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The Endocannabinoid System: Effects of Cannabis on Female Reproduction

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SUMMARY

Preliminary research into endocannabinoid system suggests a significant role in reproductive processes, especially fertility and fecundity. Although there are many psychological and physiological benefits of cannabis for a variety of health conditions, the longer-term effects on the female reproductive system are not explicated. With legislative approbations of marijuana through legalization and/or decriminalization of marijuana, ensuing uptake in use has ensued concern for these potential effects. Cannabis users and their medical providers should utilize current knowledge to help navigate the balance between benefits and possible ramifications.

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Cannabis, or marijuana, is one of the most used psychoactive substances worldwide, particularly in those of reproductive age [1-4]. Although there are ostensive documented health benefits including analgesic effects, the physiological processes of the human endocannabinoid system [ECS] are not fully understood, nor are the potential ramifications of marijuana use on human health [1,3,5]. Emerging research suggests that the ECS is crucial to the reproductive processes [6]. With increased legalization of marijuana, and subsequent increasing use, there are concerns arising about its effects [7]. Cannabis use may have harmful effects on reproduction and fertility. While there tend to be higher rates of use in men, the implications of cannabis use on female reproductive processes, fecundity and fertility appear to be more egregious [2,3,8].

The Endocannabinoid System

The endocannabinoid system (ECS) is a complex biological system affecting human health, with components found ubiquitously around the body. The ECS is associated with various physiological and cognitive processes, such as pain, memory, metabolism, growth, as well as reproduction and fertility [9]. The ECS is involved in maintaining homeostasis and consists of receptors, enzymes, and endocannabinoids [9].

Endocannabinoids

The body naturally produces cannabinoids, called endogenous cannabinoids or endocannabinoids (eCBs) which are ligands that activate receptors [5]. These eCBs are derived from unsaturated fatty acids with precursors in lipid membranes through hydrolysis [10-12]. Endocannabinoids, unlike other neurotransmitters, are synthesized de novo, as needed by postsynaptic cells, rather than produced and stored [10-15]. The primary eCBs in the body are N-arachidonoylethanolamine or anandamide [AEA], and 2-Arachidonoylgycerol [2-AG] [16]. Levels 3 of eCBs are tightly regulated by the ECS enzymes for both synthesis and degradation [9,15,16]. Fatty acid amide hydrolase [FAAH] and monoacylglyercol lipase [MAGL] degrade AEA and 2-AG, respectively When produced, eCBs bind to receptors to produce their effects in an autocrine or paracrine manner [6,10].

Receptors

AEA and 2-AG bind and activate 2 G-protein coupled receptors [GPCRs] cannabinoid receptors 1 and 2, CB1 and CB2, respectively [12,17]. CB1 receptors have been identified in endocrine tissues, including the ovaries, oviduct, endometrium, uterus, hypothalamus and anterior pituitary [2,3,12,18]. Similarly, CB2 receptors are found in the ovarian cortex, ovarian medulla, ovarian follicles, myometrium, endothelial cells of uterine blood vessels, and embryonic stem cells [6,12,17]. These receptors are also targets of exogenous cannabinoids.

Exogenous Cannabinoids

Exogenous cannabinoids are substances from outside the body, and act as ligands for the cannabinoid receptors [11,12]. Common exogenous cannabinoids, include tetrahydrocannabinol (THC) and cannabidiol (CBD), derived from cannabis. THC is an analog of eCBs, which mimics the receptor responses to AEA and 2-AG and acts as an agonist on receptors [12,19]. Although eCBs are tightly regulated by the ECS for homeostasis, exogenous cannabinoids do not have selectivity or stringent regulation [5,16,20]. Instead, they bind and modulate receptors and their expression [9,20]. Pertinently, THC can be stored in adipose tissue, prolonging effects [12,20]. This storage can alter levels of eCBs and receptor

expression, which may have broader and longer response than the elucidated effects of cannabis [12].

Cannabinoids and the Female Reproductive System

Endocannabinoids have a strong influence on the female reproductive organs, and processes of reproduction, including folliculogenesis, oocyte maturation, hormone secretion, fecundation, oviduct embryo transport, implantation, uterine decidualization, placentation and parturition [9,10,12,17,21]. The ECS affects the hypothalamus-pituitary-ovarian (HPO) axis; influencing hormone production and secretion [2,12]. The close association between sex steroid hormones and eCBs suggest a regulatory function, but this relationship appears bidirectional [2,10,14,19].

Hormones

The ECS appears to be involved in follicular maturation and development [12]. Plasma AEA levels surge periovulatory but vacillate throughout the menstrual cycle [9,10,12,14]. Following ovulation and LH surge, high levels of FAAH and lower levels of AEA are found [9,22]. AEA may be regulated by gonadotrophins or estrogen, specifically enhanced by estradiol [9,14,19,23]. However, FAAH also appears to be modulated by progesterone and estrogen [9,10,23,24]. These processes are highly specific and localized, where aberrations may induce infertility or reproductive health issues.

