Title: The Effects of Cannabis on Female Reproductive Health Across the Life Course

Author Names:

Daniel J Corsi, PhD^{a, b, c, d}, dcorsi@ohri.ca

Malia SQ Murphy, PhD^c, malmurphy@ohri.ca

Jocelynn Cook, PhD^{e, f}, jcook@sogc.com

Author Affiliations:

^aChildren's Hospital of Eastern Ontario Research Institute

^bBetter Outcomes Registry & Network (BORN) Ontario

^cOMNI Research Group, Clinical Epidemiology Program, Ottawa Hospital Research Institute

^dSchool of Epidemiology and Public Health, University of Ottawa

^eSociety of Obstetricians and Gynaecologists of Canada

^fDepartment of Obstetrics and Gynaecology, University of Ottawa

Corresponding Author:

Daniel J Corsi, PhD

Centre for Practice Changing Research, Box 241

Ottawa Hospital Research Institute

501 Smyth Road

Ottawa, Ontario, K1H 8L6

Email: dcorsi@ohri.ca

Telephone: 613-725-9466

Word Count: 4147

Declarations of interest: None

Abstract

Cannabis is commonly used for its medicinal and therapeutic benefits and is also widely used as a recreational drug. Cannabis use has been increasing in Canada, including among Canadian women of reproductive age. Post-legalization, further increases in cannabis use are expected as a result of increased availability and lowered perceptions of harm. Although cannabinoids are well known for their effects on the central and peripheral nervous systems, endocannabinoid receptors have also been characterized throughout the female reproductive tract. Cannabinoids may affect many aspects of female reproductive health, including fertility, pregnancy outcomes with neonatal implications, and menopause. The existing literature is primarily concentrated on the effect of cannabis use in pregnancy and breastfeeding, with little exploration of its impact on fertility and in later life. In this review, we consolidate the available literature to provide an overview of trends in cannabis use among women and review the impact of cannabis across the female reproductive lifespan. We searched the PubMed and Cochrane Library databases using keywords and MeSH terms. Included studies were those reporting on the potential impact of cannabinoids on female fertility, pregnancy, transmission to breastmilk, neonatal outcomes and menopause.

Keywords (4-6): cannabis, marijuana, pregnancy, fertility, breastfeeding, menopause

Introduction

Cannabis is used widely recreationally and for an array of medicinal and therapeutic purposes. Before legalization, cannabis was the most widely used illicit drug in Canada,[1] and its use was on the rise across multiple age groups, including among women of reproductive age.[1–3]

The primary psychoactive component of cannabis, tetrahydrocannabinol (THC), is rapidly absorbed by the bloodstream and spreads quickly throughout the body.[4] Cannabinoids, including THC, cannabidiol and cannabinol have a direct impact on the endogenous cannabinoid signalling system (ECSS), a broad-spectrum modulator of the central and peripheral nervous systems.[5,6] The ECSS includes two primary G-protein coupled receptors – CB1 and CB2 – which are present throughout the body. Although primarily expressed in the brain and immune system cells, these endocannabinoid receptors have also been characterized throughout various tissues of the female reproductive tract.[5] Exposure to cannabinoids may have differential impacts on female reproductive health across the life course from preconception through to pregnancy, breastfeeding, and menopause.

There is currently limited evidence on the potential short- and long-term health effects of cannabis use in women beyond of the perinatal window. In this review, we summarize the available literature to explore the impact of cannabis across a women's reproductive lifespan.

Methods

A literature search was conducted in PubMed and Cochrane Library databases using keywords and MeSH terms for publications related to cannabis use and outcomes related to fertility, pregnancy, breastfeeding and menopause. All study designs were included including clinical

68 trials, observational studies, reviews including systematic reviews and meta-analysis, guidelines,
69 and conference consensuses. Included studies were those with pregnant and breastfeeding
70 individuals as the target population, and cannabis as the intervention or exposure of interest. The
71 year of publication, location and environment of published studies were not limited. The
72 reference lists of included articles were screened publications that may have been missed by the
73 search strategy.

75 **Cannabis and Female Fertility**

76 Endocrine studies in animals have consistently shown the female reproductive system to
77 be sensitive to the effects of cannabinoids. CB1 and CB2 type endocannabinoid receptors for
78 THC are expressed in the oviduct, uterus and anterior pituitary.[7] Knockout models for CB1 and
79 CB2 receptors exhibit defects in fertilization and implantation.[8–10] Work in rodents and non-
80 human primates has shown reductions in sex hormone levels and ovulatory disruption.[11–15] In
81 women, data on the impact of cannabis use on fertility are few, and some studies are conflicting.
82 However, a summary of the available evidence suggests that cannabinoid exposure may
83 adversely affect female reproductive function.

85 *Ovulation*

86 Clinical data suggest that cannabis may affect sex hormones essential to fertility and the
87 timing of ovulation.¹ In a sample of 201 women who are planning pregnancy, Jukic *et al.* used

¹The ovarian and uterine cycles together are referred to as the menstrual cycle. They are characterized by fluctuations in sex hormones that prepare the female reproductive tract for conception and pregnancy. The follicular phase begins with the onset of menses. Estradiol rises, followed by a surge in luteinizing hormone (LH) that stimulates ovulation. Ovulation marks the

the self-reported number of times smoking cannabis in the past month and urine estradiol and progesterone levels to determine the effect of cannabis on the timing of ovulation; cannabis use was associated with longer follicular phase lengths compared to non-users.[16] Based on these data, follicular phases were 3.5 days longer among individuals reporting occasional cannabis use (1-3 times in the past three months, $p=0.04$), and 1.7 days longer among frequent cannabis users (>3 times in the past three months, $p=0.04$), with an excess of anovulatory cycles among cannabis smokers (43% vs 15% in non-smokers); ovulatory delay and potentially cycle inhibition were associated with cannabis use. Lammert *et al.* compared the menstrual cycles of premenopausal women reporting co-use of tobacco and cannabis ($n=13$) with age-matched controls who used tobacco only ($n=39$);[17] the luteal phase length was 5.4 days shorter among women who reported co-use of tobacco and cannabis ($11.4 \text{ days} \pm \text{SD } 2.2$) than women who used tobacco only ($16.8 \text{ days} \pm \text{SD } 11.3$, $p=0.002$). In contrast to the findings by Jukic *et al.*, there was no apparent suppression of the LH surge based on urine testing. Cannabis use was based on self-report (yes/no), and no additional information on timing or frequency of use was collected.

