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Cannabinoid exposure during pregnancy and its impact on immune function

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Abstract

Cannabinoids are the most commonly abused illicit drugs worldwide. While cannabis can be beneficial for certain heath conditions, abuse of potent synthetic cannabinoids has been on the rise. Exposure to cannabinoids is also prevalent in women of child-bearing age and pregnant women. These compounds can cross the placental barrier and directly affect the fetus. They mediate their effects primarily through G-protein coupled cannabinoid receptors, CB1 and CB2. In addition to significant neurological effects, cannabinoids can trigger robust immunomodulation by altering cytokine levels, causing apoptosis of lymphoid cells and inducing suppressor cells of the immune system. Profound effects of cannabinoids on the immune system as discussed in this review, suggest that maternal exposure during pregnancy could lead to dysregulation of innate and adaptive immune system of developing fetus and offspring potentially leading to weakening of immune defenses against infections and cancer later in life. Emerging evidence also indicates the underlying role of epigenetic mechanisms causing long-lasting impact following cannabinoid exposure *in utero*.

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Keywords

Fetus; immune system; marijuana; metabolites; neurological; pregnancy; perinatal; prenatal; substance abuse

Introduction

Cannabis and synthetic cannabinoids are considered one of the most common drugs of abuse [1–3]. There has also been an intense public interest with regard to their health benefits and a greater acceptance of medical cannabis in recent years [4, 5]. The current decriminalization and legalization efforts for the recreational use of cannabis as well as a renewed interest in its therapeutic use are expected to lead to an increase in the prevalence of exposure to these drugs in the coming years [6, 7]. These call for a clear understanding of risks of cannabinoid exposure during pregnancy. Historically, the constellation of effects of cannabinoid use during pregnancy has not received enough attention. While the early and long-term developmental and neurological adverse effects of prenatal cannabis abuse have been known for some time, the profound immunological implications are only beginning to emerge in recent literature. In this review, we discuss the prevalence and recent trends of abuse of cannabis and synthetic cannabinoids during pregnancy and address their impact on the endocannabinoid system (ECS) and immune function of the developing fetus and offspring. We will discuss the possible underlying mechanisms involving cytokines and cells of the immune system. Further, we will highlight the emerging role of epigenetic mechanisms of immune dysregulation caused by maternal exposure to cannabinoids during pregnancy.

Cannabis and synthetic cannabinoids

Cannabis (or marijuana) refers to the dried leaves, flowers, stems, and seeds from the plant *Cannabis sativa*, which contains the major psychoactive chemical delta-9-tetrahydrocannabinol (Δ^9THC) as well as other related compounds collectively called phytocannabinoids (Figure 1) [8–10]. It has been used for centuries not only for recreational purposes but also for its actual as well as perceived medicinal benefits [11]. It is believed to be beneficial in symptomatic relief of a variety of ailments. For instance, the use of cannabis and cannabis-derived cannabidiol (CBD) preparations for effective alleviation of seizers in children with epilepsy who do not respond to other medications is well known [12]. Cannabis and Δ^9THC are also effective in providing relief from nausea, vomiting and loss of appetite in cancer patients undergoing chemotherapy as well as in AIDS patients [13]. In fact, the synthetic Δ9THC such as Dronabinol (Marinol™, Syndros™) and Nabilone (Cesamet™) are FDA approved drugs as antiemetics and orexigenics for this purpose. A mixture of Δ^9THC and CBD (Sativex®) is approved for medical use in Europe and Canada for treating spasticity and neuropathic pain in multiple sclerosis (MS) patients [13]. Potent activity of cannabinoids in reducing inflammation has also been demonstrated in various preclinical models [14], and there is an interest in developing cannabimimetics as novel anti-inflammatory therapeutics.

Natural cannabis and a number of cannabinoid compounds including Δ^9THC and CBD are classified as Schedule I substances based on the United States federal Controlled Substances Act. It is illegal to cultivate, possess, trade and consume cannabis in majority of the countries worldwide, although the extent of implementation of such laws, and hence the prevalence of its use may vary widely. Nevertheless, it is considered the most widely cultivated and trafficked drug of abuse. According to the World Health Organization, cannabis is consumed by ~147 million people or nearly 2.5% of the global population [15]. In the United States, cannabis is the third most widely abused drug by adults, next to alcohol and tobacco. However, recent surveys since 2010 have also found that adolescents smoked cannabis more than cigarettes [16]. Approximately 46% of young adults (ages of 18–34 years) have used cannabis in their lifetime; and 2–3% of the population consumes cannabis on a daily basis [17]. The prevalence of cannabis use has also been increasing among youth and teens since 2007 [16, 18, 18–20]. There have been increasing efforts in recent years towards easing restrictions on both medical and recreational use of cannabis. Several states in America have legalized it for recreational use, and 28 states have now passed laws allowing medical cannabis for certain health conditions [21]. With more states expected to join this trend, the cannabis use and abuse is anticipated to increase. Moreover, the amount of Δ^9THC in cannabis has increased over the past decades, because of selective breeding practices for higher psychoactive content. Compared to approximately 4% in 1980s, Δ^9THC concentrations in new cultivars of cannabis tremendously increased to about 15% in 2012 [22].

