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Cannabis: An ancient friend or foe? What works and doesn't work

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ABSTRACT

Cannabis has been cultivated by mankind for a multitude of uses over a period of thousands of years. This review explores how our relationship with the cannabis plant has evolved over this period of time, including the use of cannabis for recreational purposes and for its medicinal properties. The endocannabinoid system plays a complex role in the development of the fetal, infant and adolescent brain. Use of exogenous cannabinoids has the potential to result in supra-physiological stimulation and impact on normal central nervous system development. Cannabis is the most frequently used recreational drug in western societies and its use is common amongst pregnant women. This review summaries much of the evidence about what is known of the long term effects of in utero cannabis exposure. Further, the potential impact of use of medicinal cannabis products during pregnancy is considered and the implications to health professionals caring for pregnant women and their babies are explored.

1. Ancient friend

Cannabis Sativa is a fast-growing plant that originates from central Asia. Archeological evidence indicates that the fibers of the cannabis plant were used in the production of rope, textiles and paper in China as early as 4000 BCE[1]. The medicinal properties of the cannabis plant were recognised by Emperor Sheng-Nung (2,700 BCE) and subsequently recorded in the historically important Chinese pharmacopeia, *pen-ts'ao ching*, first published during the Ming Dynasty. The seed of the plant was mostly used in the preparation of these herbal medicines. These herbal preparations were used to treat a variety of medical problems including constipation, malaria, rheumatic pain and disorders of the female reproductive system [2]. The anaesthetic effects of cannabis, when combined with wine, during surgical procedures, were first described by Hua T'o, (A.D. 110–207). The fruit of the cannabis plant, known as the achene, was considered an import food product in ancient China, and the oil extracted from the seed was used in the frying of food [1].

The medicinal properties of cannabis were recognised in India from around the time of 1000 years BC [3]. Traditional healers used cannabis plant compounds for the management of a large array of disorders, including as an analgesic, and anticonvulsant, particularly in the management of tetanus, an anti-inflammatory, a topical antibiotic, an anti-parasitic, an antispasmodic for the management of diarrhoea and colic, a diuretic and appetite stimulant and in the management of tuberculosis. The use of cannabis derived herbal medicines in India continued well into the Christian era.

From India, the medicinal use of cannabis spread to the Middle East. *The Canon of Medicine*, written by Avicenna around the time of 1000 years AD, described the use of cannabis as an analgesic, amongst other uses. In 1464, Ibn al-Badri described the use of cannabis resin to treat epilepsy. Unfortunately, Ibn al-Badri reported that whilst being cured of his epilepsy, the use of cannabis resin left the patient "an addict who could not for a moment be without the drug" [4]. From around the time of the 15th century, the use of cannabis products for medicinal purposes became evident in Africa. These herbal medicines were used in the treatment of snakebite, dysentery, malaria, fever and infection, including anthrax, asthma and to facilitate childbirth. Similarities in descriptions of preparation of these medicines in both Africa and India suggest that Arab traders may have introduced the cannabis plant into Africa [5].

In contrast, references to the use of cannabis for medicinal purposes in Europe were scarce during this period. Whilst the cannabis plant was cultivated in Europe, it was almost exclusively for its fibers. The spread of Muslim culture into Spain was associated with the introduction of paper making from cannabis plant fibers in 1150. This paper manufacturing technique subsequently spread to Italy [4].

The use of cannabis for medicinal purposes in Europe did not receive widespread recognition until an Irish physician, William B. O'Shaughnessy, wrote a series of publications on his experiences with cannabis based medicinal preparations during his time serving with the British in India. He went on to research the medicinal properties of cannabis, including use of animals to study potential toxicities and later trialing the use of cannabis products for various ailments in humans. In 1839, O'Shaughnessy published his book '*On the preparations of the Indian hemp, or gunjah*', in which he describes various successful human

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experiments using cannabis preparations predominantly in the management of muscular spasms caused by tetanus and rabies, but also for treatment of rheumatism and convulsions [6]. Around the same time, a French psychiatrist, Jacques-Joseph Moreau, observed some of the properties of the cannabis resin, hashish, whilst he was visiting the Middle East. Moreau subsequently experimented with the use of various cannabis products on both himself and later his students for the investigation and management of mental illnesses [7,8].

