International Journal of Medical Science and Clinical Invention 6(9): 4565-4569, 2019
DOI:10.18535/ijmsci/v6i9.01 **ICV 2016: 77.2**
e-ISSN:2348-991X, p-ISSN: 2454-9576

Reviwe Article

Cannabis "in utero": the fetus as a compulsive consumer

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Abstract:
Cannabis sativa, a plant known for millennia for its hallucinogenic and medicinal effects, contains widely consumed psychoactive substances worldwide, with increasing numbers among adolescents and adults, including pregnant women. Due to its potential adverse effects on users, it is of fundamental importance to know and disseminate the harm caused to humans in order to reduce the consumption of this drug. This article presents a review of the physiological and pharmacological characteristics of psychoactive substances present in cannabis, their actions on the endocannabinoid system and the placenta. It also highlights the main clinical repercussions that can occur with the fetus and, in the long run, with children whose mothers used cannabis during pregnancy.

Key Words: cannabis – cannabinoids – pregnancy – child health – abuse drugs

Introduction

Since ancient times human beings have been searching in nature for sources of pleasure and/or relief for the suffering and stress of everyday life, experimenting with the most varied substances that, isolated or combined, can be incorporated into their daily habits. Over time, and adopting social rules, these substances were designated as licit or illicit according to their pharmacological properties and effects on the organism [1].

Among the various illicit substances cannabis products has been used cannabis for centuries for spiritual, medicinal and nonmedical purposes, and over the past 60 years recreational or non-medicinal use has spread globally by adolescents and youg adults, currently being the most commonly used by pregnant women that believe cannabis is natural and safer than other substances [2-6].

Studies have observed increased prevalence of pregnant women using cannabis in different forms. This increase in consumption is directly linked to the legalization that has been taking place in many countries, the increased availability on this drug, and the lack of accurate information on health risks often overlooked by users, causing the medical and social use of cannabis is becoming more acceptable in whole world [7-10].

Cannabis, cannabinoids and endocannabinoid system

Cannabis sativa (also known as marijuana) is a plant originated in Central Asia and currently growing worldwide that contains more than 500 active herbal compounds and can consumed inhaled, ingested or applied topically to mucous membranes [11-13]. The most common route of use is smoked because is the most efficient way to achieve the desired psychoactive effects [14], although the effects depend on the mode of administration, the dose received, the previous experience, the mood state and the social setting in wich is used [14,15].

Cannabis is the generic term used to denote plant-derived psychoactive substances prepared from *C. sativa*, and consists of approximately 60 plant-derivative cannabionid compounds denominated phytocannabinoids. In addition to these, there are two other types: the endocannabinoids (naturally produced by the body) and the synthetic cannabinoids (eliciting cannabis effects, generally with a higher potency than endocannabinoids) [16]. The most important psychoactive phytocannabinoid is the delta-9-tetrahydrocannabinol (delta9THC), a partial agonist of the endocannabinoids receptors CBr1 and CBr2, the ativation of which generates central and peripheral effects [17-21]. The concentration of delta9THC varies in the diferent strains of cannabis (6% to 20%), and due to its physicochemical properties (small molecular size and lipophilic nature) has high distribution and transport capacity in the human body, quickly crossing the transplacental membranes [2,22-24]. It is estimated that one-third of delta9THC plasma concentration crosses the fetoplacental barriers exposing the fetuses of cannabis using mothers during the prenatal period. Also, there has been as increase in potency of cannabis over the past 20 years due to the novel ways of cultivating and production of synthetic substances which enhance the possibility of greater adverse effects among users [25,26].

The effects of delta9THC are due to its action on cannabinoid receptors CBr1 and CBr2 - widely distributed throughout various organs and tissues that, together with endogenously produced cannabionids and the regulatory enzymes of synthesis and degradation, constitute the endocannabinoid

system (ECS) [19,27]. The ECS is a neuromodulatory system, detected from the earliest embryonic stage and throughout pre- and postnal development, responsible for several controls related to the regulation of many important function, since its receptors has been found to play a key role in neuronal progenitor cell proliferation, pyramidal specification, axon pattering modulation of dendritic arbor, and promotion of neuronal differentiation [5,20,28,29]. Also, the ECS influences metabolism and physiology of multiple systems with its anabolic action, leading to protein and glycogen synthesis and fat deposition [30]. Moreover, plays a fundamental role in pregnancy outcome and fetal development, and over-stimulation of CBr1 in the placenta can impair fetal growth by inhibiting cytotrophoblastic proliferation [5,28,31].

