P-294 Mapping COVID-19 affected genes from blood in a Window of implantation co-expression network reveals a potentially compromised landscape

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Study question: Could the transcriptomic and functional landscape of the window of implantation be compromised by SARS-COV-2 infection?
Summary answer: Some of the main genes and pathways involved in the window of implantation are affected in blood of COVID-19 patients and receptivity could be affected.
What is known already: There is a concern whether SARS-COV-2 can disrupt assisted reproduction treatments (ARTs) and fertility in short and long terms. In the endometrium, it was found that genes related to the viral infection (ACE2, TMPRSS2/4, CTSL/B) are involved in menstrual cycle progression, especially in the Window of Implantation (WOI). However, there are no studies describing the transcriptome changes after the infection, and the changes that could affect receptivity and embryo implantation. Currently transcriptomic datasets are publicly available regarding virus infection effects in blood. The aim of this study was to integrate these blood effects with the gene expression during the WOI.
Study design, size, duration: A public dataset with blood transcriptome of 231 female COVID-19 patients and 30 female controls was downloaded from GEO. Meanwhile, 5 transcriptomic endometrial datasets in the WOI with patients without endometrial pathologies were also retrieved (n=44). Gene expression correlations (potential activations and inhibitions) were calculated in endometrium and filtered by blood differentially expressed genes for predicting the potential effects of COVID-19 in endometrial factor. Additionally, we discovered new endometrial genes involved in the infection repercussions.
Participants/materials, setting, methods: A gene co-expression network was built in Cytoscape with the WOI dataset [Pearson correlation = 0.65, only significant correlations; Power fit law R2 >= 0.8]. Differential expression was done for COVID-19 patients versus controls with limma and significant genes in blood were highlighted in the endometrial WOI network. Topological parameters were calculated by CytoHubba and network modules and related functions were analysed performing a Functional enrichment (BINGO). Statistical significance cut off was stablished in FDR<0.05.
Main results and the role of chance: After filtering by blood affected genes, 2051 genes were found differentially expressed in COVID-19 females in blood and mapped in the co-expression WOI network. Nine modules were highlighted being enriched in translational elongation, intracellular protein transport, endosome organization, vitamin D receptor binding, actin cytoskeleton organization, RNA splicing, among others. Important hubs in the endometrium that correlated with TMPRSS4 were: COBL, a gene that promotes formation of cell ruffles which are important or embryo adhesion (FC = -3.99, degree = 209); PKP2 (FC = -1.5, degree = 188) which could play a role in junctional plaques and knockdown in mice was reported to inhibit implantation; SOCS3, linked to unexplained

infertility and pregnancy loss, (FC -4.3, degree = 177); GPX3 involved in detoxification and usually highly upregulated during WOI was downregulated (FC -3.7, degree = 173). GPX3 also correlated with CTSB. TPRC/CD45, related to unexplained pregnancy loss and concentration of NK cells, was an upregulated gene (FC = 5, degree = 161) that correlated with CTSL. Upregulated genes with main connections in the network were: SERPING1 (FC = 5), which regulates complement activation and embryo-maternal immune modulation and SMARCAD1 (FC 1.5), involved in DNA repair and heterochromatin organization.

Limitations, reasons for caution: This is an in-silico descriptive study where differentially expressed genes in blood samples of COVID-19 patients were analysed in an endometrial co-expression network context. Studying a COVID-19 infected endometrium during WOI would help to confirm the results of this study.

Wider implications of the findings: Although ACE2 has been reported as not highly expressed during the WOI, this study describes potential genes and functions very important for embryo implantation affected after SARS-COV-2 infection. These findings evidenced how SARS-COV-2 could impact the efficacy of ARTs and should be taken into consideration for further research and implications.

Trial registration number: not applicable