The work of O'Shaughnessy and Moreau generated significant interest in the use of cannabis for its medicinal and psychoactive properties in Western medicine. The use of cannabis for its medicinal properties spread into Europe and subsequently into North America. The first clinical conference about use of cannabis in medicine was organised by the Ohio State Medical Society and held in the United States 1860[3].

The use of various tinctures or extracts of cannabis peaked around the late 19th and early 20th Centuries, with highly reputable companies such as Merck, Burroughs-Wellcome, Bristol-Meyers Squibb, Parke-Davis, and Eli Lilly marketing these products [6]. These products were primarily used as sedatives or hypnotics, analgesics or as more non-specific remedies for conditions such as appetite stimulants, dyspepsia, diarrhoea, impotence, diabetes, vertigo, nephritis and haematuria, and dysentery and cholera.

Following the early years of the 20th century, the use of cannabis based medical products began to decline. Vaccines were being developed and newer more effective analgesics and sedatives were being produced. Without any active principle being identified in the cannabis plant, it was not possible to produce products with reliable and consistent potency [6]. The In 1937, the Marihuana Tax Act was passed in the United States. This Act required users, including those consuming cannabis for medicinal purposes, to register and pay this tax. This was associated with a decline in the use of medicinal cannabis products. Subsequently, cannabis was removed from the American Pharmacopeia in 1941 [3].

More recently, there has been a resurgence in interest in the use of marijuana and cannabis products to manage medical conditions where mainstream medications have proved to have less than optimal efficacy. Currently in the United States, a majority of states permit the use of marijuana in the management of Alzheimer's Disease, amyotrophic lateral sclerosis, cachexia/wasting syndrome, cancer, Crohn's Disease, epilepsy and seizures, glaucoma, hepatitis C virus, human immunodeficiency virus/acquired immunodeficiency syndrome, multiple sclerosis and muscle spasticity, severe and chronic pain, severe nausea, and post-traumatic stress disorder [9]. This is despite there being limited robust evidence for the proven efficacy of medicinal cannabis in the management of many of these conditions. Most of the studies are limited to case reports or cross-sectional trials. Further, there has been limited comparative studies between medical cannabis and conventional treatment to determine whether medicinal cannabis has added benefits or overall superiority when compared to mainstream medical treatments.

2. A modern foe?

The use of cannabis as a psychoactive agent was first documented in the Chinese pharmacopeia, *pen-ts'ao ching*. Both positive and negative aspects of its hallucinogenic effects were noted: "…ma-fen (the fruit of cannabis) … if taken in excess will produce visions of devils … over a long term, it makes one communicate with spirits and lightens one's body …" [10]. In India, use of cannabis as a hallucinogenic and recreational drug paralleled its use for its medicinal properties. The use of cannabis as part of religious rituals in that region has been ongoing for over a 1000 years [2].

Until the second half of the 20th Century, the use of Cannabis as a recreational drug in Western cultures was largely limited to small fringe groups within societies. However, by the 1970s, a rapid expansion of recreational use of cannabis was occurring among the youth of the Western world [3]. In 1964, the chemical structure of the principle psychoactive compound, Δ [9] Tetrahydrocannabinol (THC), was identified by Gaoni and Mechoulam [11]. Around that time, there was a dramatic increase in scientific interest in the properties of cannabis, with growing concerns about the potential negative impacts of regular cannabis use. These concerns included an emerging interest in the potential negative impacts cannabis use during pregnancy may have on pregnancy outcomes and long-term outcomes of these infants.

Around the late 1980's, several laboratories worldwide began to synthesise multiple compounds possessing similar effects to Δ [9]-THC for research purposes. Synthetic cannabinoids are a heterogeneous group of compounds developed to further investigate the endocannabinoid system and to identify potential new therapeutic agents [12]. They interact with cannabinoid receptors and elicit similar effects to Δ [9] THC. In the early 2000's, synthetic cannabinoids produced in clandestine laboratories and sprayed on plant material first began to be marketed in Europe and later in the United States as legal alternatives to cannabis. They are typically consumed by smoking, in similar fashion to marijuana. Known as Spice and K2, the popularity of these products is attributed to their intense psychoactive effects, an inability to be detected by routine drug screening and at least for a period of time, the ability to purchase these products legally. Some of these synthetic cannabinoid compounds have extremely high potency, with relative potency ranging from 40 to 660 fold higher than Δ [9]-THC [13].

