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## RESEARCH ARTICLE

# THE EFFECT OF MATERNAL USE OF CANNABIS AND ITS DERIVATIVES DURING PREGNANCY ON HUMAN DEVELOPMENT: A SYSTEMIC REVIEW

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**ABSTRACT**

We review the literature for the association between prenatal cannabis and its derivatives use onthe human development. The psycho-active ingredient in cannabis; is prenatally transported transplacentally and later is secreted in breast milk as well. It has been found to causephysical and neuro-behavioral consequences among children.Various scientific studies in pregnancy outcome and fetal growth; and neurological, cognitive and behavioral development among children borne by cannabis users. PubMed, EBSCO, COCHRANE, MEDLINE and ProQuest databases were used to retrieve studies relevant to keywords. The data from the prospective research were taken from the three most extensive prospective longitudinal studies, namely: The Ottawa Prenatal Prospective Study (OPPS), the Maternal Health Practices and Child Development (MHPCD), and the Generation R study. The rest of the retrospective studies were selected on cannabis use in pregnancy. Beyond the postnatal period, epidemiological studies have revealed adverse effects of prenatal cannabis exposure to the brain development leading to short- and long-term cognitive impacts. Cumulative findings include exaggerated Moro's reflex, increased tremors, impaired visual habituations, sleep pattern disturbances, memory deficits, language and perceptual skills alterations, impaired reasoning abilities, low intelligence Quotient (IQ), poor academic performance and low executive functions among children of cannabis users.



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## INTRODUCTION

Despite growing awareness of the negative effects of cannabis use during pregnancy (1), cannabis remains the most frequently used illicit drugs in the United States and Canada (2). Based on the 2013 results of the Canadian Tobacco, Alcohol and Drugs Survey (CTADS), 10.6% of Canadians aged 15 years or older, reported using cannabis (3). Rates of cannabis use during pregnancy vary depending on demographic characteristics such as socioeconomic status, maternal age and race, but the universal prevalence of its use is established (4). Although the detrimental effects of cannabis have been widely debated (5), it is only recently that studies have focused on its long-term effects on the offspring of pregnant users.

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Marijuana is extracted from the cannabis plant and it contains approximately 400 different chemicals, one of which is tetrahydrocannabinol (THC), a psychoactive substance that rapidly diffuses from the lungs into the circulation before subsequent metabolization by the liver (6). It has been presumed that, since THC crosses the placenta and persists in various tissues for up to 30 days, it could lead to teratogenic effects with regular usage (7). The psychoactive ingredients of cannabis pass through the placental barrier and also can be secreted in breastmilk, hence, it could possibly interfere with the development of the fetal central nervous system and other metabolic processes (8). Aside from its well-known involvement in the neurological processes, such as movement, coordination, emotion and memory, cannabis derivatives also impact cellular processes which may lead to long-term physical and neurobehavioral consequences (9). Assessing the outcome of exposure to cannabis in-utero is a complex process (10). Due to ethical limitations, drugs cannot be deliberately administered to pregnant subjects, leaving the exact doses, amount utilized and timing of use difficult to quantify (11).

Moreover, confounding factors, such as socioeconomic influences, cannot be fully controlled for by randomization of samples (12). In some cases, cannabis is used as a single entity; other cases involve use of cannabis with other potentially teratogenic substances, e.g. tobacco and alcohol; while in still other circumstances, it is used as one of a cocktail of illicit drugs in polydrug users (13). Human studies involving the investigation of long-term effects of prenatal cannabis exposure have depended on volunteer samples and with accounted recall of marijuana use (14). Legal considerations also affect sampling. Despite these limitations, meaningful data is available from well-designed studies (15). Interpretation of results and conclusions, has to take into account the context of each study.

