



Cannabis use during pregnancy: Are we at the verge of defining a “fetal cannabis spectrum disorder”?

S. Schreiber^{a,b,c,d,*}, C.G. Pick^{d,e,f}

^a Department of Psychiatry, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

^b Dr. Miriam and Sheldon G. Adelson Clinic for Drug Abuse Treatment and Research, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

^c Tel Aviv University Sackler, Faculty of Medicine, Tel Aviv, Israel

^d Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel

^e Department of Anatomy, Tel Aviv University Sackler Faculty of Medicine, Tel Aviv, Israel

^f Dr. Miriam and Sheldon G. Adelson Center for the Biology of Addictive Diseases, Tel-Aviv University, Tel-Aviv, Israel



ARTICLE INFO

Keywords:

Cannabis
Pregnancy
Neuro-developmental disorders
Psychiatric manifestations
Fetal cannabis spectrum disorder

ABSTRACT

Cannabis is probably the drug most commonly used globally since ancient times.

Following the trend of legalization of access to cannabis in several Western countries, its use has increased in North America over the past few years. In spite of warnings of the potential hazards associated with in-utero exposure to cannabis, approximately 10% of pregnant women in an American study reported using cannabis in recent years, and most of them on a daily basis. Significant effects of prenatal cannabis exposure have been found on children's sleep, cognitive functions (memory and scholastic skills), as well as on executive (frontal lobe) functions (reasoning, attention, impulsivity, and motivation), and affective (depression) and anxiety symptoms throughout the stages of development. Following the presentation of two case vignettes, we integrate the published information on outcomes of maternal use of cannabis during pregnancy on the developing fetus and the “soft” neurological deficits and neuro-behavioral disturbances manifested by them from early childhood and evolving to peaks in adolescence. Taken together, these data serve to define what we call a heretofore unspecified “fetal cannabis spectrum disorder”.

Introduction

Cannabis is probably the drug most commonly used globally since ancient times, with an annual prevalence of 3.8% of the adult population, or an estimated 183 million people (range 128 million to 238 million) having used cannabis in 2016 [1]. Following the trend of legalization of access to cannabis (either by direct legalization or by a non-incrimination policy) in several Western countries (e.g., Amsterdam in the Netherlands, some States in the USA, Israel, etc.), its use has increased considerably in North America [2] over the past few years. In the state of Colorado, for example, cannabis use among 18-to-25-year-olds increased from 20% to 31% between 2000 and 2014 [1]. It is estimated that about 10% of people who have used cannabis in their lifetime will develop cannabis dependence [3]. The availability of new high-potency strains of cannabis with tetrahydrocannabinol (THC) levels of 20–25% higher than the “classical” marijuana [4] may mean exposure to higher THC levels with an increased risk of adverse effects.

Exposure to cannabis has been associated with medical

complications, such as cardiovascular and respiratory problems, as well as altered brain function, such as impairing the ability to drive [5], decreasing cognitive function, and decreasing memory function [4]. Initiation of cannabis use at an earlier age is associated with a clear increased risk of a cannabis use disorder development, and it has been suggested that there may be alterations of white and gray brain matter and cortical thickness [6–8]. Frequent use of high potency cannabis has been associated with increased paranoia, elevated risk for psychotic disorder, and cannabis-induced psychosis among persons with no previous psychiatric history [4,9,10].

Despite the many concerns expressed about maternal use of cannabis during pregnancy and potential harm to the fetus [11,12], together with the recommendations of the American College of Obstetricians and Gynecologists for pregnant women and women planning a pregnancy to be aware of the potential hazards of prenatal cannabis use [13], approximately 10% of pregnant women in one American study reported using cannabis in recent years, and most of them on a daily basis [14]. Maternal cannabis use has long-term impacts on both

* Corresponding author at: Department of Psychiatry, Tel Aviv Sourasky Medical Center, 6 Weizmann St., Tel Aviv 6423906, Israel.

E-mail address: shaulsch@tlvmc.gov.il (S. Schreiber).

<https://doi.org/10.1016/j.mehy.2019.02.017>

Received 21 November 2018; Accepted 2 February 2019

0306-9877/ © 2019 Elsevier Ltd. All rights reserved.

the physical and behavioral development of the child [15], as documented in a Maternal Health Practices and Child Development publication [16]. Significant effects of prenatal cannabis exposure were found on children's sleep, cognitive functions (memory, scholastic skills), as well as on executive (frontal lobe) functions (reasoning, attention, impulsivity, motivation) and affective (depression) and anxiety symptoms throughout the stages of development [15]. Furthermore, the lower attention span and the higher number of depressive symptoms during middle childhood have been associated with delinquency in early adolescence of these children [16,17]. Even though there are theoretical reasons to expect possible gender differences following prenatal exposure to cannabis [18], only few studies reported on higher rates of behavior problems for cannabis-exposed girls [19].

