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Review Article

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

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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

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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

reported on the studies performed in three different cohorts (ACOG, 2011). Further, cannabis use is often combined with smoking tobacco, which makes disentangling the specific effect of cannabis only difficult. These methodological differences across studies must be kept in mind as they may contribute to the inconsistent findings. Notably, in the past decade, levels of Δ9-tetrahydrocannabinol (THC) in cannabis products have increased (Dujourdy and Besacier, 2017; Niesink et al., 2015), and high potency products such as butane hash oil have become available (Miller et al., 2016). These potent products may influence fetal development, as cannabis metabolites are able to pass the placental barrier.

In summary, there is substantial evidence of an association between prenatal cannabis use and lower birth weight in offspring. However, the long-term effects (> 10 years) of prenatal cannabis exposure on offspring neurodevelopmental outcomes (for example, cognitive functioning or academic achievement) are less well established as there are only three longitudinal cohorts that measured different outcomes at different ages in the offspring. Specially, longitudinal studies that examine the association of prenatal cannabis exposure on health and neurodevelopment prospectively through childhood and adolescence, rather than just infant years, are needed to understand the potential long-term consequences. Thus, continued research on the potential consequences of prenatal cannabis exposure on other fetal and child health outcomes is necessary.

3. Considerations for future research

First, to capture possible long-term outcomes, prospective longitudinal studies with longer follow-up periods are necessary. The follow-up in each study was at least 8 years and some outcomes of interest, such as academic achievements, labor participation, delinquency, schizophrenia, psychotic symptoms, and addiction develop later in life. A challenge with such studies, of course, is attrition, and thus cohorts need to heavily invest in reducing participant loss in their studies. A possible solution to this challenge is using registry data: some countries, particularly the Nordic countries, have nationwide registries (Lund and Bukten, 2015) that are well-suited for longitudinal studies. The registries include comprehensive information about each citizen over the course of their lives, including detailed demographic information (e.g. education, employment, marital status, all birth and death dates), and health care utilization (e.g., contacts with primary health care, specialist health care, dispensed prescription medications). In some countries, information from the various registries can be combined at the individual and family level using the personal identification numbers that are assigned to each person at birth. However, despite many advantages with nationwide registries, they are not always able to identify risks associated with prenatal exposure to legal and illegal substances, as often this is not documented in the registries (except in cases with a parental substance use disorder). Importantly, though, most women using cannabis during pregnancy do not have a cannabis use disorder diagnosis registered in their medical record. Thus, only a small proportion will be identified with this approach. One solution to identify cannabis-using women who do not have a cannabis use disorder is to combine pregnancy cohort surveys with registry data. This would be possible if survey respondents are also asked to provide their personal identification numbers and provide consent to match information from the survey(s) to registry data. This approach has several advantages: depending on the survey questions, it can provide detailed information on maternal cannabis use and other substance use during pregnancy. Further, since follow-up can be done in registries, issues with loss to follow-up will be non-existent or negligible.

Second, to inform public health policy regarding the effect of prenatal exposure to cannabis on subsequent child outcomes, future studies that differentiate between causal and non-causal associations are necessary. Determining causality is difficult given that many women who use cannabis also use other substances (Coleman-Cowger et al., 2017; Gunn et al., 2016; Hasin, 2017; Washio et al., 2018). In addition, using cannabis in pregnancy is related to many socioeconomic and psychosocial indicators (El Marroun et al., 2008), which confound the association of prenatal cannabis exposure and maternal and child health outcomes. If associations are presented as causal associations when they are not, this may result in misguided interventions that are a waste of resources and distract attention from effective methods (Smith, 2008). To address unmeasured or residual confounding, several innovative study designs could be used. For instance, quasi-experimental designs are able to control for unmeasured familial risk factors (D'Onofrio et al., 2013; Hill et al., 2000). Mendelian Randomization (MR) is an exciting and innovative technique that was proposed in 1986, but only recently became viable following advances in the field of genetics. MR utilizes genetic variation strongly associated with a predictor variable, as a proxy or 'instrument' to test causal effects on a specified outcome variable. For example, genetic variants that modify the biological response to an environmental exposure—such as genetic variants related to alcohol metabolism can be taken as indicators of the effects of different levels of exposure (Smith and Ebrahim, 2004). In addition, a recent genome-wide association study has identified multiple genetic variants related to lifetime cannabis use (Pasman et al., 2018). Typically, observational studies are weakened by residual confounding and reverse causation, and bidirectional MR designs can be used to account for reverse causality and residual confounding (Davey Smith and Ebrahim, 2003). Other instrumental variable methods are also well-suited to overcome unmeasured confounding in epidemiological studies (Davies et al., 2017), for example using a negative control. Studies using paternal cannabis exposure as a negative exposure may give insights into the role of potential shared familial confounding and genetic predisposition (Smith, 2008). When mothers use cannabis during pregnancy almost all fathers/partners use cannabis as well. However, when fathers use cannabis, only 10% of the mothers use cannabis. This has been previously shown in the Generation R study, and thus cannabis use by the father or partner is suitable to account for non-intrauterine effects of cannabis use. Finally, a promising approach is using a sibling design in which family factors are controlled for. However, discordant siblings (i.e., being exposed and unexposed to cannabis) are rare, and statistical power is a common limitation of this approach (Frisell et al., 2012). Moreover, if the siblings are discordant on the exposure, they may also be discordant on other variables, which may lead to bias.