In another study, White *et al.* found no association between past or current cannabis use and serum anti-Mullerian hormone (AMH) levels in a cross-sectional analysis of 913 premenopausal women.[18] AMH is an indirect marker of fertility and ovarian follicular reserve, and correlates with IVF success rates and time to menopause. Cannabis smoking status, frequency, years of use or age of initiation were not associated with AMH levels. There were

beginning of the luteal phase, which is characterized by a rise in progesterone and a secondary peak in estradiol as the uterine endometrium thickens in preparation for implantation. Menstrual cycle phase durations and timing of ovulation vary between and within women and are vulnerable to physiological stressors.

very few current cannabis users in this study (<1%), limiting the ability to draw a conclusion from their findings. Another study of 17 female cannabis users reporting at least weekly cannabis use for the previous two years compared to 39 non-users, found that chronic cannabis use did not affect concentrations of serum LH, FSH, or prolactin;[19] stratification by frequency of cannabis use did not change the study findings.

The acute effects of cannabis smoking on sex hormones in reproductive-aged women have also been examined. In one of the earliest clinical studies on the topic, Mendelson *et al.* performed time-course experiments in small groups of women with an average 14 times per month frequency of cannabis use. Healthy volunteers consumed a 1g cannabis cigarette containing 1.8% THC at various time points during their menstrual cycles and submitted to sex hormone testing. In the periovulatory phases of 8 women, smoking a 1g cannabis cigarette induced a statistically significant increase in LH and prolactin levels 20 minutes after smoking initiation.[20] There were no changes in estradiol or progesterone levels. The same authors assessed the effect of cannabis smoking on female sex hormones during the luteal phases of 16 women using the same experimental design. Data revealed that smoking a 1g cannabis cigarette induced a 30% suppression in LH levels compared to smoking a placebo cigarette.[21] No changes in estradiol or progesterone levels after cannabis smoking were observed.

More recent data suggest that women expect cannabis to ameliorate pre-menopausal symptoms (PMS) such as irritability and joint and muscle discomfort.[22] With the wider availability of cannabis as many jurisdictions move toward legalization of the drug, more work is required to thoroughly evaluate the efficacy of cannabinoid products on treating PMS symptoms, particularly in light of the potential repercussions on fertility.

Time to conception

There are limited data on the impact on cannabis use on time to conception. In a population-based sample of women who completed the U.S. National Survey of Family Growth, Kasman *et al.* sought to assess the impact of cannabis use on fertility among women who were actively trying to become pregnant.[23] Using a current-duration approach to assess fecundity, the authors relied on answers to the question, “How long have you been trying to become pregnant”. 124 (12.5%) of women in this sample reported cannabis smoking in the preceding 12 months while attempting to conceive. There were no observed effects of cannabis use on time to pregnancy; adjusted time ratio of 1.03 months (95%CI 0.80-1.31). Similarly, there were not observed effects of frequency of cannabis use (monthly, weekly, daily) on time to pregnancy, and no significant interactions with respondent age, race, income, marital status, parity and infertility care were found. In contrast, Wise *et al.* used data from a web-based preconception cohort study to evaluate the association between use of cannabis and fecundability (per cycle probability of conception).[24] The authors found no clear association between female cannabis use and fecundability. Compared to non-users, individuals reporting cannabis use in the previous two months had fecundability ratios of 0.99 (95% CI 0.85-1.16) for cannabis use <1 time per week and 0.98 (95% CI 0.80-1.20) for cannabis use at least once per week. Mueller *et al.* examined a cohort of 300 women seeking evaluation for infertility challenges, and showed that those reporting smoking cannabis had an elevated risk for primary ovulatory infertility compared to those did not use cannabis (RR 1.77, 95% CI 1.0-3.0).[25] The risk for infertility was greatest among women who had used cannabis within one year of trying to become pregnant (RR 2.1 95% CI 1.1-4.0).

Increases in cannabis use are highest among individuals of reproductive age.[1,26] Progressive increases are anticipated as a result of increased availability and lowered perceptions of harm associated with the legalization of the drug across several jurisdictions. The lack of contemporary data highlights a need for a more substantive evaluation of the potential consequences of cannabis exposure and female fertility.

Cannabis Use in Pregnancy

In pregnancy, cannabinoids, including THC and cannabidiol (CBD, non-psychoactive), and their metabolic byproducts cross the placenta, enter the fetal bloodstream and distribute to fetal tissues including the brain.[6] Non-human studies show that THC reaches fetal plasma within 15 minutes of maternal exposure, equilibrating to maternal levels within 3 hours.[6] The lipophilic nature of THC, together with its half-life of up to eight days in fatty tissues, resulting in slow fetal clearance of the compound. Fetal exposure is, therefore, prolonged even after maternal discontinuation.[27,28] CBD has molecular similarities to THC, although data on maternal consumption of CBD are limited, and there is a lack of evidence for the potential benefits of products such as CBD oils. The routes and formats of cannabis use have also changed with the availability of vaporizers, tinctures, new consumables and oils, which may have implications for risk; however, robust evidence about these forms is currently lacking.