Concerns about the potential health impacts of cannabis have been escalating more recently because of an apparent change in relative potencies over the past 30 years. Data from marijuana samples collected over these decades indicates that there has been a progressive increase in mean potency, based on Δ [9]-THC content, over this time period. Mean potency of samples collected in 1985 was 2.8% Δ [9]-THC content, where as in 2008 it ranged between 5.8 and 9.3%. Further, mean potency of Sinsemilla, the flowering tops of unfertilized female plants with no seeds, has increased from 7.3% in 1985 to 11.7% in 2008, with some individual plants reaching up to 37.2% Δ [9]-THC content in 2008 [13].

3. The endocannabinoid system

The CB1 cannabinoid receptor was first identified in the brain 1990, and subsequently its immune system counterpart, the CB2 cannabinoid receptor, was identified 3 years later [14]. The discovery of cannabinoid receptors prompted the search for naturally occurring endogenous cannabinoid receptor agonists. Endocannabinoids are naturally occurring arachidonic acid metabolites, and include anandamide and 2-arachidonoylglycerol (2-AG).

Unlike classical neurotransmitters, endocannabinoids are not stored in synaptic vesicles. Anandamide and 2-AG are synthesized by neurons following membrane depolarization, and once released, travel in a retrograde fashion back into the synaptic cleft, where they bind to CB1 cannabinoid receptors on presynaptic terminals [14]. Activation of the CB1 cannabinoid receptor results in inhibition or activation of ion channels that, in turn, can inhibit neurotransmitter release from axon terminals. Following release, anandamide and 2-AG are rapidly cleared from the synaptic cleft, possibly by a carrier-mediated transport process [15]. This entire process of rapid induction of synthesis with receptor activation and rapid clearance suggests that endocannabinoids act in the brain primarily as neuromodulators with highly regulated, spatio-temporal specific patterns. which in turn play a major role in short- and long-term synaptic plasticity [14].

4. Cannabis use in pregnancy

Cannabis is the most frequently used illicit drug in western communities. Data from the 2007 to 2012 National Surveys on Drug Use and Health, a cross-sectional nationally representative survey in the

United States, indicates that approximately 1 in 10 pregnant and non-pregnant women 18–44 years of age had used marijuana in the previous 12 months to the survey period [16]. Hayatbakhsh et al. reported on the prevalence of use of illicit drugs by women of reproductive age before and during pregnancy in an Australian perinatal population [17]. They found that cannabis was the most common illicit drug used before and during pregnancy, with 9% of women engaged in regular use prior to pregnancy and with 2.5% continuing to use cannabis during pregnancy. In contrast to the use of alcohol and many other illicit drugs, women will often continue to use cannabis throughout pregnancy and while breast feeding [18]. This maybe in part due to a perception by some women that continuing cannabis use is relatively harmless [19].

The same molecular characteristics that enable psychoactive agents to readily cross the blood brain barrier also permit cannabinoids to readily cross the placental barrier.

Simultaneous sampling of human cord blood and maternal blood indicates that Δ [9] THC and its metabolite, 9-carboxy-THC, are present in cord blood at levels approximately 3–6 times lower than in maternal blood [20]. However, in a series of animal experiments, repeated dosing of rat dams, particularly at higher doses, resulted in plasma concentrations that were higher in the fetus than in the dam. This finding suggests that heavy chronic cannabis use during pregnancy may in fact result in accumulation of cannabinoids in the developing fetus [21].

Many studies in mice and epidemiological data in humans suggest a major regulatory role of cannabinoid signalling is in pregnancy [22]. In the mouse model, increased cannabinoid signalling via CB1 receptor inhibits normal mouse embryo development. Blocking or augmenting CB1 signalling results in abnormal embryo development. Similarly, inhibition or augmentation of endocannabinoid signalling impairs normal movement of the mouse embryo through the oviduct and regulated endocannabinoid signalling in both the blastocyst and uterus is required for normal blastocyst implantation in the uterus and establishment of normal placentation. Finally, in the human amnion, endocannabinoids and synthetic cannabinoids are known to significantly increase prostaglandin production, suggesting cannabinoid signalling may have an important role human parturition.