An alarming rise in the availability and abuse of highly potent synthetic cannabinoids has been considered as a public health emergency, with increasing number of overdoses and emergency room visits in large metropolitan areas [19, 23, 24]. Synthetic cannabinoids are mind-altering chemicals or mixtures of chemicals structurally related to Δ^9THC that are sprayed on dried and shredded plant material, and sold. They are known by street names such as fake weed, K2 or Spice, often wrongly promoted as legal cannabis. Synthetic cannabinoid analogs such as JWH-018, JWH-073 or HU-210 (Figure 1) are some of the most commonly found chemicals in these products [25, 26]. They are also sold as herbal or liquid incense to be vaporized and inhaled in e-cigarettes and other devices. Their abuse trend has also been associated with increasing popularity of e-cigarettes and vapes among teens and younger population [19]. Synthetic cannabinoids are much more powerful than cannabis or Δ^9THC, sometimes over 100 times stronger with potent psychoactivity and likely, with a myriad of other known and unknown adverse health effects on human body [27–29]. For example, 11-hydroxy-Δ8-THC-dimethylheptyl (HU-210) is a remarkably potent synthetic agonist which has high affinity for both CB1 (Ki 0.0608 nM) and CB2 (Ki 0.524 nM) receptors [30]. It also exhibits high relative intrinsic activities at these receptors. Moreover, HU-210 is known to exhibit long half-life and prolonged duration of action in vivo. The high affinity and efficacy at cannabinoid receptors have been mainly attributed to the replacement of the pentyl side chain of Δ8-THC with a dimethylheptyl group in HU-210 [30, 31].

Cannabinoid abuse during pregnancy

Cannabis is the most widely used illicit drug among women of childbearing age. In recent years, cannabis use appeared to increase among women in their reproductive years. In one of the Monitoring the Future Studies by NIDA, 10.4% of women aged 19 to 32 years reported using cannabis [32]. A recent survey has documented that approximately 4.9% of women of childbearing age regularly smoke cannabis [33]. The prevalence of substance abuse during pregnancy may vary from 5–16% [34]. It is estimated that five million women of childbearing age use illicit drugs and that approximately half a million infants in the United States are exposed to one or more illicit drugs *in utero*. Hence, the impact of maternal substance abuse on both the mother and offspring is of major public health concern. Based on National Pregnancy and Health Survey conducted by National Institute on Drug Abuse (NIDA), the prevalence and substance use patterns among women delivering live-born infants in the US, the self-reported cannabis use during pregnancy was 2.9% compared with 0.9–1.1% for cocaine [35, 36]. While the proportion of substance abuse treatment admissions for pregnant women in the United States remained stable at 4% during 1992–2012, those pregnant women reporting cannabis use increased significantly from 29% to 43% [37]. These studies have also found that pregnant women who use illicit drugs are more likely to use cannabis compared to other substances. This is often due to the perception that cannabis may be less harmful to the developing embryo and fetus compared to other drugs such as cocaine, heroin, or methamphetamine. With the legalization and decriminalization of medical and recreational cannabis in several states, its use among women and during pregnancy is expected to further increase in the coming years [38].

Accumulating evidence suggests that cannabis exposure during pregnancy may significantly impact fetal brain development causing neurological impairments, hyperactivity, poor cognitive function and changes in dopaminergic receptors in children [35, 39–44]. Notably, recent experimental evidence in rodents point to significant impact of stimulation of cannabinoid system on learning and reward-related explicit memory [45, 46]. While cannabis use during pregnancy did not increase risk of perinatal mortality, regular use of cannabis throughout pregnancy was associated with significant decrease in birth weight [35, 47]. However, a recent study found that cannabis use, after adjusting for tobacco and other illicit drug use, was associated with neonatal morbidity or death [48].

Endocannabinoid system (ECS) and pregnancy

The effects of cannabis on reproductive and immune functions may be closely related to the processes that are modulated by the ECS. Endogenous cannabinoids (endocannabinoids) together with cannabinoid receptors, metabolic enzymes and membrane transporters form the ECS [49, 50]. Anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are the two major endocannabinoids (Figure 1) [51, 52]. AEA is metabolized by fatty acid amide hydrolase (FAAH) to arachidonic acid (AA) and ethanolamine, while 2-AG is mainly degraded by monoacyl glycerol lipase (MAGL) to AA and glycerol [53, 54]. Although the precise mechanisms are not fully known, it is agreed that ECS plays a pivotal role in reproduction [55, 56]. The components of ECS are involved in fertilization, oviduct transport,

implantation, embryo development, maintenance and immune regulation during pregnancy [57–59].