Data on cannabis use in pregnancy have primarily relied on maternal self-report. Although economical and reasonably valid for epidemiological studies,[29] it is important to note that self-reports can suffer from bias and measurement error. Misreporting or inaccuracies in reporting perinatal cannabis use may arise due to related to feelings of guilt; fear of legal

action, later child apprehension, or social stigmatization; poor recall of drug-use details, poorly constructed screening tools; or inadequate training of interview staff.[29–31]

Prevalence of Cannabis Use in Pregnancy

Current data suggest that rates of cannabis consumption are increasing among women of reproductive age, those who are pregnant, and those who are breastfeeding. In Canada, pre-legalization provincial data from Ontario demonstrate that cannabis use in pregnancy increased from 1.2% in 2012 to 1.8% in 2017; a relative risk increase of 61%.[2] Similar increases have been observed in British Columbia and in other countries, where available data suggest that peripartum cannabis use based on self-reports and toxicology varies from 1 to 8%.[3,29,32–36]

The US National Survey on Drug Use and Health from 2002-2014 included 4,971 pregnant women, 3.9% of whom reported last-month cannabis use. The prevalence of cannabis use was highest at 7.4% in the first trimester of pregnancy.[35] The National Birth Defect Prevention Study, also based in the US, reported that 4% of the 15,208 mothers reported cannabis use in the periconceptional period.[37] An international multi-centre prospective study of nulliparous women (n=5,888) assessed cannabis use at 15 and 20 weeks' gestation. Self-reported cannabis use in pregnancy during this time was 3.9%.[33] A substance use survey conducted 2-3 days postpartum among mothers in France (n=13,545) found a self-reported rate of 1.2% for cannabis use in pregnancy.[32] In Australia, a retrospective cohort study (n=24,874) showed the prevalence of ever-use cannabis among women to be 9.5%, and while in pregnancy to be 2.6%.[34] Finally, the longitudinal Generation R Study from Rotterdam, Netherlands, also relied on self-report to collect data on cannabis use in pregnancy. In this cohort, 214 (2.9%) of

the 7,452 participants reported cannabis use before and during the first trimester of pregnancy. A total of 41 (19%) of cannabis users continued to use throughout pregnancy.[38]

Associations with maternal conditions in pregnancy and perinatal outcomes

A recent meta-analysis of 24 case-control, cross-sectional and cohort studies indicated that women who reported cannabis use during their pregnancy had higher odds of being anemic (pooled OR 1.36) compared to non-users.[39] An increased incidence of stillbirth has been noted by a case-control study which confirmed cannabis use via umbilical cord toxicology analysis (odds OR 2.83).[40] Multiple studies have shown an association between cannabis use and preterm labour.[32–34] An interview survey study in France,[32] which included women with singleton pregnancies from all maternity units in the country (n=13,545) found a higher rate of spontaneous preterm birth (adjusted odds ratio [aOR] 2.15) among the 1.2% of women who reported cannabis use during pregnancy. A prospective cohort study in Australia, which stratified cannabis use by gestational age, showed that cannabis use has an adjusted odds ratio of 2.28 with spontaneous preterm birth, and for women who reported marijuana use at 20 weeks' gestation, the association is even stronger (aOR 5.44).[33] Similarly, a separate study from Australia showed increased preterm birth (aOR 1.5) with population attributable risk of 1.5%.[34] An extensive and recent study indicated an increased risk of poor birth outcomes among mothers self-reporting cannabis in Ontario. The rate of preterm birth less than 37 weeks' gestation was 12% among women reporting cannabis use compared to 6% among non-users, the rate of small-for-gestational-age infants was 18% vs 9% in users and non-users, respectively, and transfer to neonatal intensive care was 25% vs 12%, respectively. These associations remained statistically

significant after accounting for differences in age, socioeconomic status, body mass index, and use of tobacco between women who reported cannabis use and those who did not).[41]

Associations with neonatal outcomes

The use of cannabis during pregnancy has been associated with adverse neonatal outcomes including preterm birth,[3,33,34,41] lower birth weights compared to infants born to mothers who did not use during pregnancy,[34,38] small-for-gestational-age,[33,34,41] shorter neonatal lengths,[39,42] smaller head circumference,[43] and increased admission to neonatal intensive care unit.[39,41]

Fetal and infant exposure to cannabis during pregnancy and breastfeeding can disrupt the fetal ECSS, which is present and active from the early embryonic stage and modulates neurodevelopment into adulthood.[6] Perturbations to this system have a range of cellular effects and may affect cognitive, behavioural, and emotional development in childhood.[6,44,45] Several longitudinal studies have reported on associations between prenatal cannabis exposure and childhood neurodevelopmental outcomes.[46,47] None have included population-level or postpartum exposure analyses. The Ottawa Prenatal Prospective Study followed children born from 1980-83 to 2000 predominantly healthy, Caucasian, middle-class women. The study included women selected for use of cannabis, alcohol, or tobacco and a comparison group of 50 non-users.[48] Based on maternal self-report, 47 of 250 children had documented prenatal cannabis exposure, averaging about 1 joint/week during pregnancy. Exposed neonates had increased startle response, tremors, and poor habituation to visual stimuli versus unexposed neonates.[48] The Maternal Health Practices and Child Development Study (Pittsburgh, USA; initiated in 1982), interviewed 1360 randomly selected women from an inner-city out-patient

prenatal clinic.[42] Participants were predominantly un-married, low-income and 50% were African American. Women who self-reported >2 joints/month in the first trimester were followed and a random sample of women who used “less than this amount” served as controls.[42] The authors reported negative effects of cannabis exposure on child performance on Stanford-Binet Intelligence Scale at 3 years old. Effects were limited to exposure during the first and second trimesters.[49] Second trimester exposure was also associated with increased impulsivity, hyperactivity and delinquency; and decreased concentration, IQ score, verbal and visual reasoning at 6-10 years of age.[50] The Generation R study (Rotterdam, Netherlands; initiated in 2002) also relied on self-report to collect data on cannabis use in pregnancy.[51] Among exposed children (88 of 4077), only girls exhibited significant increases in attention problems at 18-months of age based on the Child Behaviour Checklist (CBCL; OR 2.75, 95%CI 1.27-5.96).[51] Aggressive behaviour was also increased among girls at this age but the association was not statistically significant (OR 1.66, 95%CI 0.38-7.26).

