Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Infection xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Letter to the Editor

Coronavirus disease 2019 vaccination and live birth outcome after fresh embryo transfer

Dear editor,

Coronavirus disease 2019 (COVID-19) has become a global pandemic and vaccination is a key strategy to reduce morbidity and mortality from the disease. This is especially important for reproductive-aged women planning to conceive, since COVID-19 could result in unfavorable obstetric and neonatal outcomes during pregnancy as addressed by a living systematic review with meta-analysis[1] and two recent articles published in the *Journal of Infection*.[2,3] However, vaccination coverage remains slow-moving despite of increased access, with fertility concern identified as a major source of hesitancy.[4] Among *in vitro* fertilization (IVF) cycles, accumulating studies have demonstrated no significant association of COVID-19 vaccines with ovarian response, oocyte quality, and embryo implantation.[5–8] Nonetheless, data on live birth, the key outcome of IVF treatment, is still lacking due to the short follow-up period. The purpose of our study was to evaluate the effect of inactivated COVID-19 vaccination on live birth outcome after fresh embryo transfer (ET).

This was a retrospective cohort study of all infertile women undergoing fresh ET cycles from June 1st to October 18th 2021 at our reproductive center with ISO 9001:2015 quality control. Study approval was obtained from the Ethics Committee of Jiangxi Maternal and Child Health Hospital (No. 2021–02), and all patients provided written informed consents. The study group consisted of patients who completed two full doses of inactivated COVID-19 vaccines (Sinopharm or Sinovac) before ET, while those unvaccinated were categorized into the control group. We excluded patients with partial vaccination, other vaccine types, self-reported COVID-19 history, donor sperm or oocyte, repeated cycles, loss to follow-up, and missing IVF data. The primary outcome was the rate of live birth, defined as the delivery of a viable infant at $\geq$24 weeks of gestation. Details on vaccination status ascertainment, routine IVF protocol, and other outcome measures have been described in our previous study of the same cohort.[8]

For between-group comparison, we used Student's *t*-test, Mann-Whitney U-test, Pearson's Chi-square test, or Fisher's exact test as appropriate. Multiple logistic regression analysis was applied to control for potential confounders. Based on an overall live birth rate (LBR) of 55% in our center, a sample size of 117 patients *per* group was estimated to detect a 18% post-vaccination decrease with 80% power and alpha of 0.05. Data analysis was conducted in SAS version 9.4 (SAS Institute, USA), and a two-sided $P < 0.05$ was considered as statistically significant.

Of the 1385 patients included, 124 were vaccinated and 1261 were unvaccinated. The two groups differed significantly in female age, uterine factor infertility, previous transfer times, ovarian stimulation protocol, fertilization method, and male vaccination status. No significant differences were observed in other baseline demographics, cycle characteristics, as well as laboratory outcomes (Table 1).

LBR was 49.2% and 54.4% in vaccinated and unvaccinated patients respectively ($P = 0.267$), resulting in a crude odds ratio (OR) of 0.81 (95% confidence interval [CI] 0.56–1.77) and an adjusted OR of 0.97 (95% CI 0.62–1.51). Similarly, there were no significant differences in biochemical pregnancy, clinical pregnancy, and miscarriage rates, which remained consistent on crude and adjusted analyses (Table 2). Obstetric and neonatal outcomes were also followed-up during pregnancy, and no evidently increased complications were observed in the vaccinated group (Supplementary Table S1).

For vaccinated patients, the mean time interval between complete vaccination and ET was 126.5 $\pm$ 64.0 (range 13–246) days. As demonstrated in Supplementary Table S2, both laboratory and pregnancy outcomes remained comparable when these patients were subdivided into $\leq$2-month and $>$2-month groups.

For the first time, our study showed that COVID-19 vaccination had no measurable effect on LBR in IVF cycles, which adds to the growing evidence on its reproductive safety and provides reassurance for fertility-seeking women. Consistent with guidelines from the American Society for Reproductive Medicine and European Society of Human Reproduction and Embryology,[9,10] our preliminary data also demonstrated no significant impact of vaccination interval on IVF outcome, as long as the immune response was stabilized after several days.