FAAH activity has been linked to early pregnancy success with a strong correlation between its decrease in maternal peripheral blood mononuclear cells and spontaneous miscarriage in women [60]. The levels and activity of FAAH were significantly lower in patients undergoing embryo transfer following in vitro fertilization who failed to achieve successful implantation as compared to those who became pregnant [61]. FAAH is considered as a critical metabolic gatekeeper of AEA levels in the uterus throughout menstrual cycle, as well as during pregnancy [62, 63]. In a major study, uterine AEA levels were shown to be highest during non-receptive stage and in inter-implantation sites, but lowest at the site of embryo implantation [64]. Thus, downregulation of AEA is associated with uterine receptivity, and its elevated levels with uterine refractoriness to embryo implantation. This suggests that the down-modulation of uterine AEA at the implantation sites may be the mechanism by which embryos protect themselves from detrimental effects of this endocannabinoid [64]. AEA also modulates decidualization of rat and human endometrial stromal cells [65, 66]. AEA signaling has also been shown to regulate sperm functions required for fertilization in human reproductive tracts [67]. Deregulation of metabolic enzymes of endocannabinoids following exposure to cannabis has been therefore implicated in potential negative impacts on human fertility [65]. In fact, Δ^9THC is known to significantly influence bioactive lipid profile or induce endocannabinoid levels [68, 69]. Unlike endocannabinoids, Δ^9THC is metabolized slowly and may mimic situations in which an excess of endocannabinoids are produced or when re-uptake or removal of endocannabinoids is impaired [58]. Further, THC and CBD can have non-CB1/CB2 targets which may produce a more complex signaling cascade and additional implications for pregnancy.

Several studies have explored the role of intricate endocannabinoids-sex hormone-cytokine regulatory axis during pregnancy [57, 70]. Sex steroid hormones, progesterone and estrogen, are involved in the maintenance of endocannabinoid levels [71]. Progesterone promotes lymphocyte FAAH activity involving transcription factors Stat3 and Ikaros, which results in lower AEA levels [72–74]. These studies indicate regulation of immune cytokine network by endocannabinoids during reproduction which appears to be one of the important mechanisms controlling implantation and the maintenance of healthy pregnancy [75]. Animal studies have shown the presence of constituents of ECS in early embryo before neurogenesis indicating its involvement in early embryogenesis [76–78]. Thus, maternal abuse of cannabis and synthetic cannabinoids can cause adverse reproductive, developmental and immune consequences also by significantly altering the components of the ECS.

Pregnancy and immunity

The maternal immune system actively tolerates the semiallogeneic fetus during pregnancy. This includes changes in local immune responses in the uterine mucosa as well as alterations in peripheral immune responses [79, 80]. The innate immune system is activated during pregnancy [81, 82]. Cells of the granulomonocytic lineage significantly increase during normal pregnancy and undergo phenotypic and functional activation [83], whereas the dendritic cell numbers decrease [84]. Further, the number of natural killer (NK) T cells and

the production of interferon (IFN)-γ by NK cells is decreased in pregnant women [85]. Pregnant women are more sensitive to certain infections and immune dysregulation caused by either proinflammatory or immunosuppressive stimuli. Thus, a significantly altered immune system is essential during pregnancy for normal placentation and maintenance of a healthy pregnancy. However, interfering with the maternal immune system could disturb the balance between tolerance and immunity during pregnancy and may affect the outcome.

Prenatal cannabinoid exposure and immune dysregulation

Exogenous cannabinoids, such as Δ^9THC, have been shown to cross the fetal-placental barrier in humans and other mammals [86–89]. Significant effects of prenatal, intrauterine exposure to cannabinoids on the growth and development of the fetus, as well as on learning and memory, neuronal, behavioral and endocrine aspects of the progeny have been studied and reviewed [43, 90–92]. In addition to its effects on central nervous system (CNS), cannabinoids also profoundly alter immune function [93–96]. While CB1 receptor is expressed in brain and CB2 in the peripheral tissues, immune cells express both the receptors [97–99]. Moreover, reproductive tissues such as the uterine endometrium, human placenta and ovaries express functional cannabinoid receptors [100–103]. However, only a few studies have investigated its impact on maternal and developing immune systems under normal or disease conditions. These studies as discussed below suggest that maternal Δ^9THC exposure may have long-lasting effects on the immune system of the offspring.

T cells play a significant role in implantation, with the shift from Th1 to Th2 helper T cell response at the fetal-maternal interface contributing significantly to a successful pregnancy [104]. It is suggested that a Th2 shift inhibits Th1 cytokine responses, allowing the survival of the fetal allograft [105]. It has also been found that FAAH expression is regulated by the Th1 and Th2 cytokines, with IL-4 and IL-10 enhancing its activity and IL-2 and INF-γ reducing its expression [74]. A recent study has shown that expression of CB1 and CB2 receptors in B lymphocytes is differentially regulated during pregnancy [106]. Moreover, B cells from pregnant mice were shown to produce elevated levels of anti-inflammatory cytokine IL-10 following activation of CB1 receptors by select agonists [106]. Maternal exposure to synthetic cannabinoid HU-210 in rats was found to result in detectable changes in the development of the immune system, and long-lasting alterations to the functional status of the hypothalamus-pituitary-adrenal axis. Particularly, prenatal exposure to HU-210 caused reduction in the T-helper subpopulation in the spleen and a dose-related decrease in the ratio of T helper/ cytotoxic T cells in the peripheral blood of adult male offspring [107].

