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# The Effects of Prenatal Exposure to Marijuana on Early Childhood Development: A Systematic Literature Review

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## ABSTRACT

To assess the effect of prenatal marijuana exposure (PME) on the newborn, infant and early childhood development through review of current literature. A systematic literature review was conducted in the electronic database from 1996 to 2017 for the effects of PME and their fetal and early childhood outcomes. 7% of pregnant women self-reported using marijuana in the last year, while 16% of them reported near-daily use. Marijuana use has been reported to: a) interfere with normal placentation leading to miscarriage, preeclampsia and preterm labor through imbalance in Cannabinoid receptor type 1 (CBR1) stimulation; b) could lead to reduction of fetal growth and head circumference due to increased plasticity and resistance of uterine artery; c) be associated with impaired memory function, decreased verbal scores, increased aggression and hyperactivity, impaired abstract and visual reasoning; and d) could alter sleep patterns. Finally, there is no consensus regarding the effects of marijuana through breastfeeding exposure and no postpartum withdrawal effects in the newborn were reported. Research on the effects of PME on offspring has been limited by several confounding factors including self-reporting bias, concomitant use of other illicit drugs and psychosocial factors. Overall, PME may lead to negative consequences on the developing offspring. Public health messages to health care providers and pregnant women regarding the harmfulness of PME should become a high priority. Further research is needed to reinforce the existing data and examine additional potential negative effects on the developing child.

**Key words:** cannabis exposure; pregnancy; early childhood

Dramatic reductions in perceived harmfulness of cannabis as well as its increased availability have made it a widely used psychoactive substance (Patrick et al., 2016; Warner et al., 2014). The cannabis legalization debate continues worldwide, while various legislative enactments of new regulations proceed. New types of cannabis with increased potency of its psychoactive component tetra hydro cannabinol (THC) as well as advanced cannabis delivery devices (e.g., E-cigarettes vaping, JUUL) emerge rapidly (Warner et al., 2014). At this juncture the need to attend to

the risks and negative health consequences related to cannabis use is arguably more important than ever.

An important subpopulation of marijuana users are pregnant women where use has been growing during the last decade (Jarlenski et al., 2017). Although marijuana has been the most commonly used illicit drug during pregnancy, the effect of prenatal marijuana exposure (PME) on the offspring has been understudied. A cross sectional study report based on self-report states that seven percent of pregnant women used

marijuana during the last year (Ko et al., 2015). Sixteen percent of them reported near daily use. A recent study reported that the prevalence rate of marijuana during pregnancy when studied by age was, 16.2% for those aged 15 to 17, 7.4% for those aged 18-25 and 1.9% for those ages 26 to 44 (Calvigioni et al., 2014). Notably, 48–60% of the women continued to use during pregnancy, believing that it is relatively safe to use (Committee opinion no. 637, 2015). The proportion of treatment admissions for women who were pregnant remained stable at 4%, however the admissions of pregnant women reporting marijuana use increased substantially from 29% to 43% (Martin et al., 2015). This alarming increase in use could be attributed to the continued trend of reduction in the perception of harm caused by cannabis use as well as increased access to marijuana (Ko et al., 2015). Furthermore, these changes in perception of harmfulness and increased availability of marijuana are related to the increase in number of states that have legalized marijuana for medicinal or recreational purposes. For example, the most recent data provided by the state of Colorado where cannabis use is legal shows a high use of 12.8% among pregnant women between the ages of 15-24 years (Gosh et al., 2017). A growing concern for marijuana use in pregnancy has been its consumption for anti-emetic effects. A clinical retroactive self-assessment survey of marijuana use in “hyperemesis gravidarum” was conducted in Canada. 75% of the respondents reported that marijuana was ‘extremely effective’ as a therapy for nausea during pregnancy.

The objective of this review is to critically appraise and summarize the literature on the impact of prenatal marijuana exposure on fetal, infant and early childhood development. We recognize that there are some methodological confounds that challenge finding reported on the psychological and neurobiological consequences in exposed offspring. It includes recall and self-reporting bias by pregnant women; co-consumption of other drugs like opioids (12%), stimulants (10%), alcohol (4%) or cigarettes (Burns et al., 2006; Godding et al., 2006) which may have independent effect on the growing fetus. Also adverse socioeconomic like poverty, malnutrition, lower levels of education, lower household income, less likely use of folic acid supplementation may have additional risk on

adverse pregnancy outcome conditions (Van Gelder et al., 2010). Nevertheless, it is imperative from a public health perspective to assess, understand, and disseminate the present findings regarding the harmfulness of perinatal exposure to cannabis to the public in general and to healthcare providers and pregnant women in particular.

