

# O Cannabis: What have we done by legalizing marijuana in pregnancy?

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*"The Canadian government is taking a public health approach to legalizing, strictly regulating, and restricting access to cannabis."<sup>1</sup>*

Those were the words of Minister of Health Ginette Taylor in November 2017, spoken as the government of Canada began to put together Bill 45, known as The Cannabis Act.

Over a year has passed since the enactment of Bill 45 and questions still remain regarding the safety of legal cannabis to our pregnant population, both in the short- and long-term.<sup>2</sup> Even preceding the legalization of cannabis in Canada, a 2017 survey by the Centre for Addiction and Mental Health (CAMH) indicated that from 1996–2017, adults of reproductive age (i.e., 18–29 years) in Ontario reported the biggest increase in cannabis use, from 18.3% to 39.1%.<sup>3</sup> Moreover, in 2017, the proportion of Ontarians reporting cannabis use in a span of just 1 year rose from 15.7% to 19.4%, representing a total of 2 million people.<sup>3</sup>

These trends in usage are of great concern, especially when considering that over the last decade, cannabis use has progressively increased in pregnant women, along with the perception that it poses no risk in perinatal life.<sup>4,5</sup> In the United States, the rates of self-reported or screened cannabis use in pregnant mothers aged 18–24 years varied from as low as 6% to as high as 22%, with some women acknowledging taking 1–2 joints per day.<sup>3,6</sup> Among nursing mothers, a cross-sectional study from the Colorado Pregnancy Risk Assessment Monitoring System indicated that the incidence of cannabis use was ~5%.<sup>7</sup> In pre-legalization Ontario, a population-based study using the Better Outcomes Registry and Network (BORN) database indicated a self-reported cannabis rate of 6.7% in pregnant mothers aged 15–24 years in the lowest two area-level income quintiles.<sup>8</sup> More striking, of all the cannabis users surveyed in that study, the majority (52%) were aged 15–24 years.<sup>8</sup> While post-legalization data is not available, surveys suggest that more women intend to use cannabis in pregnancy, due in part to the perception that if it is legal, it must be safe.<sup>9,10</sup>

A recent Southwestern Ontario study has revealed that maternal cannabis use in pregnancy is the third highest risk factor for low birth weight babies [odds ratio (OR) 2.72; 95% confidence interval (CI) 1.67–4.42].<sup>11</sup> While three systematic reviews and meta-analyses have further validated the relationship of maternal cannabis use with low birth weight and adverse neurodevelopmental outcomes,

these studies are confounded by sociodemographic factors and the fact that users often use other drugs (e.g., tobacco).<sup>11,15</sup> In the state of Colorado, where cannabis has been legal for more than 5 years, one study demonstrated that prenatal cannabis exposure is associated with a 50% increased chance of having low birth weight children independent of the level of education, age, race/ethnicity, and tobacco consumption [OR 1.5; 95% CI 1.1–2.1].<sup>7</sup> So the question remains, given the risk to fetal development, why do mothers use cannabis in pregnancy?

Many continue to use cannabis given the common perception that it will reduce anxiety and pregnancy-induced nausea.<sup>16,17</sup> Cannabis use in pregnancy is also thought to improve mood, and a recent study suggests that depressed women are 2.5 times more likely to use cannabis in pregnancy.<sup>17,18</sup> For others, cannabis is 'herbal', 'natural', and a welcome part of a 'pro-vegan' diet.<sup>9,17</sup> A member of CannaMama, a support group in Colorado consisting of more than 5,000 women who advocate for cannabis use in pregnancy, has been recently quoted as saying:

*"Cannabis is not crack. Cannabis is not heroin. Cannabis is not alcohol. Our movement is to help women make a choice that they feel is safer than pharmaceuticals and over-the-counter medications."<sup>19</sup>*

The bigger issue regarding the perception of the safety of cannabis by pregnant mothers emerges from a recent Canadian integrative review.<sup>20</sup> The authors found that the uncertainty of adverse postnatal outcomes along with a lack of counselling by healthcare providers were main drivers of their decision to use cannabis in pregnancy.<sup>20</sup> Other reasons for using cannabis in that review included its supposed therapeutic effects and its lower cost compared to tobacco.<sup>20</sup> One of the overall conclusions from that study was that "women perceived a lack of counselling as an indication that adverse outcomes were not significant."<sup>20</sup> Herein lays a significant issue. The message from our governing bodies regarding the safety of cannabis in pregnancy just may be too passive. For example, the Health Canada website states that, "until more is known about the short and long-term effects of cannabis, it is safest to avoid using cannabis when pregnant and breastfeeding."<sup>21</sup> But is that a strong enough message in the interim?

Moving forward, two essential issues require immediate attention. First, the paucity of research examining the specific contributions of components of cannabis (i.e.,  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC) and cannabidiol (CBD)) on short-term pregnancy outcomes should be examined, but more importantly, its long-term effects on the exposed offspring must be studied. This needs to be addressed explicitly in animal models given the confounding issues of clinical studies.<sup>8,11–15</sup> The second issue – an issue that is always problematic in biomedical research

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– is a lack of knowledge translation (i) from the bench to the clinic, and (ii) from the clinician to the patient.