The endocannabinoid receptors can be found on both presynaptic neurons and postsynaptic locations and are densely expressed in various regions within the brain [4], and its key function in mature neurons is modulate the release of neurotransmitters [18]. These receptors has been detected in the fetal human brain as early as 14 weeks of gestation and changes across development indicating important roles in fetal central nervous system (CNS) development events [5,32] such as neuronal proliferation, migration and synaptogenesis [18,33]. Cannabis exposure during pregnancy has the potential to induce supra-physiological stimulation of the ECS, wich can break the ontogeny of endogenous endocannabinoid signalling and compromisse the synaptogenesis and the development of neural interconections [17,31,33,34].

Due to the mode of cultivation, preparation and handling some products derived from cannabis can deliver chemical and biological contaminants to the user such as pesticides, yeasts, bacteria, metals and solvents, increasing the harmfulness and the possibility of synergistic effects with other substances [35-38]. Cannabis, with its hundreds of compounds, has the property of interacting with many substances and when consumed in inhaled form, pyrolysis can produce more harmful substances [35].

Pharmacokinetics of cannabinoids and pregnancy

Cannabis consumption during pregnancy may negatively impact the fetus since the effects may be subtle and do not be detectable for many months to years after birth [28]. Cannabis can affect the normal transport functions and physiologic status of the placenta where it arrives by passive diffusion or, less commonly, through active transport or pinocytosis [2,19], and its concentrations varies by the permeability and biological capacity of the placenta. In addition, when cannabis is smoked, serum carbon monoxide concentrations in the pregnant woman is very high, resulting potentially in impaired maternal respiratory gas exchange and subsequent adverse effect on the fetus [2].

Other effects observed are increased resistance and pulsatility index of the uterine artery, with resulting potential effects on uterine blood flow, resulting in increased placental resistance and reduced placental circulation [2], besides impair fetal growth by inhibiting cytotrophoblastic proliferation [36].

Effects on pregnant woman and fetus

For pregnant women, as for any adult, cannabis use can cause many short-term and long-term biopsychosocial problems (impairment of motor coordination and memory, altered judgement, risk of psychosis, myocardial infaction, arrhythmias, acute coronary syndrome, perpheral arteritis, stroke and cerebrovascular accident) besides predispose to the development of addition and adversely affect a mother's ability to care for the child [39,40].

Several studies have reported associations between cannabis use during pregnancy and fetal outcomes, congenital anomalies and teratogenic effects [19,34,41]. The effects may vary depending on duration, route administration, timing and overall magnitude of exposure, and the extent to wich the fetus and the fetal SNC are exposed [19], since prenatal exposure to exogenous cannabinoids can modify the maturation of neurotransmitter system and their functions through the activation of receptors that arise early in the developing brain [5].

Alterations on fetal neuroendocrine and neurotransmitters systems, decrease in insulin-like growth factors and effects on direct effects on central nervous system are the main mechanisms that compromise the fetus during pregnancy. The main effects on the fetus caused by cannabis use by pregnant women are presented in Table 1.

Table 1. Effects of cannabis on the fetus

Growth restriction
Decreased birth weight
Small for gestatinal age
Decreased head circumference
Reduced grey matter volume
Lower apgar scores
Preterm delivery
More likely to require admission to neonatal intensive care unit
stillbirth
Risk of congenital malformations
Ref. 2,3,8,14,17,31-33,42-56

Long term effects on the child

In addition to the immediate effects on the intrauterine environment, the consumption of cannabis use by pregnant women may lead to development abnormalities: tremors, startle, altered responses to visual stimuli, and high-pitched cry after birth [14]. In children have been observed decreased attention and motivation, gaps in problem-solving skill and memory, increased depressive and anxiety symptoms, impulsivity, aggressiveness, disturbed sleep [17,32,46,49,57,58].

Conclusion

All early chemical exposure can result in injuries to the fetus that are expressed as changes in postnatal development [18]. External stimuli can affect embryonic signalling systems, resulting in long-lasting or even permanent alterations to

organogenesis leading to the in uteroadaptation of the fetus to an anticipated non-physiological environment after birth [46]. Therefore, in addition to its harmful effects, cannabis can enhance the placental barrier permeability to pharmacologic agents and recreational substances, potentially placing the fetus at risk from other agents or drugs [2].

It is urgent to spread the potential repercussions of cannabis use on maternal and fetal health during pregnancy [44]. There is mounting evidence to suggest that perinatal cannabis exposure can have negative effects and the combination of increasing trends in consume, potency, and acess poses an important public health and clinical practice challenge [33,59]. Whereas the general population increasingly views cannabis as safe, measures to disseminate reliable information on the harm caused by cannabis use during pregnancy are urgently needed, preventing thousands of children from being exposed to the harmful effects that begin during the intrauterine period [18,53,61].

Preventive programs should provide education about the potential adverse effects on the health of pregnant women and their future or current fetus or newborn [62,63]. During the initial prenatal all women should be asked about use of cannabis and medical community should advise pregnant women to avoid perinatal cannabis exposure [36,64]. Besides that it is very important education of health providers in the care and management of women with evidence of drug use before, during and after pregnancy.

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