Cannabis Use Disorder During the Perinatal Period

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Introduction

Cannabis use in the perinatal period has been increasing in recent years, coincident with increasing legalization in the USA for medical or recreational purposes [1]. Marijuana is the most commonly used illicit drug during pregnancy [2], and among some populations, it is used more frequently than tobacco [3, 4]. Although the prevalence of cannabis use during pregnancy is difficult to ascertain with accuracy, rates of marijuana use range from 2.6% to 28% or higher [3, 5] depending on the population studied and/or screening practices. According to the 2013 National Survey on Drug Use and Health, the rate of marijuana and hashish use among pregnant women in the USA was 5.2% [6].

Marijuana use is more prevalent among nonpregnant than pregnant women of child-bearing age in the general population. However, among past-year users, near daily use rates are higher in pregnant versus nonpregnant women (16.2% versus 12.8%), as is the percentages of women meeting criteria for cannabis abuse and dependence (18.1% versus 11.4%) [7]. These statistics indicate that for the population of women using marijuana during pregnancy, many are chronic users who are likely to have a cannabis use disorder (CUD). Young adolescents (ages 15–17) have the highest rate of marijuana use during pregnancy (16.5%), more than double the rate for 18- to 25-year-olds (7.5%) [6, 8]. During pregnancy, rates of marijuana use are higher during the first trimester than the second or third trimester (6.44% vs. 3.34% and 1.82%, respectively) [9]. Given that the percentage of unplanned pregnancies is very high (almost half of pregnancies in the general population and higher in substance using/abusing populations), many fetuses are likely to be exposed to cannabis during the first trimester of pregnancy, before the mother is aware of being pregnant.

The effects of cannabis mainly depend on its major psychoactive cannabinoid (delta-9-tetrahydrocannabinol or THC) content. Novel ways of cultivating the *Cannabis sativa* plant have produced more potent varieties of cannabis [10], and the legal cannabis market has implemented selective growing methods to boost psychoactive potency. In the USA, the potency of cannabis has increased steadily over the past 50 years [11], and this trend has translated to increased fetal THC exposure. For example, tetrahydrocannabinolic acid concentrations were significantly increased in marijuana-positive meconium samples originating from Colorado hospitals compared with specimens sent from the rest of the USA during the first 9 months post legalization in Colorado [12]. The proportion of THC in the commonly used herbal cannabis (marijuana) and its resin (hashish) was 3% or less in the 1960s but reached a potency of 12% by 2014 [10, 13]. This means that marijuana today is at least 4 times more potent than it was 4 decades ago [14], which has implications for the interpretation of older studies on the effects of prenatal marijuana exposure on child development that form the large bulk of our current knowledge.

The emergence on the drug market of synthetics cannabinoids (SCBs) in the early 2000s represents a new public health challenge. Whereas THC generally acts as a partial cannabinoid receptor agonist, SBCs are often full cannabinoid receptor agonists and can have greater cellular actions and behavioral effects. The concentrations of SCBs can vary widely, even within batches of the same product [15]. Some SCBs have extremely high potency, ranging from 40- to 660-fold higher than Δ9-THC in cannabis strains [16]. SCBs are cheap and easily purchased on the Internet, potent, and addictive and possess different toxicity profiles from naturally grown marijuana [17]. These substances appear to produce multiple dose-dependent congenital anomalies in

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I. D. Montoya, S. R. B. Weiss (eds.), *Cannabis Use Disorders*, https://doi.org/10.1007/978-3-319-90365-1_17

rodents [18], and there is no current information on the effects of SCBs in exposed human fetuses or infants.

Despite its controversial nature, the use of medical marijuana and cannabis-derived medicinal products is also becoming more popular in the USA. Nausea, a common complaint in pregnant women, is a medically approved indication for marijuana in all states where medical use of this drug has been legalized [19]. A study carried out in Hawaii, a state where marijuana is legal, found that women with severe nausea during pregnancy, compared with other pregnant women, were significantly more likely to use marijuana (3.7% vs 2.3%, respectively) [20].

Taking this information together, the current landscape of the risks of marijuana use during the perinatal period is not clear because of the recent changes in the patterns of marijuana use, the increase in prevalence of cannabis use in women during the perinatal period, the production and use of more potent forms of cannabis, and the introduction of synthetic cannabinoids. It is well-established that THC crosses the placental barrier, and while a preponderance of studies have established harmful effects of prenatal cannabinoid exposure in animal (e.g., rodent) models, further research is urgently needed to determine the effects of the increased fetal THC exposure.

Prenatal Cannabis Exposures: Impact on the Pregnancy and the Fetus

Cannabis has more than 540 constituents [10]. The plant's behavioral and psychotropic effects are attributed to the major psychoactive cannabinoid, THC. THC has a lipophilic nature and, when inhaled rapidly, enters the bloodstream resulting in swift distribution from the blood to the tissue. In both animals and humans, THC crosses the placenta and transfers to the fetus; however, there is a lack of complete understanding of the pharmacokinetics and maternal-fetal transfer and disposition of THC and its metabolites [21]. Animal studies indicate great variability in THC distribution to fetal tissues across species, although THC concentrations in the fetus have been documented to be lower than maternal concentrations in those animal studies [21, 22]. In studies done in humans when the mother smoked marijuana daily during the third trimester of pregnancy, THC levels in maternal blood were 2.5 to 6 times greater than in cord blood [23].

Biological (Fig. 17.1) and neurodevelopmental/neurobehavioral (Fig. 17.2) effects of prenatal THC exposure have been described across the life span of the developing organism. There are several mechanisms by which THC exposure

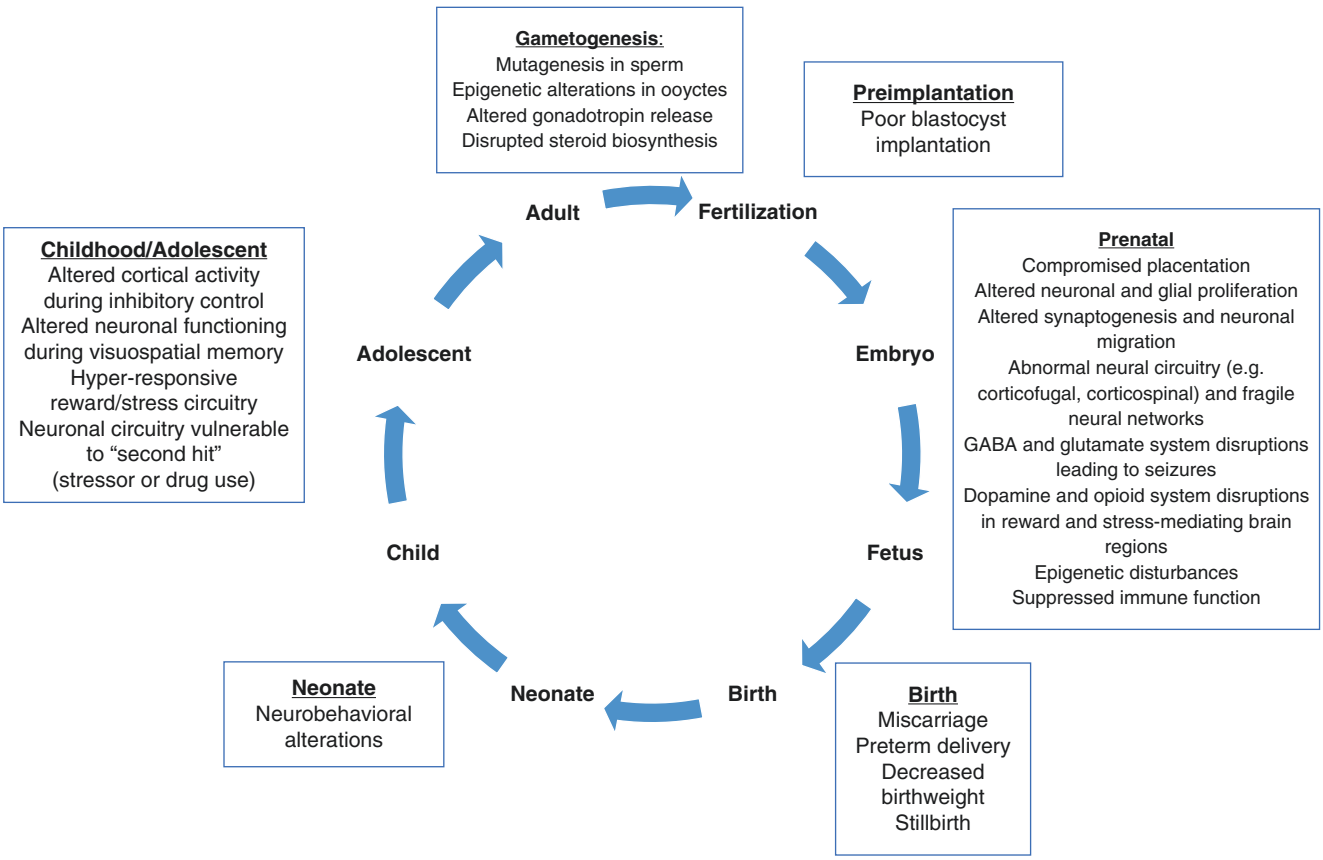

Fig. 17.1 Reported biological disruptions due to prenatal cannabinoid exposure across the human and/or animal life span