Murine fetal thymocytes express high levels of the CB1 and CB2 receptors [108]. Acute exposure to Δ^9THC on gestation day 16 was shown to significantly impact fetal immune components as demonstrated by significant thymic atrophy and marked alterations in T cell subpopulations in fetuses on gestational days 16–18 as well as in pups on post-gestational day 1 [108]. Thymic atrophy was characterized by significant dose-dependent (20–50 mg/kg of Δ^9THC) decrease in thymic cellularity which correlated with caspase-dependent apoptosis of thymocytes. Δ^9THC exposure significantly decreased the number of single-positive CD8, double-positive CD4CD8 and double-negative T cell subsets of fetal thymocytes. Δ^9THC (5–20μM) also induced apoptosis in *ex vivo* fetal thymic organ cultures

in a dose-dependent manner. These effects were mainly mediated by activation of CB1 and CB2 receptors as *in vivo* receptor blocking experiments using intraperitoneal injections of CB1 antagonist SR141716A (20 mg/kg) or CB2 antagonist AM630 (40 mg/kg) one hour prior to Δ^9THC (50 mg/kg) administration attenuated these immunological changes. Importantly, exposure to Δ^9THC in pregnant mice had a significant and persistent effect on the postnatal immune response. For example, subchronic perinatal exposure to Δ^9THC with the dosing regimen of 25 mg/kg on gestation day 16 and 10 mg/kg every day thereafter until the pups were born for a total of four injections resulted in significant decrease in thymic and splenic cellularity in 1-week-old offspring, thus negatively affecting the immune system of the progeny. Moreover, decreased proliferative and antibody responses to HIV gp120 antigens by peripheral T cells from the offspring demonstrated significant immune dysregulation. Thus, exposure to 20–50 mg/kg Δ^9THC in pregnant mice seems to trigger profound T cell dysfunction in the developing fetus and the immune system of the offspring, thereby suggesting that cannabinoid exposure during pregnancy may cause significant and long-lasting effects on immune function [108].

Human epidemiological observations linking cannabis use, HIV immunity and development of AIDS have been contradictory. In a retrospective study that evaluated the link between cannabis use and sexually transmitted diseases in pregnant women entering prenatal care in which 86 women using only cannabis as an illicit substance were compared to 441 drug-free women with regards to the prevalence of gonorrhea, chlamydia, syphilis, human immunodeficiency virus (HIV), hepatitis B surface antigen, human papilloma virus, and herpes virus. No significant differences were found in the prevalence of these sexually transmitted infectious diseases between pregnant women who used cannabis and the drug-free pregnant women [109]. However, an association between cannabis use and HIV progression and the development of symptomatic AIDS was reported in homosexual men [110]. HIV positive men who progressed to AIDS and to have used cannabis for 3 months or more were more likely to have a lower percentage of CD4 T cells and a higher percentage of CD8 T cells [110]. However, several other studies reported no statistically significant links between cannabis or synthetic cannabinoids and HIV infection or associated immune parameters [111, 112]. For example, a randomized and placebo-controlled intervention trial involving 67 patients with HIV-1 infection, cannabis smoking and oral Dronabinol did not appear to adversely affect HIV RNA levels, CD4+ or CD8+ cell counts, or protease inhibitor levels [113]. *In vitro* studies on the effects of cannabinoids on HIV have also been contradictory. One study noted that several cannabinoid receptor agonists, including Δ^9THC, may enhance HIV infection of a human T cell line [114], whereas others have reported that the synthetic cannabinoid receptor agonist WIN55,212–2 inhibited HIV expression in CD4 T lymphocytes and microglial cell cultures [115, 116]. However, in a hybrid mouse model in which human peripheral blood leukocytes were implanted into severe combined immunodeficient mice (huPBL-SCID), exposure to Δ^9THC could suppress immune function, increase HIV co-receptor expression, and act as a cofactor to significantly enhance HIV replication [117]. HIV+ patients who were also cannabis users had lower circulating CD16 monocytes and IFN-γ-inducible protein 10 (IP-10) levels when compared to those not using cannabis [118]. Daily cannabis use was strongly associated with moderate to severe fibrosis in hepatitis C virus-infected individuals [119] and with liver fibrosis progression in

patients with chronic hepatitis C [120]. The CB1 receptors were found to promote the progression of fibrosis as CB1 antagonism was able to attenuate liver fibrogenesis primarily by decreasing hepatic TGF-β [121]. CB1 and CB2 receptors have also been shown to play opposite roles in the pathogenesis of alcoholic liver disease via regulation of reinforcing properties of alcohol in the brain as well as hepatic cell injury and inflammation by endocannabinoids [122].