5. Cannabis and the developing brain

From very early on in fetal development, endogenous cannabinoids and CB1 receptors are identifiable in white matter and regions of cellular proliferation. They are thought to play key roles in crucial events such as neuronal proliferation, migration and synaptogenesis [23]. Trans-placental exposure to Δ [9] THC and other cannabis metabolites has the potential to result in supra-physiological stimulation and impact on normal development of endogenous endocannabinoid signalling with downstream effects on synaptogenesis and normal development of neuronal interconnections [24].

The normal development of other neurotransmitter systems may also be impacted on by fetal exposure to cannabis. Dopaminergic neurones are expressed in the developing brain from very early on in fetal life and exert trophic effects on other developing neuronal cells [23]. Cannabis use early in pregnancy potentially affects maturation of dopaminergic target cells by disruption of tyrosine hydroxylase activity, which is the rate-limiting enzyme in dopamine synthesis. Disorders of dopamine function have been associated with increased risk of depression, schizophrenia and drug dependency [19]. Further, animal data indicates that fetal exposure to Δ [9] THC impacts on endogenous encephalin precursor expression and expression of opioid and serotonin receptors [23]. The significance of these findings is yet to be determined, but raise the possibility of future predisposition to depression and addictive behaviours in affected individuals.

6. Cannabis and the developing immune system

Following the initial identification of the endocannabinoid system, it was first believed that its expression was largely limited to the central nervous system. Subsequently, it has been recognised that cannabinoid receptors are also expressed in the immune and reproductive systems The CB2 receptor is most prominently expressed on cells of the immune system. Stimulation and activation of the CB2 receptor can result in modulation of immune responses including impacts on apoptosis, cytokine suppression, altered T cell differentiation, induction of Myeloid-Derived Suppressor Cells (MDSCs) and a shift of the immunological status from a proinflammatory to an antiinflammatory profile [25].

Animal experiments indicate that Δ [9] THC exposure during pregnancy may have lasting impacts on T cell function. When pregnant mice were exposed to Δ [9] THC, thymic cellularity was reduced in mouse pups resulting in thymic atrophy mediated by apoptosis of thymocytes. This was associated with decrease in T cell proliferation and decreased T cell and antibody responses to HIV-1 antigens in the mouse pups [26]. Such T cell dysfunction could potentially lead to increased susceptibility to certain infections and cancers in offspring.

More concerning, is the potential for environmental insults affecting immune status during pregnancy to have transgenerational effects. DES exposure during pregnancy has had well documented transgenerational effects with DES-mothers becoming more susceptible to breast cancers and DES-daughters and even granddaughters becoming more susceptible to cervical cancers [27]. The transgenerational effects of DES are best explained by epigenetic changes acting not only on somatic cells but also on germinal cells [25].

7. The impact of cannabis use during pregnancy

Cannabis consumption during pregnancy is not associated with an increased risk of overt birth defects [28]. However, cannabis use has been associated with other negative birth outcomes. Hayatbakhsh et al., reported on birth outcomes in a large cohort of women presenting for antenatal care in a large tertiary referral hospital in Brisbane, Australia [17]. At the time of their first antenatal visit, 2.6% of women prospectively reported the use of cannabis. These authors reported that use of cannabis during pregnancy strongly and significantly predicted negative birth outcomes, including low birth weight, preterm birth, small for gestational age, and admission to the Neonatal Intensive Care. These negative outcomes persisted even with adjustment for mothers' socio-demographic characteristics, smoking, alcohol consumption, and use of other illicit drugs.

Fergusson et al. reported somewhat different outcomes in a cohort of women, who were prospectively surveyed for cannabis use prior to and during pregnancy in Bristol-based health districts of Avon [29]. Based on a self-reporting survey, approximately 5% of the women identified as using cannabis before pregnancy with a slightly smaller number reporting using cannabis at some time during pregnancy. In this cohort, cannabis use was not associated with preterm delivery or admission to Special Care Nursery, and as identified in other studies, and there was no increase in perinatal death rates. However, a decrease in birth weight and length was associated with cannabis use. These authors did acknowledge the potential impact of confounding variables on birth weight and length outcomes, in particular the strong association between cannabis use and cigarette smoking. In a systematic review of the impact of cannabis use on pregnancy outcomes, maternal cannabis use was not found to be an independent risk factor for low birth weight or other pregnancy outcomes [30]. Rather, adverse outcomes appeared to be secondary to concomitant tobacco use and other confounding factors.

