *Am J Obstet Gynecol.* 2015; 213, 761–778.
37. Mourh J, Rowe H. Marijuana and breastfeeding: applicability of the current literature to clinical practice. *Breastfeed Med.* 2017; 12, 582–596.
38. Liston J. Breastfeeding and the use of recreational drugs—alcohol, caffeine, nicotine and marijuana. *Breastfeed Rev.* 1998; 6, 27–30.
39. Ayonrinde OT, Oddy WH, Adams LA, et al. Infant nutrition and maternal obesity influence the risk of non-alcoholic fatty liver disease in adolescents. *J Hepatol.* 2017; 67, 568–576.
40. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda. *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research,* 2017. National Academies Press (US), Washington, DC. Recommendations to Support and Improve the Cannabis Research Agenda. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK425745/> (accessed 10 February 2020).
41. Canadian Institutes of Health Research. Integrated Cannabis Research Strategy, 2019. Available from: <https://cihr-irsc.gc.ca/e/51352.html> (accessed 8 June 2020).
42. Gunn JK, Rosales CB, Center KE, et al. Prenatal exposure to cannabis and maternal and child health outcomes: a systematic review and meta-analysis. *BMJ Open.* 2016; 6, e009986.
43. Food Standards Agency Newsletter, 2020. Available from: <https://www.food.gov.uk/print/pdf/node/3721> (accessed 8 June 2020).
44. Zurolo E, Iyer AM, Spliet WG, et al. CB1 and CB2 cannabinoid receptor expression during development and in epileptogenic developmental pathologies. *Neuroscience.* 2010; 170, 28–41.
45. Marsicano G, Goodenough S, Monory K, et al. CB1 cannabinoid receptors and on-demand defense against excitotoxicity. *Science.* 2003; 302, 84–88.
46. Oka S, Ishima Y, Waku K, Sugiura T. Endocannabinoids as retrograde messengers in synaptic transmission. In *Endocannabinoids: The Brain and Body's Marijuana and Beyond* (eds. Onaivi ES, Sugiura T, Di Marzo V), 2006; pp. 133–149. CRC: Boca Raton, FL.

47. Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature*. 1990; 346, 561–564.
48. Klein TW, Newton C, Larsen K, *et al.* The cannabinoid system and immune modulation. *J Leukoc Biol*. 2003; 74, 486–496.
49. Lombard C, Nagarkatti M, Nagarkatti P. CB2 cannabinoid receptor agonist, JWH-015, triggers apoptosis in immune cells: potential role for CB2-selective ligands as immunosuppressive agents. *Clin Immunol*. 2007; 122(3), 259–270.
50. Tomar S, Zumbrun EE, Nagarkatti M, Nagarkatti PS. Protective role of cannabinoid receptor 2 activation in galactosamine/lipopolysaccharide-induced acute liver failure through regulation of macrophage polarization and microRNAs. *J Pharmacol Exp Ther*. 2015; 353(2), 369–379.
51. World Health Organization. *The Health and Social Effects of Nonmedical Cannabis Use*, 2016. World Health Organization. <https://apps.who.int/iris/handle/10665/251056>.
52. Taylor AH, Amoako AA, Bambang K, *et al.* Endocannabinoids and pregnancy. *Clin Chim Acta*. 2010; 411, 921–930.
53. Maia J, Midão L, Cunha SC, *et al.* Effects of cannabis tetrahydrocannabinol on endocannabinoid homeostasis in human placenta. *Arch Toxicol*. 2019; 93(3), 649–658.
54. Benevenuto SG, Domenico MD, Martins MA, *et al.* Recreational use of marijuana during pregnancy and negative gestational and fetal outcomes: an experimental study in mice. *Toxicology*. 2017; 376, 94–101.
55. Carter RC, Wainwright H, Molteno CD, *et al.* Alcohol, Methamphetamine, and Marijuana Exposure Have Distinct Effects on the Human Placenta. *Alcohol Clin Exp Res*. 2016; 40, 753–764.
