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Education

Consequences of foetal and neonatal cannabis exposure

EDUCATION

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ABSTRACT

Summary:

The increasing social and legal acceptance of cannabis around the world is driven by a growing body of research that points to several medical benefits, however, there remain significant risks to certain members of the population. More specifically, the maternal use of cannabis during pregnancy is associated with several adverse foetal and neonatal health consequences. While the volume of evidence is mixed, infants from women who used cannabis during pregnancy were more likely to be anaemic, have decreased birth weight and be placed in neonatal intensive care compared to infants whose mothers did not use cannabis. Findings from human and animal trials suggest that tetrahydrocannabinol (THC) and cannabidiol (CBD) may be the key chemicals responsible for many of the abnormal neurodevelopment issues such as long-term impairment in cognitive function resulting from structural alterations in synaptic plasticity. There is limited information available in the literature around the assessment of safe threshold limits, the effects of cannabis exclusive of other drugs and the long-term outcomes in the offspring. As the popularity of cannabis increases, it is important that these data gaps be addressed to provide proper guidance to women and their health care team during pregnancy.

Relevance:

The societal trend towards cannabis use raises the probability that medical students and practicing physicians will encounter pregnant women using cannabis in some form. Understanding the potential risks of maternal cannabis exposure on foetal development and pregnancy outcomes provides the knowledge required to share appropriate information and guidance with female patients during preconception, pregnancy and lactation. This in turn allows for the implementation of more comprehensive optimum wellness plans for the mother and child.

Take Home Messages:

As societies and lawmakers around the world increasingly accept the use of cannabis, it's important that medical professionals have a basic knowledge of the possible risks posed to certain vulnerable members of the population. This article provides a step in that direction.

Cannabis is a flowering plant that generally includes three species - sativa, indica, and ruderalis. The flowering buds of the female plant have high concentrations of trichomes, which are resin-filled glands containing a rich source of pharmacologically active cannabinoid compounds. The most active of these are tetrahydrocannabinol (THC) and cannabidiol (CBD), which are known for their psychoactive and non-psychoactive effects respectively. (1) As a recreational drug cannabis has for generations been used to alter sensory perception and cause elation and euphoria. This is most vividly described by the 19th century French poet Charles Baudelaire in his book Les Paradis Artificiels. (2) Most recently, research has pointed to several medical benefits including the relief of neuropathic pain. (3)

Although cannabis is still an illicit substance in most parts of the world there is growing social and legislative acceptance for its use for medical and recreational use. (4) It is the most commonly used illicit drug among women of childbearing age in developed countries, and while estimates vary, one study by Ko et al. estimates that more than 10% of pregnant women use cannabis – in fact, pregnant women who were smokers of tobacco, and used illicit drugs and alcohol were 2-3 times more likely to use cannabis. (5) Typically, cannabis is used during the first trimester as a treatment for nausea and morning sickness. (6) The legalization and commercialization of cannabis is expected to attract for-profit corporations and could result in aggressive marketing to encourage demand, similar to practices implemented by the tobacco industry. (7) For example, according to the National Survey on Drug Use and Health the use of cannabis among pregnant women in the United States has increased by 62% between 2002 and 2014. According to the study, 3.85% of pregnant women in 2014 reported cannabis use in the previous month compared with only 2.37% of pregnant women in 2002. (8, 9) Another population survey reported that pregnant users of cannabis were younger, had a lower level of education and a lower household income. (10) While it appears that the use of cannabis is growing, there continues to be a paucity of reliable evidence available regarding the use and frequency of cannabis use during pregnancy.

Impact of Cannabis Use on Foetal and Neonatal Mechanisms

As part of the human endocannabinoid system there are specific cannabinoid receptors in the body acted on by cannabinoids that affect the homeostasis of biological functions. The cannabinoid receptors are widely distributed throughout the central nervous system and the peripheral nervous system. Their greatest concentration is around the hippocampus, cortex, olfactory areas, basal ganglia, cerebellum and spinal cord, which accounts for the effects of cannabinoids on memory, emotion, cognition and movement. (11) In the foetal human brain cannabinoid receptors were detectable at 14 weeks gestation, however the receptor levels were very low throughout the second trimester. (12) The region showing a receptor density close to that seen in adults was the globus pallidus. (12) Cannabinoids can cross the placental barrier and be secreted into maternal milk to affect the expression of key genes for neural development. (13) Cannabinoid receptors are expressed in white matter and cell proliferative regions and are integral to critical neurodevelopmental events, such as neuronal proliferation, migration, and synaptogenesis. (14) Endogenous endocannabinoids also play a key role in regulating neural progenitor cell commitment and survival. (15) Thus, exposure to exogenous cannabis during pregnancy has the potential to induce supra-physiological stimulation of the endogenous cannabinoid system, which may disrupt the ontogeny of endogenous endocannabinoid signalling, and interfere with synaptogenesis and the development of neuronal interconnections. (16)

Embryonic and foetal life represents a crucial period of development involving the greatest number of cell divisions. An aspect of the impact of cannabis that has not been studied in detail involves the effects on developing organs as they progress through key stages of growth - cellular hyperplasia, non-committal cellular hyperplasia, and hypertrophy. (17) Due to the lipophilic nature of cannabis, the active ingredient THC can readily cross many types of cell barriers including the placental barrier and can directly affect the foetus. (18) An unfavourable intrauterine environment could leave the foetus vulnerable to structural and functional anomalies that can have life-long consequences. A 1988 study by Wu et al. also associated marijuana smoking to a nearly fivefold greater increment in the blood carboxyhaemoglobin level, and a near threefold increase in the amount of tar inhaled, compared to tobacco smoking. (19) This study was limited to male subjects and further study would be required to confirm whether these pulmonary hazards would also adversely impact pregnant women.