Hypothesis

The increasing rate of admissions to the psychiatric day hospital of young people affected since early childhood by a combination of neurodevelopmental disorders and severe anxiety, the ever increasing numbers of children (and adults) diagnosed with ADHD, and the 'epidemic-like' expansion of autistic spectrum disorder during the last decade, call for a search for possible direct hazards, especially during pregnancy.

We propose to integrate the growing published information (both basic- and clinical-studies) on the outcomes of maternal use of cannabis during pregnancy on the developing fetus and the "soft" neurological deficits and neurobehavioral disturbances manifested since early childhood and evolving to peak in adolescence to define a "fetal cannabis spectrum disorder". The following two vignettes (out of many seen in the clinic over the years) will illustrate the gradual emergence of this disorder by early adulthood as monitored in the clinical setting.

Patients and methods

Vignette 1

YC was a 20-year-old single male referred by an outpatient clinic in the community to the psychiatric daycare hospital following the exacerbation of his abnormal mental condition and behavior. He had been diagnosed in early childhood as having mixed specific neuro-developmental disorders (speech articulation, mixed scholastic skills, fine motor function, conduct, and emotions), depressive conduct disorder (DSM-5 Disruptive Mood Dysregulation Disorder [DMDD]), attention deficit and hyperactivity disorder (ADHD) and post-traumatic stress disorder. He had been treated in various psychiatric ambulatory settings throughout most of his life. Upon the index admission, his mother reported that his was not a premature birth and that there had been no complications during delivery. However, he was considered as being a "not OK" newborn and was put in an incubator for several days (she did not know why). She mentioned that he had undergone repeated diagnostic procedures since early childhood, and there have never been any clear-cut diagnoses for the many difficulties he manifested, such as failure to identify facial expressions, restlessness and hyperactivity, impaired scholastic skills, inadequate social skills, and mood swings accompanied by death ideation (no suicide attempt ever), low arousal threshold and repeated, life-long episodes of temper tantrums. Prolonged treatment with neuroleptics and SSRIs was only partially effective, and at the age of 14 years he was transferred to a boarding school for adolescents with special needs, where he stayed for 5 years. Both the patient and his mother insisted that he never used either alcohol or drugs of any kind (he did smoke tobacco for several years), however, his mother was concerned that he might start smoking weed, since both she and the children's father, as well as some relatives and various friends and guests at home often do ("It is always on the table in the living room"). When questioned explicitly, she admitted that smoking weed is a regular habit of hers since she was a teenager, that

both she and her children's father (and some of their relatives and many of their friends) do it as a life-long habit, and that she definitely did not quit during her pregnancy or lactation period after having given birth to the patient and to his younger sister. The patient's mother adamantly denied the possibility that there might be any association between her use of cannabis during pregnancy and lactation (and thereafter) and her son's neurodevelopmental disorders, as well as her daughter's (relatively minor) difficulties.

Vignette 2

AS was a 19-year-old single female who had been referred to the psychiatric daycare hospital for evaluation, diagnosis and treatment recommendations. Her past history revealed repeated psychiatric diagnostic procedures since the age of 3 years, as a result of which she was first diagnosed with severe prolonged diffuse anxiety and separation anxiety, restlessness and hyperactivity accompanied by repeated episodes of temper tantrum, and later (in addition) with oppositional defiant disorder. At the age of 6 years, she began having auditory hallucinations with full insight, and they have continued to date. She was later diagnosed with depressive conduct disorder (DSM-5, DMDD) accompanied by social skills impairment and mood swings (the diagnosis was changed to bipolar II affective disorder when she was 10 years of age), and she has been treated in various psychiatric ambulatory settings throughout most of her life. When asked about her family's medical and mental history, she disclosed that her mother has been habitually smoking cannabis since she was a teenager (including throughout her 3 pregnancies). When AS was 13 years old, her mother was additionally heavy on cocaine and LSD for around two years at which point she quit using them and continued on with cannabis alone. AS reported having sporadically smoked cannabis since she was 13 years of age, and using cocaine for one year when she was 17 years of age. A battery of psycho-diagnostic tests revealed a significant gap between her intellectual potential and actual abilities, with impaired learning capacity mainly due to low scholastic skills (dyscalculia, dysgraphia) accompanied by prominent difficulties in executive functions.