**Extent of Cannabis use**

Cannabis or marijuana is the world's most prevalent illicit drug [2,16]. In the CTADS 2013 results, approximately 10.6% Canadians aged 15 years or more claimed to have used cannabis, with a rate of 22.4% among 15-19-year-old and 26.2% among young adults aged 20-24. [17] Among pregnant women aged 15 to 44 years old in the United States, cannabis is still ranked first among the illicit drugs taken, with a recorded rate of 5.2% from the 2012 National Survey on Drug Use and Health. [18] Cannabis use was highest in the first trimester that is 10.7%, with 2.8% and 2.3% in the second and third trimesters respectively. [18] Eleven percent of Canadian women are in the reproductive age group of 15-44 years, and 5% of these report cannabis use during pregnancy period. [19] The Substance Abuse and Mental Health Services Administration [18] states that more than 10 percent of unborn children in Europe and United States are exposed to cannabis. [20]. At present, the cannabis in use is 6-7 times more potent than the drug available in the 1970s. There are increasing number of studies suggesting cannabis is a teratogen and that exposure to this substance during the intrauterine period results in risks to the fetal development, although the exact adverse fetal impact is still unclear. Prenatal exposure has been linked to fetal growth problems, infertility and placental complications. [21] This systematic review aims to examine the potential adverse effects of cannabis and its derivatives use during pregnancy on early human development, including the prenatal, and early postnatal periods.

**Criteria for inclusion of studies in the review**

Studies from the fields of nursing, medicine and psychology were accessed, using both quantitative and qualitative papers. Criteria for selection were that the paper had to include pregnant women who had been smoking cannabis or marijuana below 35 years of age, and information on their children. Effects of cannabis use on children focused on the following areas: pregnancy outcome and fetal growth, neurological, cognitive (3) and behavioral development.

**Search Strategy**

Search engines MEDLINE, CINAHL, EBSCO, PubMed, Ovid and ProQuest were utilized for retrieving the articles. The MeSh terms used were cannabis use during pregnancy, effects of marijuana in prenatal development, substance abuse in pregnancy, adverse effects of cannabis on newborn, teratogenic effects of marijuana, and smoking pot during pregnancy. Reference lists in related published papers were also scrutinized for additional sources.

**Assessment of methodological quality critical appraisal**

To choose relevant studies the following definition was used: 'papers whose primary focus was the effect of cannabis use during pregnancy on the early human development during the antenatal, neonatal and postnatal periods'.The systematic review shall be using qualitative methods of data collection and analysis in standalone studies including those of larger mixed-method studies. Thematic analysis methods will be used to explore and synthesizes data from 1980 to 2015. Themes shall be established by integrating components of views, experiences and findings contained in the gathered data. The body of evidence presented in this study was derived from retrospective and prospective researches presenting the effects of prenatal cannabis use on the subjects' birth outcomes, physical, neurological, cognitive and behavioral development of children. The data from the prospective research were taken from the three most extensive prospective longitudinal studies, namely: the Ottawa Prenatal Prospective Study (OPPS), the Maternal Health Practices and Child Development (MHPCD), and the Generation R study. The rest of the retrospective studies were selected on cannabis use in pregnancy.

These three major studies gave more reliable measurements in terms of the timing and extent of cannabis use, taking into consideration other cofounding variables, such as socioeconomic status, maternal health status, other substances used by the mothers, and lifestyle. The developmental and behavioral changes among the offspring were also monitored within specified developmental stages of the studies. The retrospective counterparts drew interpretations from comparisons of identified groups of subjects for deviations from expected developmental traits and relating these to cannabis use. The three longitudinal studies were launched when the women subjects were still pregnant, with a continuous follow up on the status of their children into their childhood for generation R, adolescent period for MHPCD, and for OPPS, up to the early adult period. OPPS commenced in 1978, with the study focusing mostly on Caucasian subjects from the middle-class families. [22] The MHPCD, which started in 1982, was a cohort study of the children of women from the African-American origin belonging to lower socioeconomic status. [22] The latest of the three, the Generation R study, which was spearheaded in 2001, covered mothers and their children from Netherlands with multi-ethnic backgrounds, most of which were from the higher socioeconomic level [24]

**Cannabis Prenatal Mechanism**

Recent discoveries and investigations of the endocannabinoid system, which refers to the endogenous human brain cannabinoid receptors linked with neurotransmitters similar to THC, has shed light on the mechanisms involved in prenatal cannabis exposure effects. [2] The endocannabinoid system has a vital role in the embryonic development, particularly of the nervous system, cellular proliferation and cell differentiation. Use of cannabis floods the endocannabinoid system, which alters the normal neurological development. [25] The adverse effects of cannabis in the prenatal period has been associated to impaired cognitive and memory brain functions. [26]