Various human and non-human studies confirm the transfer of THC across the placenta. A study by Fisher et al. indicates that THC will cross the placenta to reach a concentration equal to or higher than that of the maternal circulation. It also indicates that THC has the potential to be placento-toxic as it accumulates in the placenta and could interfere with the transfer of essential amino acids and other macromolecular precursors. (20) In another study, researchers injected THC into late-term (gestational days 146-151) rhesus monkeys to measure its placental transfer to the foetus. After analyzing for THC and 11-nor-9-carboxy-THC (11-nor), a major metabolite, they observed that maternal and foetal plasma THC levels were equal at 37ng/ml after 3 hours. However, less than 5ng/ml of 11-nor was detected in foetal plasma, with none

being detected in the placenta, foetal liver, or foetal brain. This data supports that THC rapidly diffuses through the placenta, entering the foetus. It also suggests that 11-nor does not travel through the placenta because the foetus does not readily metabolise THC into 11-nor at this late developmental stage. (21) Furthermore, from a study of the human endocannabinoid system there is evidence that THC affects trophoblast proliferation, apoptosis, differentiation, and function. (22) A study by Costa et al. found that THC impaired cytotrophoblast differentiation into synctiotrophoblast. This was caused by a reduction in the expression of syncytialisation biomarkers via a cannabinoid receptor-dependent mechanism. (23) Another study by Almada et al. found that the use of synthetic cannabinoids, such as WIN-55,212, induced cell cycle arrest through the activation of CB1 receptors. Specifically, they determined that this apoptosis was associated with a mitochondrial membrane potential disruption and the activation of caspase proteins without reactive oxygen species or recruitment of the endoplasmic reticulum stress marker CHOP. (24)

Because of the increased teratogenic action of THC on the proper functioning of the placenta, cannabis use during the first trimester of pregnancy may result in miscarriage and congenital malformations, while use after the first trimester would more likely cause delays in foetal growth and functional development. (25) A comprehensive Australian study which analyzed 416,834 live births over a 5-year period confirmed that 2,172 of all births that were associated with maternal cannabis use resulted in neonates with a higher level of foetal distress. (26) Compared with infants whose mothers did not use cannabis during pregnancy, in-utero exposure to cannabis usually resulted in pre-term birth requiring placement of newly born infants in neonatal intensive care units. (26, 27) A systematic review and meta-analysis by Gunn et al. which reviewed 24 case-controlled, cross-sectional and cohort studies also found similar findings. (28) Most studies reflect participants characterised by concurrent polysubstance use including tobacco and alcohol. To achieve more accurate conclusions future research is required that evaluates neonatal outcomes only from cannabis users exclusive of these confounding factors.

Weight & Growth Outcomes

Various studies reveal that high levels of THC exposure may result in adverse pregnancy outcomes including preeclampsia, pre-term birth, and low birth weight. Animal studies show that high doses of THC in pregnant mice and rats result in lower birth weight among offspring. (29) While some human studies showed a null association, others demonstrated a decrease in foetal weight when exposed to cannabis in-utero. (30) A 2009 Dutch study of 7,452 infants exposed to cannabis during pregnancy indicated that birth weight for those infants exposed to cannabis throughout pregnancy was on average 277 grams lower compared with non-exposed infants, and 156 grams lower for infants exposed to cannabis in early pregnancy only. (31) This is a significant effect as lower birth weight has also been associated with an increase in morbidity and mortality in infants. (32) A twin study has also shown that it is the smaller twin at birth that has the highest blood pressure later in life. (33) Other lasting consequences of lower birth weight may include lower IQ and academic achievement, higher rates of neurosensory impairments and chronic conditions. (34) Other studies by Day et al. and Gray et al. have reported a decrease in gestational length from exposure to cannabis in-utero. (35, 36)

Definitive conclusions from maternal cannabis studies on foetal growth and birth weight are limited due to many confounding variables across studies related to nutrition, prenatal care, multi-substance use and the duration and frequency of use involving these substances. An Australian multi-hospital study of pregnant women using cannabis indicated that over 33.5% of cannabis users were multidrug users. (37) As a result, it is difficult to separate the direct impact of cannabis relative to other substances.