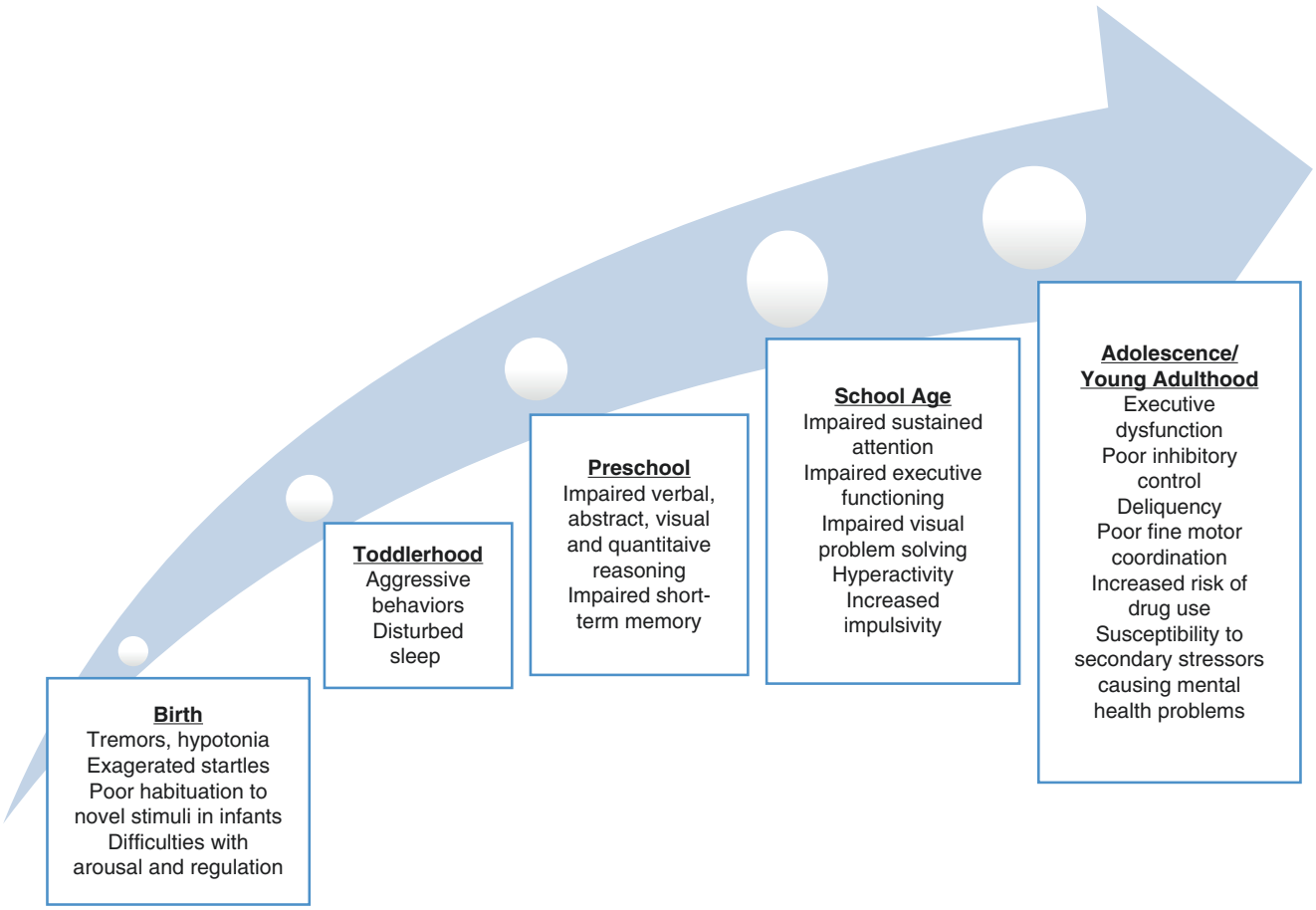

Fig. 17.2 Reported neurobehavioral effects of prenatal cannabinoid exposure across the developmental life span of the child

causes developmental harm in children, including effects of cannabis on the developing endocannabinoid system, effects on neurotransmitters and neural circuit connectivity, and persistent epigenetic modifications which may alter gene expression across the life span.

Mechanisms of Harm

Effects of Prenatal THC Exposure on the Fetal Endocannabinoid System

The endocannabinoid (EC) system describes the body's endogenous or naturally produced cannabinoid system and includes the endocannabinoid retrograde neurotransmitters, their receptors, and the enzymes involved in their synthesis and degradation. The EC system has been detected from the earliest embryonic stage and throughout pre- and postnatal development [24, 25]. Data from both animal and human research indicate that EC system signaling plays a critical role in pregnancy outcome and fetal development. The EC system undergoes significant changes in expression and activity of its components during sequential developmental stages, suggesting ECs play a major role in the formation of specific anatomical regions at timepoints in pregnancy. A fine-tuned orchestration of this system during brain development is essential.

The EC system works both in the central nervous system and peripherally to regulate a myriad of vital functions. Endocannabinoids and plant-derived cannabinoids exert their effects by activating predominantly cannabinoid (CB) receptors. In the fetal nervous system of animals and humans, CB receptor distribution is different from that in the adult, suggesting that endogenous and exogenous cannabinoids may have different effects prenatally than in a mature organism. Expression of CB1 receptors has been detected in the fetal human brain as early as 14 weeks of gestation and changes dynamically across development in different parts of the brain [26] indicating critical roles in orchestrating fetal brain development. In developing fetal human brains not exposed to cannabis, the distribution of CB1 receptor mRNA at approximately 20 weeks of gestation is elevated in limbic structures (including the hippocampal CA region and basal nuclear group of the amygdaloid complex) compared to the rest of the brain. High CB1 receptor concentrations are also present on several white matter neuronal tracts of the human

fetus but had disappeared by infancy [27]. Thus, differences in localization of CB1 receptor expression seem to be a transitory phenomenon, with progressive increases occurring from the fetal period through adulthood. In the adult human brain, CB1 mRNA expression is relatively widespread and is particularly apparent in the frontal cortex, hippocampus, basal ganglia, and cerebellum [27, 28]. Together these findings suggest that CB1 receptors have unique and changing roles in regulating pre- and postnatal development that significantly differ from adulthood.

The two main ECs are N-arachidonoylethanolamine (anandamide, AEA) and 2-arachidonoylglycerol (2-AG). They are produced on demand, and their levels are tightly regulated by enzymes involved in their synthesis and degradation. Brain AEA levels are low at midgestation but gradually increase during postnatal development, reaching a maximum in adulthood. In contrast, brain 2-AG synthesis gradually increases during embryonic development, peaks immediately after birth, and normalizes during postnatal development [29]. Prenatally, EC signaling plays a critical role in stimulating the proliferation of progenitor cells, differentiation of these cells toward both glia and neurons, and myelinogenesis. EC signaling also appears to regulate neural cell migration and is involved in the control of axon elongation and guidance, the establishment of synaptic communication, and the acquisition of specific neurotransmitter phenotypes [30–32].