Cannabis and Breastfeeding

The low molecular weight and high lipid solubility of cannabinoids contribute to its propensity for transfer into breastmilk.[4,52–54] The pharmacokinetics of cannabinoids in breastmilk are not well understood, however, transfer of cannabinoids to maternal breastmilk are likely subject to maternal dosing and frequency of dosing. The variable fat composition of human milk and the milk sample type (hind milk has a substantially higher lipid content than foremilk)[55,56] can further affect the cannabinoid content of a given sample. In a field where determining cannabis exposure is still largely reliant on self-reported data that do not include

comprehensive use profiles, it is unsurprising that data related to cannabis and breastmilk are lacking.

Limited data are available on the effects of postpartum exposure to cannabis through breastmilk. A paper by Astley and Little identified a difference in infant motor development at one year of age between infants based on the level of cannabis exposure in breastmilk.[57] These findings may be confounded by maternal consumption during pregnancy and have not been well replicated.[58] Distinguishing the effects of prenatal and postnatal exposures is challenging when women are unlikely to begin using cannabis de novo in the postpartum period after abstaining in the periconceptional and gestational periods.

Transfer to breastmilk and the neonate

Case-reports confirming the presence of cannabinoids in the breastmilk of mothers who consume cannabis during lactation[52,59] have prompted more recent development and validation of new methods for cannabinoid detection in this matrix,[60] and investigation into its pharmacokinetic properties.[54,61]

In a 1982 correspondence in the New England Journal of Medicine, Perez-Reyez *et al.* reported the presence of THC in the breastmilk of two chronic cannabis users.[59] Cannabinoid concentrations in breastmilk were as high as 8 times higher than in maternal serum concentrations. Fecal samples from one of the infants were also positive for THC and its principal metabolites 11-hydroxy-THC and 9-carboxy-THC. More recently, Crume *et al.* investigated the prevalence of maternal cannabis use in the early postnatal period among a population-based sample of mothers responding to the 2014-2015 Colorado Pregnancy Risk Assessment Monitoring System survey.[62] The prevalence of postnatal cannabis use in this

cohort of 3285 respondents was 5% (95%CI, 4.1-6.2). Among women who breastfed in the first 8 weeks, prevalence of postnatal cannabis use was 10.2% (95%CI, 7.1-14.6). Prenatal and postnatal cannabis use were also associated with a shorter duration of breastfeeding. Bertrand *et al.* used samples from a human milk biorepository to quantify cannabinoids in the samples of mothers who had reported cannabis use within 14 days of collection.[54] Cannabinoids were detectable in 34 (63%) of the 54 analyzed samples, up to 6 days after the last reported use. Frequency of cannabis use and time between consumption and sample collection were significant predictors of THC milk concentrations. Finally, in a pilot pharmacokinetic study, Baker *et al.* evaluated the transfer of THC metabolites into the breastmilk of 8 volunteers after a known THC dose.[61] Participants were 18-45 years old, a median 5 months postpartum (range 3-5 months) and all reported smoking cannabis while exclusively breastfeeding. Participants were instructed to purchase a pre-weighed 0.1g sample of cannabis with 23.18% THC content from a pre-specified dispensary. After abstaining from cannabis for 24 hours, samples were smoked using a provided glass pipe and milk samples collected at 0 hour (before smoking), 20 minutes, 1 hr, 2 hr and 4 hr after inhalation. THC concentrations in maternal milk peaked at 1 hour (mean 94 ng/mL, range 21.2-420.3 ng/mL) and declined slowly over the remaining study period.

Cannabis exposure through breastmilk and infant outcomes

Data regarding outcomes in infants exposed to cannabis through breastmilk are conflicting. Astley and Little used Psychomotor Developmental Index scores to demonstrate motor deficits at 12 months of age among 68 infants exposed to cannabis during lactation in the first month postpartum compared with 81 controls who were not exposed. The effects of postnatal cannabis exposure were difficult to delineate from prenatal exposures however; 84% of

individuals who used cannabis in pregnancy continued to use the drug during lactation.[57] In contrast, Tennes *et al.* used the Bayley Infant Scale of Mental and Motor Development to assess infant outcomes following prenatal and postnatal cannabis exposure in a population of pregnant women known to include a high proportion of cannabis users.[63] 62 infants were breastfed and 27 (43.5%) mothers reported using cannabis during breastfeeding. The authors reported no differences in the psychomotor development of 12-month old infants whose mothers reported cannabis use while breastfeeding compared to unexposed infants. The authors cited statistical limitations as a result of small sample size and lack of comparability across cases for duration and dose of cannabis consumption.

Clinical recommendations

The paucity of data has made it challenging for professional organizations to provide definitive information to maternity care providers and their patients. In the absence of such data, the Society for Obstetricians and Gynaecologists of Canada[64] and the American College of Obstetricians and Gynecologists[65] both encourage that cannabis be avoided during lactation. The guidelines do not, however, recommend against breastfeeding while using cannabis. Women who use cannabis and breastfeed should be supported to breastfeed well, and this can be supported for example through referral to a lactation consultant.