## Fetal development and pregnancy outcomes

The evidences on the use of cannabis during pregnancy, associated with risk of miscarriage, premature delivery and gross physiologic abnormalities are scarce. [27,28] In a related study on the mortality rates in the first 2 years of life related to cannabis, no significant result was noted. [29] Use of cannabis can disrupt the circulation of nutrients and oxygen to the developing fetus, which can subsequently result to reduced fetal growth. There is a noted significant reduction of the age gestation by around one week among the newborns of the maternal subjects in the OPPS who reported cannabis use of at least 6 times a week. [30] The group of Hayat bakhsh [1] conducted a large cohort study of Australian mothers in a public tertiary hospital from 2000 to 2006, revealing negative birth outcomes, such as incidence of premature deliveries, SGA, low birth weight, and higher admission rate to the NICU.

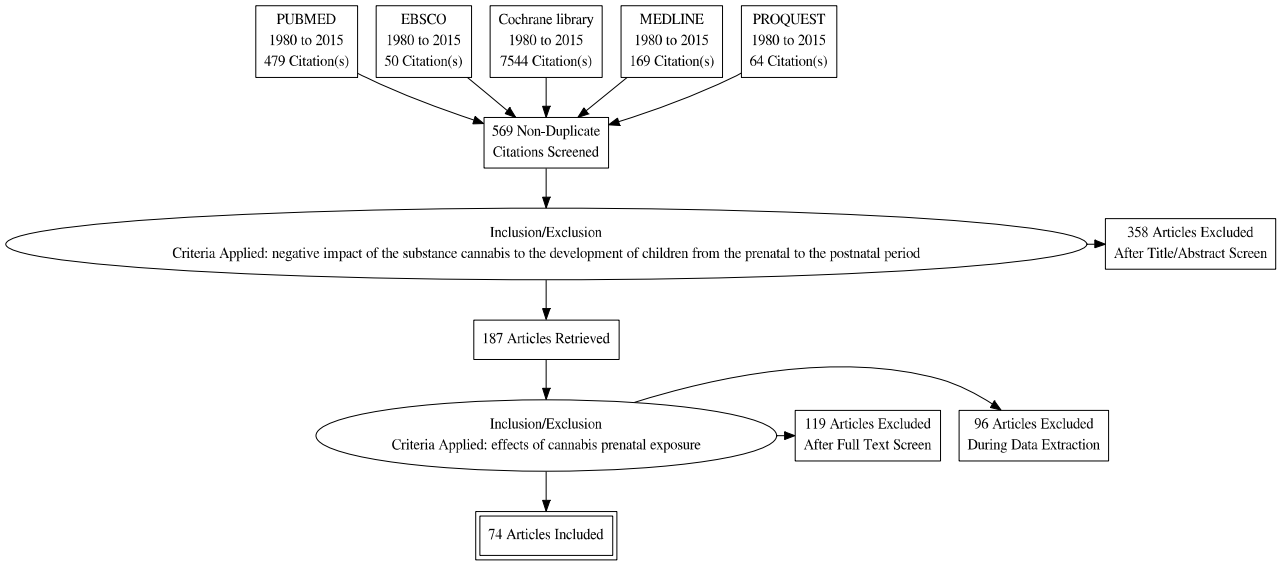


**Figure 1. Prisma diagram for the selection of studies in the systematic review**

MHPCD also stated a decrease in the birth length with cannabis use in the first trimester. [27] The average reported reduction in the birth weight [31] of newborns of mothers using cannabis was 48g, with a larger reduction of 131 g to 209 g for those who use cannabis at least four times a day. From the meta-analysis of 10 studies by English et.al, the link between prenatal cannabis exposure and negative birth outcomes are not definitive [32]. On the other hand, OPPS found no significant differences in the growth measurements of the offspring of the cannabis users and non-users. [33] Hingson *et al*. [34] also presented that the newborns of mothers who used marijuana during pregnancy have a mean birth weight lighter by 105g compared to newborns of non-users, with additional presenting manifestations likened to that of Fetal Alcohol Syndrome. In a study by Zuckerman *et al*. [35] on the effects of marijuana to fetal growth, among 202 infants who were exposed, there was no significant serious physical malformation noted compared to infants born of non-marijuana users. Two studies [36,37] claimed that marijuana exposure resulted to decrease in birth weight and increased incidence of malformations, but no significant relationship was noted when cofounding factors were considered. Although there are findings showing possible physical