EC (particularly 2-AG) signaling has mechanistically been implicated in the differentiation of dopaminergic and basal forebrain (cholinergic) and cortical (glutamatergic and GABAergic), cerebellar (GABAergic), and hypothalamic (orexinergic) neurons during late gestational and early-postnatal periods in rodents. Therefore, ECs are important neuromodulators of multiple central neurotransmitter systems that are essential for normal fetal brain development. Studies also indicate that a cross talk between the ECs and other neurotransmitters (acetylcholine, dopamine, and serotonin) is essential for proper embryo development.

In addition to the EC system's role in central nervous system development, other systems (e.g., immune and reproductive systems) also have cannabinoid receptors and produce endocannabinoids which could be altered by prenatal exposure to exogenous cannabinoids (e.g., cannabis or SCB consumption) [33–37]. In rodents, the CB1R is present and functionally active in the preimplantation embryo and in the uterus [38]. ECs modulate several reproductive events from gonadotropin release and sex steroid production to the formation of quality gametes and successful pregnancy. Thus, ECs influence reproductive processes from gametogenesis to fertilization and from embryo implantation to the final outcome of pregnancy. Normal physiological EC levels appear necessary in order to achieve optimal neurophysiological outcomes. It is known, for example, that in order to guarantee a receptive uterine environment, AEA levels must be kept low, and this is attained through a tight regulation mediated by N-acyl-phosphatidylethanolamine-specific phospholipase (NAPE-PLD), the enzyme responsible for AEA synthesis, and fatty acid amide hydrolase (FAAH), in charge of AEA degradation. Significant changes in AEA levels have been detected at the end of pregnancy in maternal blood, suggesting that the endocannabinoid system could modulate physiological functions during pregnancy and labor.

Because pre- and postnatal development is critically regulated by the EC system, there are concerns among clinicians and researchers that disturbing the delicate balance of ECs due to exogenous cannabinoids, such as through parental marijuana or SCB use, could negatively impact reproductive potential and fetal brain growth as well as structural and functional neurodevelopment [9]. Disruptions of the EC system by cannabis use may have many negative consequences for pregnancy outcome, including delayed embryo development, poor blastocyst implantation, miscarriage, and altered placenta formation [39].

An understanding of the molecular pathophysiological events that underlie the alterations in embryonic/fetal development related to cannabis prenatal exposure is just unfolding [40, 41]. However, animal and human studies suggest that perinatal cannabis exposure may disrupt the precise temporal and spatial control of EC signaling at critical stages of neural development, leading to negative effects on later nervous system functioning [42].

Prenatal THC Exposure and Effects on Neurotransmitters

Prenatal exposure to exogenous cannabinoids can modify the maturation of neurotransmitter systems and their related functions through the activation of CB1 receptors that emerge early in the developing brain. Animal studies have revealed alterations of neurotransmitter systems associated with behavioral changes relevant to the human condition after administration of cannabinoids, at doses similar to those found in cannabis users. For example, THC binding to CB1R during gestation alters development of central dopamine and opioid neurotransmitter systems in brain areas regulating reward and motivation, which may increase vulnerability to future drug use and addiction in later life [43, 44]. In addition to evidence from animal studies, postmortem examination of human fetal brains with prenatal cannabis or THC exposure reveals reduced dopamine D2 receptor mRNA in the basal nuclear complex of the amygdala, accompanied by a lesser reduction in the nucleus accumbens. Reduced D2 receptor mRNA was correlated with the amount of maternal marijuana intake and was more prominent in males [43]. This gender-specific imbalance in dopaminergic development might

explain why boys exhibit greater deficits in attention, learning, and memory following in utero marijuana exposure. Moreover, because the amygdala and nucleus accumbens are critical in the development of behavioral and mood disorders, a shift in dopamine receptor expression in these regions following prenatal THC exposure might explain increases in depressive symptoms and impaired social behaviors reported in children upon longitudinal follow-up [45].

Postmortem human studies have also discovered that maternal marijuana use affects fetal expression of opioid-related genes in areas of the brain highly involved in emotional regulation, reward, goal-directed behavior, and motivation [43]. Broadly, opioids influence nociception, motor control, emotions, behavioral reinforcement, and cognition. Altered fetal expression of opioid-related genes can therefore have long-lasting impact on developmental outcomes [44]. Furthermore, alterations in the limbic organization of THC-exposed fetuses, including opioid and dopamine D2 receptor changes in the striatum and amygdala, indicate increased susceptibility for neuropsychiatric impairments in later life.

Prenatal THC Exposure and Neural Circuit Connectivity

During prenatal and postnatal development, CB receptors play a fundamental role in hardwiring the developing brain and contribute postnatally to the regulation of synaptic plasticity throughout the life span [30, 46]. Signaling within the EC system dynamically controls neuronal connectivity during prenatal development in pathways such as the cortico-striatal-thalamic circuitry and several cortical regions involved in addiction and psychiatric disorders [41]. Prenatal cannabis exposure may impact the formation and functions of neuronal circuitries by targeting CB receptors. If EC signaling is significantly altered in the fetus, the loss of particular neurons and glia, cellular redirecting during long-distance migration or interference with synaptogenesis, and disturbed development of neuronal interconnections may lead to subsequent disorder phenotypes [42]. For example, CB1 receptor signaling controls long-range neuronal (e.g., corticofugal, corticospinal) connectivity, and animal studies have shown that prenatal THC resulted in long-lasting alterations in the structure and function of cortical circuitry [46].

Administration of THC to pregnant mice during a demarcated time window disrupts the mouse cortical development, leading to long-term consequences in the fine motor functioning and an increased vulnerability to seizures in the adult offspring [47]. THC exposure may impede the normal development of corticospinal connectivity and increase seizure susceptibility by interfering with CB1R-dependent regulation of both glutamatergic and GABAergic neuron development [47]. This alteration in the corticospinal connectivity is considered to be due to direct impact of THC on the developing embryo, which does not rely on maternal programming and is evident without the need of a secondary insult (e.g., environmental adversity or drug abuse).

Prenatal THC Exposure and Epigenetic Effects

A growing body of evidence suggests that the risk of initiation and progression of a variety of chronic physical and psychiatric diseases depends on epigenetic modifications triggered by environmental signals during early (prenatal or postnatal) life sensitive stages. Epigenetic mechanisms consist of the regulation of gene expression without altering the genetic code. Epigenetic alterations that can regulate gene expression levels consist of DNA methylation, nucleosomal structure and positioning, histone replacement, and small RNA molecules that influence protein production.

Recent studies indicate that cannabis exposure at sensitive periods of development is associated with long-term epigenetic disturbances. The association between prenatal cannabis exposure and addiction vulnerability has been explained, at least in part, by cannabis-induced alterations in the epigenetic regulation of the dopamine D2 receptor (DRD2) gene in the nucleus accumbens. Studies of adult rat brains prenatally exposed to THC showed disturbances in the histone modification profile and decreased D2 receptor mRNA in the nucleus accumbens, which was associated with increased heroin seeking during adulthood [43, 44, 48]. Therefore, cannabis exposure can initiate epigenetic alterations that contribute to long-term disruptions of the D2R in adulthood, predisposing the individual to addiction and other psychiatric disorders [43, 48].

Other evidence exists demonstrating that histone modification plays an important role in the mechanism by which cannabinoids exert immunological effects. Data from various animal models suggests that in utero exposure to cannabinoids results in important T cell dysfunction and a greatly reduced immune response to viral antigens, likely through modifications at the CB2 receptor [49, 50]. Furthermore, evidence from animal studies indicates that the immunosuppressive effects of cannabinoids can be mediated through epigenetic mechanisms such as altered microRNA, DNA methylation, and histone modification profiles. Such studies support the hypothesis that parental or prenatal exposure to cannabis can activate epigenetic changes that could have immunological consequences for offspring as well as long-term transgenerational effects [48, 50–52]. Finally, environmental factors can induce epigenetic alterations in the germ cells that can potentially be transmitted trans-generationally. Germ cells (sperm, oocytes) are also sensitive to cannabinoids, but the exact underlying epigenetic mechanisms remain to be determined [48, 50, 51].