56. El Marroun H, Tiemeier H, Steegers EA, *et al.* A prospective study on intrauterine cannabis exposure and fetal blood flow. *Early Hum Dev*. 2010; 86, 231–236.
57. Brar BK, Patil PS, Jackson DN, Gardner MO, Alexander JM, Doyle NM. Effect of intrauterine marijuana exposure on fetal growth patterns and placental vascular resistance. *J Matern Fetal Neonatal Med*. 2019; 1–5.
58. Natale BV, Gustin KN, Lee K, *et al.* Δ 9-tetrahydrocannabinol exposure during rat pregnancy leads to symmetrical fetal growth restriction and labyrinth-specific vascular defects in the placenta. *Sci Rep*. 2020; 10, 544.
59. Roncero C, Valriberas-Herrero I, Mezzatesta-Gava M, Villegas JL, Aguilar L, Grau-López L. Cannabis use during pregnancy and its relationship with fetal developmental outcomes and psychiatric disorders. A systematic review. *Reprod Health*. 2020; 17, 25.
60. Hahn T, Barth S, Graf R, *et al.* Placental glucose transporter expression is regulated by glucocorticoids. *J Clin Endocrinol Metab*. 1999; 84, 1445–1452.
61. Darke S, Duflou J, Farrell M, Peacock A, Lappin J. Characteristics and circumstances of synthetic cannabinoid-related death. *Clin Toxicol (Phila)*. 2020; 58, 368–374.
62. Tait RJ, Caldicott D, Mountain D, Hill SL, Lenton S. A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment. *Clin Toxicol (Phila)*. 2016; 54, 1–13.
63. Neradugomma NK, Drafton K, Mor GG, Mao Q. Marijuana-derived cannabinoids inhibit uterine endometrial stromal cell decidualization and compromise trophoblast-endometrium cross-talk. *Reprod Toxicol*. 2019; 87, 100–107.
64. Lojpur T, Easton Z, Raez-Villanueva S, Laviolette S, Holloway AC, Hardy DB. Δ 9-Tetrahydrocannabinol leads to endoplasmic reticulum stress and mitochondrial dysfunction in human BeWo trophoblasts. *Reprod Toxicol*. 2019; 87, 21–31.
65. Almada M, Costa L, Fonseca BM, Amaral C, Teixeira N, Correia-da-Silva G. The synthetic cannabinoid WIN-55,212 induced-apoptosis in cytotrophoblasts cells by a mechanism dependent on CB1 receptor. *Toxicology*. 2017; 385, 67–73.
66. Fonseca BM, Fernandes R, Almada M, *et al.* Synthetic cannabinoids and endometrial stromal cell fate: dissimilar effects of JWH-122, UR-144 and WIN55,212-2. *Toxicology*. 2019; 413, 40–47.
67. Almada M, Alves P, Fonseca BM, *et al.* Synthetic cannabinoids JWH-018, JWH-122, UR-144 and the phytocannabinoid THC activate apoptosis in placental cells. *Toxicol Lett*. 2020; 319, 129–137.
68. Gray KA, Day NL, Leech S, Richardson GA. Prenatal marijuana exposure: effect on child depressive symptoms at ten years of age. *Neurotoxicol Teratol*. 2005; 27, 439–448.
69. Goldschmidt L, Richardson GA, Cornelius MD, Day NL. Prenatal marijuana and alcohol exposure and academic achievement at age 10. *Neurotoxicol Teratol*. 2004; 26, 521–522.
70. Day NL, Goldschmidt L, Thomas CA. Prenatal marijuana exposure contributes to the prediction of marijuana use at age 14. *Addiction*. 2006; 101, 1313–1322.
71. Derauf C, Kekatpure M, Neyzi N, Lester B, Kosofsky B. Neuroimaging of children following prenatal drug exposure. *Semin Cell Dev Biol*. 2009; 20, 441–454.
72. Warshak CR, Regan J, Moore B, Magner K, Kritzer S, Van Hook J. Association between marijuana use and adverse obstetrical and neonatal outcomes. *J Perinatol*. 2015; 35, 991–995.