Cannabis and Menopause

Symptoms associated with the hormonal changes that occur during the transitional period into menopause range broadly from hot flashes, irritability, depressed moods, poor sleep, joint and muscle pain, vaginal dryness and urinary symptoms. The duration of the menopausal

transition varies between individuals, typically lasting 2-6 years.[66] Treatment options include hormone replacement therapy, anti-depressant medications, and herbal and other alternative therapies. Although the efficacy of cannabis has been cited for a number of health concerns that are also commonly described in perimenopausal women (e.g., sleep, irritability, joint pain, depression),[67] little work has explored the use, efficacy and safety of cannabis in women seeking treatment for menopausal symptoms.

In a small double-blinded cross over study, Mendelson evaluated the acute effects of cannabis smoking in 10 healthy menopausal volunteers with naïve cannabis use histories.[68] Cannabis smoking (1g cigarette with 1.83% THC) did not elicit changes in plasma LH levels compared to smoking a placebo cigarette.[68] Effect on symptoms of menopause were not collected. The authors noted that their findings did not rule out the possibility that natural or synthetic cannabinoids may be useful for menopausal symptoms. They suggested that cannabis may be helpful in ameliorating menopausal symptoms via non LH-mediated mechanisms. In the same sample of women, Benedikt *et al.* reported a 14 beat/min pulse rate increase.[69] More recently, Slavin and colleagues surveyed 115 menopausal and post-menopausal women with favourable perceptions toward cannabis use to evaluate expectancy-mediated effects of cannabis on menopausal symptoms.[67] Frequency of self-reported cannabis use was significantly correlated to menopausal symptoms. Expectancy of cannabis-induced amelioration of menopausal symptoms was also correlated to severity of menopausal symptoms. Cannabis was not perceived to be equally effective for all symptoms. Whereas cannabis was perceived to be largely beneficial for treating joint/muscle discomfort, irritability, sleep problems, depression, anxiety and hot flashes, this was not the case for other symptoms such as heart discomfort, exhaustion vaginal dryness and bladder problems. Given that individual expectancies for positive

outcomes may influence frequency and quantity of cannabis use, the authors concluded that effort is warranted to ensure that consumer expectancies are in line with supported evidence.

Summary

Approximately 11% of all women in Canada use cannabis, increasing to 16% among women 15-49 years of age. Cannabis use may have health implications for women, and these may vary across the life course. In this review, we summarized the effects of cannabis on female health from fertility, pregnancy and neonatal outcomes, breastfeeding, and menopause. Although there appears to be little evidence of an overall association between cannabis use and female fertility and fecundability, there are limited studies in this area. Cannabis use in pregnancy appears to be associated with adverse neonatal outcomes, in particular, low birth weight, preterm birth, admission to neonatal intensive care, and small for gestational age. Some studies report inconsistent associations between cannabis use and outcomes. This difference may be related to statistical adjustment for confounding factors, exposure ascertainment, or other significant differences between women who use cannabis and those who do not. International studies have also shown that women who use cannabis are more likely to be younger, unmarried, have lower income and education, and concurrently use alcohol, tobacco and other illicit substances. We found evidence that cannabis and its metabolites may transfer to breastmilk. To date, however, there are limited studies on potential effects on infants who may be exposed to maternal cannabis through breastmilk. Finally, studies on cannabis and menopause indicate that cannabis was not associated with plasma LH levels, but may be used to some benefit to alleviate specific symptoms of menopause. Cannabis use is increasing, and this is concurrent with raised social acceptability and lowered perceptions of harm. There remain critical gaps in the literature about

379 the potential risks of cannabis use, particularly in vulnerable populations, including pregnant
380 women, women who are breastfeeding, and their infants.

381 **Acknowledgements**

382 This work was supported in part by the Public Health Agency of Canada. The funding source
383 had no involvement in the study design; in the collection, analysis and interpretation of data; in
384 the writing of the report; and the decision to submit the article for publication.

References

- [1] Canadian Tobacco Alcohol and Drugs (CTADS) Survey: 2017 summary - Canada.ca [Internet]. [cited 2019 Apr 29]. Available from: <https://www.canada.ca/en/health-canada/services/canadian-tobacco-alcohol-drugs-survey/2017-summary.html#n5>
- [2] Corsi DJ, Hsu H, Weiss D, Fell DB, Walker M. Trends and correlates of cannabis use in pregnancy: a population-based study in Ontario, Canada from 2012 to 2017. *Can J Public Health* [Internet]. 2019 Feb;110(1):76–84. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/30387034>
- [3] Luke S, Hutcheon J, Kendall T. Cannabis Use in Pregnancy in British Columbia and Selected Birth Outcomes. *J Obstet Gynaecol Can* [Internet]. 2019 Feb 7; Available from: <http://www.ncbi.nlm.nih.gov/pubmed/30744979>
- [4] Battista N, Sergi M, Montesano C, Napoletano S, Compagnone D, Maccarrone M. Analytical approaches for the determination of phytocannabinoids and endocannabinoids in human matrices. *Drug Test Anal*. 2014;6(1–2):7–16.
- [5] Walker OLS, Holloway AC, Raha S. The role of the endocannabinoid system in female reproductive tissues. *Journal of Ovarian Research*. 2019.
- [6] Richardson KA, Hester AK, McLemore GL. Prenatal cannabis exposure - The “first hit” to the endocannabinoid system. *Neurotoxicology and Teratology*. 2016.
- [7] Brents LK. Marijuana, the endocannabinoid system and the female reproductive system. *Yale J Biol Med*. 2016;89(2):175–91.
- [8] Xie H, Sun X, Piao Y, Jegga AG, Handwerger S, Ko MSH, et al. Silencing or amplification of endocannabinoid signaling in blastocysts via CB1 compromises

407 trophoblast cell migration. J Biol Chem. 2012;