As compared to the extensive number of studies looking at impact of maternal cigarette smoking or alcohol consumption long-term neurobehavioral outcomes in children, there are a limited number of studies that have investigated the relationship between prenatal exposure to cannabis and these outcomes in humans. Currently, three significant prospective longitudinal studies exist that report on follow-up assessments of children beyond the early infancy.

The earliest study of significance was the Ottawa Prenatal Prospective Study (OPPS) conducted by Fried et al. in the late 1970s. A total of 698 low risk Caucasian middle class pregnant women participated in this study. Cannabis usage was reported as number of joints per week smoked. Of the original cohort, a subgroup of 140 women identified as consuming tobacco, cannabis or a significant amount of alcohol. A control group of 50 women who abstained from all of these substances was also identified. Cannabis usage was stratified into the following groups: 1) no use, (2) mild/moderate use up to 6 joints/week, and (3) heavy use of at least 6 joints/week. Follow up of offspring continued until the cohort reached an age of 18–22 years age [31].

In 1982, the Maternal Health Practices and Child Development Study (MHPCD) was commenced [32]. In contrast to the OPPS study, this study focused on a high risk cohort of pregnant women of low socioeconomic status, mixed ethnicity (57% of African-American ethnicity) and who were mostly single. Of the initial cohort interviewed, those who used two or more joints per month were selected, with a random selection of remaining participants selected as a comparison group, resulting in a total of 564 participating women. Again prenatal cannabis use was reported as number of joints per day smoked. Heavy used was defined as one or more joints per day, and light to moderate use as 1 to 6.9 joints per week. Follow up data has been reported to 14 years of age.

The Generation R study is the most recent of cohort studies, commencing in 2001, with a total of 9778 mothers enrolled between 2002 and 2006. The authors describe this study as a multi-ethnic population-based prospective cohort study from fetal life until adulthood, based in Rotterdam, the Netherlands. Part of this study specifically focuses on maternal cannabis use during pregnancy (220 women) and fetal and offspring behavioural outcomes, comparing cannabis-exposed offspring with tobacco-exposed and non-exposed offspring [33].

The OPPS and MHPCD studies reported no impact on newborn growth parameters with the exception of decreased birth length in the MHPCD subgroup comparing 1st trimester only use to those who abstained. In contrast, the Generation R study, which also monitored fetal growth via ultrasound, identified a statistically significant reduction in fetal growth parameters, particularly where maternal cannabis use continued throughout pregnancy. This was associated with an increased fetal pulsatility index and resistance index of the uterine artery, which suggests an increased placental resistance during pregnancy [34].

In the neonatal period, neither the OPPS nor MHPCD studies demonstrated any consistent pattern of disturbed behaviour in cannabis exposed newborns. Some subtle disturbances in sleep patterns, and increased tremors and startles were noted but these findings are of uncertain significance [34]. These findings do not support the existence of a true abstinence syndrome in cannabis exposed newborn.

During infancy, there was limited evidence for negative effects of cannabis on neurobehavioral outcomes. Between the age of 3 and 4 years old, OPPS and MHPCD studies indicated that verbal and memory function was affected by daily maternal cannabis use but there were no overall effects on composite intelligence scores. However, the Generation R study did not identify a similar effect. The Generation R study was the only study to assess behaviour in this age group and demonstrated increased aggression and inattention in girls in cannabis using groups.

As yet, the Generation R study has not reported on outcomes beyond infancy. In both OPPS and MHPCD study groups, behavioural disturbances, including increased impulsivity and hyperactivity, were noted in children around 6 years old. Additionally, the MHPCD study group reported more delinquency amongst 10 year olds in their high risk subgroup. In the MPHCD study group, there was some indication that maternal cannabis use impacted on abstract and visual reasoning at age 10. Similarly, impaired visuoperceptual functioning was identified in 9–12-year old OPPS children exposed to daily cannabis use in pregnancy [34]. These domains are of particular importance to the mental processes of executive functioning, and impairment in these domains has the potential to impact on educational outcome and hence future employment potential.