Immunomodulatory activity of both plant-derived and endocannabinoids have been also studied in animal models of inflammation such as allergic contact dermatitis, autoimmune hepatitis and graft-versus-host disease [14, 123–130]. Cannabinoids have been shown to typically act by suppressing proinflammatory cytokines, decreasing effector CD4/CD8 T cell population by inducing apoptosis and inhibiting their proliferation [124, 128]. Moreover, they can also upregulate certain chemokines or growth factors (G-CSF) and induce regulatory T cells or immunosuppressive myeloid cells [124, 127]. While most cannabinoids exert these effects via activation of cannabinoid receptors (CB1/CB2) [123, 124, 128, 130], CBD has been shown to function through vanilloid (Trpv1) receptors to ameliorate inflammation [127]. The robust anti-inflammatory activity of cannabinoids can have significant impacts during pregnancy. For example, use of non-steroidal anti-inflammatory drugs (NSAIDS) during pregnancy has been linked to miscarriages and other adverse outcome [131, 132]. According to a nested case-controlled study of 47,050 women, the risk of miscarriage was 2.4 times greater for those who took NSAIDS in early pregnancy [133]. The synthesis of prostaglandin is important in later stages of pregnancy and for fetal maturation [134]. Therefore, exposure to NSAIDS during the third trimester can affect fetal development and cause fetal ductal constriction [135]. Clinical evidence supports the association of changes in fetal ductus arteriosus flow and maternal consumption of foods rich in natural anti-inflammatory substances such as polyphenols [136–138]. Maternal dietary intervention during the third trimester of pregnancy by restricting potent anti-inflammatory foods for a period two weeks or more had a beneficial outcome with improved fetal ductal flow dynamics and reduced dimensions of the right ventricle [137]. Pro and anti-inflammatory conditions are tightly controlled *in utero* during pregnancy. Such fine-tuned regulation of inflammatory milieu is critical for optimal maintenance of pregnancy, fetal health, development and normal labor. While intrinsic changes in endocannabinoid levels appear to be an important component of this regulatory process, exposure to exogenous immunomodulatory cannabinoids could significantly alter this balance.

Increased frequency of mutant lymphocytes were observed in cannabis-smoking mothers and their newborns, suggesting a link between maternal cannabis smoking and somatic mutations, with a potentially elevated risk of developing malignancies [139]. Feinshtein et al., examined the influence of short-term exposure of human placental epithelial cell lines to CBD, and found that CBD inhibited placental breast cancer resistance protein function. Further, CBD significantly enhanced glyburide transport across human placenta ex vivo, suggesting that cannabinoids could enhance placental barrier permeability to other xenobiotics and endanger the developing fetus [140]. The association between maternal cannabis use and incidence of certain childhood malignancies such as rhabdomyosarcoma, astrocytoma and leukemia have been studied [141–144]. Trans-generational assessment of the effect of maternal cannabis use in 204 case-controlled women during and one year

preceding pregnancy showed as much as an 11-fold increased risk of childhood acute non-lymphoblastic leukemia in offspring [141]. In cases of childhood acute myeloid leukemia, the risk of association was not observed with maternal cannabis use 3 months prior to or during pregnancy [89]. An evaluation of the self-reported use of recreational drugs in the mothers of 538 children with neuroblastoma showed that cannabis use during the first trimester of pregnancy was associated with significantly increased risk of neuroblastoma in the offspring, whereas its use during late pregnancy did not increase the risk. The association of gestational cannabis exposure with cancer incidence was particularly strong in children diagnosed with neuroblastoma before the age of 1 year [145]. However, these epidemiological studies have major limitations in that the data were mainly obtained by hospital surveys and information on amount of exposure was not available or dose-response evaluations were not performed, and therefore did not establish a causative link.

Potential impact of metabolites of exogenous cannabinoids

The detection of metabolites of Δ^9THC and CBD in human hair and body fluids, and their precise quantitation methods have been well-developed particularly in the context of clinical toxicology and forensics of cannabis abuse [146–148]. However, unlike in the case of parent cannabinoids, there is limited literature on the biological activities of their metabolites.

11-Nor-9-carboxy-Δ9-tetrahydrocannabinol also known as THC-11-oic acid (11-COOHTHC) is the most abundant metabolite of Δ^9THC [149–151]. As such 11-COOH-THC in body fluids is the clinical and forensic marker for cannabis exposure. Δ^9THC is primarily metabolized by liver cytochrome P-450 (CYP450) isoenzymes into Phase I metabolites, which are oxidative and/or hydroxylated derivatives [152]. The initial oxidative metabolite is 11-hydroxy-Δ^9THC (11-OH-THC), which is psychoactive. Further oxidative metabolism gives rise to 11-COOHTHC, which is inactive at CB1 and hence non-psychoactive [153]. This and other oxidized metabolites can also get converted to glucuronide esters as Phase II metabolites before excretion. 11-COOH-THC could be detected in the newborn meconium to determine the maternal exposure to cannabis [154], which suggested its placental transfer. Although 11-COOH-THC is psychotropically inactive, it exhibits analgesic and anti-inflammatory properties and hence considered as a biologically active metabolite. Similar to Δ^9THC and CBD, 11-COOH-THC suppressed melatonin biosynthesis in rat pineal gland preparations ex vivo [155]. Orally administered 11-COOH-THC showed higher activity than Δ^9THC in preventing platelet-mediated edema [156]. Moreover, 11-THC-COOH showed topical anti-inflammatory effects in vivo in experimental ear edema model in mice [157]. Certain synthetic cannabinoids such as ajulemic acid (AjA), endocannabinoids, and 11-THC-COOH have been shown to also influence eicosanoid biosynthesis. Endocannabinoids 2-AG and AEA can serve as a source of AA as well as metabolized by most eicosanoid biosynthetic enzymes, yielding additional lipids that regulate inflammatory cell functions [158]. AjA can increase the steady state levels of COX2 mRNA and AA release, and can selectively and markedly upregulate 15d-PGJ2, an eicosanoid which facilitates resolution of inflammation [159]. While AjA could induce 2–7 fold increase in the production of anti-inflammatory eicosanoid lipoxin A4 [160], 11-COOH-THC was found to inhibit cyclooxygenase and 5-lipoxygenase activities

involved in prostaglandin biosynthesis, and hence decrease the production of proinflammatory prostaglandin eicosanoids [161].

