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Clearing the Smoke on Cannabis

Maternal Cannabis Use during Pregnancy – An Update

Amy J. Porath-Waller, Ph.D.
Director, Research and Policy, CCSA

Key Points

- Cannabis is the most commonly used illicit drug during pregnancy.
- Prenatal exposure to cannabis has adverse effects on cognitive development and academic achievement.
- There are also effects on behaviour, including attention deficits, increased hyperactivity and impulsivity.
- There is also emerging evidence of an increased likelihood of smoking, substance abuse and delinquency among adolescents who were prenatally exposed to cannabis.
- Information on the effects of cannabis use during pregnancy is essential to help healthcare providers advise patients about the impact of cannabis use and improve the health and well-being of patients' children.

Background

After alcohol, cannabis (also referred to as marijuana) is the most widely used psychoactive substance in Canada. According to the 2013 Canadian Tobacco, Alcohol and Drugs Survey (CTADS), 10.6% of Canadians aged 15 years and older reported using cannabis at least once in the past year (Statistics Canada, 2015), virtually unchanged from 10.2% in 2012. The use of cannabis is generally more prevalent among young people, with 22.4% of youth aged 15 to 19 and 26.2% of young adults aged 20 to 24 reporting past-year use. Approximately 28% of Canadians aged 15 and older who used cannabis in the past three months reported that they used this drug every day or almost every day.

A growing body of evidence suggests that cannabis use may negatively impact several aspects of people's lives, including mental and physical health, cognitive functioning, ability to drive a motor vehicle, and pre- and post-natal development among children. In this report—one in a series reviewing the effects of cannabis use on various aspects of human functioning and development (see Beirness & Porath-Waller, 2009; Diplock & Plecas, 2009; Kalant & Porath-Waller, 2014; Porath-Waller, 2009)—the effects of

This is the second in a series of reports that reviews the effects of cannabis use on various aspects of human functioning and development. This report on the effects of maternal cannabis use during pregnancy on children provides an update of a previous report with new research findings that validate and extend our current understanding of this issue. Other reports in this series address the effects of chronic cannabis use on cognitive functioning and mental health, cannabis use and driving, and respiratory effects of cannabis use. This series is intended for a broad audience, including health professionals, policy makers and researchers.

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prenatal cannabis exposure on offspring the birth outcomes, neurocognitive development, behaviour and mental health of children are explored. Following a review of the evidence, this report discusses implications for policy and practice.

Much of the available evidence on this topic is derived from three prospective longitudinal cohort studies that describe the impact of cannabis use during pregnancy on child development and behaviour. The first was the Ottawa Prenatal Prospective Study (OPPS). This study was initiated in 1978 and involved a group of Caucasian, predominantly middle-class families (Fried, 2002). The Maternal Health Practices and Child Development (MHPCD) study in Pittsburgh commenced in 1982 and was based on a cohort of children of mostly African-American women from low socioeconomic backgrounds (Day, Sambaoorthi, Taylor, et al., 1991). More recently, the Generation R study, which commenced in 2001, consisted of a multi-ethnic cohort of mothers and children with a predominantly higher socio-economic status from the Netherlands (El Marroun, Tiemeier, Steegers, et al. 2009). All three of these studies began when the women were pregnant and have followed their children into early childhood (Generation R), adolescence (MHPCD) and early adulthood (OPPS).

The prospective longitudinal nature of these three studies is preferred over retrospective research designs because it follows the same group of mothers and children over a long period of time. This allows for reliable measurement of the extent and timing of cannabis exposure, as well as numerous lifestyle variables (e.g., maternal health, socioeconomic status, maternal use of drugs other than cannabis, etc.) during pregnancy and assesses developmental differences in children's behaviour and functioning over time. On the other hand, retrospective research designs compare groups of subjects who differ on some developmental characteristic and draw inferences based on an examination of exposure to potential risk factors (including cannabis use) at some previous point in time.