408 [9] Wang H, Guo Y, Wang D, Kingsley PJ, Marnett LJ, Das SK, et al. Aberrant cannabinoid
409 signaling impairs oviductal transport of embryos. Nat Med. 2004;

410 [10] Paria BC, Song H, Wang X, Schmid PC, Krebsbach RJ, Schmid HHO, et al. Dysregulated
411 Cannabinoid Signaling Disrupts Uterine Receptivity for Embryo Implantation. J Biol
412 Chem. 2001;

413 [11] Asch RH, Smith CG, Siler-Khodr TM, Pauerstein CJ. Effects of delta 9-
414 tetrahydrocannabinol during the follicular phase of the rhesus monkey (*Macaca mulatta*). J
415 Clin Endocrinol Metab [Internet]. 1981 Jan;52(1):50–5. Available from:
416 <http://www.ncbi.nlm.nih.gov/pubmed/6256405>

417 [12] Ayalon D, Nir I, Cordova T, Bauminger S, Puder M, Naor Z, et al. Acute effect of Δ 1-
418 tetrahydrocannabinol on the hypothalamo-pituitary-ovarian axis in the rat.
419 Neuroendocrinology. 1977;

420 [13] Smith CG, Almirez RG, Berenberg J, Asch RH. Tolerance develops to the disruptive
421 effects of Δ 9- tetrahydrocannabinol on primate menstrual cycle. Science (80-). 1983;

422 [14] Chakravarty I, Sheth AR, Ghosh JJ. Effect of acute Δ 9 tetrahydrocannabinol treatment on
423 serum luteinizing hormone and prolactin levels in adult female rats. Fertil Steril. 1975;

424 [15] Dalterio SL, Mayfield DL, Bartke A. Effects of delta 9-THC on plasma hormone levels in
425 female mice. Subst Alcohol Actions Misuse [Internet]. 1983;4(5):339–45. Available from:
426 <http://www.ncbi.nlm.nih.gov/pubmed/6322366>

427 [16] Jukic AMZ, Weinberg CR, Baird DD, Wilcox AJ. Lifestyle and reproductive factors
428 associated with follicular phase length. J Women’s Heal. 2007;16(9):1340–7.

- 429 [17] Lammert S, Harrison K, Tosun N, Allen S. Menstrual Cycle in Women Who Co-use
430 Marijuana and Tobacco. *J Addict Med.* 2018;12(3):207–11.
- 431 [18] White AJ, Sandler DP, D'Aloisio AA, Stanczyk F, Whitworth KW, Baird DD, et al. Anti-
432 Müllerian Hormone (AMH) in relation to tobacco and marijuana use and sources of
433 indoor heating/cooking. *Fertil Steril.* 2016;106(3):723–30.
- 434 [19] Block RI, Farinpour R, Schlechte JA. Effects of chronic marijuana use on testosterone,
435 luteinizing hormone, follicle stimulating hormone, prolactin and cortisol in men and
436 women. *Drug Alcohol Depend.* 1991;28(2):121–8.
- 437 [20] Mendelson J, Mello N, Cristofaro P, Ellingboe J, Benedikt R. Acute Effects of Marijuana
438 on Pituitary and Gonadal Hormones During the Periovulatory Phase of the Menstrual
439 Cycle. In: *Problems of Drug Dependence* 1984. 1985.
- 440 [21] Mendelson JH, Mello NK, Ellingboe J, Skupny AS, Lex BW, Griffin M. Marijuana
441 smoking suppresses luteinizing hormone in women. *J Pharmacol Exp Ther.*
442 1986;237(3):862–6.
- 443 [22] Slavin M, Barach E, Farmer S, Luba R, Earleywine M. Cannabis and symptoms of PMS
444 and PMDD. *Addict Res Theory.* 2017;25(5):383–9.
- 445 [23] Kasman AM, Thoma ME, McLain AC, Eisenberg ML. Association between use of
446 marijuana and time to pregnancy in men and women: findings from the National Survey
447 of Family Growth. *Fertil Steril [Internet].* 2018;109(5):866–71. Available from:
448 <https://doi.org/10.1016/j.fertnstert.2018.01.015>
- 449 [24] Wise LA, Wesselink AK, Hatch EE, Rothman KJ, Mikkelsen EM, Sørensen HT, et al.
450 Marijuana use and fecundability in a North American preconception cohort study. *J*

451 Epidemiol Community Health. 2018;72(3):208–15.

452 [25] Mueller B, Daling J, NS W, Moore D. Recreational drug use and the risk of primary
 453 infertility. *Epidemiology*. 1990;1:195–200.

454 [26] Young-Wolff KC, Sarovar V, Tucker L-Y, Conway A, Alexeeff S, Weisner C, et al. Self-
 455 reported Daily, Weekly, and Monthly Cannabis Use Among Women Before and During
 456 Pregnancy. *JAMA Netw Open* [Internet]. 2019 Jul 19;2(7):e196471. Available from:
 457 <https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2738343>

458 [27] Friedrich J, Khatib D, Parsa K, Santopietro A, Gallicano GI. The grass isn't always
 459 greener: The effects of cannabis on embryological development. *BMC Pharmacology and*
 460 *Toxicology*. 2016.

461 [28] Sithisarn T, Granger DT, Bada HS. Consequences of prenatal substance use. *International*
 462 *Journal of Adolescent Medicine and Health*. 2012.

463 [29] El Marroun H, Tiemeier H, Jaddoe VWV, Hofman A, Verhulst FC, Van Den Brink W, et
 464 al. Agreement between maternal cannabis use during pregnancy according to self-report
 465 and urinalysis in a population-based cohort: The generation R study. *Eur Addict Res*.
 466 2010;

467 [30] Price HR, Collier AC, Wright TE. Screening Pregnant Women and Their Neonates for
 468 Illicit Drug Use: Consideration of the Integrated Technical, Medical, Ethical, Legal, and
 469 Social Issues. *Front Pharmacol* [Internet]. 2018 Aug 28;9. Available from:
 470 <https://www.frontiersin.org/article/10.3389/fphar.2018.00961/full>

471 [31] Gray TR, Eiden RD, Leonard KE, Connors GJ, Shisler S, Huestis MA. Identifying
 472 prenatal cannabis exposure and effects of concurrent tobacco exposure on neonatal

473 growth. Clin Chem. 2010 Sep;56(9):1442–50.