There is also the issue of reluctance and accurate disclosure by study participants, driven by fear of legal consequences especially since cannabis use is illegal in many jurisdictions. For example, in a Brazilian hospital study, only 1 of 26 mothers who used cannabis during pregnancy reported their use. (38) A potential solution in future studies could be the use of more reliable laboratory assessments to determine cannabis use. This could include toxicological analysis of body specimens such as hair and urine, as self-reported cannabis use had poor correlation with corresponding urinalysis results. (39)

Neurobehavioural Outcomes

As exogenous cannabis binds to the receptors of the foetal endocannabinoid system it alters neurodevelopment by interfering with proper neural circuitry formation in the early brain. This adversely impacts the creation and movement of neurons, the outgrowth of their axons and dendrites and axonal pathfinding. This predisposes offspring to abnormalities in cognition and altered emotionality. (40)

A neonatal study by Fried and Makin examining 250 infants born to middle-class women showed that prenatal cannabis exposure was connected with increased tremors, startles and a poorer ability to adapt to visual stimuli. (41) Another Brazilian study of adolescent mothers with babies born at term found that neonates exposed

to cannabis during pregnancy required more time for testing and showed adverse reactions relative to arousal, regulation, and excitability. (38) Examining a different social class, yet another study by Coles et al. examining 107 infants born to low-income predominantly black women also showed that prenatal cannabis exposure resulted in a reduced ability of the neonate to focus and track external stimuli. (42) In contrast to these studies, a study by Dotters-Katz et al. found no adverse neonatal or childhood outcomes from foetal exposure to cannabis in neonates. (43) These discrepancies could be the result of confounding factors previously mentioned or even the use of different neurobehavioral scales and inconsistent follow-up periods to access deficits in cognitive functioning.

A study by El Marroun et al. showed that by early childhood, cannabis-exposed children, especially girls, develop more slowly in terms of visual–perceptual tasks and language skills, and demonstrate increased levels of aggression and poor attentiveness. (44) Cognitive and intellectual deficits seem to also be related to the timing and amount of in-utero exposure. Heavy use (defined as one or more cannabis cigarettes per day) during the first trimester was associated with lower verbal reasoning scores in children at 6 years of age when compared with their non-exposed peers, while second trimester use was associated with deficits of composite, short-term memory, and quantitative scores. (45)

Various longitudinal studies including the Ottawa Prenatal Prospective Study (OPPS) by P.A. Fried have also shown adverse effects of cannabis use. In the OPPS, involving an initial sample of 698 women, the effects of cannabis used during pregnancy was studied and offspring assessed repeatedly during the neonatal period. The results suggest that in the neonates, state alterations and altered visual responsiveness may be associated with in utero exposure to cannabis, however there was no association between cannabis exposure and infant development at 1 year. Beyond the absence-of-effect during early childhood, at the age of 4 and older there were increased behavioural problems and decreased performance on visual perceptual tasks. (46) Another epidemiological, developmental and clinical overview by El Marroun et al. also found that cannabis use in pregnancy poses major health concerns for developing children, however it was pointed out that findings have been inconsistent or difficult to interpret due to methodological issues. (47)

Overall, the inconsistent neurobehavioral results could be explained by differing population sizes and characteristics, varied assessment techniques, prevalence of concurrent maternal multidrug use, frequency and timing of cannabis exposure, maternal age, or even the socioeconomic and educational profile of the mother. Even the type and potency of cannabis used may have played a role as improved greenhouse technology in recent years has increased the THC potency of cannabis. (48)

Conclusion

Although the body of literature regarding the consequences of cannabis use during pregnancy is limited, foetal and neonatal exposure may have the potential to cause long-term growth, neurodevelopmental, and behavioural harm. For instance, at present there is evidence to indicate that cannabis is responsible for causing low birth weight, and the need for neonatal intensive care of newborns. In addition, the THC and CBD present in cannabis may be linked to long-term impairments in cognitive function. In 2017, because of the concerns regarding impaired neurodevelopment, the American College of Obstetricians and Gynecologists published Committee Opinion Number 722 that discourages physicians from prescribing cannabis for medicinal purposes during preconception, pregnancy, and lactation. (49)

The results of the limited number of studies are conflicting and complicated since they often reflect participants characterized by polysubstance use. There is inadequate conclusive research on the specific perinatal impacts of THC and CBD, excluding other bioactive compounds. Thus, further research is needed to isolate the effect of THC and CBD exclusive of tobacco, alcohol and other drug consumption. Future studies could also determine the neurodevelopmental effect of high-potency formulations and low-cost synthetic cannabinoids, as their effects may pose different risks to the foetus.

Given the nature of maternal polysubstance use, coupled with legislation trends that are likely to increase the use of cannabis, there is a need for more through screening and substance management for women of reproductive age. There is also a need for more focused research to comprehensively evaluate the long-term effects of prenatal cannabis exposure on foetal development and pregnancy outcomes. This will allow maternal decisions on the use of cannabis to be made on firmer scientific grounds. In the interim, because of the potential adverse foetal and neonatal health consequences, there should be increased action on the part of governments, medical associations and physicians to inform women of the potentially harmful impact of cannabis exposure use during pregnancy.

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