Review Article

An epidemiological, developmental and clinical overview of cannabis use during pregnancy

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ARTICLE INFO

ABSTRACT

The objective of the current narrative literature review is to provide an epidemiological, developmental and clinical overview on cannabis use during pregnancy. Cannabis use in pregnancy poses major health concerns for pregnant mothers and their developing children. Although studies on the short- and long-term consequences of prenatal cannabis exposure are increasing, findings have been inconsistent or difficult to interpret due to methodological issues. Thus, consolidating these findings into clinical recommendations based on the mixed studies in the literature remains a challenge. Synthesizing the available observational studies is also difficult, because some of the published studies have substantial methodological weaknesses. Improving observational studies will be an important step toward understanding the extent to which prenatal exposure to cannabis influences neurodevelopment in the offspring. Therefore, further research on prenatal cannabis exposure and the long-term consequences to offspring health in representative samples are needed to guide and improve clinical care for pregnant women and their children. Future research should also investigate the role of policies on prenatal cannabis use.

Cannabis use during pregnancy is an important health issue as it may affect the health of pregnant women and their offspring. The idea of this narrative review of the literature was raised during round table discussions on cannabis use in pregnancy at the 10th Annual International Women's and Children's Health and Gender (InWomen's) Group Conference in June 2017 in Montreal. The mission of the InWomen's Group is to address issues in substance use among women, children, youth, and Lesbian Gay Bisexual Transgender Queer (LGBTQ) populations, and also examine gender differences globally. Issues that were addressed during this round table discussion included: What is the current scientific knowledge on prenatal cannabis use? How can we improve the scientific information and knowledge transfer? And, what are problems in clinical practice? Therefore, the purpose of the current

paper is to provide an epidemiological, developmental, and clinical overview of published research on cannabis use during pregnancy. In addition, the authors of this paper suggest directions for future research and offer evidence-based clinical guidance for providers working with reproductive age women.

1. Epidemiological overview

Rates of cannabis use among pregnant women are increasing just as fast as they are among non-pregnant women of reproductive age (Brown et al., 2017b). For example, in a US nationally representative study among reproductive-age women 18 to 44 years old, numbers showed that the prevalence of current cannabis use (i.e. past month

use) in pregnancy increased from 2.37% in 2002 to 3.85% in 2014, while the prevalence of cannabis use among non-pregnant women increased from 6.29% in 2002 to 9.27% in 2014 (Brown et al., 2017b). Considering the lower prevalence of cannabis use among pregnant women, compared to their non-pregnant counterparts, pregnancy might be viewed as a protective factor. However, this view may be overly liberal, given that rise in cannabis use over time appears to be similar between pregnant and non-pregnant women in the US (Brown et al., 2017b). In the Netherlands, a country that is considerably tolerant toward the use of cannabis, maternal cannabis use during pregnancy was approximately 3% in 2002 to 2006 (El Marroun et al., 2008). Unfortunately, there are no recent prevalence estimates of prenatal cannabis use in the Netherlands. Data suggests that women using cannabis during pregnancy are often daily users (El Marroun et al., 2008; Ko et al., 2015), and, cannabis-using pregnant women are more likely to meet criteria for cannabis use disorders relative to non-pregnant women of reproductive age (18.1% as compared to 11.4% in non-pregnant reproductive-age women) (Ko et al., 2015).

Given the increase of cannabis use among pregnant women and concerns about the potential negative fetal and child health consequences associated with prenatal cannabis exposure (Gunn et al., 2016), it is important to understand who may be at risk for using cannabis while pregnant. Younger age has been consistently associated with increased prenatal cannabis use (Brown et al., 2017b). For example, from 2002 to 2014 in a representative sample in the US, cannabis use during pregnancy was higher among 18 to 25 year-olds (7.47%) as compared to 26 to 44 year-olds (2.12%) (Brown et al., 2017b). In addition, low income or socioeconomic disadvantage; being divorced, separated, widowed, or never married; and tobacco, alcohol, and other illicit drug use were associated with increased past-year cannabis use (i.e. cannabis use during or around the time of pregnancy) among pregnant women (El Marroun et al., 2008; Ko et al., 2015). In addition, past-year psychiatric diagnoses, including any anxiety or mood disorder, antisocial personality disorder, and borderline personality disorder, have been associated with increased past-year cannabis use among pregnant women as well (Brown et al., 2017a). Delinquency and childhood trauma have also been associated with cannabis use during pregnancy (El Marroun et al., 2008). In addition to demographic risk factors (being married or single), the behaviours of others family members or friends in the social network of individuals can also pose a risk for prenatal cannabis use. For example, having a partner who uses cannabis is one of the strongest predictors of cannabis use during pregnancy (El Marroun et al., 2008).