deformities related to prenatal cannabis exposure, cannabis is not yet implicated as a major teratogen to human due to the absence of established homogenous pattern of anomalies for intrauterine cannabis exposure. [38,31] Reported physical anomalies include abnormally increased distance between the eyes or hypertelorism and presence of exaggerated epicanthal folds of the upper eyelids. [39] Heavy users of cannabis were linked to giving birth to children with short eye width or small palpebral fissures, thin upper lip, and smooth groove between the upper lip and the nose. [34] In a case-control study of the relationship of rhabdomyosarcoma among children and prenatal exposure to marijuana, there was a noted increased risk of developing rhabdomyosarcoma.[40] However, this case failed to isolate marijuana as the sole cause from other drugs taken by the maternal subjects. Cannabis can also be secreted in breastmilk up to eight times more potent than the levels in the maternal blood. [41] This has been associated with delayed motor development among breastfed infants. [42]

## CNS adverse effects

Animal studies and human epidemiological studies have revealed that prenatal exposure to cannabis can adversely affect the brain development resulting to short- and long-term cognitive impacts. [43] Initial findings from OPPS in 1980 from the examination of 4-day old babies of 12 mothers who regularly used marijuana, revealed increased tremors, exaggerated moro reflex and impaired visual habituations.[44] With the use of Prechtl neurologic assessment in the same Ottawa sample [45], related observations included increased hand-to-mouth behavior among 9 to 30 days of age babies. Similar neurological indicators were also seen in related studies with added manifestations of mild withdrawal [46], but were not significant in other researches. [47,48] In the Generation R study, prenatal exposure to marijuana was linked to alteration in acoustic cries among infants along with significant reduction in fetal growth.[49]

Dahl et.al. [47] were able to establish the relationship of marijuana exposure in the first trimester to newborns presenting with altered sleep cycles, greater awake period, indeterminate sleep, more movements, as further reflected in the abnormal EEG sleep measurements among subjects. Observations were taken within 24 to 36 hours after birth for three-hour period among newborns in the nursery.