Cannabis is a greenish or brownish material consisting of the dried flowering, fruiting tops and leaves of the cannabis plant, Cannabis sativa. Hashish or cannabis resin is the dried brown or black resinous secretion of the flowering tops of the cannabis plant. The acute effects of cannabis include euphoria and relaxation, changes in perception, time distortion, deficits in attention span and memory, body tremors, and impaired motor functioning. It is a controlled substance under the Controlled Drugs and Substances Act—meaning that the acts of growing, possessing, distributing and selling cannabis are illegal. There is an exception for those possessing cannabis for medical purposes as supported by a physician.

Caution is urged when comparing the results from the OPPS and MHPCD to the Generation R study. The Δ9-tetrahydrocannabinol (THC) content in cannabis preparations has steadily increased over the past few decades (European Monitoring Centre for Drugs and Drug Addiction, 2014; University of Mississippi, National Centre for Natural Products Research, 2013), so it is possible that the children enrolled in the Generation R study were exposed to higher levels of THC as compared to those participating in the other two studies.

Prevalence of Cannabis Use during Pregnancy

Cannabis is the most frequently used illicit drug during pregnancy. Based on data averaged across the 2011 and 2012 National Survey on Drug Use and Health in the United States, 5.2% of pregnant women aged 15-44 years reported past-month cannabis use, a rate that is slightly higher than that reported when combining the data from 2009 and 2010 (3.6%) (Substance Abuse and Mental Health Services Administration [SAMHSA], 2013). The use of cannabis was reportedly highest during the first trimester (10.7%) as compared to the second (2.8%) and third (2.3%) trimesters (SAMHSA, 2013).

In Canada, approximately 11% of women of childbearing age (i.e., 15-44 years) reported past-year use of cannabis (Health Canada, 2013). The 2008 Canadian Perinatal Health Report noted that 5% of pregnant women reported illicit drug use during pregnancy; however, it did not specify the actual percentage that had used cannabis (Ordean & Kahan, 2011). A report from the Reproductive Health Working Group (2006) in Alberta indicated that 2.3% of women who gave birth in 2006 reported using street drugs while pregnant, with cannabis being the most commonly used substance. These figures, however, are considerably below those reported by a number of prospective, longitudinal cohort studies investigating cannabis use during pregnancy, which state rates of use ranging from 10–16% in middle-class samples to 23–30% in inner-city populations (Day, Leech & Goldschmidt, 2011; Fried, 2002).

Errata: The following corrections have been made to this publication. Page 1, end of first paragraph: "Approximately 27% … every day in 2012" changed to "Approximately 28% … every day or almost every day"; reference removed.

Effects on Pregnancy, Fetal Development and Birth Outcomes

After controlling for maternal tobacco, alcohol and other illicit drug use and various demographic covariates, there is little evidence to suggest an association of cannabis use during pregnancy with an increased risk of premature birth, miscarriage or major physical abnormalities (Day et al., 1991; Fried, Buckingham, & Von Kulmiz, 1983). However, Fried, Watkinson and Willan (1984) have noted a statistically significant reduction of approximately one week in the gestational age of infants born to mothers in the OPPS who used cannabis six or more times per week. There have also been some reports indicating hypertelorism (increased distance between the eyes) and severe epicanthus (skin fold of the upper eye lid) (O'Connell & Fried, 1984) and a five-fold increase in features consistent with fetal alcohol syndrome (e.g., smooth philtrum or groove between the nose and upper lip, thin upper lip and small palpebral fissures or short eye width) (Hingson et al., 1982) in children of heavy cannabis-using mothers.

There is evidence suggesting an adverse effect of prenatal cannabis exposure on fetal growth and birth outcomes, although the findings are somewhat mixed. In the Generation R study, maternal cannabis use during pregnancy was associated with reduced fetal growth in mid and late pregnancy as well as a lower birth weight, and these associations were independent of various lifestyle and socio-economic factors (El Marroun et al. 2009). The results from this study also suggested a dose–response relationship such that heavier cannabis use during pregnancy was particularly associated with lower birth weight. Findings from the MHPCD study noted a small but significant negative relationship between cannabis use during the first trimester and length of the child at birth (Day et al. 1991). In a study of a large cohort of Australian women presenting for public prenatal care at a large hospital between 2000 and 2006, Hayatbakhsh and colleagues (2011) reported that use of cannabis during pregnancy significantly predicted negative birth outcomes, including low birth weight, preterm birth, small size for gestational age and admission to the neonatal intensive care unit. These effects were independent of the mother's socio-demographic characteristics, cigarette smoking, alcohol consumption and the use of other illicit drugs. In contrast, the OPPS did not observe any differences in growth measures at birth between newborns born to cannabis-using mothers and non-users (Fried & O'Connell, 1987). Moreover, the results from a meta-analysis of 10 studies found only weak evidence suggesting that any maternal use of cannabis during pregnancy was associated with either a reduction in birth weight or low birth weight (English, Hulse, Milne, Holman & Bower, 1997).