Furthermore, mothers who use cannabis during pregnancy may also use it while breastfeeding, but very little information is available on this topic. A recent survey indicated that approximately 15% of breastfeeding mothers reported past year cannabis use in the US (Bergeria and Heil, 2015). It is important to further study breastfeeding and cannabis use as infants receiving breast milk of cannabis-using mothers are exposed at approximately 0.8% of maternal exposure (Djulus et al., 2005).

2. Developmental overview

Studies investigating prenatal cannabis exposure and pregnancy and birth outcomes are increasing. For example, in a systematic review and meta-analyses, it has been shown that children exposed to cannabis in utero have lower birth weight (but no difference in neonatal length or head circumference) and they need placement in the neonatal intensive care unit (Gunn et al., 2016). In addition, women who used cannabis had higher odds of anemia compared to women who did not use cannabis while pregnant (Gunn et al., 2016). However, no associations have been found between prenatal cannabis exposure and other birth outcomes such as stillbirth (Varner et al., 2014; Warshak et al., 2015) or fetal distress (Gunn et al., 2016).

However, information on neurodevelopmental outcomes in children exposed to cannabis in utero is sparse and has been researched in a few

longitudinal cohorts worldwide (reviewed in Calvigioni et al., 2014; Huizink, 2014; Jutras-Aswad et al., 2009; McLemore and Richardson, 2016; Trezza et al., 2008): a) The Ottawa Prenatal Prospective Study (OPPS) in Ottawa, Canada; b) The Maternal Health Practices and Child Development Study (MHPCD) in Philadelphia, the US; and (c) The Generation R Study in Rotterdam, the Netherlands. Offspring in the OPPS were followed until the ages 18–22 years (with expected attrition); follow-up data of the MHPCD study have been reported up to the age of 14; data reported on the children from the Generation R study is up to the age of 8 years, and data collection is still ongoing. These reviews (reviewed in Calvigioni et al., 2014; Huizink, 2014; Jutras-Aswad et al., 2009; McLemore and Richardson, 2016; Trezza et al., 2008) show that, at birth, newborns show increased tremors accompanied by exaggerated and prolonged startles or altered sleep patterns. In infancy, children exposed to cannabis in utero are more likely to have problems with executive functioning including lower memory scores, as well as more attention problems, hyperactivity and impulsivity in early childhood. In the longer-term, adolescents exposed to cannabis during pregnancy have a higher risk of problems with executive functioning, and are also more likely to develop emotional and behavioral problems, such as depression and delinquent behavior. However, studies are inconsistent; the OPSS found no association between cannabis exposure in pregnancy and infant mental development at 1 year. Likewise, the MHPCD cohort found no association of prenatal cannabis use and the mental scores of the Bayley Scales of Infant Development (reviewed in Huizink, 2014; Trezza et al., 2008). In addition, prenatal cannabis use has been related to more advanced motor skills (reviewed in Huizink, 2014).

Neurodevelopmental changes may be underlying these problems, and structural and functional neuroimaging studies suggest that the frontal part of the brain might develop and function differently in children and adolescents exposed to cannabis as compared to non-exposed controls (El Marroun et al., 2016; Smith et al., 2006; Smith et al., 2010). These studies suggest that the endocannabinoid system plays an essential role in the ontogeny of the nervous system during fetal brain development and that early gestational exposure to cannabis is able to induce lasting but subtle neurodevelopmental alterations. Indeed, a growing body of evidence indicates that the endocannabinoid system plays a role in a broad array of critical neurodevelopmental processes, from early neural stem cell survival and proliferation to the migration and differentiation of both glial and neuronal lineages as well as neuronal connectivity and synaptic function (Lubman et al., 2015). Moreover, animal studies are in agreement with these findings, as they show that exposure to low doses of THC in a narrow temporal window during prenatal development (embryonic day 12.5 to 16.5) negatively impacts mouse cortical development (de Salas-Quiroga et al., 2015), and this, in turn, has long-term functional consequences on mature offspring (Wu et al., 2011).

Nevertheless, while information on prenatal cannabis use and fetal outcomes is becoming increasingly available, little information is present on maternal cannabis use during pregnancy and the long-term physiological and neurodevelopmental consequences in offspring. Although the number of high-quality studies is increasing, many of the published studies are limited by methodological problems. These methodological problems include small sample sizes, biases (e.g. selection bias, confounding or misclassification are often major limitations), have different study designs (e.g. cross-sectional, retrospective or prospective studies), assessment of different outcomes, and differences in exposure assessment (self-report or urinalysis) (Beatty et al., 2012; El Marroun et al., 2011) making it difficult to synthesize information and make valid conclusions regarding the health effects of prenatal cannabis exposure. In a recent report of the National Academies of Sciences (National Academies of Sciences, Engineering, and Medicine, et al., 2017), the committee did not identify a good- or fair-quality systematic review that reported on the association between prenatal cannabis exposure and later outcomes for children and thus