Unlike THC, the metabolism of CBD is extremely complex, with more than 100 different metabolites identified [162]. The major metabolites of CBD are water soluble, hydroxylated 7-COOH derivatives [163]. Similar to natural enantiomer (−) CBD, the 7-COOH metabolites had very low affinities for CB1 and CB2 receptors. Whereas, those derived from synthetic (+) CBD enantiomer exhibited high (K_i = 13.2 nM) and modest (K_i = 156 nM) affinities respectively for CB1 and CB2. Moreover, while both CBD enantiomers were good agonists of vanilloid (Trpv1) receptors, the 7-COOH metabolites showed no Trpv1 binding [164]. The 7-COOH CBD metabolites may also have anti-nociceptive and anti-inflammatory activities as they were found to inhibit the generation of nitric oxide and reactive oxygen species as well as production of TNF-α in vitro in a dose-dependent manner [164].

A number of human metabolites of synthetic cannabinoids have been reported [165, 166]. However, studies on their biological effects are limited. Mass spectrometric analysis of human urine specimens of individuals exposed to JWH-018 has identified monohydroxylated and carboxylated derivatives as the major metabolites, with hydroxylated primary metabolites exhibiting potent CB1 receptor agonistic activity [165, 167]. The metabolites of synthetic cannabinoids can also produce stronger activation of CB1 and CB2 receptors than Δ^9THC, and may possess distinct pharmacology and higher toxicity [168–170].

While studies investigating the direct impact of metabolites of exogenous cannabinoids are lacking, their known biological activities as discussed above have the potential to interfere during pregnancy. It is likely that the immunosuppressive activity of bioactive cannabinoid metabolites may interfere with normal inflammatory changes and eicosanoid-prostaglandin homeostasis during pregnancy. Whether or not these metabolites affect fetal development or have specific neuronal and immune-related effects impacting the offspring needs further investigation.

Emerging role of epigenetic mechanisms

Epigenetics refers to stable, long-term alterations in the cell or individual that involves mechanisms of gene regulation by post-transcriptional and post-translational modifications, but not direct changes to the DNA sequence [171, 172]. The epigenetic regulatory machinery includes DNA methylation, histone modifications and non-coding RNAs. Recent studies have explored the impact of phytocannabinoids, synthetic cannabinoids and endocannabinoids on the epigenetic components [173–177].

Using a combined computational and experimental approach, it was shown that myocardial CB1 receptors were regulated by microRNA(miR)-494 and that CB2 receptors were targeted by miR-665, with miR-494 enhanced and miR-665 significantly repressed in chronic heart failure [178]. In Simian immunodeficiency virus-infected macaques, miRNA expression was profiled in intestines at 14, 30, and 60 days post-infection with or without chronic Δ^9THC administration [179]. Chronic Δ^9THC exposure was found to significantly increase the total

number of differentially expressed miRNAs, selectively enhancing the expression of miR-10a, miR-24, miR-99b, miR-145, miR-149 and miR-187, that were found to target pro-inflammatory pathways, suggesting that the selective upregulation of anti-inflammatory miRNAs may contribute to Δ^9THC-induced attenuation of gastrointestinal inflammation and maintenance of intestinal homeostasis [179].

The immunomodulatory effect of Δ^9THC in experimental superantigen-elicited immune response in mice was shown to be mediated by epigenetic regulation [176]. In this study, changes in histone modifications in activated lymphocytes from mice following staphylococcal enterotoxin B superantigen challenge with or without Δ^9THC administration were studied using ChIP-Seq approach. Global histone methylation and acetylation were found to be altered by Δ^9THC, which caused increase in active histone modification marks (H3K4me3) in Th2-associated genes and of suppressive modification signals (H3K27me3) in Th1-associated genes, suggesting for the first time that Δ^9THC might modulate immune response through epigenetic histone modifications. In humans, the regulation of increased proenkephalin (Penk) expression, which is an opioid neuropeptide gene, was found to be mediated via decreased histone H3K9 methylation in the brain nucleus accumbens of adults following adolescent Δ^9THC exposure, thereby disrupting the normal developmental pattern of this epigenetic mark. It was suggested that epigenetic dysregulation of Penk underlies the long-term effects of Δ^9THC particularly in the neurobiological mechanisms of vulnerability to abuse of other drugs associated with cannabis abuse [180]. Rotter et al., have investigated the CB1/CB2 receptor promoter methylation status in peripheral blood cells of individuals with Δ^9THC dependence and non-smoking control subjects. A significant negative correlation between mean promoter methylation frequency and CB1 expression was noted with a higher CB1 expression associated with cannabis consumption. Thus, altered CB1 expression associated with Δ^9THC dependence was found to be mediated by changes to promoter methylation status [181].