## METHOD

A systematic review of the literature was performed using PubMed and Scopus database for relevant articles between 1996 to 2017 for the effects of prenatal marijuana exposure and their fetal and childhood outcomes through 3 years of age. Broad range of keywords that focused on cannabis or marijuana and prenatal or perinatal or fetal or neonatal or early childhood and outcomes were used to search each data base. Studies that included review articles, randomized controlled trials (RCT), case control studies and cross-sectional studies were searched. After carefully reviewing 133 article titles and abstracts, 42 articles were excluded due to duplication or their irrelevance to the selection criteria. 91 articles were included in this review (see Figure 1).

## RESULTS AND DISCUSSION

### *Marijuana Use and Its Generally Known Negative Consequences*

The potency of marijuana has substantially increased in the past 40 years in the United States (McLaren et al., 2008). The psychoactive potency of marijuana is measured by the percentage of the THC content. THC is a small and highly lipophilic molecule, it is rapidly distributed to the brain and fatty tissues and it freely crosses placenta (Hutchings et al., 1989). The mean concentration of THC has increased from 4% to 12% in the last 20 years (El Sohly et al., 2016). It was reported that in Colorado’s legal bud, the average concentration of THC is 18.7% and some retail pot contains 30% THC or more (Briggs, 2015). This trend of increased THC concentration is likely to continue. There is also an increase in the amount of marijuana consumed due to the growing popularity of blunts (marijuana filled cigars) compared to joints and pipes (Warner et al., 2014).

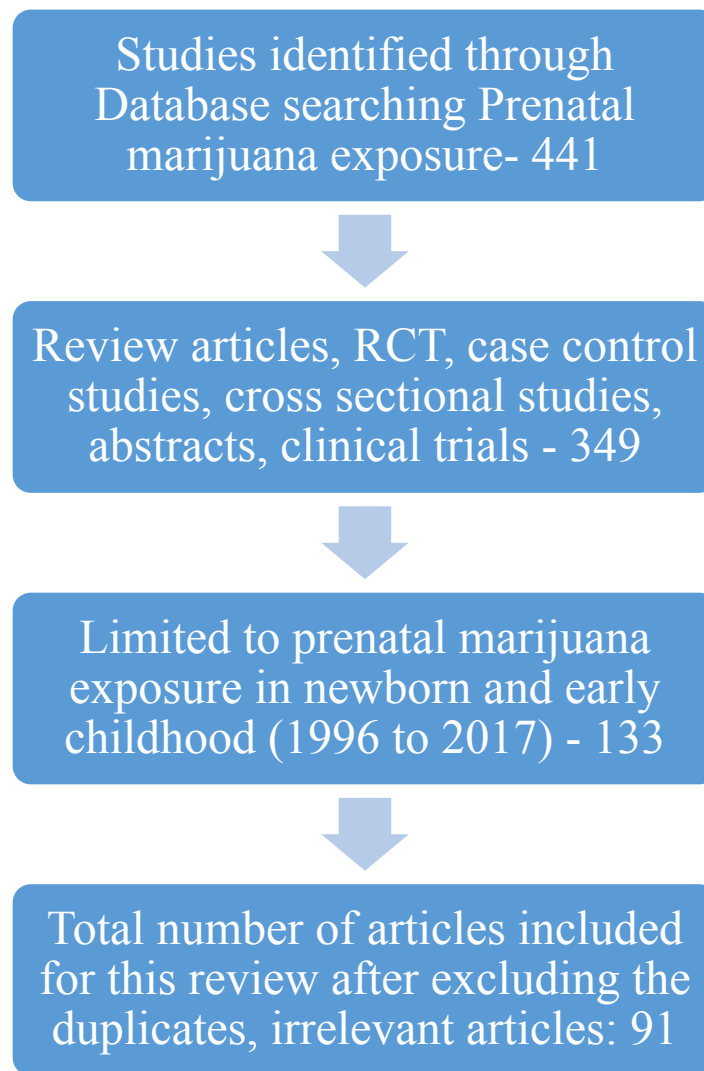


Figure 1. Explains the Selection Process of Relevant Articles on Prenatal Marijuana Exposure and the Effect on Offspring

The blunt has greater amount of marijuana – up to 1.5 times more than joints and 2.5 times more than pipes (Mariani, 2011). Not only there are different ways to consume marijuana including smoking, vaporization, dabbing (i.e., vaporizing concentrated marijuana), edibles, topical applications etc., there are different delivery systems including e-cigarettes, dab, bongs (i.e., specialized waterline with large chamber where smoke is suspended prior to its release) or needle which attracts anyone including pregnant women to consume marijuana (Gosh, 2017).