**Table 1. Effects of Marihuana & other abused substances**

| Studies | Year | No of women Included | Substance Type | Impacts of Abused Substances |
|---|---|---|---|---|
| Hingson *et al*. | 1982 | 1690 | Marijuana, Alcohol, Cigarette smoking | • Adverse fetal growth,short eye width or small palpebral fissures, thin upper lip<br>• Shorter duration of gestation |
| Zuckerman *et al*. | 1989 | 1226 | 27 % Marijuana<br>18% cocaine during pregnancy | • 79-g decrease in birth weight (P = 0.04) and<br>• 0.5-cm decrement in length (P = 0.02)<br>• Women who had positive assays for cocaine, as compared with nonusers, had infants with a 93-g decrease in birth weight (P = 0.07),<br>• 0.7-cm decrement in length (P = 0.01), and<br>• 0.43-cm-smaller head circumference (P = 0.01). |
| Day *et al*. | 1994 | 655 | Marijuana | • Negative effects of prenatal marijuana exposure on the performance of 3-year-old children on the Stanford-Binet Intelligence Scale |
| English *et al*. | 1997 | 32,483 | cannabis | • Reduction in birth weight 48 g (95% confidence interval (CI) 83-14 g) |
| Fried *et al*. | 2001 | Not mentioned | Marijuana | • Impulsivity ,memory retention |
| Porath | 2005 | 152 | marijuana utilization,Cigarettes smoking during Pregnancy | • Risk of substance abuse is high with prenatal drug exposurecigarette smoking (OR=2.58) andmarijuana use (OR=2.76) |
| Goldschmidt *et al*. | 2008 | 648 | Marijuana | • Significant nonlinear relationship between marijuana exposure and child intelligence<br>• Heavy marijuana use (one or more cigarettes per day) during the first trimester was associated with lower verbal reasoning scores on the Stanford-Binet Intelligence Scale.<br>• Heavy use during the second trimester predicted deficits in the composite, short-term memory, and quantitative scores<br>• Third-trimester heavy use was negatively associated with the quantitative score |
| Derauf *et al*. | 2009 | Not mentioned | Alcohol, tobacco, cocaine, methamphetamine, and marijuana | • Neuro-teratogenic effects |
| Gould *et al*. | 2010 | Not mentioned | Alcohol, marijuana | • Deficits in cognitive flexibility and<br>• Memory deficit |
| Crean *et al*. | 2011 | Review | Marijuana | • Impaired cognitive function |
| Day *et al*. | 2011 | 829 | Marijuana, tobacco | • 8% were premature (<37 weeks gestation),<br>• 10% were small-for-gestational age (SGA: birth weight <10th percentile for gestational age)<br>• The average birth weight in the sample was 3210 grams (7.1 lbs) (range 1150-4990 gm)<br>• Few infants had major anomalies, 7% had two or more minor physical anomalies |
| Minnes *et al*. | 2011 | Not mentioned | Tobacco, marijuana, stimulants opiates | • Decreased birth weight,<br>• Sudden Infant death syndrome,<br>• Increased infant mortality rate,<br>• prematurity,<br>• Intra Ventricular Hemorrhage,<br>• Small for gestational; age |
| Leech *et al*. | 2011 | 829 | Marijuana, Alcohol, Tobacco | • Lower Stanford-Binet Intelligence Scale composite scores Commissionerror, Omissionerror, attentional processes |
| Hayat Bakhsh *et al*. | 2012 | 24,874 | 26.3% use of Cannabis use in past<br>2.6% current use of Cannabis | • Low birth weight (OR = 1.7; 95% CI: 1.3–2.2),<br>• preterm birth (OR = 1.5; 95% CI: 1.1–1.9),<br>• SGA (OR = 2.2; 95% CI: 1.8–2.7), and<br>• admission to the NICU (OR = 2.0; 95% CI: 1.7–2.4) |
| Ross *et al*. | 2015 | Review | Marijuana | • Stunted growth,<br>• Decreased gestation lengths,<br>• Low birth weights |

Scher et.al. [12] reported sleep cycling and motility disturbances among newborns exposed to marijuana, which related studies confirms sleep pattern disturbance up to 3 years old were still associated to prenatal marijuana exposure.[50] One study suggested that attention and impulsivity processes were effected by prenatal substance abuse [51]. In a longitudinal study [52] marijuana intake in first and second trimester of pregnancy were associated with the physical and cognitive development of three year old.In a study by Goldschmidt *et al*, increased hyperactivity, intention and impulsivity symptoms were found to be related to marijuana intake during prenatal period [53]. In a recent study involving functional MRI of the brains of children exposed to marijuana and other drugs in utero, results showed a reduction in the cortical gray matter and brain parenchyma. [43] In as much as there are evidences on the neurological effects of prenatal cannabis exposure to children, several research results have failed to establish strong links of central nervous system dysfunction related to prenatal marijuana exposure among newborns [47, 48]

**Cognitive effects of prenatal marijuana exposure**

The effects of cannabis to the brain development of offspring of users during pregnancy extends to cognitive difficulties.

From the OPPS and MHPCD studies, children born of heavy cannabis users from 3 to 4 years of age, presented with memory deficits, language and perceptual skills alterations, and impaired visual and verbal reasoning abilities [54,55], while Generation R study found no significant association of cannabis use in these areas. [56] In the study conducted by Day & Richardson [54] involving sleep study samples, adverse effects to children's IQ was noted at 3 years old. MHCPD further reported verbal and short-term memory deficits and quantitative reasoning impairment among six years old children of mothers who claimed to be smoking at last one marijuana cigarette during the prenatal period. [57].