474 [32] Saurel-Cubizolles MJ, Prunet C, Blondel B. Cannabis use during pregnancy in France in
475 2010. BJOG An Int J Obstet Gynaecol. 2014;

476 [33] Leemaqz SY, Dekker GA, McCowan LM, Kenny LC, Myers JE, Simpson NAB, et al.
477 Maternal marijuana use has independent effects on risk for spontaneous preterm birth but
478 not other common late pregnancy complications. Reprod Toxicol. 2016;

479 [34] Hayatbakhsh MR, Flenady VJ, Gibbons KS, Kingsbury AM, Hurriion E, Mamun AA, et
480 al. Birth outcomes associated with cannabis use before and during pregnancy. Pediatr Res.
481 2012;

482 [35] Ko JY, Farr SL, Tong VT, Creanga AA, Callaghan WM. Prevalence and patterns of
483 marijuana use among pregnant and nonpregnant women of reproductive age. Am J Obstet
484 Gynecol [Internet]. 2015 Aug;213(2):201.e1-201.e10. Available from:
485 <http://www.ncbi.nlm.nih.gov/pubmed/25772211>

486 [36] Young-Wolff KC, Tucker L-Y, Alexeeff S, Armstrong MA, Conway A, Weisner C, et al.
487 Trends in Self-reported and Biochemically Tested Marijuana Use Among Pregnant
488 Females in California From 2009-2016. JAMA [Internet]. 2017;318(24):2490–1.
489 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/29279917>

490 [37] van Gelder MMHJ, Reefhuis J, Caton AR, Werler MM, Druschel CM, Roeleveld N, et al.
491 Maternal periconceptional illicit drug use and the risk of congenital malformations.
492 Epidemiology [Internet]. 2009 Jan;20(1):60–6. Available from:
493 <http://www.ncbi.nlm.nih.gov/pubmed/19057385>

494 [38] El Marroun H, Tiemeier H, Steegers EAP, Jaddoe VW V, Hofman A, Verhulst FC, et al.

495 Intrauterine Cannabis Exposure Affects Fetal Growth Trajectories: The Generation R
496 Study. *J Am Acad Child Adolesc Psychiatry*. 2009;

497 [39] Gunn JKL, Rosales CB, Center KE, Nuñez A, Gibson SJ, Christ C, et al. Prenatal
498 exposure to cannabis and maternal and child health outcomes: A systematic review and
499 meta-analysis. *BMJ Open*. 2016.

500 [40] Varner MW, Silver RM, Hogue CJR, Willinger M, Parker CB, Thorsten VR, et al.
501 Association between stillbirth and illicit drug use and smoking during pregnancy. *Obstet*
502 *Gynecol*. 2014;

503 [41] Corsi DJ, Walsh L, Weiss D, Hsu H, El-Chaar D, Hawken S, et al. Association Between
504 Self-reported Prenatal Cannabis Use and Maternal, Perinatal, and Neonatal Outcomes.
505 *JAMA [Internet]*. 2019 Jun 18 [cited 2019 Jun 19]; Available from:
506 <http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2019.8734>

507 [42] Day N, Sambamoorthi U, Taylor P, Richardson G, Robles N, Jhon Y, et al. Prenatal
508 marijuana use and neonatal outcome. *Neurotoxicol Teratol*. 1991;

509 [43] Fergusson DM, Horwood LJ, Northstone K. Maternal use of cannabis and pregnancy
510 outcome. *BJOG An Int J Obstet Gynaecol*. 2002;

511 [44] Boa-Amponsem O, Zhang C, Mukhopadhyay S, Ardrey I, Cole GJ. Ethanol and
512 cannabinoids interact to alter behavior in a zebrafish fetal alcohol spectrum disorder
513 model. *Birth Defects Res [Internet]*. 2019 Jul 15;111(12):775–88. Available from:
514 <https://onlinelibrary.wiley.com/doi/abs/10.1002/bdr2.1458>

515 [45] Breit KR, Zamudio B, Thomas JD. The effects of alcohol and cannabinoid exposure
516 during the brain growth spurt on behavioral development in rats. *Birth Defects Res*

517 [Internet]. 2019 Jul 15;111(12):760–74. Available from:
 518 <https://onlinelibrary.wiley.com/doi/abs/10.1002/bdr2.1487>

519 [46] McLemore GL, Richardson KA. Data from three prospective longitudinal human cohorts
 520 of prenatal marijuana exposure and offspring outcomes from the fetal period through
 521 young adulthood. *Data Br.* 2016;

522 [47] Fine JD, Moreau AL, Karcher NR, Agrawal A, Rogers CE, Barch DM, et al. Association
 523 of Prenatal Cannabis Exposure With Psychosis Proneness Among Children in the
 524 Adolescent Brain Cognitive Development (ABCD) Study. *JAMA Psychiatry* [Internet].
 525 2019 Jul 1;76(7):762. Available from:
 526 <http://archpsyc.jamanetwork.com/article.aspx?doi=10.1001/jamapsychiatry.2019.0076>

527 [48] Fried PA, Makin JE. Neonatal behavioural correlates of prenatal exposure to marihuana,
 528 cigarettes and alcohol in a low risk population. *Neurotoxicol Teratol.* 1987;