Although difficult to demonstrate causality, research across multiple domains highlights the short- and long-term deleterious effects associated

with cannabis use. Early age of use initiation has been associated with increased risk for early onset psychosis in adolescents (Bagot et al., 2015). Regular cannabis use is associated with poorer academic performance and greater likelihood of dropping out of high school, increased family conflict, increased probability of high-risk behaviors including intoxicated driving, legal problems, unprotected sex, and higher health-care costs (Ammerman et al., 2015).

#### *Endocannabinoid System During Prenatal and Postnatal Development*

The endocannabinoid system (ECS) is a group of endogenous cannabinoid receptors located in

mammalian brain and throughout the central and peripheral nervous system. Among the cannabinoid receptors, the CBR1 plays a major role in normal brain development and neurotransmitter system including neuronal proliferation, migration, differentiation, and survival (Campolongo et al., 2011). CBR1 regulates the neural progenitor differentiation into neurons and glia and guides axonal migration and synaptogenesis (Fride, 2008). This receptor is exhibited in the human fetus and the placenta as early as 14 weeks of gestation with increasing receptor density with advancing gestational age (Wilford, 2010). Manipulating the ECS by pre and post-natal administration of cannabinoids through maternal external marijuana exposure has significant effects on the offspring (Fride, 1999).

### *Prenatal Marijuana Exposure*

As the THC freely crosses placenta, the fetal plasma THC levels are 10% of maternal level and it significantly increases after repeated exposure (Hutchings et al., 1989). This explains why the prenatal marijuana exposure affects the growing fetus. A national survey conducted in 2012 by the Substance Abuse and Mental Health Services Administration reported marijuana abuse in each trimester and concluded that its prevalence is higher during the first trimester (10.7%) as compared to 2.8% and 2.3% in second and third trimester respectively (Substance Abuse and Mental Health Services Administration, 2013). This is because many women report cessation of marijuana use on discovery of pregnancy by the end of the first or early second trimester.

### *Effect on Pregnancy and Implantation*

Both animal and human studies (Sun et al., 2010; Fonseca et al., 2013) found that the stimulation of CBR1 receptor by exogenous cannabinoids like THC causes disruption in trophoblast proliferation and differentiation thereby inhibiting successful placentation. This leads to several pregnancy related complications like miscarriage, pre-eclampsia, growth restriction and preterm labor (Fonseca et al., 2013). Marijuana use in pregnancy is associated with increased fetal pulsatility index and increased uterine artery resistance index

suggestive of increased placental resistance (El Morroun et al., 2010; Behnke et al., 2013). This provides a partial explanation for intra uterine growth retardation.

### *Effect on Growing Fetus*

Marijuana use in pregnancy affects the fetal growth (Hurd, 2005). This study examined fetal weight and height on elective mid gestational aborted fetus (17-22 weeks) who were exposed to marijuana, tobacco and alcohol and showed decrease in both weight (by 14.53gm) and foot length (by 0.08cm). Moreover, fetal foot length development was negatively correlated with the amount and frequency of marijuana use reported by the mothers.

### *Effect on Head Circumference in Neonates*

A longitudinal study on the growth parameters found that cannabis-exposed children have statistically significant smaller head circumferences at birth (Fried et al., 2011). It should be noted that the head growth especially in first month of life is significantly associated with future intelligence quotient (Smithers et al., 2013).

### *Effect on Neonatal Withdrawal and Sleep*

Neonatal withdrawal including irritability, anxiety, and restlessness from prenatal marijuana exposure alone has not been reported in any of the prospective, longitudinal studies in our search domain. There are studies addressing sleep changes in newborns attributed to prenatal marijuana exposure with concomitant alcohol use. This included altered sleep patterns of the newborn including decreased quiet sleep, increased body movements during sleep and increased nighttime arousals (Warner et al., 2014).