Effects on Neurocognitive Functioning

Maternal cannabis use during pregnancy has subtle effects on children's neurocognitive functioning. Beginning at age three to four, children of mothers who used cannabis heavily while pregnant in the OPPS and MHPCD have demonstrated deficits in memory, verbal and perceptual

Neurocognitive and Behavioural Effects

18 months	3–6 years	9–10 years	14–16 years	17-22 years
Increased aggressive behaviour[c] Attention deficits (females)[c]	Deficits in: • Verbal and perceptual skills[ab] • Verbal reasoning[ab] • Visual reasoning[ab] • Verbal and quantitative reasoning[b] • Short-term memory[ab] Hyperactivity[ab] Attention deficits[ab] Impulsivity[ab] Impaired vigilance[b]	Deficits in: • Abstract and visual reasoning[ab] • Executive functioning[ab] • Reading[ab] • Spelling[ab] Hyperactivity[ab] Attention deficits[b] Impulsivity[b] Depressive and anxious symptoms[b]	Deficits in: • Visual-cognitive functioning[a] • Academic achievement[b] • Information processing speed[b] • Visual motor coordination[b] Delinquency[b]	Deficits in: • Executive functioning[a] • Response inhibition[a] • Visuospatial working memory[a] Smoking[ab] Substance use[ab] Early initiation of substance use[ab]

[a] OPPS [b] MHPCD [c] Generation R

skills, and verbal and visual reasoning after adjusting for potentially confounding variables[1] (Day et al., 1994; Fried & Watkinson, 1990). In contrast, the results from the Generation R study did not find evidence of such cannabis-related deficits when children were assessed at about age three (El Marroun, 2010). Impaired performance in verbal and quantitative reasoning and short-term memory has also been found in the MHPCD among six-year-old children whose mothers reported smoking one or more marijuana cigarettes per day while pregnant (Goldschmidt, Richardson, Willford, & Day, 2008). Both the OPPS and MHPCD studies reported that in children around the age of nine, prenatal cannabis exposure has been linked with impaired abstract and visual reasoning, poor performance on tasks reflecting executive functioning (i.e., visual-motor integration, nonverbal concept formation and problem solving), and deficits in reading, spelling and academic achievement (Fried, Watkinson & Gray, 1998; Fried & Watkinson, 2000; Goldschmidt, Richardson, Cornelius, & Day, 2004; Richardson, Ryan, Willford, Day & Goldschmidt, 2002). Vulnerability in visual-cognitive functioning has been shown to persist into early adolescence among those children heavily exposed to cannabis (Fried, Watkinson, & Gray, 2003).

Prenatal exposure to heavy maternal cannabis use during the first trimester also predicted significantly poorer scores on a test of academic achievement (particularly in reading) at the age of 14 in the MHPCD (Goldschmidt, Richardson, Willford, Severtson & Day, 2012). Interestingly, these latter effects were found to be related to the effects of prenatal cannabis exposure on intelligence test performance at age six, attention problems and depression symptoms at age 10, and early initiation of marijuana use. At the age of 16, deficits in information processing speed, interhemispheric transfer of information and visual-motor coordination have been linked with prenatal exposure to cannabis, and these effects were found at light to moderate levels of prenatal cannabis exposure in the MHPCD (Willford, Chandler, Goldschmidt & Day, 2010).

