MON-010: Effects of Delta-9-Tetrahydrocannabinol (THC) on Oocyte Competence and Early Embryonic Development

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Cannabis is the highest used recreational drug amongst individuals of reproductive age. Fertility clinics advise against cannabis use when undergoing fertility treatments, but the literature backing this statement is weak. This rise in cannabis use has occurred simultaneously with the increase in the percentage of the main psychoactive component of cannabis, delta-9 tetrahydrocannabinol (THC).[1] Current literature suggests that THC mimics the effects of endogenous cannabinoids, binding to cannabinoid receptor 1 (CB1), which has been identified in reproductive tissues.[2]

Our research aims to study the impact of THC on oocyte maturation and pre-implantation embryonic development. An in vitro bovine system was used as it is the most appropriate translational model to humans for in vitro reproductive toxicity studies. Bovine oocytes were collected and matured under five treatment groups: control, vehicle (1:1:18 ethanol: TWEEN: saline), low THC (0.032uM), mid THC (0.32uM) and high THC (3.2uM). These doses mimic plasma concentrations reached after therapeutic (0.032uM) or low/high recreational (0.32uM and 3.2uM) cannabis use.[3] We hypothesize that THC affects oocyte competence and proper early embryonic development in vitro.

A negative THC dose-dependent response in cleavage rate was observed, with the highest THC group cleaving at 70.2% rate compared to 86.8% and 85.5% of control and vehicle groups, respectively ($p<0.0001$, $n=7$). There was no significant difference in blastocyst rate, suggesting that oocyte THC exposure affects the numbers of oocytes capable of development, but those able to cleave will properly reach blastocyst stage. We analyzed changes in gene expression, i) by a full RNA transcriptome analysis (24,128 transcripts screened) and ii) by quantification of Connexin 37 (CX37) and 43 (CX43) mRNA levels. Connexin expression is correlated to oocyte competence.[4] RNA transcriptome analysis showed 62 genes that were significantly downregulated only in the low THC group. CX mRNA levels were measured via droplet digital PCR in both cumulus-oocyte complexes (COCs) and blastocysts. No significant differences were detected in blastocysts, however, a significant decrease in both CX37 and CX43 levels was measured in the low THC group in COCs ($p<0.05$, $n= 9$). Differences seen exclusively at the low THC dose suggest a role of THC as partial agonist of CB1.

This research aims to understand the effects of cannabis on fertility, as current knowledge during pre-implantation development is limited, making it difficult for physicians to properly advise patients undergoing IVF.

Reference: 1. ElSohly et al., *Biol Psychiatry*. 2016 Apr 1;79(7):613-9. 2. El-Talatini et al., *PLoS ONE*. 2009 Feb 24;4(2):e4579. 3. Whan et al., *Fertil Steril.* 2006 Mar;85(3):653-60. 4. Wang et al., *Am J Physiol Endocrinol Metab*. 2012 Jun 15;302(12):1511-8.