Results and discussion

A growing body of evidence supports the notion that substances, such as alcohol and cannabis that are generally considered only moderately harmful when consumed at low doses by adults, may pose severe threats to the developing fetus when consumed at the same low doses by the pregnant mother-to-be [20]. The effects of alcohol on the developing fetal brain during pregnancy may manifest since early childhood as an evolving cascade of neurodevelopmental impairments, and they have already been studied in depth and were well-described (fetal alcohol spectrum disorders, for review see [21]). The teratological and perinatal toxicological effects of cannabis on the developing fetal brain during pregnancy in rats have been studied and described by Abel in a series of pioneer and seminal studies during the 1970s [22] (for review of findings in rat, mouse, rabbit and hamster, see [23]). The possible effects of cannabis use by pregnant women on their fetuses have been described as well (for review see [24]), however, integration of all the available knowledge and support for a potential "fetal cannabis spectrum disorder" by basic laboratory studies on animal models are still lacking.

The last 20–30 years have been characterized by a persistent increase in the frequency of diagnosing ADHD and autistic spectrum disorder among children and adolescents, reaching 2–3 folds higher than before the 1980's [25–29]. Based on the accumulated published data and the clinical experience with many young adult psychiatric patients who were exposed to cannabis in-utero, we hypothesize the existence of a "fetal cannabis spectrum disorder". Moreover, in the face of the trend in some Western countries to legalize cannabis use, we stress an urgent need for targeted studies, both basic science (animal

models) and clinical, to investigate this hypothesis. If “fetal cannabis spectrum disorder” emerges as a valid diagnosis, flags must be raised about the liberal use of that drug worldwide.

Conflict of interest statement

Both Shaul Schreiber (M.D.) and Chaim G. Pick (Ph.D.) declare no conflict of interest of any kind.

Funding

No financial support was offered (or needed) for this study.

Disclosures and acknowledgments

Both authors contributed equally to the development of the concept, data (PubMed) search and integration, conclusions reached and manuscript writing and reviewing. Both have read and approved the submitted version.

We wish to thank Esther Eshkol for editorial assistance.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2019.02.017>.