Findings from brain imaging studies of young adults aged 18–22 enrolled in the OPPS indicate that *in utero* cannabis exposure negatively impacts the neural circuitry involved in aspects of executive functioning, including response inhibition and visuospatial working memory (Smith, Fried, Hogan, & Cameron, 2004, 2006). These findings are particularly noteworthy as they demonstrate the long-term impairing effects of prenatal exposure to cannabis on children's neurocognitive functioning. General intelligence does not appear to be impacted by prenatal cannabis exposure (Fried et al., 1998, 2003).

Behavioural Effects

The behavioural effects of prenatal cannabis exposure have also been documented, although it is unclear as to how early such effects first present themselves. The Generation R study has reported that prenatal exposure to cannabis is associated with an increased risk of aggressive behaviour and attention problems as early as 18 months of age in girls, but not boys (El Marroun et al., 2011). At the age of four, the OPPS failed to find evidence of a negative relationship between cannabis exposure and attention (Fried & Watkinson, 1990), whereas the MHPCD has reported impaired vigilance among exposed children at this age (Noland et al., 2005). When children reach age six, the effects of maternal cannabis use during pregnancy become much more evident. Compared to children of non-users, children born to cannabis users— particularly heavy users—have been found to be more hyperactive, inattentive and impulsive (Fried, Watkinson, & Gray, 1992; Leech, Richardson, Goldschmidt, & Day, 1999). At age 10, prenatally exposed children display increased hyperactivity, inattention and impulsivity, and show increased rates of delinquency and externalizing problems as reported by their mothers and teachers, compared to those children who were not exposed prenatally to cannabis (Fried et al., 1998; Goldschmidt, Day, & Richardson, 2000). More recently, the MHPCD reported that the children of heavier cannabis users during the first trimester (i.e., one or more joints per day) were almost twice as likely to display delinquent behaviour at the age of 14 as the children who were not exposed to cannabis or those who were exposed to lesser amounts (Day et al., 2011). The study authors also noted that the relationship between prenatal exposure to cannabis and delinquent behaviour also appears to be mediated by the effects of cannabis on depressive symptoms and by attention deficits in the cannabis-exposed children. In children aged 13–16, however, the effects of prenatal cannabis exposure on some aspects of attention (i.e., flexibility, encoding and focusing) appear to wane (Fried et al., 2003).

There is accumulating evidence that indicates prenatal cannabis exposure may contribute to the initiation and frequency of subsequent substance use during adolescence. Porath and Fried (2005) reported that 16- to 21-year-old children (particularly males) of cannabis users were at increased risk, in a dose-related manner,

[1] In all three longitudinal studies, the analyses controlled for various covariates such as the children's gender and ethnicity, home environment, maternal socioeconomic status, prenatal exposure to tobacco and alcohol, and current maternal substance use.

for the initiation and daily use of cigarette smoking and cannabis use, compared to children of non-using mothers. Similar results were noted by Day, Goldschmidt, and Thomas (2006). At age 14, children of mothers who used cannabis heavily while pregnant not only reported using this substance more frequently than children of non-users, but they also initiated use at an earlier age. These findings were also evident when the offspring were 22 years of age and the likelihood of cannabis use was related to the extent of prenatal exposure (Sonon, Richardson, Cornelius, Kim & Day, 2015).

Effects on Mental Health

There is emerging evidence linking *in utero* cannabis exposure to depressive and anxious symptomatology. After controlling for prenatal exposure to other drugs and risk factors for childhood depression, children of maternal cannabis users expressed significantly more depressive and anxious symptoms at age 10 compared to children of non-users (Gray, Day, Leech & Richardson, 2005; Leech, Larkby, Day & Day, 2006). The potential impact of prenatal marijuana exposure on the mental health of children is critical to their long-term health and well-being and needs to be examined closely in longitudinal studies.