Our seminal study demonstrated that cannabinoid receptor activation by Δ^9THC in mice leads to a rapid and massive expansion of $CD11b^+Gr\text{-}1^+$ myeloid-derived suppressor cells (MDSC) expressing functional arginase and exhibiting potent immunosuppressive properties both *ex vivo* and upon adoptive transfer *in vivo* [182]. Further, the induction of MDSCs by Δ^9THC in vivo was associated with robust upregulation of chemokines, particularly G-csf and Cxcl1. Thus, induction of certain chemokines and MDSCs was identified as a major mechanism of immunomodulation by Δ^9THC. MDSCs are the major immunosuppressive innate cell population induced in cancer, where they play a critical role in cancer immune escape [183, 184]. Epigenetic changes involving microRNA in MDSCs that are induced *in vivo* following exposure to Δ^9THC have been studied in mice [175]. Δ^9THC-induced MDSCs were found to exhibit distinct global microRNA expression profile compared to other myeloid cells and control bone marrow myeloid progenitor cells, with the targets of differentially expressed miRNA significantly associated with hematopoiesis and myeloid cell function Gene Ontology clusters as well as myeloid differentiation biological pathways. In fact, several of the altered miRNA were found to directly target crucial transcription factors involved in myeloid differentiation and function. Importantly, miRNA-690, highly overexpressed in Δ^9THC-MDSCs, was found to target and regulate CCAAT/enhancer-binding protein α (C/EBPα), a master regulator of myeloid differentiation. The functional

nature of this regulatory circuit was further confirmed by *ex vivo* miR-690 knockdown in primary MDSCs [175]. Moreover, endocannabinoid 2-AG has been recently shown to increase the presence and suppressive potency of MDSCs in brain [185], and AEA was shown to suppress Th17 cell-mediated experimental delayed type hypersensitivity response in vivo in mice by inducing IL-10 which in turn triggered a set of miRNA specifically targeting pro-inflammatory pathways [186].

Concluding remarks and Perspective

Currently accepted theories of the fetal origins of adult diseases involve *in utero* exposure and response to environmental factors that ultimately lead to persistent effects with increased susceptibility to certain diseases later in life. Although precise mechanisms are not completely known, accumulating evidence in recent years suggests the involvement of epigenetic regulatory pathways [187, 188]. Studies on the effects of cannabinoids on the epigenome thus far have been mostly performed in adults. As epigenetic changes are stable and have sustained effects, these early results suggest that cannabis abuse could have a trans-generational impact, and that such events early in life in utero might have a significant impact on fetal health and progeny, including the critical immune components (Figure 2). Importantly, immune system and inflammation also plays a critical role in the etiology of number of neurological and psychiatric illnesses. Women during pregnancy could potentially get exposed to high potency cannabis and synthetic cannabinoids. Robust controlled human studies involving drug abuse patients on the specific effects of cannabis and synthetic cannabinoids on immune function in neonates and offspring are lacking. Future studies with a balanced approach are needed to examine the dose and duration-dependent effects cannabis components and synthetic cannabinoids on immune function and other health aspects to further clearly understand their harmful impact and pregnancy risks, as well as any potential beneficial effects.

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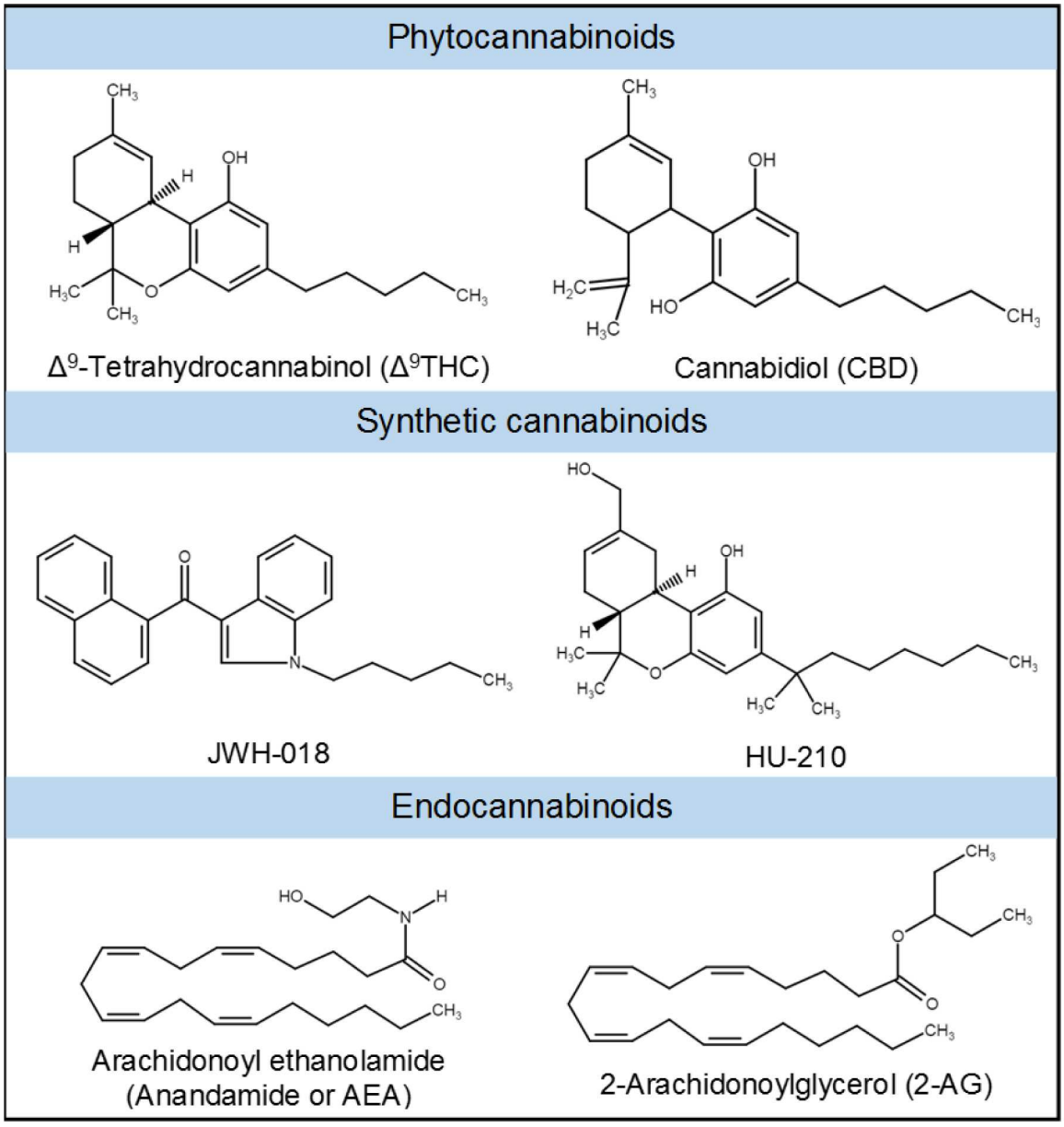