Prenatal Cannabis Exposure and Developmental Effects

Although the relationship between maternal cannabis use during pregnancy and the effects on pregnancy and child outcome is complex, there is increasing evidence from epidemiological and experimental studies suggesting negative effects on the pregnancy and the prenatally exposed individual [53, 54].

The Impact of Cannabis Exposure on the Infant

Cannabis does not appear to produce an increased risk for physical birth defects in exposed infants [54]. Stillbirth [55], shorter gestation lengths, decreased birth weight, and deficits in other growth measures have been reported in some studies [56, 57], although others have shown little to no effect on these birth outcomes [21, 54].

Using the NICU Network Neurobehavioral Scale, a tool to assess infant neurobehavior in at-risk, particularly substance-exposed infants from birth until 1 month of age [58], negative effects of prenatal cannabis exposures indicating neurotoxicity have been reported. These include deficits in visual functioning, tremors, jitteriness, hypotonia, lethargy, and difficulties with arousal and regulation [59, 60]. One Jamaican study found enhanced neurobehavioral functioning; however, possible confounding variables associated with socioeconomic status were reported [61]. Prenatal cannabis exposure has been associated with sleep disturbances during the neonatal period [62] and at 3 years of age [63].

The Impact of Cannabis Exposure on the Developing Child

Evidence for cannabis effects on child growth and development is often difficult to interpret and fraught with confounding factors such as socioeconomic status, psychosocial conditions, and other substance abuse including tobacco use. In longitudinal studies, other confounding factors include genetic vulnerability, parenting and lifestyle issues, economic disadvantage, and stress. However, there are similarities in results of these studies indicating cognitive, behavioral, emotional, and substance use problems in prenatally exposed children and adolescents [64, 65].

Much of the data collected on the effects of prenatal exposure to cannabis come from three longitudinal studies: the Ottawa Prenatal Prospective Study (OPPS) in the 1970s [64, 66], the Maternal Health Practices and Child Development (MHPCD) Study in the 1980s [67–69], and the Generation R (GenR) Study in the early 2000s [70, 71]. The OPPS [59] evaluated a low-risk white middle-class population of 698 pregnant women with 140 selected for follow-up. The use of a low-risk sample that self-reported heavy cannabis use allowed the evaluation of drug effects in relative isolation, without the stressors seen in higher risk populations; but it did not control for nicotine or alcohol exposures. The MHPCD Study [67] followed 564 high-risk, mixed-race pregnant women of low socioeconomic status. The use of a high-risk study group allowed more generalizability of results, but multiple confounders are inherently difficult to fully control for. The GenR Study [70] is a prospective cohort of 9778 multiethnic pregnant women, following 220 who used cannabis during pregnancy, the majority (177) using cannabis only during the first trimester. This study, still in progress, is evaluating the effects of behavior on health including healthcare and maternal determinants for cannabis smoking, and the interplay of factors that can affect both are complex and challenging.

The three studies produced variable results particularly in early childhood development, perhaps due to population differences, differences in dose/potency of THC in the cannabis used, route of administration, and the multiple confounders often affecting child development observations in substance-exposed populations. However, all three noted variable deleterious effects of prenatal cannabis exposure on offspring. Using the Bayley Scales of Infant Development, developmental testing that assesses development in cognitive, language, motor, social-emotional, and adaptive behavior domains, the OPPS found no differences in scores at 12 and 24 months between exposed and non-exposed children, advanced motor skills at 36 months, and lower memory functioning and verbal scores at 48 months in exposed children. At 6 years, exposed children had more impulsivity and hyperactivity, and at 9–12 years, they had impaired visual perceptual functioning [59, 66]. The MHPCD Study [67] found lower Bayley scale scores at 9 months, no differences at 19 months, and lower short-term memory functioning and verbal reasoning in African American participants only at 36 months. At 6 years, cannabis-exposed children overall were more impulsive and hyperactive. The GenR Study found more aggression and inattention for exposed girls only at 18 months, and at 30 and 36 months, no differences between exposed and non-exposed children were observed [70]. However, the literature offers little support for a direct relationship between prenatal or perinatal marijuana exposure and childhood aggression, particularly after accounting for potential confounders.

In opposition to the variability of effects of cannabis on earlier childhood development, prenatal exposure effects for adolescents and young adults have been fairly consistently described. This "unmasking" of earlier deficits [66] with onset of effects during school age or adolescence, especially on executive functioning, may be explained by the theories of "early programming" or the "Developmental Origins of

Health and Disease" [72]. This theory proposes that adverse exposures early in life may reprogram the fetus or infant for immediate adaptation to prenatal and/or neonatal environmental perturbations but enhance the risk of subsequent pathologies. The OPPS found reduced visual perception and increased impulsivity at 9–12 years; decreased concentration, visual memory, and verbal reasoning at 13–16 years; and reduced response inhibition at 18–22 years. The MHPCD Study found diminished abstract and visual reasoning, concentration, internalization, learning and memory, and IQ scores, along with elevated externalization, depression, impulsivity, hyperactivity, and delinquency at 10 years. At 14 years enhanced delinquency persisted, and at 16 years, there was slightly diminished fine motor coordination [73]. The GenR population data for older children has not yet been reported.

Postnatal Cannabis Exposure and Effects on the Developing Child

Maternal Cannabis Use Disorder (CUD)

Acute and chronic effects of cannabis use on the mother are important to consider, as they are likely to affect her ability to care for and develop a relationship with the infant. There are multiple short-term effects of cannabis use that would impact parental care, including impairment of key executive functions such as attention, memory, and decision-making. Impaired judgment, motor coordination, and reaction time have also been associated with impaired driving ability, putting the mother and the unborn/born child or children at risk. In high THC doses, paranoia and psychosis are possible. Some of these impairments have been found to persist after acute intoxication, particularly in chronic users. Effects of long-term or heavy use may include addiction and affiliated behaviors, increased likelihood of depression and anxiety, diminished memory and impaired executive functioning, high-risk sexual behavior, and aggressive behavior during withdrawal [74, 75]. Women with CUD also often have comorbid psychiatric disorders, which may predate cannabis use or result from chronic cannabis abuse.

It is easy to understand how any one of these conditions, or any combination, could harmfully affect the mother's decision-making prior to pregnancy, during pregnancy, or when parenting and could ultimately negatively affect child safety and development. Altered ability to respond appropriately and contingently to infant cues due to periodic changes in consciousness or mood can result in developmental harm, i.e., effects on emerging infant language. Acute effects of THC exposure, combined with risk taking and poor judgment, can result in physical harm to the infant, i.e., inability of the mother to respond appropriately to infant distress. Finally, impairments observed in parenting among women with SUDs may be secondary to the dysregulation of stress and reward-related neural circuits in addiction. The reward-stress dysregulation model of addicted parenting proposes that given anomalous connectivity in brain regions that mediate rewarding vs. stressful cues and experiences, including the nucleus accumbens and amygdala, parenting or caring for a child is less rewarding and more stressful. Women with addiction disorders frequently find normally rewarding infant cues to be stressful, creating a risk for relapse to substance use, which by experience, brings relief from stress [76].

Lactation and the Cannabis-Using Women

As cannabis use in the USA becomes more common, numbers of lactating cannabis-using women and concerns regarding the safety of lactation in cannabis-using women for the child have also increased. There is evidence that chronically cannabis-using women do not decrease use during lactation [77]. Consequently, it is difficult to sort out the effects of postnatal cannabis exposure via breast milk from prenatal exposures, as the two are likely to occur sequentially. It is important to consider that women who use cannabis while breastfeeding are likely to be chronic users who have CUD with reduced control over their use and that postnatal exposures may compound with prenatally acquired deficits. Additionally, there is evidence that lactation care providers are promoting lactation for cannabis users regardless of active or chronic use status 85% of the time [78].

