

The role of the endocannabinoid system during pregnancy

The number of countries decriminalizing and/or legalizing the use of cannabis for recreational or medical purposes is constantly increasing. Although medical use of cannabis has been proven to alleviate certain pathological conditions, it has also been reported a diminished fertility capacity and reproductive failure in frequent and/or heavy cannabis consumers. Therefore, it is imperative to fully understand the effects of cannabinoids in female fertility and the different stages of pregnancy. This is of particular importance for women currently consuming cannabis for medical reasons and who are seeking becoming pregnant.

In the late 1980's and early 1990's two binding sites for cannabis main psychoactive component were characterized and named CB1 and CB2. Shortly after these discoveries, the main ligands for these receptors, anandamide (AEA) and 2-arachydonoyl glycerol (2-AG), were isolated and chemically characterized; as well as their respective biosynthesis and degradation enzymes. Together, they comprise the endocannabinoid system (eCS).

The eCS is present in the reproductive tissue of both male and female. In particular, the endometrium expresses higher levels of AEA than any other reproductive tissue. Interestingly, AEA levels, as well as the expression of other components of the eCS, fluctuate with the menstrual cycle, which indicates that this system is under hormonal control. Moreover, components of the eCS have been detected in all stages of oocyte maturation and fertilized eggs express high levels of CB1. The precise role of the eCS in female reproductive physiology still remains elusive; however, several studies have demonstrated that an adequate "AEA tone" is required throughout gestation for a successful and healthy pregnancy. Thus, during implantation (when the blastocyst adheres and invades the uterine wall), the uterine AEA level are tightly regulated by the uterine expression of the fatty acid amide hydrolase (FAAH), since too high or too low levels of AEA are deleterious for gestation. The implantation site shows increased FAAH activity and low levels of AEA, whereas the opposite is true for the surrounding tissue. Moreover, the blastocyst regulates its CB1 expression in order to detect the appropriate level of AEA for a successful implantation.

A tightly regulated "endocannabinoid tone" is also required for other events during pregnancy, such as decidualization and placentation. It has been shown that too low levels of AEA, via CB1-dependent mechanisms, induce apoptosis-like molecular changes in decidual cells, whereas too high concentrations trigger the release of lactate dehydrogenase from these cells, a characteristic of a necrotic process. Similar observations have been reported for 2-AG. Furthermore, alterations in the eCS have been shown to affect several aspects of the placentation process, compromising pregnancy outcome.

Data from patient studies highlight the negative impact that an imbalance of the "endocannabinoid tone" has on the normal course of pregnancy. Accordingly, it has been reported that women with non-viable first-trimester pregnancies have elevated serum levels of AEA. Similarly, women subjected to a successful in vitro fertilization of intracytoplasmic sperm injection show lower serum

levels of AEA at the time of implantation when compared to those in which the procedure failed. Additionally, women in risk of miscarriage show higher plasma levels of AEA than women with a normal pregnancy. Furthermore, increased levels of plasma levels of AEA and related endocannabinoids have been reported in women with ectopic pregnancies.

The precise role of the eCS system at different stages of pregnancy remains elusive and further research is warranted. Nevertheless, cumulative evidence point towards the need to prevent drastic changes in the eCS homeostasis at every stage of gestation in order to prevent negative consequences and to ensure a healthy gestation.

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