Follow up of the OPPS cohort has now continued into adult age. Smith et al., reported on outcomes in a group of 18–22 year olds using functional MRI brain assessment whilst performing a series of 4 executive functioning tasks [35]. Whilst both cannabis exposed and control groups were both able to perform each functional MRI task, increased activity in posterior regions of the brain were noted with each task in the prenatally exposed group, suggesting a need for compensatory responses through increased activity in these regions or involvement of additional brain regions in these tasks. These authors concluded that this study provides evidence of long term impact of prenatal cannabis exposure that persists into adult life.

8. Beyond the womb

Depending on the amount ingested by the lactating mother, cannabis and its metabolites are excreted into breast milk in significant quantities. Human milk Δ [9] TCH concentrations have been reported to be as high as 8 times maternal serum concentrations when cannabis is consumed regularly whilst breast feeding [19].

There is limited data about the impact breast feeding whilst consuming cannabis. This is in part due to the complexity of confounding variables, including in utero exposure predating postnatal exposure. Two studies have reported conflicting outcomes. Whilst 1 reported no differences in mental or motor development at 1 year of age, the second reported that infants exposed during the first month of lactation had significantly lower mean Psychomotor Development Index scores at a similar age [36]. Of note, both the OPPS and MHPCD studies indicated that the impacts of in utero exposure do not become apparent until 3–4 years of age. To date, there is insufficient data to indicate that breast feeding whilst regularly consuming cannabis does not have impacts on neurodevelopmental outcomes. The Academy of Breast Feeding and most other professional bodies counsel against breast feeding whilst regularly consuming cannabis, but do recognise that there is very limited data to support this stance.

Whilst a well recognised link exists between prenatal and postnatal cigarette smoking and an increased risk of SIDS, this association has not been identified in cannabis users [37]. However, a strong association exists between SIDs and co-sleeping and recent parental use of alcohol or drugs. Such data must be considered when advising new parents on safe sleeping practices [38].

9. What does and doesn't work?

Unlike management strategies for opioid addiction, to date no effective substitutional therapy had been identified to assist users in reducing or abstaining from use of cannabis. Currently, interventions mostly focus on harm reduction strategies. Cognitive behavioural therapy based interventions have shown some promise. A randomized controlled trial comparing a basic skills training approach to group-delivered cognitive behavioural therapy demonstrated significant reductions in number of days of cannabis use at 12 months follow up in the cognitive behavioural therapy group, but no difference in abstinence rates [39]. Similar results occurred with brief one-session intensive intervention accompanied by a self-help booklet. Although abstinence rates were low, there was a significant impact on amount and frequency of use.

These findings have some significance in the management of women presenting for antenatal care who identify as regular cannabis users. Although the safety of intermittent use has not been fully established, prospective longitudinal studies indicate that the greatest risk of harm is associated with regular heavy use of cannabis during pregnancy.

10. A new friend?

Currently a majority of states in the United States permit use of cannabis for management for a number of medical problems. Whilst the US Food and Drug Administration requires robust evidence before approving a drug for medical use in specific clinical problems, the same standards have not been applied when legalising marijuana for medicinal use. Evidence exists to support the use of cannabis to manage nausea and vomiting related to chemotherapy, specific pain syndromes, and spasticity from multiple sclerosis. However, approval for use in other conditions largely relies on low-quality scientific evidence, anecdotal reports, individual testimonials, legislative initiatives, and public opinion [40].

There is some evidence that legalisation of cannabis in the United States has been associated with an increased perception amongst pregnant and non-pregnant women that regular cannabis use is safe [41]. Further, there are some indications that women who report severe nausea during pregnancy are significantly more likely to use of cannabis during pregnancy than those who do not experience these symptoms [41]. It is possible that cannabis is being used as an antiemetic among women experiencing severe morning sickness [42]. When a random selection of Colorado cannabis dispensaries was contacted in 2017 about use of cannabis products to treat nausea in the first trimester, nearly 70% recommended cannabis to callers [43]. Of note, only a small number of these dispensaries suggested that their clients should discuss the use of cannabis for this purpose with a health care provider without prompting. Currently there is very limited safety data on the use of cannabis to manage nausea in the first trimester or severe morning sickness.