Finally, future research should examine the role of policies (e.g., medical and recreational cannabis laws) on prenatal cannabis use. Cannabis use during pregnancy has been increasing (Brown et al., 2017b) in the context of US states adopting more permissive cannabis legislation, despite continued federal prohibition of cannabis use. In the past two decades, more than half of the US states have implemented medicinal marijuana laws and 8 states plus the District of Columbia have legalized adult recreational cannabis use. Some evidence suggests that medical marijuana laws are associated with increased cannabis use and cannabis use disorder among adults, whereas data are insufficient to determine the effects of recreational legalization (Carliner et al., 2017). Other possible consequences of the changing cannabis policy landscape in the US are potential modifications in modes of cannabis use (inhalation through a wide array of devices, vaping, dabbing, or oral delivery by ingestible oils and edibles), increased potency of cannabis products, and increased cannabis availability (Budney and Borodovsky, 2017). A potential unintentional consequence of increasingly permissive marijuana use laws could be the increased use of high potency cannabis during and around the time of pregnancy; however, research has not yet directly examined this hypothesis.

The 'coffee shop system' in the Netherlands, which is a system that was introduced in 1976 and does not fully prohibit nor fully legalize use of cannabis, could give us some hints at what might happen in the US (MacCoun, 2011). The best available evidence paints a nuanced picture. Although life-time prevalence in the Netherlands is relatively high (28.0%), the Dutch 'continuation rate' is lower relative to their

counterparts in Europe and the United States (MacCoun, 2011).

4. Considerations for clinical practice

4.1. Identification of pregnant cannabis users

Healthcare providers have an important opportunity to address prenatal cannabis use in a prenatal care setting. However, providers may face a dilemma of having to develop rapport with a pregnant cannabis-using patient while meeting mandatory requirements to report prenatal substance use to a state agency in some states (Mark and Terplan, 2017). Developing rapport and therapeutic relationship with healthcare providers is essential to reduce fear of stigmatization or other consequences and increase disclosure of use (Mark and Terplan, 2017; McLafferty et al., 2016). Providers must also be educated in order to inform their pregnant patients on possible medical, social, and legal consequences of cannabis use while empathizing and attenuating the feeling of guilt or shame related to their cannabis use (McLafferty et al., 2016). Sole use of biochemical screening to identify prenatal substance use might not be ideal, since it may interfere with the process of developing a therapeutic relationship with a patient who screened positive for use while denying the use (Terplan, 2012). Further, sole use of urine screening, does not provide a comprehensive estimate of cannabis use in pregnancy. The combination of self-reported information with urinalysis is needed to improve the quality of cannabis use assessment as self-reported information may add information on frequency, quantity and products used (El Marroun et al., 2011; Young-Wolff et al., 2017). Further, THC detection using urine, blood, saliva or hair is possible (Musshoff and Madea, 2006; Teixeira et al., 2007), but these methods do not provide accurate information on timing of cannabis use during pregnancy. Therefore, Screening, Brief Intervention, and Referral to Treatment (SBIRT) if necessary may be ideal to identify prenatal cannabis use and engage women in a discussion of their use, including reasons for use, providing feedback on the possible consequences of prenatal cannabis use, discouraging cannabis use and encourage additional treatment as appropriate. Because many women who report prenatal cannabis use also tend to smoke tobacco while pregnant, providers should be prepared to address both cannabis and tobacco use (Coleman-Cowger et al., 2017).

4.2. Barriers to medical providers

Notably, providers state that they lack knowledge of definitive health risks of cannabis use during and around the time of pregnancy (Holland et al., 2016). Therefore, health care provider education is needed on the risks of cannabis use on reproductive health. A targeted approach to treating prenatal cannabis use should be developed, as this area remains under developed (McLafferty et al., 2016). Further, to promote optimal maternal and child health, states should dismantle mandatory reporting laws that criminalize women for prenatal substance use. Punitive laws discourage women from disclosing use of cannabis (or other substances) during prenatal check-ups, ultimately leading to missing opportunities for treatment and prevention. Such laws have been demonstrated to be ineffective and inappropriate (ACOG, 2011). Finally, the environmental context should also be considered as cannabis use may be serving specific functions for pregnant women (e.g., relief of nausea (Westfall, 2004; Westfall et al., 2006), or potentially reducing anxiety or stress), that must be addressed in conjunction with the recommendations for abstinence from cannabis use by the American Congress of Obstetricians and Gynecologists (Committee on Obstetric Practice, 2017). Considering that cannabis use is discouraged during preconception, pregnancy, and lactation (ACOG, 2015), health care providers should have a discussion about cannabis use with all women of reproductive age, including those who are planning for pregnancy and those who are postpartum.

5. Summary

The aim of narrative review was to describe the findings from epidemiological and developmental perspectives, and to provide suggestions for future studies and clinical practice. 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 the published studies have substantial methodological weaknesses and gaps remain in the literature. Improving observational studies and addressing unanswered questions will be important steps toward understanding the extent to which prenatal exposure to cannabis influences neurodevelopment in the offspring.

In conclusion, 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.

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Conflict of interest statement

All authors declare that they have no competing interests.

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