There are several difficulties that face providers when caring for cannabis-using women who desire lactation. The first is unclear and inconsistent guidelines. While AAP and ACOG policies are consistent in advising that cannabis use is contraindicated during breastfeeding [54, 79] as have recommendations from Hale's and LactMed [80, 81], other guidelines have changed to include the possibility of cannabis use during lactation [82, 83]. Current literature includes recommendations for absolute cessation of marijuana use during lactation [84] to continued breastfeeding with concurrent use [85]; however, much of it is based on opinion. Pumping and dumping until maternal toxicology comes back negative for substance use may be prolonged and problematic due to the extended half-life of THC in chronic users [86, 87].

THC readily appears in breastmilk at concentrations up to 7.5 times plasma concentrations and is absorbed and metabolized by the infant [88]; metabolites (e.g., tetrahydrocannabinolic acid) are found in infant stool. THC delivered via lactation to the infant may affect various neurotransmitter systems leading to changes in neurobiological functioning of the infant [24], as described above. Secondhand exposures should also be considered, as THC is present in exhaled breath for 2 h after a single cannabis cigarette, which corresponds to a

newborn feeding schedule. Secondhand exposures may be significant, mimicking active cannabis smoking in extreme circumstances [89].

Studies evaluating effects of cannabis delivered via lactation on infant development are variable. Infant effects including sedation, growth delay, low tone, and poor sucking [90] have been reported. Both effects on motor development [91] and no effects on development [92] have been reported. Infant safety is another concern. Breastfeeding necessarily means that the dyad is in close proximity, and for women with CUD and active cannabis use, this may portend harmful environmental exposure.

Identification and Treatment of Pregnant/Parenting Women with CUD

Based on the effects of cannabis on the mother and concerns about the potential negative effects of maternal marijuana use on the child, there is substantial justification for the implementation of systematic identification and treatment of the mother and child affected by marijuana use. Screening, brief intervention, and referral to treatment are evidence-based approaches to effectively manage substance use disorders.

Optimal identification of CUD and compassionate, nonjudgmental counseling or referral for treatment can have a crucial impact on pregnancy and long-term health outcomes for both the mother and her child. Identifying the pregnant women with a CUD can be difficult. Self-report is the most economic and common method to screen substance use during pregnancy, but maternal interview may be unreliable. In one report evaluating 422 first obstetric visits, 11% of women disclosed any current or past cannabis use, but 27% tested positive for THC. Thirty six percent of the women who were positive for cannabis did not disclose current use [93].

Although disputed by some due to the legal consequences in regions in which marijuana use is banned [94], the American College of Obstetricians and Gynecologists [54] recommends that before pregnancy and during pregnancy, all women should be asked about their use of tobacco, alcohol, and other drugs, including marijuana and other medications used for nonmedical reasons. This committee emphasizes "that the women should be informed that the purpose of screening is to allow treatment of the substance use disorder, not to punish and persecute her. Women need to be informed of the potential consequences of a positive screen, including any mandatory requirements" [54].

Screening tools used in the periconceptional settings are generally questionnaires that are designed to be administered face-to-face by the provider to the woman. They should be administered multiple times during gestation, because patients may be more willing to disclose substance use problems once they develop rapport with a provider [95].

Screening tests can also provide an opportunity to educate the patient. Studies indicate that women frequently use the Internet, social media, friends, or relatives to seek information about marijuana and pregnancy. Pregnant women seeking information regarding gestational cannabis use reported little concrete information from providers [96], and one study showed that the majority (74%) of information delivered was vague and unclear [97]. In another study, nearly half of patients reporting marijuana use during pregnancy received no specific counseling or information, although among those who reported both marijuana and nicotine use, 86% received tobacco counseling [98]. Providers tend to focus more on legal than health risks when counseling pregnant patients and generally believe marijuana to be less harmful than other substances [98]. Consequently, women continue to use cannabis during pregnancy. In one study evaluating 306 surveys of women attending an urban OB clinic, 35% of women reported current use of cannabis and 34% of those women continued to use, with only 27% noting a doctor's recommendation as motivation to quit [99]. Cannabis use in pregnancy is frequently accompanied by the use/abuse of other substances, such as tobacco and alcohol [100].

With changing legal landscapes, the role of the provider in identifying, evaluating, and treating cannabis-using pregnant women has become less clear. There is evidence that providers are more willing to accept cannabis use during pregnancy and lactation [78] largely due to ambiguous information, misperception of risk, lack of training, or scarcity of time or resources to address detected substance use.

Toxicology screening for the determination of drugs and metabolites in maternal and neonatal biological samples offer a more objective and reliable approach; however, there is no good way to understand maternal marijuana use using biomatricies. Neonatal specimens (meconium, cord, and urine) directly reflect fetal exposure to drugs during pregnancy. Urine toxicology testing is most commonly used; however, THC can remain positive in urine drug screens for long periods of time after cessation of use in chronic users. Meconium and umbilical cord testing can detect use during the second and third trimesters but does not differentiate patterns of abstinence closer to delivery and as such are matrices of limited use when evaluating women in substance use disorder treatment. Meconium passage may be delayed up to 5 days after birth, and if passed before birth, drug testing cannot be performed. Newborn toxicology screening primarily focuses on identifying families at risk of ongoing drug use, to address child protection concerns that may be associated with parental drug use and to provide appropriate treatment for suspected cases of withdrawal or intoxication. Synthetic cannabinoids, which are more psychoactive than

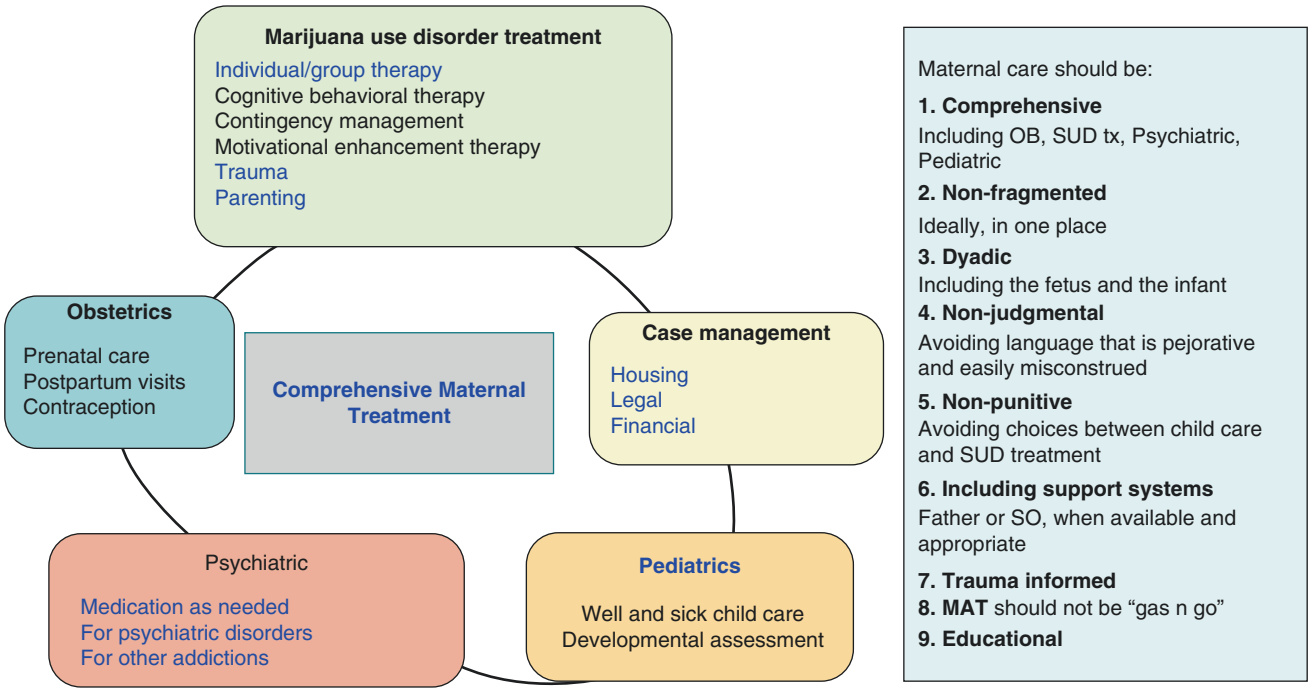

Fig. 17.3 A model of comprehensive treatment for the pregnant woman with a cannabis use disorder

cannabis, are currently non-detectable in standard urine toxicological tests now available.