References

- [1] United Nations Office on Drugs and Crime. World Drug Report 2017; 2018. https://www.unodc.org/wdr2017/field/Booklet_2_HEALTH.pdf last [accessed on October 1, 2018].
- [2] Hasin SH. US epidemiology of Cannabis use and associated problems. *Neuropsychopharmacol Rev* 2018;43:195–212. <https://doi.org/10.1038/npp.217.198>.
- [3] Wanger FA, Anthony JC. Into the world of illegal drug use: exposure opportunity and other mechanisms linking the use of alcohol, tobacco, marijuana, and cocaine. *Am J Epidemiol* 2002;155:918–25.
- [4] Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. *N Engl J Med* 2014;370:2219–27. <https://doi.org/10.1056/NEJMra1402309>.
- [5] Le Strat Y, Dubertret C, Le Foll B. Impact of age at onset of cannabis use on cannabis dependence and driving under the influence in the United States. *Accid Anal Prev* 2015;76:1–5. <https://doi.org/10.1016/j.aap.2014.12.015>.
- [6] Cooley J, Bernier D, Tibbo PG. White matter changes in early phase schizophrenia and cannabis use: an update and systematic review of diffusion tensor imaging studies. *Schizophr Res* 2014;156:137–42. <https://doi.org/10.1016/j.schres.2014.04.026>.
- [7] Jacobus J, Squeglia LM, Meruelo AD, et al. Cortical thickness in adolescent marijuana and alcohol users: a three-year prospective study from adolescence to young adulthood. *Dev Cogn Neurosci* 2015;16:101–9. <https://doi.org/10.1016/j.dcn.2015.04.006>.
- [8] Lopez-Larson MP, Bogorodzki P, Rogowska J, et al. Altered prefrontal and insular cortical thickness in adolescent marijuana users. *Behav Brain Res* 2011;220:164–72. <https://doi.org/10.1016/j.bbr.2011.02.001>.
- [9] Freeman TP, Winstock AR. Examining the profile of high-potency cannabis and its association with severity of cannabis dependence. *Psychol Med* 2015;45:3181–9. <https://doi.org/10.1017/S0033291715001178>.
- [10] Di Forti M, Marconi A, Carra E, et al. Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. *Lancet Psychiatry* 2015;2:233–8. [https://doi.org/10.1016/S2215-0366\(14\)00117-5](https://doi.org/10.1016/S2215-0366(14)00117-5).
- [11] Volkow ND, Compton WM, Wargo EM. The risks of marijuana use during pregnancy. *JAMA* 2017;317:129–30. <https://doi.org/10.1001/jama.2016.18612>.
- [12] Eiden RD, Zaho J, Casey M, Shisler S, Schuetze P, Colder CR. Pre- and postnatal tobacco and cannabis exposure and child behavior problems: bidirectional associations, joint effects, and sex differences. *Drug Alcohol Depend* 2018;185:82–92. <https://doi.org/10.1016/j.drugalcdep.2017.11.038>.
- [13] College American. of Obstetricians and Gynecologists Committee on Obstetric Practice. Committee opinion no. 637: marijuana use during pregnancy and lactation. *Obstet Gynecol* 2015;126:234–8. <https://doi.org/10.1097/01.AOG.0000467192.89321.a6>.
- [14] Ko JY, Farr SL, Tong VT, Creanga AA, Callaghan WM. Prevalence and patterns of marijuana use among pregnant and nonpregnant women of reproductive age. *Am J Obstet Gynecol* 2015;213:e210. <https://doi.org/10.1016/j.ajog.2015.03.021>.
- [15] US Department of Health and Human Services. The Health Consequences of Smoking – 50 Years of Progress: A report of the Surgeon General. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, Atlanta, GA; 2014. p. 17. <https://www.surgeongeneral.gov/library/reports/50-years-of-progress/index.html> [last accessed on October 1, 2018].
- [16] Day NL, Leech SL, Goldschmidt L. The effects of prenatal marijuana exposure on delinquent behaviors are mediated by measures of neurocognitive functioning. *Neurotoxicol Teratol* 2011;33:129–36. <https://doi.org/10.1016/j.ntt.2010.07.006>.
- [17] Fried PA, Watkinson B. 36- and 48-month neurobehavioral followup of children prenatally exposed to marijuana cigarettes. *J Dev Behav Pediatr* 1990;11:49–58.
- [18] Craft RM, Marusich JA, Wiley JL. Sex differences in cannabinoid pharmacology: a reflection of differences in the endocannabinoid system? *Life Sci* 2013;92:467–81. <https://doi.org/10.1016/j.lfs.2012.06.009>.
- [19] El Marroun H, Freeman TP, Winstock AR. Examining the profile of high-potency cannabis and its association with the severity of cannabis dependence. *Psychol Med* 2015;45:3181–9. <https://doi.org/10.1017/S0033291715001178>.
- [20] Singer LT, Min MO, Minnes S, et al. Prenatal and concurrent cocaine, alcohol, marijuana, and tobacco effects on adolescent cognition and attention. *Drug Alcohol Depend* 2018;191:37–44. <https://doi.org/10.1016/j.drugalcdep.2018.06.022>.
- [21] Lange S, Rovet J, Rehm J, Popova S. neurodevelopmental profile of fetal alcohol spectrum disorder: a systematic review. *BMC Psychol* 2017;5:22. <https://doi.org/10.1186/s40359-017-0191-2>.
- [22] Abel EL. Behavioral teratology of marihuana extract in rats. *Neurobehav Toxicol* 1979;1:285–7.
- [23] Abel EL. Prenatal exposure to Cannabis: a critical review of effects on growth, development, and behavior. *Behav Neural Biol* 1980;29:137–56.
- [24] Alpar A, Di Marzo V, Harkany T. At the tip of an iceberg: prenatal marijuana and its possible relation to neuropsychiatric outcome in the offspring. *Biol Psychiatry* 2016;79:e33–45. <https://doi.org/10.1016/j.biopsych.2015.09.009>.
- [25] Bachmann CJ, Gerste B, Hoffmann F. Diagnoses of autism spectrum disorders in Germany: time trends in administrative prevalence and diagnostic stability. *Autism* 2018;22:283–90. <https://doi.org/10.1177/1362361316673977>.
- [26] Davidovitch M, Koren G, Fund N, Shrem M, Porath A. Challenges in defining the rates of ADHD diagnosis and treatment: trends over the last decade. *BMC Pediatr* 2017;17:218. <https://doi.org/10.1186/s12887-017-0971-0>.
- [27] May T, Williams K. Brief Report: gender and age of diagnosis time trends in children with autism using Australian medicare data. *J Autism Dev Disord* 2018. <https://doi.org/10.1007/s10803-018-3609-7>.
- [28] Nevison CD, Blaxill M. Diagnostic substitution for intellectual disability: a flawed explanation for the rise in autism. *J Autism Dev Disord* 2017;47:2733–42. <https://doi.org/10.1007/s10803-017-3187-0>.
- [29] Vasilidiadis HM, Diallo FB, Rochette L, et al. temporal trends in the prevalence and incidence of diagnosed ADHD in children and young adults between 1999 and 2012 in Canada: a data linkage study. *Can J Psychiatry* 2017;62:818–26. <https://doi.org/10.1177/0706743717714468>.