With regards to the role of  $\Delta 9$ -THC, the major psychoactive cannabinoid in cannabis, on fetal development, animal models have demonstrated that exposure of pregnant dams to cannabis or  $\Delta 9$ -THC leads to placental dysfunction and low birth weight offspring.<sup>22–24</sup> This is alarming considering that the concentration of  $\Delta 9$ -THC in cannabis has increased from 3% up to 22% over the last decade due to selective plant breeding.<sup>25</sup> Moreover, animal studies have indicated that  $\Delta 9$ -THC can cross the placenta and 10–28% of maternal concentrations are detected in the fetal plasma, with 2–5-fold higher concentrations in fetal tissues.<sup>26,27</sup> In human studies, it has also been demonstrated that  $\Delta 9$ -THC can pass into breast milk, and that chronic use of cannabis results in 8-fold higher concentrations in milk compared to maternal circulation.<sup>28</sup> In addition to the limited research related to  $\Delta 9$ -THC, little is known regarding the contributions of CBD, the major non-psychoactive component of cannabis, alone on fetal or neonatal development. Furthermore, it is uncertain how the content of CBD, a phytocannabinoid known to counteract many of the negative effects of  $\Delta 9$ -THC, may influence cannabis-induced fetal growth restriction.

For the past couple of decades, there has been a growing body of research examining the role of the endocannabinoid system in pregnancy on neurodevelopment in postnatal life. The endocannabinoid system is involved in a diverse range of physiological processes including cognition, learning, memory, nociception, mood, inflammation, energy and balance, and metabolism.<sup>29</sup> While both cannabinoid receptors (CB1R and CB2R) are expressed in peripheral tissues (i.e., placenta, pancreas, adipose, liver, and heart) in fetal and postnatal life, CB1R is primarily detected in the brain during development and in postnatal life.<sup>30–36</sup> Both CB1R and CB2R can bind to  $\Delta 9$ -THC with greater affinity than CBD.<sup>32</sup> In rats, CB1R is first detected in the forebrain around gestational days 11–14, coinciding with the increased expression of neurotransmitters.<sup>36</sup> CB1R in humans is detected by week 14 of gestation in the hippocampus with subsequent expression in the amygdala by week 20.<sup>37</sup> In both species, the higher expression of CB1R in fetal compared to postnatal life has been suggested to play a key role in developmental events including cell proliferation and migration, metabolic support, axonal elongation, and ultimately, synaptogenesis and myelogenesis.<sup>38</sup> While activation of CB1R by  $\Delta 9$ -THC might seem to be beneficial to the fetus in the short-term, chronic exposure to cannabis in pregnancy leads to several deficits in brain function in postnatal life.<sup>6,39–41</sup> The Mental Health Practices and Child Development Study (MHPCD) demonstrated that cannabis use in pregnancy results in decreased mental scores (e.g., Bayley Scales of Infant Development) as early as 9 months of age.<sup>6</sup> As these children get older, maternal cannabis use led to lower scores in short-term memory and verbal and abstract/visual reasoning in 3 year old children, with deficits in sustained attention by 6 years, and problems in abstract and visual reasoning in 10 year olds.<sup>6,40,41</sup> Another study demonstrated long-lasting effects, as young 18–22 year olds exposed to cannabis in pregnancy exhibited altered neuronal functioning during visuospatial working memory processing.<sup>39</sup>

However, given the intrinsic limitations of these clinical studies, including the fact that cannabis users also use other drugs, and due

to the variations in cannabinoid composition between patients, animal studies are highly valued for their ability to delineate the specific contribution of perinatal  $\Delta 9$ -THC and/or CBD towards neurodevelopment and postnatal brain function. The pregnant rat dam has been a useful model to examine the effects of exposure of  $\Delta 9$ -THC in pregnancy on several indices of social behavior and mental capacity in postnatal life. Specifically, perinatal  $\Delta 9$ -THC-exposed offspring exhibit increases in anxiety (decreased time in inner part of open field test and increased investigation time), impaired social interaction, anxiogenic-like profile (elevated plus maze test), and have enhanced presynaptic dopamine D2 receptor responses including immobility and inhibition of locomotion.<sup>42–45</sup> With respect to addiction, elegant studies have demonstrated that only  $\Delta 9$ -THC-exposed females exhibited greater morphine self-administration behavior due to sex-specific increases in the density and binding of mu opioid receptors in the prefrontal cortex, hippocampus (CA3 area), and the amygdala.<sup>46</sup> To date, these studies have assessed long-term hippocampal function after perinatal  $\Delta 9$ -THC exposure, but future studies are needed to address the short and long-term effects of cannabinoid exposure during the lactation period alone. This is imperative considering the behavior patterns of women who smoke in pregnancy, especially those who think that smoking during breastfeeding alone is safe in the long-term for offspring health.<sup>47</sup> Moreover, adolescent rodent studies from our Addiction Research group at Western University indicate that exposure to  $\Delta 9$ -THC or other CB1R agonists adversely impacts working memory, spatial working memory, and cognitive flexibility,<sup>48</sup> suggesting that the brain in early life could be quite vulnerable to  $\Delta 9$ -THC or CBD during lactation, a period of developmental plasticity.

