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Study question: What is the effect of COVID-19 infection on pregnancy rates in frozen embryo transfer (FET) cycles?

Summary answer: Past COVID-19 infection decreased pregnancy rates in FET cycles, especially in patients with recent infection.

What is known already: ACE2 and TMPRSS2 are expressed in the endometrium, potentially enabling SARS-COV-2 viral invasion of the cells. Unlike with bacterial infections, the effect of viral infections in general on implantation and pregnancy rates is unclear. Some evidence suggests that early embryonic and trophoblastic infection, may result in impaired implantation or placentation. A recently published study including both recovered and vaccinated patients did not find an effect of COVID-19 immunity on FET cycle outcomes. The study did not stratify by time from infection thus the immediate consequences of infection on pregnancy rates could not be properly evaluated.

Study design, size, duration: A retrospective cohort study, including 41 COVID-19 recovered women, aged 20-42 years that underwent FET cycles, and 41 controls between January 1, and June 31, 2021, at a large IVF unit.

Participants/materials, setting, methods: Embryos transferred were the product of fresh cycles performed prior to infection. Maximal time from infection to transfer was defined as one year. The study group was matched by age, number of embryos transferred and day of transfer, to unvaccinated patients, with no history of past infection that underwent FET cycles during the same period. Demographics and cycle characteristics were recorded. Clinical and ongoing pregnancy rates were compared, with further stratification by time from infection.

Main results and the role of chance: Clinical pregnancy rates were 29.3% and 48.8% for the recovered and control patients respectively ($p = 0.070$). Ongoing pregnancy rates were 26.6% vs. 43.4% ($p = 0.093$). Mean age at ovum pickup (30.72 vs. 30.69; $p = 0.929$) and at transfer (31.56 vs. 31.58; $p = 0.966$) was similar between groups, as were the demographic characteristics and previous retrievals and transfers. The predominant transfer protocol used was different between groups with higher rates of natural cycle (NC) protocol in the COVID group (61% vs. 33.3%; $p = 0.013$. All other cycle characteristics including endometrial width, number of embryos transferred, day of embryo transfer and embryo grade were similar. Stratification by time from COVID-19 infection to transfer into ≤ 60 and >60 days revealed a significant difference in pregnancy rates, with recovered women having lower pregnancy rates if infected in proximity to the transfer (20.7% vs. 55.2%; $p = 0.006$). In a logistic regression model, infection was a significant variable ($p = 0.05$, OR 0.325, 95% CI 0.106-0.998). Logistic regression applied on the subgroup of women infected in proximity to the transfer, further strengthened the univariate results, with COVID-19 infection remaining a significant parameter ($p = 0.005$, OR 0.072, 95% CI 0.012-0.450).

Limitations, reasons for caution: A retrospective study, with a limited sample size, but nevertheless our results showed significant differences.

Wider implications of the findings: Further studies with larger groups are warranted to support these findings. Pending further information, in cases of FET cycles with limited numbers of embryos (advanced age, embryo donation, fertility preservation, embryos following sperm extraction), postponing embryo transfer for at least 60 days following recovery might be considered, if feasible.

Trial registration number: HMC-0010-21

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