In children at nine years old, OPPS and MHCPD linked prenatal cannabis use to abstract and visual reasoning problems, low academic performance and poor executive function performance, which covers visual-motor coordination, problem solving and nonverbal conception. [58-61] Children who were exposed to heavy cannabis use in the prenatal period showed persistence of visual and cognitive function problems into early adolescent period. [62] MHPCD also regarded the heavy use of cannabis in the first trimester as an associated cause low intelligence test results at six years old, depression and attention deficits at ten years old, poor academic achievement test results of children at age 14, and early use of marijuana among adolescents. [63] Light to moderate use of cannabis in the prenatal period among mothers in the MHPCD is also linked to slow information processing, visual-motor coordination problems and difficulty in interhemispheric transition of information at 16 years of age.[64] Long standing effects of prenatal cannabis exposure were evident in the brain scans of young adults from 18-22 years of age from the OPPS who were exposed to cannabis in the intrauterine development revealed altered neural circuitry related to brain's executive function, response inhibition and spatial memory.[65]

**Behavioral affects in children**

Literature studies related to the behavioral effects of prenatal marijuana exposure are far from definitive. There were reported findings on the behavioral effects of prenatal cannabis exposure among children, although the delineation of their commencement is not clear. The Generation R study attention deficits and aggressive behaviors to cannabis use during pregnancy, which were noted starting at 18 months of age among girls, but was not significant among boys. [49] MHPCD stated exposed children at four years of age manifests vigilance impairment. [66] At age six, children of heavy cannabis users during pregnancy became more impulsive, hyperactive and inattentive. [67] At 10 years old, the exposed children showed increased problems on attention span, impulsivity, hyperactivity, delinquency and acting out as claimed by mothers and teachers. [58] By 14 years of age, the MHPCD findings revealed that children with heavy prenatal cannabis exposure in the first trimester were twice at risk of developing delinquency compared to those with no or little exposure. [48] By 13 to 16 years of age, the behavioral effects and attention deficits begin to decline. [63] Subsequent substance abuse behavioral patterns were noted among 16 to 21 years old children, with the incidence higher among males, according to Porath & Fried [64]. This is further supported by Day *et al*. [65], with their findings on children who initiated using substances at age 14, earlier compared to their unexposed counterparts.

**Conclusion**

Early human development is characterized by a complex cascade of processes, which can be greatly affected by environmental and prenatal factors, leading to a possible impact in the prenatal and postnatal development, as well as various aspects behaviors and cognitive development in children. Cannabis has been used for its psychoactive effects since antiquity, primarily for its spiritual and medicinal properties. However, a recent surge in the interest of cannabis as medicine as well as for its public acceptance of its recreational use has made it ubiquitous in all strata of society and geographic locations.

This systematic review presented a body of evidence derived from retrospective and prospective studies on the negative effects of prenatal cannabis exposure on the subjects' birth outcomes, physical, neurological, cognitive and behavioral development of pediatric population. Recent advances in the understanding of human endocannabinoid system has made it possible to study the effects of cannabis use during pregnancy and its effects on the developing endocannabinoid system, and the resulting adverse effects in the embryonic development, especially the development of the central nervous system and cellular proliferation. Our meta-analysis revealed a significant reduction in the age of gestation, incidences of premature deliveries, low birth weight and length, SGA, and higher admission rate to the NICU.

**Recommendations**

It is essential for healthcare professionals to educate expectant mothers on the negative impacts of cannabis use during pregnancy and to provide necessary care for those who are already exposed to this illicit substance. With the rising confusion on the benefits and disadvantages of cannabis use during pregnancy, there is a need to establish clinical guidelines in the prenatal cannabis exposure for women as well as a strong need for training among health care professionals on the management of cannabis use among pregnant women. Despite the recorded high incidence of cannabis use among females of reproductive age, there is still a need to further shed light on the potential impact of this substance to the early human development and its long-term effect on the children. Thus, more research must be performed on the specific areas of children's development, focusing on the long-term effects of prenatal cannabis exposure.

**Abbreviations**

- **CTADS:** Canadian Tobacco, Alcohol and Drugs Survey
- **OPPS:** Ottawa Prenatal Prospective Study
- **MHPCD:** Maternal Health Practices and Child Development
- **IQ :** Intelligence Quotient
- **THC:** Tetrahydrocannabinol
- **NICU :** Neonatal intensive care unit

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