73. Conner SN, Bedell V, Lipsey K, Macones GA, Cahill AG, Tuuli MG. Maternal marijuana use and adverse neonatal outcomes: a systematic review and meta-analysis. *Obstet Gynecol*. 2016; 128(4), 713–723.
74. Varner MW, Silver RM, Rowland Hogue CJ, *et al.* Association between stillbirth and illicit drug use and smoking during pregnancy. *Obstet Gynecol*. 2014; 123, 113–125.
75. Crean RD, Crane NA, Mason BJ. An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. *J Addict Med*. 2011; 5, 1–8.
76. Cohen K, Weinstein A. The effects of cannabinoids on executive functions: evidence from cannabis and synthetic cannabinoids—a systematic review. *Brain Sci*. 2018; 8, 40.
77. Forrester MB, Merz RD. Risk of selected birth defects with prenatal illicit drug use, Hawaii, 1986–2002. *J Toxicol Environ Health A*. 2007; 70(1), 7–18.
78. Reece AS, Hulse GK. Gastroschisis and autism—dual canaries in the Californian coalmine. *JAMA Surg*. 2019; 154(4), 366–367.
79. David AL, Holloway A, Thomasson L, *et al.* A case-control study of maternal periconceptual and pregnancy recreational drug use and fetal malformation using hair analysis. *PLoS One*. 2014; 9, e111038.
80. Siega-Riz AM, Keim-Malpass J, Lyons GR, Alhusen J. The association between legalization of recreational marijuana use and birth outcomes in Colorado and Washington state. *Birth Defects Res*. 2020; 112(9), 660–669.
81. Baker T, Datta P, Rewers-Felkins K, *et al.* Transfer of inhaled cannabis into human breast milk. *Obstet Gynecol*. 2018; 131, 783.
82. Bertrand KA, Hanan NJ, Honerkamp-Smith G, Best BM, Chambers CD. Marijuana use by breastfeeding mothers and cannabinoid concentrations in breast milk. *Pediatrics*. 2018; 142(3), e20181076.
83. Tennes K, Avitable N, Blackard C, *et al.* Marijuana: prenatal and postnatal exposure in the human. *NIDA Res Monogr*. 1985; 59, 48–60.
84. Astley SJ, Little RE. Maternal marijuana use during lactation and infant development at one year. *Neurotoxicol Teratol*. 1990; 12, 161.
85. World Health Organization. *Guidelines for the Identification and Management of Substance Use and Substance Use Disorders in Pregnancy*, 2014. World Health Organization. <https://apps.who.int/iris/handle/10665/107130>.
86. Gunasekaran N, Long LE, Dawson BL, Hansen GH, Richardson DP, Li KM, Arnold JC, McGregor IS. Reintoxication: the release of fat-stored delta(9)-tetrahydrocannabinol (THC) into blood is enhanced by food deprivation or ACTH exposure. *Br J Pharmacol*. 2009; 158, 1330–1337.
87. Hirsch S, Tam J. Cannabis: from a plant that modulates feeding behaviors toward developing selective inhibitors of the peripheral endocannabinoid system for the treatment of obesity and metabolic syndrome. *Toxins (Basel)*. 2019; 11, 275.
88. Bermudez-Silva FJ, Viveros MP, McPartland JM, Rodriguez de Fonseca F. The endocannabinoid system, eating behavior and energy homeostasis: the end or a new beginning? *Pharmacol Biochem Behav*. 2010; 95, 375–382.

89. Christensen R, Kristensen PK, Bartels EM, Bliddal H, Astrup A. Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. *Lancet*. 2007; 370, 1706–1713.
90. Julien B, Grenard P, Teixeira-Clerc F, et al. Antifibrogenic role of the cannabinoid receptor CB2 in the liver. *Gastroenterology*. 2005; 128, 742–755.