529 [49] Day NL, Richardson GA, Goldschmidt L, Robles N, Taylor PM, Stoffer DS, et al. Effect
 530 of prenatal marijuana exposure on the cognitive development of offspring at age three.
 531 *Neurotoxicol Teratol.* 1994;

532 [50] Richardson GA, Ryan C, Willford J, Day NL, Goldschmidt L. Prenatal alcohol and
 533 marijuana exposure: Effects on neuropsychological outcomes at 10 years. *Neurotoxicol*
 534 *Teratol.* 2002;

535 [51] Marroun H El, Hudziak JJ, Tiemeier H, Creemers H, Steegers EAP, Jaddoe VWV, et al.
 536 Intrauterine cannabis exposure leads to more aggressive behavior and attention problems
 537 in 18-month-old girls. *Drug Alcohol Depend.* 2011;

538 [52] Marchei E, Escuder D, Pallas CR, Garcia-Algar O, Gómez A, Friguls B, et al.

539 Simultaneous analysis of frequently used licit and illicit psychoactive drugs in breast milk
 540 by liquid chromatography tandem mass spectrometry. *J Pharm Biomed Anal* [Internet].
 541 2011 May;55(2):309–16. Available from:
 542 <https://linkinghub.elsevier.com/retrieve/pii/S0731708511000537>

543 [53] Ramnarine RS, Poklis JL, Wolf CE. Determination of Cannabinoids in Breast Milk Using
 544 QuEChERS and Ultra-Performance Liquid Chromatography and Tandem Mass
 545 Spectrometry. *J Anal Toxicol* [Internet]. 2019 Aug 21; Available from:
 546 <https://academic.oup.com/jat/advance-article/doi/10.1093/jat/bkz072/5552450>

547 [54] Bertrand KA, Hanan NJ, Honerkamp-Smith G, Best BM, Chambers CD. Marijuana use by
 548 breastfeeding mothers and cannabinoid concentrations in breast milk. *Pediatrics*. 2018;

549 [55] Andreas NJ, Kampmann B, Mehring Le-Doare K. Human breast milk: A review on its
 550 composition and bioactivity. *Early Hum Dev* [Internet]. 2015 Nov;91(11):629–35.
 551 Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0378378215001772>

552 [56] Ballard O, Morrow AL. Human milk composition: nutrients and bioactive factors. *Pediatr*
 553 *Clin North Am* [Internet]. 2013 Feb;60(1):49–74. Available from:
 554 <http://www.ncbi.nlm.nih.gov/pubmed/23178060>

555 [57] Astley SJ, Little RE. Maternal marijuana use during lactation and infant development at
 556 one year. *Neurotoxicol Teratol*. 1990;12(2):161–8.

557 [58] Ordean A, Kim G. Cannabis Use During Lactation: Literature Review and Clinical
 558 Recommendations. *J Obstet Gynaecol Canada*. 2020;

559 [59] Perez-Reyes M, Wall M. Presence of delta9-tetrahydrocannabinol in human milk. *N Engl*
 560 *J Med*. 1988;307(13):819–20.

- 561 [60] Silveira G de O, Loddi S, de Oliveira CDR, Zucoloto AD, Fruchtengarten LVG,
562 Yonamine M. Headspace solid-phase microextraction and gas chromatography–mass
563 spectrometry for determination of cannabinoids in human breast milk. *Forensic Toxicol.*
564 2017;35(1):125–32.
- 565 [61] Baker T, Datta P, Rewers-Felkins K, Thompson H, Kallem R, Hale T. Transfer of Inhaled
566 Cannabis Into Human Breast Milk. *Obstet Gynecol.* 2018;132(3):780–1.
- 567 [62] Crume TL, Juhl AL, Brooks-russell A, Hall KE, Wymore E, Borgelt LM. Cannabis Use
568 During the Perinatal Period in a State With Legalized Recreational and Medical
569 Marijuana: The Association Between Maternal Characteristics, Breastfeeding Patterns,
570 and Neonatal Outcomes. *J Pediatr* [Internet]. 2018;197:90–6. Available from:
571 <https://doi.org/10.1016/j.jpeds.2018.02.005>
- 572 [63] Tennes K, Avitable N, Blackard C. Marijuana: Prenatal and postnatal exposure in the
573 human. *NIDA Res Monogr Ser.* 1985;NO. 59:48–60.
- 574 [64] Legal Cannabis Not Worth Risk for Pregnant Women. Why Risk It? [Internet]. [cited
575 2019 Oct 15]. Available from: [https://www.sogc.org/en/content/featured-news/legal-](https://www.sogc.org/en/content/featured-news/legal-cannabis-not-work-risk.aspx)
576 [cannabis-not-work-risk.aspx](https://www.sogc.org/en/content/featured-news/legal-cannabis-not-work-risk.aspx)
- 577 [65] ACOG Committee Opinion: Marijuana use during pregnancy and lactation. Vol. 130,
578 *Obstetrics and Gynecology.* 2017.
- 579 [66] Perlman B, Kulak D, Goldsmith LT, Weiss G. The etiology of menopause: not just
580 ovarian dysfunction but also a role for the central nervous system. *Glob Reprod Heal.*
581 2018;
- 582 [67] Slavin MN, Farmer S, Earleywine M. Expectancy mediated effects of marijuana on

- 583 menopause symptoms. *Addict Res Theory*. 2016;24(4):322–9.
- 584 [68] Mendelson JH, Cristofaro P, Ellingboe J, Benedikt R, Mello NK. Acute effects of
585 marihuana on luteinizing hormone in menopausal women. *Pharmacol Biochem Behav*.
586 1985;23(5):765–8.
- 587 [69] Benedikt RA, Cristofaro P, Mendelson JH, Mello NK. Effects of acute marijuana smoking
588 in post-menopausal women. *Psychopharmacology (Berl)*. 1986;90(1):14–7.