This study is limited by its small sample size in a single center and retrospective design with potential residual confounding and selection bias. Moreover, the generalization of our finding could be restricted by the inclusion of only inactivated vaccines and the majority of double cleavage-stage embryo transfer. Further larger prospective cohort studies are needed to confirm our conclusion.

https://doi.org/10.1016/j.jinf.2022.09.023

Table 1
Baseline demographics, cycle characteristics, and laboratory outcomes of included patients.

	Vaccinated (n = 124)	Unvaccinated (n = 1261)	P-value
Age (years)	31.8 ± 4.3	31.0 ± 4.4	0.017
Body mass index (kg/m^2)	21.9 ± 3.2	22.2 ± 3.1	0.101
Antral follicle count	13.5 ± 6.1	13.9 ± 5.8	0.238
Infertility duration (years)	4.4 ± 2.9	4.2 ± 3.0	0.338
Type of infertility, n (%)			0.959
Primary	47 (37.9)	475 (37.7)	
Secondary	77 (62.1)	786 (62.3)	
Infertility diseases			
Tubal factor, n (%)	88 (71.0)	917 (72.7)	0.677
Male factor, n (%)	30 (24.2)	301 (23.9)	0.936
Ovulatory dysfunction, n (%)	14 (11.3)	175 (13.9)	0.423
Diminished ovarian reserve, n (%)	10 (8.1)	105 (8.3)	0.920
Endometriosis, n (%)	13 (10.5)	85 (6.7)	0.121
Uterine factor, n (%)	25 (20.2)	145 (11.5)	0.005
Male vaccination status, n (%)			<0.001
Unvaccinated	42 (33.9)	1115 (88.4)	
Partially vaccinated	10 (8.1)	77 (6.1)	
Fully vaccinated	72 (58.1)	69 (5.5)	
Previous retrievals	1.2 ± 0.5	1.2 ± 0.6	0.209
Previous transfers	0.3 ± 0.8	0.2 ± 0.6	0.043
Ovarian stimulation protocol, n (%)			0.001
Agonist	120 (96.8)	1255 (99.5)	
Antagonist	4 (3.2)	6 (0.5)	
Fertilization method, n (%)			0.015
IVF	96 (77.4)	946 (75)	
ICSI	27 (21.8)	222 (17.6)	
IVF+ICSI	1 (0.8)	93 (7.4)	
Stimulation duration (days)	10.9 ± 1.9	11 ± 2.0	0.746
Total gonadotropin dose (IU)	2175.8 ± 731.2	2136.2 ± 809.4	0.389
Trigger day estradiol level (pg/mL)	1658.6 ± 901.1	1780.7 ± 845.7	0.081
Trigger day progesterone level (ng/mL)	0.4 ± 0.3	0.4 ± 0.3	0.497
Trigger day endometrial thickness (mm)	10.8 ± 2.8	11.0 ± 2.5	0.160
Number of oocytes retrieved	10.8 ± 4.9	11.4 ± 4.6	0.174
ICSI mature oocyte rate (%)	75.0 ± 12.8	77.9 ± 19.8	0.192
Normal fertilization rate (%)	68.6 ± 20.5	67.3 ± 19.8	0.376
Cleavage rate (%)	96.1 ± 7.8	96.7 ± 8.0	0.180
Day 3 good-quality embryo rate (%)	29.5 ± 25.1	28.1 ± 23.5	0.699
Blastocyst formation rate (%)	74.3 ± 29.4	72.7 ± 30.3	0.683
Number of viable embryos	3.9 ± 2.2	3.7 ± 2.0	0.333
Number of embryos transferred, n (%)			0.497
Single	40 (32.3)	370 (29.3)	
Double	84 (67.7)	891 (70.7)	
Embryo developmental stage, n (%)			0.688
Cleavage	92 (74.2)	956 (75.8)	
Blastocyst	32 (25.8)	305 (24.2)	
Transfer of at least 1 good-quality embryo, n (%)	80 (64.5)	883 (70.0)	0.204

Note: Data are presented as mean ± standard deviation or number (percentage). IVF = *in vitro* fertilization; ICSI = intracytoplasmic sperm injection.

Table 2
Pregnancy outcomes of vaccinated *versus* unvaccinated patients after fresh embryo transfer.