Mechanisms of Action

The mechanisms responsible for the effects of prenatal cannabis exposure are becoming better understood with the discovery and investigation into the endocannabinoid system (our own endogenous cannabinoid receptors and THC-like neurotransmitters). This research has shown that the endocannabinoid system plays a significant role in a broad array of developmental processes in the embryonic brain, including cell proliferation and differentiation. Cannabis exposure floods this system and alters its ability to undergo "normal" neurodevelopment. Cannabinoids are able to cross the placental barrier and may also affect the expression of key genes for neural development, leading to neurotransmitter and behavioural disturbances (Gomez et al. 2003). The presence of cannabinoid receptors in the placenta and fetal brain may also mediate adverse actions of prenatal cannabis exposure (Park, Gibbons, Mitchell, & Glass, 2003), as these receptors are associated with aspects of brain functioning including cognition and memory (Kumar, Chambers, & Pertwee, 2001). Animal studies have documented that cannabinoids can lead to changes in dopamine activity and impaired functioning of the hypothalamus-pituitary-adrenal axis (Kumar et al., 2001), which may affect mood and neurobehavioural outcomes in children. Other studies have also demonstrated that prenatal cannabinoid exposure may lead to alterations in GABAergic,[2] glutamatergic, serotonergic and opioidergic systems in children (Fernández-Ruiz, Berrendero, Hernández & Ramos, 2000; Jutras-Aswad, Dinieri, Harkany & Hurd, 2009; Trezza, Cuomo, & Vanderschuren, 2008). Alterations to these systems may possibly explain the effects that cannabis is having on the children exposed to this drug. It is also possible that an as yet undetermined underlying genetic factor may account for both the lifestyle habits of the pregnant mother (including cannabis use) and her child's neurodevelopment and behaviour. This possibility needs further investigation.

Conclusions and Implications

Early brain development involves a complex cascade of events that can be influenced by prenatal and environmental factors. These events can have downstream effects, influencing postnatal development and behaviour (for reviews, see Finnegan, 2013; Leyton & Stewart, 2014). The scientific evidence indicates that prenatal exposure to cannabis (particularly heavy exposure) has subtle adverse effects, beginning as early as age three, on subsequent cognitive functioning, behaviour, mental health and substance use during adolescence. Cannabis-related deficits in the cognitive domain could impair a child's academic functioning and may require educational remediation, enrichment or placement to help protect against future learning problems.

Prevention efforts directed towards reducing maternal cannabis use during pregnancy could have significant effects in reducing such cognitive impairment. Prevention and intervention programs aimed at reducing prenatal cannabis exposure could also help reduce the percentage of youth who experience mental health conditions and other comorbid problem behaviours, such as substance use and delinquency.

It has been reported that at least half of all pregnancies in North America are unplanned (Walker, Rosenberg, & Balaban-Gil, 1999). That, combined with the fact that nearly 11% of Canadian women of childbearing age (15–44 years) reported past-year use of cannabis in 2011 (Health Canada, 2013) indicates the potential risk for children to be prenatally exposed to cannabis use. The maternal use of this drug during pregnancy is a preventable prenatal risk factor; the findings from the literature suggest that it is prudent to advise pregnant women and women thinking of becoming pregnant of the risks associated with

[2] GABA (gamma aminobutyric acid) is an inhibitory neurotransmitter.

cannabis use during pregnancy. To this end, it is vitally important that professionals who provide health care to pregnant women are well informed of the latest clinical evidence and research. The results from a recent survey of gynecologists, obstetricians, midwives and general practitioners practicing in France, however, suggest that there is a strong need for training in the management of cannabis use during pregnancy. This study revealed that only 51% of healthcare professionals asked their pregnant patients about drug use and approximately 68% did not feel sufficiently informed about the risks of cannabis use during pregnancy to provide advice to their patients and lacked the means to inform and take care of their patients who used cannabis (Gérardin, Victorri-Vigneau, Louvigné, Rivoal, & Jolliet, 2011). Pregnancy can offer a window of opportunity during which a woman's motivation for behaviour change—including her substance use patterns—may be heightened. Thus, healthcare professionals need to explore these issues with patients and provide unbiased, compassionate information to women of childbearing age and their partners.

Despite the high prevalence of marijuana use among women of childbearing age, the potential impact of cannabis on the developing brain and the long-term influence on cognition, behaviour and mental health are still not well-appreciated. With the increasing accessibility to cannabis, together with the increasing THC concentration in cannabis, decreased perceptions of risk, and the advent of potent synthetic cannabinoid products, there is a critical need for further research addressing the longer-term consequences associated with prenatal cannabis exposure.

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