Cannabidiol is the main non-psychotropic cannabinoid produced by the Cannabis sativa plant. It binds with a low affinity to both CB1 and CB2 receptors, but may exert anti-inflammatory properties through its interaction with the CB2 receptor. Additionally, cannabidiol exerts significant antioxidant effects [44]. Cannabidiol demonstrates very low toxicity and has not been demonstrated to cause teratogenic or mutagenic effects. This, combined with its lack of cognitive and psychoactive effects, makes it potentially an ideal pharmacological agent.

Currently, there is very limited data about the safety of prescribing cannabidiol during pregnancy. Arguably, its low affinity for CB1 and CB2 receptors may mitigate against potential impacts on the developing brain. However, evidence indicates that this proposition may be falsely reassuring. BCRP and P-gp play a key roles in the transport of drugs and endogenous compounds, including fetal hormonal precursors in the human placenta, and therefore have important roles in the outcome of pregnancy [45]. It has been demonstrated that cannabidiol modulates expression of these two transporters in an in vitro model used in trophoblast toxicology studies. Potentially, this may permit increased penetrance of drugs that are P-gp substrates, as well as lead to altered transport of BCRP substrates, such as medications, naturally occurring carcinogens, hormonal precursors and apoptotic molecules and impact on pregnancy outcomes.

There is emerging evidence that cannabinoids may have a neuroprotective role in adult animal models of acute and chronic neurodegenerative conditions. This has stimulated interest in the potential for cannabinoids to have a therapeutic role in management of neonatal hypoxic ischemic injury. The cannabinoid agonist WIN, when administered after induction of injury, has been demonstrated to significantly reduce brain injury, as assessed by MRI, in a neonatal rat model of hypoxic ischemic encephalopathy [46]. This effect was dependent on the activation of CB1 and CB2 receptors. This finding indicates that cannabinoids may have potential therapeutic benefits in the management of neonatal hypoxic ischemic injury.

11. Summary

Products of the cannabis plant have been used through the ages for a myriad of purposes, with the popularity of these products waxing and waning over the centuries. In many of its forms, products of the cannabis plant have been a friend. Recently there has been a resurgence in interest in cannabinoids in the management of a spectrum of medical problems. However, cannabis can also been considered a foe. With the endocannabinoid system being identified as having a key role in the developing brain of the fetus, infant and adolescent, there is good reason to be concerned about exposure of the unborn child to regular cannabis use during pregnancy and ongoing use whilst breast feeding.

Health professionals caring for pregnant women and newborn infants will continue to be confronted by the perception that cannabis use during pregnancy is relatively harmless, despite mounting evidence that regular use may well cause harm that persists into adult life. There is a strong need have a good understanding of these possible risks and an ability to discuss them in a non-threatening and non-judgemental manner. Women should be advised that regular use, particularly on a daily basis, is particularly associated with adverse outcomes, and where abstinence is not possible, significant reduction is still beneficial. The use of targeted cognitive behavioural therapy may achieve substantial reduction in frequency and quantity of cannabis use.

Evidence suggests that cannabis is being recommended to women for management of nausea and vomiting in early pregnancy. Health professionals must familiarise themselves with how use of cannabis for medicinal purposes may influence cannabis consumption in pregnancy and whilst lactating and the potential implications of this use. There is a pressing need for robust research into the use of medicinal products including cannabidiol as mainstream use becomes more common and established.

Research directions

1. Impact of prenatal cannabis use on long-term outcomes of children, including mental and physical health including immunity
2. Impact of prenatal medicinal cannabis on short and long-term childhood outcomes
3. Potential use of cannabinoids as therapeutic agents for neonatal problems, such as hypoxic ischemic encephalopathy or neonatal abstinence syndrome.

Practice points

- Cannabis is the most frequently used recreational drug in western cultures.
- The endocannabinoid system plays a role in the development of the fetal, infant and adolescent brain.
- Regular use of cannabis during pregnancy can impact on cognitive outcomes of exposed children.
- There is limited data about impact of use of medicinal cannabis and cannabinoids during pregnancy.

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