For instance, AEA levels have been found to be more consistently elevated in individuals with polycystic ovarian syndrome [PCOS] and patients with inexplicable infertility [6,10,12,24]. Similarly, defective or atypical eCB signaling have been associated with inflammatory conditions, such as endometriosis and preeclampsia [12,15,16,23]. Elevated peripheral levels of AEA showed a greater increase of miscarriage This indicates a close involvement of the ECS in fertility and pregnancy outcomes [12,17].

Implantation

AEA is thought to be vital to uterine receptivity and implantation; serving as a connection between a developing embryo and the endometrium, and pregnancy maintenance [1,6,9,10]. Low expression of CB1 in fallopian tubes and endometrium has been associated with ectopic pregnancy [14]. Precise eCB signaling is required for embryo oviduct transport, preimplantation embryo development and subsequent blastocyst implantation [9,10,16]. The blastocyst may reciprocally influenceAEA levels in the uterus, where AEA concentration is localized, low in receptive implantary areas [9,10,16]. This evidence furthers the regulatory hypothesis of the ECS and reproduction, specifically fecundity.

Pregnancy

AEA level patterns show low levels for pregnancy maintenance, with high levels associated with miscarriage in early pregnancy and the onset of labor in late pregnancy [10,23,24,37]. The high AEA may be influenced by progesterone levels, where low levels correlate with failure to implant, or miscarriage [10,24]. Additional evidence demonstrates that women undergoing In-vitro fertilization [IVF] required low AEA levels at the time of implantation for successful pregnancy [14,17]. These patterns suggest a strong regulatory role of the ECS in reproduction where AEA and FAAH might act as biomarkers for pregnancy success, and fertility [9,15,25,26].

Cannabis Use

Cannabis use introduces exogenous cannabinoids, such as THC, into the body and the ECS. THC offsets receptor signaling, silencing, and enhancing these receptors, and influencing eCB concentrations [16,23]. THC has been found to decrease the secretion of gonadotrophin-releasing hormone [GnRH], LH, and FSH, which have significant effects on the delicate hormone cycles that permit reproductive processes like folliculogenesis, oocyte maturation and ovulation [8,10,27]. Studies investigating cannabis and IVF treatment have found users have produced poorer quality oocytes, decreased oocyte retrieval, and lower pregnancy rates [2,12,20,28]. Similar results found in an NIH study, where women using cannabis were less likely to conceive [20]. Cannabis users are more likely to have disrupted menstrual cycles, including an ovulatory cycles that may contribute to infertility [2,8,29]. Animal studies have shown concordant effects [7,8,19,20,27].

Unfortunately, the safety of cannabis is overstated, and use during pregnancy has ramifications for both mother and child. Use during pregnancy is associated with pre-term birth, low birth weight, fetal growth restriction, stillbirth, and placental abruption. Cannabis use may also have epigenetic effects on developing fetuses [2,4,7,27]. Cannabis exposure is linked to specific DNA methylation in immune cells, and the brain, which can have significant effects on fetal development, neonatal outcomes, and health conditions later in life [2,27,30,31].

The identification of eCB receptors in embryonic tissues, as early as the preimplantation period, and the fetal-maternal interface indicate early ECS involvement suggesting no safe perinatal period of use [2,4,7,10,21,32]. These potential effects must be balanced with the medicinal benefits of cannabis, such as anti-emetic or analgesic effects that promote use preconception and during pregnancy.

Limitations

Current research coherently elucidates involvement of the ECS in female reproductive processes and neonatal outcomes but has clear limitations. THC is the most widely studied cannabinoid derived from marijuana but there are 100 more, with limited understanding about their mechanism or influence on the ECS [27,33]. Ethical experimental design limits the use of human participants, and alternate study design may be influenced by self-report, and the potential for social desirability bias, especially as cannabis use may be associated with other substance use [3,8,23,29,34,35].

Continued reliance on animal studies has limited applicability in humans due to biological differences or alterations in effects of drugs between species [15,36]. However, human studies could be influenced by confounding factors. Tolerance from chronic use could modify ECS regulation, and present variable results when combined with sporadic users [12,22]. Factors that influence cannabis use may be more significant than the effects of cannabis on the ECS [34]. For example, health conditions where cannabis can provide symptomatic relief, like endometriosis, or broader factors that predispose cannabis-use, such as depression or anxiety [1,4,5,24,34]. These conditions may be linked through other mechanisms not currently identified, that may exert influence over the ECS system. Continued research of cannabis with various study design are essential to discerning the significance of the ECS, reproductive processes, related health conditions and potential pharmacological treatments [7,21,24].

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