Figure 1.

Chemical structures of major cannabinoids. Phytocannabinoids are natural cannabinoids derived from Cannabis plant. Synthetic cannabinoids are potent cannabimimetics commonly present in designer street drugs such as K2 or Spice. Natural cannabinoids endogenously produced in humans and other animals are referred to as endocannabinoids. Most cannabinoids typically signal through cannabinoid receptors, CB1 and/or CB2.

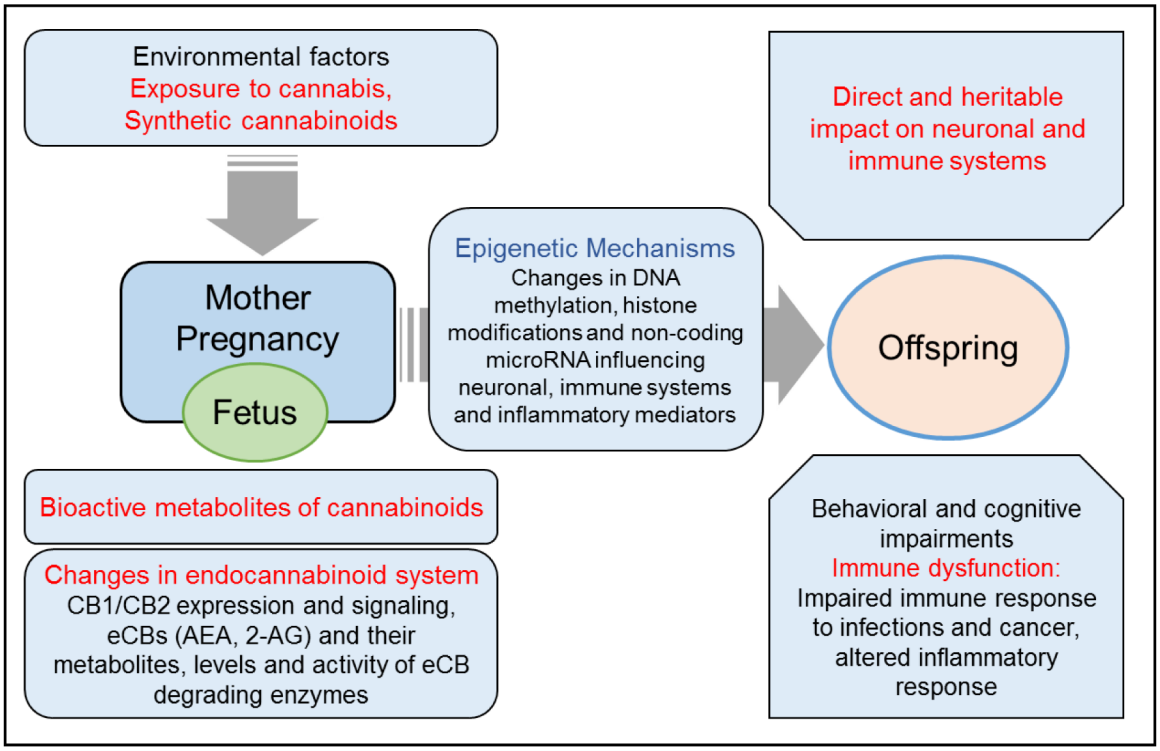

Figure 2.

Potential health impacts of cannabis and synthetic cannabinoid abuse during pregnancy. Cannabinoids are known to cross the maternofetal placental barrier. Maternal exposure to cannabinoids may exert direct as well as heritable impact on the developing fetus and offspring with significant neuronal impairment and immune dysfunction involving epigenetic mechanisms.