91. Dai E, Zhang L, Ye L, et al. Hepatic expression of cannabinoid receptors CB1 and CB2 correlate with fibrogenesis in patients with chronic hepatitis B. *Int J Infect Dis*. 2017; 59, 124–130.
92. Jeong WI, Osei-Hyiaman D, Park O, et al. Paracrine activation of hepatic CB1 receptors by stellate cell-derived endocannabinoids mediates alcoholic fatty liver. *Cell Metab*. 2008; 7, 227–235.
93. Lee SM, Kim BJ, Koo JN, et al. Nonalcoholic fatty liver disease is a risk factor for large-for-gestational-age birthweight. *PLoS One*. 2019; 14, e0221400.
94. Bhatt S., Queen J. Cannabinoid hyperemesis syndrome. *Curr Emerg Hosp Med Rep*. 2019; 7, 14–18.
95. Aziz I, Palsson OS, Whitehead WE, Sperber AD, Simrén M, Törnblom H. Epidemiology, clinical characteristics, and associations for Rome IV functional Nausea and vomiting disorders in adults. *Clin Gastroenterol Hepatol*. 2019; 17, 878–886.
96. Patel RS, Goyal H, Satodiya R, Tankersley WE. Relationship of cannabis use disorder and irritable bowel syndrome (IBS): an analysis of 6.8 million hospitalizations in the United States. *Subst Use Misuse*. 2020; 55, 281–290.
97. Adejumo AC, Ajayi TO, Adegba OM, Bukong TN. Higher odds of irritable bowel syndrome among hospitalized patients using cannabis: a propensity-matched analysis. *Eur J Gastroenterol Hepatol*. 2019; 31, 756–765.
98. Russo EB. Clinical endocannabinoid deficiency reconsidered: current research supports the theory in migraine, fibromyalgia, irritable bowel, and other treatment-resistant syndromes. *Cannabis Cannabinoid Res*. 2016; 1, 154–165.
99. Goyal H, Singla U, Gupta U, May E. Role of cannabis in digestive disorders. *Eur J Gastroenterol Hepatol*. 2017; 29, 135–143.
100. Fogel JS, Kelly TH, Westgate PM, Lile JA. Sex differences in the subjective effects of oral Δ^9 -THC in cannabis users. *Pharmacol Biochem Behav*. 2017; 152, 44–51.
101. Cooper ZD, Haney M. Investigation of sex-dependent effects of cannabis in daily cannabis smokers. *Drug Alcohol Depend*. 2014; 136, 85–91.
102. Meier MH, Pardini D, Beardslee J, Matthews KA. Associations between cannabis use and cardiometabolic risk factors: a longitudinal study of men. *Psychosom Med*. 2019; 81, 281–288.
103. Hernandez JM, Paty J, Price IM. Cannabinoid hyperemesis syndrome presentation to the emergency department: a two-year multicentre retrospective chart review in a major urban area. *CJEM*. 2018; 20, 550–555.
104. Fattore L, Fratta W. How important are sex differences in cannabinoid action? *Br J Pharmacol*. 2010; 160, 544–548.
105. Cuttler C, Mischley LK, Sexton M. Sex differences in cannabis use and effects: a cross-sectional survey of cannabis users. *Cannabis Cannabinoid Res*. 2016; 1, 166–175.
106. Craft RM, Marusich JA, Wiley JL. Sex differences in cannabinoid pharmacology: a reflection of differences in the endocannabinoid system? *Life Sci*. 2013; 92, 476–481.
107. Bara A, Manduca A, Bernabeu A, et al. Sex-dependent effects of in utero cannabinoid exposure on cortical function. *Elife*. 2018; 7, e36234.
108. Pacheco M, Childers SR, Arnold R, Casiano F, Ward SJ. Aminoalkylindoles: actions on specific G-protein-linked receptors. *J Pharmacol Exp Ther*. 1991; 257, 170–183.
109. Mackie K. Mechanisms of CB1 receptor signaling: endocannabinoid modulation of synaptic strength. *Int J Obes (Lond)*. 2006; 30(Suppl 1), S19–S23.