Achieving abstinence in the treatment of CUD is difficult, and it should be recognized that complete cessation or abstinence of cannabis use is not possible for many women. It has been reported that most marijuana users seeking treatment had multiple quit attempts and perceived themselves as unable to stop [101]. Nevertheless, early detection of a CUD during pregnancy can initiate ongoing support and may produce potentially valuable lifestyle changes that go beyond the perinatal period. It is advised that all pregnant women should be offered screening and support for cessation and relapse prevention at each antenatal visit throughout pregnancy.

Regular users of cannabis may be offered a range of alternate interventions including information, brief intervention, counseling, and psychologically based treatment for cannabis dependency. Pregnant women who are regular users of cannabis or have a CUD should be referred for comprehensive substance use disorder treatment. The proportion of admissions to substance use treatment facilities for pregnant women reporting any cannabis use, in addition to the proportion of admissions for pregnant women reporting cannabis use as a primary substance, has increased dramatically in the last two decades [102].

To date the most successful treatments for CUD have included combinations of motivation enhancement treatment (MET) plus cognitive-behavioral coping skills training (CBT) and/or contingency management (ContM) approaches [75, 103]. In addition to the CUD treatment, the mother will need obstetric and gynecologic care including contraception post-pregnancy, psychiatric evaluation/treatment (if warranted), pediatric care for all children, and referral to necessary services such as housing, legal assistance, trauma-related treatment, etc. (Fig. 17.3).

The CUD intervention should be comprehensive, supportive, and nonjudgmental. Asking the woman to comment on her perceived level of severity may allow for more open discussion of other important problem areas and high-risk situations, which will subsequently allow for the development of strategies for change, including coping with cravings, and goal setting. Treating mental health disorders with standard treatments involving medications and behavioral therapies may help reduce or eliminate cannabis use, particularly among those involved with heavy use and those with chronic mental health disorders. Finally, knowledgeable pediatric care that includes close developmental follow-up and attention to maternal substance use and its effects on parenting and child development should be instituted for all cannabis-exposed children.

Summary

Marijuana use and CUD are common among pregnant and lactating women in the USA. There are several identified mechanisms of potential harm resulting from THC exposure

to the fetus and developing child, and the acute and long-term effects of prenatal THC exposure to child development have been described. It is recommended to minimally advise the cessation of marijuana use for all pregnant and lactating women and to further advise women caring for developing children to continue abstinence. Failing to seek out or to address the problems associated with marijuana use by pregnant and postpartum women when they are identified, regardless of its legal status, is missing an opportunity for intervention for a woman needing treatment, a child at risk for neurobiological and developmental problems, or a dyad at risk for negative outcomes associated with an untreated maternal substance use disorder. Healthcare providers should have training and resources available to be able to screen, identify, and provide readily available and comprehensive treatment for women with CUD in the perinatal period. Additionally, providers should have access to interpretable guidelines based on empirically derived evidence and be able to present a balanced and informed risk assessment to pre-pregnant, pregnant, and postpartum women, with available treatment options for women who may have difficulty abstaining from use.

References

1. Brown QL, Sarvet AL, Shmulewitz D, Martins SS, Wall MM, Hasin DS. Trends in marijuana use among pregnant and nonpregnant reproductive-aged women, 2002-2014. JAMA. 2017;317(2):207–9.
2. McCabe JE, Arndt S. Demographic and substance abuse trends among pregnant and non-pregnant women: eleven years of treatment admission data. Matern Child Health J. 2012;16(8):1696–702.
3. Beatty JR, Svikis DS, Ondersma SJ. Prevalence and perceived financial costs of marijuana versus tobacco use among urban low-income pregnant women. J Addict Res Ther. 2012;3(4)
4. Johnston LDOMP, Bachman JG, Schulenberg JE. Monitoring the future National Results on adolescent drug use: overview of key findings, 2011. Ann Arbor: Institute for Social Research, The University of Michigan; 2012.
5. Hayatbakhsh MR, Flenady VJ, Gibbons KS, Kingsbury AM, Hurrion E, Mamun AA, et al. Birth outcomes associated with cannabis use before and during pregnancy. Pediatr Res. 2012;71(2):215–9.
6. Substance Abuse and Mental Health Services Administration (SAMHSA). Results from the 2012 national survey on drug use and health: summary of national findings, NSDUH series H-46, HHS publication no. (SMA) 13–4798. Rockville; 2013.
7. Ko JY, Farr SL, Tong VT, Creanga AA, Callaghan WM. Prevalence and patterns of marijuana use among pregnant and nonpregnant women of reproductive age. Am J Obstet Gynecol. 2015;213(2):201.e1–e10.
8. Warner TD, Roussos-Ross D, Behnke M. It's not your mother's marijuana: effects on maternal-fetal health and the developing child. Clin Perinatol. 2014;41(4):877–94.
9. Volkow ND, Han B, Compton WM, Blanco C. Marijuana use during stages of pregnancy in the United States. Ann Intern Med. 2017;166(10):763–4.
10. ElSohly MA, Mehmedic Z, Foster S, Gon C, Chandra S, Church JC. Changes in Cannabis potency over the last 2 decades (1995-2014): analysis of current data in the United States. Biol Psychiatry. 2016;79(7):613–9.
11. Calvigioni D, Hurd YL, Harkany T, Keimpema E. Neuronal substrates and functional consequences of prenatal cannabis exposure. Eur Child Adolesc Psychiatry. 2014;23(10):931–41.
12. Jones JTBA, Shu I. A comparison of meconium screening outcomes as an indicator of the impact of state-level relaxation of marijuana policy. Drug Alcohol Depend. 2015;156:e104–5.
13. Murray RM, Quigley H, Quattrone D, Englund A, Di Forti M. Traditional marijuana, high-potency cannabis and synthetic cannabinoids: increasing risk for psychosis. World Psychiatry. 2016;15(3):195–204.
14. ElSohly M. Potency monitoring program quarterly report no.123 — reporting period: 09/16/2013–12/15/2013. Oxford: University of Mississippi, National Center for Natural Products Research; 2014.
15. Choi H, Heo S, Choe S, Yang W, Park Y, Kim E, et al. Simultaneous analysis of synthetic cannabinoids in the materials seized during drug trafficking using GC-MS. Anal Bioanal Chem 2013;405(12):3937–3944.
16. Psychoyos D, Vinod KY. Marijuana, spice 'herbal high', and early neural development: implications for rescheduling and legalization. Drug Test Anal. 2013;5(1):27–45.
17. Ustundag MF, Ozhan Ibis E, Yucel A, Ozcan H. Synthetic cannabis-induced mania. Case Rep Psychiatry. 2015;2015:310930.
18. Gilbert MT, Sulik KK, Fish EW, Baker LK, Dehart DB, Parnell SE. Dose-dependent teratogenicity of the synthetic cannabinoid CP-55,940 in mice. Neurotoxicol Teratol. 2016;58:15–22.
19. Volkow ND, Compton WM, Wargo EM. The risks of marijuana use during pregnancy. JAMA. 2017;317(2):129–30.
20. 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):283–7.
21. Grant KS, Petroff R, Isoherranen N, Stella N, Burbacher TM. Cannabis use during pregnancy: pharmacokinetics and effects on child development. Pharmacol Ther. 2017;
22. Hutchings DE, Martin BR, Gamagaris Z, Miller N, Fico T. Plasma concentrations of delta-9-tetrahydrocannabinol in dams and fetuses following acute or multiple prenatal dosing in rats. Life Sci. 1989;44(11):697–701.
23. Blackard C, Tennes K. Human placental transfer of cannabinoids. N Engl J Med. 1984;311(12):797.
24. Fernandez-Ruiz J, Berrendero F, Hernandez ML, Ramos JA. The endogenous cannabinoid system and brain development. Trends Neurosci. 2000;23(1):14–20.
25. Jutras-Aswad D, DiNieri JA, Harkany T, Hurd YL. Neurobiological consequences of maternal cannabis on human fetal development and its neuropsychiatric outcome. Eur Arch Psychiatry Clin Neurosci. 2009;259(7):395–412.
26. Biegon A, Kerman IA. Autoradiographic study of pre- and postnatal distribution of cannabinoid receptors in human brain. NeuroImage. 2001;14(6):1463–8.
27. Mato S, Del Olmo E, Pazos A. Ontogenetic development of cannabinoid receptor expression and signal transduction functionality in the human brain. Eur J Neurosci. 2003;17(9):1747–54.
28. Wang X, Dow-Edwards D, Keller E, Hurd YL. Preferential limbic expression of the cannabinoid receptor mRNA in the human fetal brain. Neuroscience. 2003;118(3):681–94.
29. Friedrich J, Khatib D, Parsa K, Santopietro A, Gallicano GI. The grass isn't always greener: the effects of cannabis on embryological development. BMC Pharmacol Toxicol. 2016;17(1):45.
30. Berghuis P, Rajnicek AM, Morozov YM, Ross RA, Mulder J, Urban GM, et al. Hardwiring the brain: endocannabinoids shape neuronal connectivity. Science 2007;316(5828):1212–1216.