### *Neuro-Developmental Findings in the Offspring*

There are studies including animal studies and longitudinal prospective studies confirming that PME influences the neuro-cognition of the offspring. Persistent use of cannabis may impact brain development and neuropsychological functioning including executive functions,

memory, processing speed, perceptual reasoning, and verbal comprehension (Jarlenski et al., 2017). This process is due to altering the dopamine pathway in the nigrostriatum (DiNieri et al., 2011). It also causes changes in prefrontal area and impaired functioning of the hypothalamic pituitary axis. This also explains the association with attention deficit and hyperactivity (nigrostriatum pathway) and mood disturbances (prefrontal cortex). A cohort study reported that intrauterine exposure to cannabis was associated with an increased risk for aggressive behavior and attention problems as early as 18 months of age in girls, but not boys (El Marroun et al., 2011). This finding was reported in other studies as well (Fried et al., 2008; Goldschmidt et al., 2000).

A prospective study reported that the level of cognitive and intellectual deficits in children exposed to prenatal marijuana is also related to timing and degree of the in utero exposure (Goldschmidt et al., 2000). The study concluded that heavy use (defined as >1 joint/ day) during the first trimester was associated with low verbal reasoning scores whereas the second trimester use was associated with deficits of composite, short-term memory and quantitative scores. There was also a report on defects in visual problem solving, visual motor coordination and visual analysis (Wilford et al., 2010).

With regards to learning difficulties in early school years, its less clear if caused by prenatal marijuana exposure alone due to co-consumption of other substances during pregnancy. However, a prospective study reported that prenatal marijuana exposure significantly interferes with school achievement scores as early as 6 years of age (Goldschmidt, 2008).

A recent report found a dose–response relation between PME and expression of a dopamine gene in the amygdala, demonstrating an effect of prenatal exposure on the systems that regulate emotional behavior (Wang et al., 2004).

### *Neuro Psychiatric Illness in Future*

In utero cannabis exposure alters neurotransmitter homeostasis, including ventral striatal dopamine D2 gene regulation and expression which is involved in major reward pathway causing increased vulnerability to addiction (DiNieri et al., 2011; Wang et al., 2004). This not only leads to impulse control disorders

and addiction behaviors, but also increases sensitivity to drug abuse in the future (Hansen et al., 2008; Szutorisz et al., 2014). Hence it is necessary to further study the dosage and timing of prenatal marijuana exposure to further understand the drug seeking behavior and impaired executive functions.

A prospective study reported that children born following PME showed depressive symptomatology that did not meet the criteria for MDD and that this early onset depression might predict the subsequent development of psychiatric disorders and problem behaviors such as substance abuse (Gray et al., 2005).

### *Maternal Marijuana use and Lactation*

The passage of THC in breast milk has not been extensively studied so far. The American College of Obstetrics and Gynecology committee urges all breastfeeding women to discontinue marijuana use as the potential risks of exposure to its metabolites are unknown (Committee opinion no 637, Results from National survey 2012).

### *Prevention*

A most recent phone survey of 400 dispensaries in Colorado reported that in 70% of contacts the workers recommended cannabis products to treat nausea in the first trimester (Dickson et al., 2018). Few dispensaries encouraged discussion with a health care provider without prompting. It is important to understand the status of public health (PH) messages regarding perinatal marijuana use in an evolving policy context (Jarlenski et al., 2017 ). The American Academy of Pediatrics has concluded that perinatal marijuana exposure has negative effects on short-term and longer-term neurobehavioral development and cognition in childhood (Behnke and Smith, 2013). Following a most recent systematic search of 51 states and 5 federal public health agencies' web sites Jarlenski et al., 2017 concluded that the volume of PH messages about perinatal marijuana use is low, content of messages differs across state agencies, and perinatal marijuana is seldom addressed in content published by federal agencies.

### Conclusion

Although marijuana has been viewed by many as a harmless recreational drug, it is found that prenatal marijuana exposure is associated with several negative consequences in the offspring. Further studies are needed to reinforce the existing data. Guidelines for positive parenting attitude and practices among pregnant women should be developed and emphasized in the antenatal period. Finally, health-care professionals have a responsibility to identify those women and inform them of the possible risks of their cannabis use in a non-threatening and non-judgmental manner.

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