	Vaccinated (n = 124)	Unvaccinated (n = 1261)	P-value	cOR (95% CI)	aOR (95% CI) [a]
Biochemical pregnancy, n (%)	89 (71.8)	928 (73.6)	0.662	0.91 (0.61–1.38)	1.39 (0.84–2.31)
Clinical pregnancy, n (%)	76 (61.3)	799 (63.4)	0.648	0.92 (0.63–1.34)	1.26 (0.80–2.00)
Embryo implantation, n/N (%)	98/208 (47.1)	1027/2152 (47.7)	0.867	–	–
Miscarriage, n/N (%)	14/76 (18.4)	104/799 (13.0)	0.187	1.51 (0.82–2.79)	1.40 (0.71–2.76)
Live birth, n (%)	61 (49.2)	686 (54.4)	0.267	0.81 (0.56–1.17)	0.97 (0.62–1.51)

Note: cOR = crude odds ratio; CI = confidence interval; aOR = adjusted odds ratio.
[a] Adjusted for age, body mass index, infertility type, duration of infertility, infertility diseases, male vaccination status, previous retrievals and transfers, ovarian stimulation protocol, fertilization method, trigger day estradiol and progesterone level, number of oocytes retrieved, endometrial thickness, number of embryos transferred, embryo developmental stage, and embryo quality.

Funding

This study was funded by the National Natural Science Foundation of China (82,260,315).

Disclosure statement

None declared.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.09.023.

References

1. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *BMJ* 2020;**370**:m3320.
2. Huang W, Zhao Z, He Z, Liu S, Wu Q, Zhang X, et al. Unfavorable outcomes in pregnant patients with COVID-19. *J Infect* 2020;**81**:e99–e101.
3. Liu Y, Chen H, Tan W, Kuang Y, Tang K, Luo Y, et al. Clinical characteristics and outcome of SARS-CoV-2 infection during pregnancy. *J Infect* 2021;**82**:e9–e10.
4. Diaz P, Zizzo J, Balaji NC, Reddy R, Khodamoradi K, Ory J, et al. Fear about adverse effect on fertility is a major cause of COVID-19 vaccine hesitancy in the United States. *Andrologia* 2022;**54**:e14361.
5. Orvieto R, Noach-Hirsh M, Segev-Zahav A, Haas J, Nahum R, Aizer A. Does mRNA SARS-CoV-2 vaccine influence patients' performance during IVF-ET cycle? *Reprod Biol Endocrinol* 2021;**19**:69.
6. Aizer A, Noach-Hirsh M, Dratviman-Storobinsky O, Nahum R, Machtinger R, Yung Y, et al. The effect of coronavirus disease 2019 immunity on frozen-thawed embryo transfer cycles outcome. *Fertil Steril* 2022;**117**:974–9.
7. Avraham S, Kedem A, Zur H, Youngster M, Yaakov O, Yerushalmi GM, et al. Coronavirus disease 2019 vaccination and infertility treatment outcomes. *Fertil Steril* 2022;**117**:1291–9.
8. Huang J, Xia L, Lin J, Liu B, Zhao Y, Xin C, et al. No Effect of inactivated SARS-CoV-2 vaccination on *in vitro* fertilization outcomes: a propensity score–matched study. *J Inflamm Res* 2022;**15**:839–49.
9. Coronavirus/COVID-19 Task Force of the American Society for Reproductive Medicine. ASRM patient management and clinical recommendations during the coronavirus (COVID-19) pandemic: upate no. 13—Variants, vaccines, and vaccination February 22, 2021. https://www.asrm.org/globalassets/asrm/asrm-content/news-and-publications/covid-19/covidtaskforceupdate13.pdf (accessed August 31, 2022).
10. ESHRE COVID-19 Working Group. Eshre statement on COVID-19 vaccination and medically assisted reproduction. https://www.eshre.eu/Europe/Position-statements/COVID19/vaccination (accessed August 31, 2022).

Jialyu Huang[1]
Leizhen Xia[1]
Yan Zhao
Xingwu Wu
Jia Chen
Mengxi Li
Lifeng Tian
Qiongfang Wu*
Center for Reproductive Medicine, Jiangxi Maternal and Child Health Hospital, Nanchang Medical College, Nanchang, China
*Corresponding author.
E-mail address: wuqfivf@126.com (Q. Wu)
[1] J.H. and L.X. should be considered as co-first authors.