31. Bernard C, Milh M, Morozov YM, Ben-Ari Y, Freund TF, Gozlan H. Altering cannabinoid signaling during development disrupts neuronal activity. Proc Natl Acad Sci U S A. 2005;102(26):9388–93.
32. Watson S, Chambers D, Hobbs C, Doherty P, Graham A. The endocannabinoid receptor, CB1, is required for normal axonal growth and fasciculation. Mol Cell Neurosci. 2008;38(1):89–97.
33. Nagarkatti P, Pandey R, Rieder SA, Hegde VL, Nagarkatti M. Cannabinoids as novel anti-inflammatory drugs. Future Med Chem. 2009;1(7):1333–49.
34. Smita K, Sushil Kumar V, Premendran JS. Anandamide: an update. Fundam Clin Pharmacol. 2007;21(1):1–8.
35. Sido JM, Nagarkatti PS, Nagarkatti M. Role of endocannabinoid activation of peripheral CB1 receptors in the regulation of autoimmune disease. Int Rev Immunol. 2015;34(5):403–14.
36. Pandey R, Mousawy K, Nagarkatti M, Nagarkatti P. Endocannabinoids and immune regulation. Pharmacol Res. 2009;60(2):85–92.
37. Rieder SA, Chauhan A, Singh U, Nagarkatti M, Nagarkatti P. Cannabinoid-induced apoptosis in immune cells as a pathway to immunosuppression. Immunobiology. 2010;215(8):598–605.
38. Paria BC, Dey SK. Ligand-receptor signaling with endocannabinoids in preimplantation embryo development and implantation. Chem Phys Lipids. 2000;108(1–2):211–20.
39. Correa F, Wolfson ML, Valchi P, Aisemberg J, Franchi AM. Endocannabinoid system and pregnancy. Reproduction. 2016;152(6):R191–200.
40. Harkany T, Keimpema E, Barabas K, Mulder J. Endocannabinoid functions controlling neuronal specification during brain development. Mol Cell Endocrinol. 2008;286(1–2 Suppl 1):S84–90.
41. Morris CV, DiNieri JA, Szutorisz H, Hurd YL. Molecular mechanisms of maternal cannabis and cigarette use on human neurodevelopment. Eur J Neurosci. 2011;34(10):1574–83.
42. Keimpema E, Mackie K, Harkany T. Molecular model of cannabis sensitivity in developing neuronal circuits. Trends Pharmacol Sci. 2011;32(9):551–61.
43. DiNieri JA, Wang X, Szutorisz H, Spano SM, Kaur J, Casaccia P, et al. Maternal cannabis use alters ventral striatal dopamine D2 gene regulation in the offspring. Biol Psychiatry 2011;70(8):763–769.
44. Spano MS, Ellgren M, Wang X, Hurd YL. Prenatal cannabis exposure increases heroin seeking with allostatic changes in limbic enkephalin systems in adulthood. Biol Psychiatry. 2007;61(4):554–63.
45. Wu CS, Jew CP, Lu HC. Lasting impacts of prenatal cannabis exposure and the role of endogenous cannabinoids in the developing brain. Future Neurol. 2011;6(4):459–80.
46. Tortoriello G, Morris CV, Alpar A, Fuzik J, Shirran SL, Calvigioni D, et al. Miswiring the brain: Delta9-tetrahydrocannabinol disrupts cortical development by inducing an SCG10/stathmin-2 degradation pathway. EMBO J 2014;33(7):668–685.
47. de Salas-Quiroga A, Diaz-Alonso J, Garcia-Rincon D, Remmers F, Vega D, Gomez-Canas M, et al. Prenatal exposure to cannabinoids evokes long-lasting functional alterations by targeting CB1 receptors on developing cortical neurons. Proc Natl Acad Sci U S A 2015;112(44):13693–13698.
48. Szutorisz H, DiNieri JA, Sweet E, Egervari G, Michaelides M, Carter JM, et al. Parental THC exposure leads to compulsive heroin-seeking and altered striatal synaptic plasticity in the subsequent generation. Neuropsychopharmacology 2014;39(6):1315–1323.
49. Olah A, Szekanecz Z, Biro T. Targeting cannabinoid signaling in the immune system: "high"-ly exciting questions, possibilities, and challenges. Front Immunol. 2017;8:1487.
50. Zumbrun EE, Sido JM, Nagarkatti PS, Nagarkatti M. Epigenetic regulation of immunological alterations following prenatal exposure to marijuana cannabinoids and its long term consequences in offspring. J Neuroimmune Pharmacol. 2015;10(2):245–54.
51. Szutorisz H, Hurd YL. Epigenetic effects of Cannabis exposure. Biol Psychiatry. 2016;79(7):586–94.
52. Murphy LL, Gher J, Szary A. Effects of prenatal exposure to delta-9-tetrahydrocannabinol on reproductive, endocrine and immune parameters of male and female rat offspring. Endocrine. 1995;3(12):875–9.
53. Chasnoff IJ. Medical marijuana laws and pregnancy: implications for public health policy. Am J Obstet Gynecol. 2017;216(1):27–30.
54. Braillon A, Bewley S. Committee opinion no. 722: marijuana use during pregnancy and lactation. Obstet Gynecol. 2018;131(1):164.
55. Varner MW, Silver RM, Rowland Hogue CJ, Willinger M, Parker CB, Thorsten VR, et al. Association between stillbirth and illicit drug use and smoking during pregnancy. Obstet Gynecol 2014;123(1):113–125.
56. Gunn JK, Rosales CB, Center KE, Nunez A, Gibson SJ, Christ C, et al. Prenatal exposure to cannabis and maternal and child health outcomes: a systematic review and meta-analysis. BMJ Open 2016;6(4):e009986.
57. 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(12):991–5.
58. Lester BM, Tronick EZ, Brazelton TB. The neonatal intensive care unit network neurobehavioral scale procedures. Pediatrics. 2004;113(3 Pt 2):641–67.
59. Fried PA. Marihuana use by pregnant women: neurobehavioral effects in neonates. Drug Alcohol Depend. 1980;6(6):415–24.
60. de Moraes Barros MC, Guinsburg R, de Araujo Peres C, Mitsuhiro S, Chalem E, Laranjeira RR. Exposure to marijuana during pregnancy alters neurobehavior in the early neonatal period. J Pediatr. 2006;149(6):781–7.
61. Dreher MC, Nugent K, Hudgins R. Prenatal marijuana exposure and neonatal outcomes in Jamaica: an ethnographic study. Pediatrics. 1994;93(2):254–60.
62. Scher MS, Richardson GA, Coble PA, Day NL, Stoffer DS. The effects of prenatal alcohol and marijuana exposure: disturbances in neonatal sleep cycling and arousal. Pediatr Res. 1988;24(1):101–5.
63. Dahl RE, Scher MS, Williamson DE, Robles N, Day N. A longitudinal study of prenatal marijuana use. Effects on sleep and arousal at age 3 years. Arch Pediatr Adolesc Med. 1995;149(2):145–50.
64. Fried PA. Marihuana use by pregnant women and effects on offspring: an update. Neurobehav Toxicol Teratol. 1982;4(4):451–4.
65. Huizink AC, Mulder EJ. Maternal smoking, drinking or cannabis use during pregnancy and neurobehavioral and cognitive functioning in human offspring. Neurosci Biobehav Rev. 2006;30(1):24–41.
66. Fried PA. Adolescents prenatally exposed to marijuana: examination of facets of complex behaviors and comparisons with the influence of in utero cigarettes. J Clin Pharmacol. 2002;42(11 Suppl):97S–102S.
67. Day NL, Richardson GA. Prenatal marijuana use: epidemiology, methodologic issues, and infant outcome. Clin Perinatol. 1991;18(1):77–91.
68. Day NL, Richardson GA, Goldschmidt L, Robles N, Taylor PM, Stoffer DS, et al. Effect of prenatal marijuana exposure on the cognitive development of offspring at age three. Neurotoxicol Teratol 1994;16(2):169–175.
69. Goldschmidt L, Richardson GA, Cornelius MD, Day NL. Prenatal marijuana and alcohol exposure and academic achievement at age 10. Neurotoxicol Teratol. 2004;26(4):521–32.
70. Hofman A, Jaddoe VW, Mackenbach JP, Moll HA, Snijders RF, Steegers EA, et al. Growth, development and health from early fetal life until young adulthood: the generation R study. Paediatr Perinat Epidemiol 2004;18(1):61–72.
71. El Marroun H, Tiemeier H, Steegers EA, Jaddoe VW, Hofman A, Verhulst FC, et al. Intrauterine cannabis exposure affects fetal