Aside from the brain, activation of cannabinoid receptors by  $\Delta 9$ -THC or CBD in peripheral tissues (e.g., pancreas, heart, adipose, and liver) during pregnancy could also directly influence the development of those organs, and consequentially, their function in postnatal life.<sup>30–36</sup> In addition,  $\Delta 9$ -THC in pregnancy may have indirect effects on long-term non-communicable diseases given that it impedes fetal growth, which is a strong predictor of metabolic disease risk in human offspring.<sup>23,49</sup> With respect to heart development, the role of CB1R and CB2R has been scarcely explored. One *in vitro* study has indicated that the cannabinoid receptor ligand anandamide impairs neonatal cardiomyocyte size, but the effects of  $\Delta 9$ -THC or CBD in pregnancy on the developing heart is unknown.<sup>50</sup> We recently investigated if exposure to  $\Delta 9$ -THC in pregnant rats influences postnatal cardiovascular function. Part of our rationale came from recent *in vitro* studies that demonstrated that  $\Delta 9$ -THC directly leads to endoplasmic reticulum stress and mitochondrial dysfunction, which are key instigators of fetal growth restriction and cardiac dysfunction.<sup>51–53</sup> We demonstrated that daily injections of 3 mg/kg  $\Delta 9$ -THC from gestational day 6 to birth leads to fetal growth restriction without any adverse effects to maternal food intake, weight gain, gestational length, or litter size.<sup>54</sup> Others have demonstrated that this dose of  $\Delta 9$ -THC in rats results in circulating concentrations of 8.6–12.4 ng/ml  $\Delta 9$ -THC, which is consistent with that reported in (i) cannabis smokers (13–63 ng/ml from a 7%  $\Delta 9$ -THC content cigarette) 0–22 hours post inhalation, and (ii) in fetal tissues (4–287 ng/ml) of pregnant cannabis smokers.<sup>55–57</sup> At birth, there was an approximate 25% decrease in the heart to body weight ratio in

these Δ9-THC exposed offspring while echocardiographic analysis revealed this was accompanied by lower cardiac stroke volume.<sup>54</sup> By 3 weeks of age, after the Δ9-THC offspring exhibited postnatal catch-up growth, both a decrease in stroke volume and cardiac output were observed.<sup>54</sup> Given the short-term impact of Δ9-THC on heart function, future studies are warranted to examine the effects of perinatal exposure of Δ9-THC and/or CBD on long-term cardiovascular function along with adiposity, glucose/insulin homeostasis, and liver function including drug metabolism.

**Future Directions**

As previously mentioned, future research is required to examine the effects of cannabis components on fetal developmental and postnatal health. While animal studies have shed some light on the adverse effects of Δ9-THC in perinatal life on long-term neurodevelopmental outcomes, the safety of CBD in pregnancy also needs to be addressed. As the majority of cannabis strains are high in Δ9-THC and low in CBD,<sup>25</sup> such studies would collectively help identify which strains of cannabis may or may not be linked to adverse perinatal outcomes. Furthermore, as cannabinoid receptors are also expressed in peripheral organs,<sup>30-36</sup> research must be aimed at exploring the different development windows (i.e., gestation, lactation, or both) of cannabinoid exposure on postnatal metabolic health. This is critical given Δ9-THC can cross into maternal, fetal, and neonatal circulation to influence organ development.<sup>26-28</sup> Moreover, as researchers determine the effects of cannabinoids on long-term disease risk, it is imperative that we also identify any sex-specific outcomes resulting from these clinical and animal studies. To date, ~70% of the studies examining the effects of perinatal Δ9-THC exposure on neurodevelopmental outcomes in rodents only looked at male offspring,<sup>42-46</sup> even though we now know there are sex-specific effects.<sup>46</sup>

In Canada, while we still have a long way to go in providing a healthy research budget for our biomedical researchers, the Canadian Institutes for Health Research (CIHR) has just recently recognized cannabis research as a priority with the release of both Team and Catalyst grants related to “Cannabis Research in Urgent Priority Areas”. With that said, it would have been beneficial to have these research initiatives well in place preceding the passing of Bill 45. Regardless, the outcomes of these current and future studies will be important for clinical and regulatory agencies around the world, such as Health Canada, for providing functional evidence to support policy and decision-making.

However, research and policy will have limited impact on maternal-fetal health if information is not properly disseminated to the patient. Given what underlies a patient’s decision to use cannabis in pregnancy,<sup>17,20</sup> all stakeholders in Obstetrics and Gynaecology, Pediatrics, and Family Medicine must be well informed to counsel patients with evidence-based data. Secondly, through open dialogue we further need to understand why these patients are choosing to use cannabis pre- and postpartum, especially given that socioeconomic status may influence their decisions.<sup>8,11-15</sup> With greater counseling and evidence, we should be able to reduce the incidence of neurodevelopmental and metabolic adversity in a generation of children, who without choice, are exposed to cannabinoids in fetal life.

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