growth trajectories: the generation R study. J Am Acad Child Adolesc Psychiatry 2009;48(12):1173–1181.
72. Barker DJ. In utero programming of chronic disease. Clin Sci (Lond). 1998;95(2):115–28.
73. McLemore GL, Richardson KA. Data from three prospective longitudinal human cohorts of prenatal marijuana exposure and offspring outcomes from the fetal period through young adulthood. Data Brief 2016;9:753–757.
74. Volkow ND, Compton WM, Weiss SR. Adverse health effects of marijuana use. N Engl J Med. 2014;371(9):879.
75. Litt MD, Kadden RM, Petry NM. Behavioral treatment for marijuana dependence: randomized trial of contingency management and self-efficacy enhancement. Addict Behav. 2013;38(3):1764–75.
76. Rutherford HJ, Williams SK, Moy S, Mayes LC, Johns JM. Disruption of maternal parenting circuitry by addictive process: rewiring of reward and stress systems. Front Psych. 2011;2:37.
77. Demont-Heinrich C BJ, editor. Marijuana use among WIC clients: a survey following legalization of recreational marijuana in Colorado. Council of State and Territorial Epidemiologists (CSTE) conference; 2015.
78. Bergeria CL, Heil SH. Surveying lactation professionals regarding marijuana use and breastfeeding. Breastfeed Med. 2015;10(7):377–80.
79. American Academy of Pediatrics (AAP). American Academy of Pediatrics Reaffirms Opposition to Legalizing Marijuana for Recreational or Medical Use 2018. Available from: https://www.aap.org/en-us/about-the-aap/aap-press-room/pages/American-Academy-of-Pediatrics-Reaffirms-Opposition-to-Legalizing-Marijuana-for-Recreational-or-Medical-Use.aspx.
80. Hale TWRH. Medications and Mother's milk. 16th ed. Plano: Hale Publishing; 2014.
81. LactMed. LactMed: A ToxNet database. In: National Institutes of Health. Bethesda: US National Library of Medicine; 2015.
82. Jansson LM. Academy of breastfeeding medicine protocol (ABM) clinical protocol #21: guidelines for breastfeeding and the drug-dependent woman. Breastfeed Med. 2009;4(4):225–8.
83. Reece-Stremtan S, Marinelli KA. Academy of breastfeeding medicine (ABM) clinical protocol #21: guidelines for breastfeeding and substance use or substance use disorder, revised 2015. Breastfeed Med. 2015;10(3):135–41.
84. Garry A, Rigourd V, Amirouche A, Fauroux V, Aubry S, Serreau R. Cannabis and breastfeeding. J Toxicol. 2009;2009:596149.
85. Hill M, Reed K. Pregnancy, breast-feeding, and marijuana: a review article. Obstet Gynecol Surv. 2013;68(10):710–8.
86. Lowe RH, Abraham TT, Darwin WD, Herning R, Cadet JL, Huestis MA. Extended urinary Delta9-tetrahydrocannabinol excretion in chronic cannabis users precludes use as a biomarker of new drug exposure. Drug Alcohol Depend. 2009;105(1–2):24–32.
87. Kelly P, Jones RT. Metabolism of tetrahydrocannabinol in frequent and infrequent marijuana users. J Anal Toxicol. 1992;16(4):228–35.
88. Perez-Reyes M, Wall ME. Presence of delta9-tetrahydrocannabinol in human milk. N Engl J Med. 1982;307(13):819–20.
89. Cone EJ, Bigelow GE, Herrmann ES, Mitchell JM, LoDico C, Flegel R, et al. Nonsmoker exposure to secondhand Cannabis smoke. III. Oral fluid and blood drug concentrations and corresponding subjective effects. J Anal Toxicol 2015;39(7):497–509.
90. Liston J. Breastfeeding and the use of recreational drugs--alcohol, caffeine, nicotine and marijuana. Breastfeed Rev. 1998;6(2):27–30.
91. Astley SJ, Little RE. Maternal marijuana use during lactation and infant development at one year. Neurotoxicol Teratol. 1990;12(2):161–8.
92. Tennes K, Avitable N, Blackard C, Boyles C, Hassoun B, Holmes L, et al. Marijuana: prenatal and postnatal exposure in the human. NIDA Res Monogr 1985;59:48–60.
93. Chang JC, Holland CL, Tarr JA, Rubio D, Rodriguez KL, Kraemer KL, et al. Perinatal Illicit Drug and Marijuana Use. Am J Health Promot 2017;31(1):35–42.
94. Stadterman JM, Hart CL. Screening women for marijuana use does more harm than good. Am J Obstet Gynecol. 2015;213(4):598–9.
95. Colorado Department of Health. Marijuana Pregnancy and Breastfeeding Guidance 2017. Available from: www.colorado.gov/pacific/sites/default/files/MJ_RMEP_Pregnancy-Breastfeeding-Clinical-Guidelines.pdf.
96. Jarlenski M, Tarr JA, Holland CL, Farrell D, Chang JC. Pregnant Women's access to information about perinatal marijuana use: a qualitative study. Womens Health Issues. 2016;26(4):452–9.
97. Holland CL, Rubio D, Rodriguez KL, Kraemer KL, Day N, Arnold RM, et al. Obstetric health care Providers' counseling responses to pregnant patient disclosures of marijuana use. Obstet Gynecol 2016;127(4):681–687.
98. Holland CL, Nkumsah MA, Morrison P, Tarr JA, Rubio D, Rodriguez KL, et al. "Anything above marijuana takes priority": obstetric providers' attitudes and counseling strategies regarding perinatal marijuana use. Patient Educ Couns. 2016;99(9):1446–51.
99. Mark K, Gryczynski J, Axenfeld E, Schwartz RP, Terplan M. Pregnant Women's current and intended Cannabis use in relation to their views toward legalization and knowledge of potential harm. J Addict Med. 2017;11(3):211–6.
100. Jaques SC, Kingsbury A, Henshcke P, Chomchai C, Clews S, Falconer J, et al. Cannabis, the pregnant woman and her child: weeding out the myths. J Perinatol 2014;34(6):417–424.
101. Budney AJ, Roffman R, Stephens RS, Walker D. Marijuana dependence and its treatment. Addict Sci Clin Pract. 2007;4(1):4–16.
102. Martin CE, Longinaker N, Mark K, Chisolm MS, Terplan M. Recent trends in treatment admissions for marijuana use during pregnancy. J Addict Med. 2015;9(2):99–104.
103. Litt MD, Kadden RM, Kabela-Cormier E, Petry NM. Coping skills training and contingency management treatments for marijuana dependence: exploring mechanisms of behavior change. Addiction. 2008;103(4):638–48.