Received: 7 January 2023 | Accepted: 17 March 2023

DOI: 10.1111/jebm.12528

WILEY

LETTER

Effects of inactivated COVID-19 vaccinations on the IVF/ICSI-ET live birth rate and pregnancy complication in a population of southern China: A retrospective cohort study

The devastating health impact of COVID-19 pandemic in early 2020 shortened the bench-to-clinic process of vaccine development from 10–20 years to ~10 months. The efficacy of such vaccines in preventing disease severity and mortality has been appreciated by both clinicians and end users. However, for infertile couples ready to undergo assisted reproductive technology, there is hesitation about vaccination due to the lack of comprehensive follow-up studies and clinical evidence on its safety during this procedure. Even the recommendations are not consistent between different fertility and obstetric societies. For example, the European Society of Human Reproduction and Embryology published a recommendation of at least a 2-month delay before starting assisted reproductive therapy after vaccination.[1] However, the American Society for Reproductive Medicine encourage women who are undergoing assisted reproductive quality to receive vaccination.[2]

Acute respiratory syndrome coronavirus 2 (SARS-CoV-2) invades target host cells via angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) that are present in the reproductive system, such as the epithelium of the urogenital tract and endometrium. Thus, SARS-CoV-2 infection may affect endometrial regeneration, proliferation and, subsequently, fetal implantation.[3] The virus may also infect the placenta resulting in preeclampsia, miscarriage, fetal distress, and preterm birth.[4] Vaccination remains the main strategy to reduce SARS-CoV2 transmission and prevent severe symptoms; however, there is a structural similarity between the spike protein of SARS-CoV-2 and human syncytidin-I related to placenta formation,[5] which may cause a cross-reaction between the anti-spike protein antibodies produced by the vaccine and human syncytidin-I leading to implantation failure or miscarriage. In China, two inactivated COVID-19 vaccines (CoronaVac (Sinovac Life Sciences) and Sinopharm vaccine (The Beijing Institute of Biological Products)) have been widely used and recognized by WHO, which contain viruses that have lost their ability to infect or replicate but can still induce immune responses. Most studies outside China have focused on mRNA vaccines due to their local availability,[6–8] which showed the safety amount infertile patients who require assisted reproductive technology. However, those studies did not include fetal growth, birth outcome and pregnancy complications. In addition, it is unclear whether the same applies to inactivated vaccines for such patients.

The research on the impact of COVID-19 vaccines on pregnancy outcomes in patients undergoing in vitro fertilization/intracytoplasmic sperm injection—embryo transfer (IVF/ICSI-ET) treatment is limited. One single-center study has investigated the effects of CoronaVac and Sinopharm vaccines on pregnancy outcomes in a small Chinese population; however, the study utilized the human chorionic gonadotropin or decapeptyl protocol, which is not a common treatment protocol.[9] Conversely, the early-follicular phase long-acting Gonadotropin-releasing hormone (GnRH) agonist protocol has been increasingly used due to its robust control and stable pregnancy outcomes.[10,11] How the success of the latter is impacted by inactivated COVID-19 vaccines (i.e., CoronaVac and Sinopharm) among couples with existing fertility is unclear, which formed the rationale of this study.

Here, we extended beyond previous research by not only evaluating fertilization and embryo quality, but also assessing pregnancy success, gestational complications, intrauterine fetal growth, and live birth rate among infertile couples requiring IVF/ISCI treatments using the early-follicular phase long-acting GnRH-agonist protocol. In this retrospective cohort study, we studied 802 couples treated with IVF/ICSI-ET using the early-follicular phase long-acting GnRH-agonist protocol in the Second Affiliated Hospital of Wenzhou Medical University from 1/June/2021 to 31/December/2021. The couples were divided into four groups according to their vaccination status (CoronaVac and/or Sinopharm); both partners fully vaccinated (Group A, $n = 237$), only male partner fully vaccinated (Group B, $n = 152$), only female partner fully vaccinated (Group C, $n = 13$), and neither partner vaccinated (Group D, $n = 400$). Inclusion and exclusion criteria are in the Supplementary materials. At baseline, there was no significant difference in age, body mass index, type of infertility, infertile duration, number of failed embryo transplantations, and basal sex hormone levels among the four groups (Supplementary Table S1). There were no differences in ovulation induction procedure and outcomes, including sex hormone levels and endometrial thickness on the day of human chorionic gonadotropin (hCG) injection, as well as the incidence of moderate to severe ovarian hyperstimulation syndrome, among four groups (Supplementary Table S2).

Four groups recorded similar numbers of oocytes retrieved, maturation, fertilization, cleavage, high-quality embryos on Day 3, mature

TABLE 1 Outcome of ovulation induction and fertilization, pregnancy outcomes, and pregnancy complications

Variable	Group A ($n = 237$)	Group B ($n = 152$)	Group C ($n = 13$)	Group D ($n = 400$)	*p* Value
Fertilization method, *n* (%)					0.081
IVF	181 (76.37%)	118 (77.63%)	9 (69.23%)	334 (83.50%)	
ICSI	39 (16.46%)	30 (19.74%)	4 (30.77%)	56 (14.00%)	
IVF/ICSI	17 (7.17%)	4 (2.63%)	0 (0.00%)	10 (2.50%)	
No. of oocyte retrieved	14.68 ± 6.93	14.06 ± 6.50	12.15 ± 4.18	13.75 ± 6.46	0.344
No. of oocyte matured	12.68 ± 6.48	12.08 ± 6.06	10.77 ± 4.32	12.03 ± 5.92	0.549
No. of oocyte fertilized	10.28 ± 5.53	9.73 ± 5.39	8.92 ± 3.71	9.57 ± 4.96	0.467
No. of oocyte cleaved	10.08 ± 5.40	9.49 ± 5.25	8.92 ± 3.71	9.38 ± 4.86	0.492
No. of high-quality embryos on Day 3	7.74 ± 4.88	7.27 ± 4.45	6.15 ± 2.97	7.46 ± 4.44	0.583
No. of blastocyst	4.91 ± 3.21	4.46 ± 2.93	4.15 ± 2.44	4.64 ± 3.03	0.563
No. of embryos transferred	0.73 ± 0.49	0.74 ± 0.53	0.85 ± 0.38	0.78 ± 0.54	0.697
No. of high-quality embryos transferred	0.65 ± 0.48	0.69 ± 0.54	0.62 ± 0.51	0.69 ± 0.54	0.839
Mature oocyte rate (%)	2321/2686 (86.41%)	1353/1575 (85.90%)	140/158 (88.61%)	3540/4043 (87.56%)	0.274
Normal fertilization rate (%)	1882/2686 (70.07%)	1090/1575 (69.20%)	116/158 (73.42%)	2817/4043 (69.68%)	0.715
Cleavage rate (%)	1844/1882 (97.98%)	1063/1090 (97.52%)	116/116 (100%)	2763/2817 (98.08%)	0.31
High-quality embryo rate (%)	1409/1887 (74.67%)	814/1099 (74.07%)	80/118 (67.80%)	2188/2841 (77.02%)	0.206
Blastocyst formation rate (%)	899/1887 (47.64%)	500/1099 (45.50%)	54/118 (45.76%)	1366/2841 (48.08%)	0.514
Pregnancy outcomes					
Fresh embryo transfer rate, *n* (%)	167 (70.46%)	105 (69.07%)	11 (84.62%)	289 (72.25%)	0.69
Biochemical pregnancy rate, *n* (%)	120 (50.63%)	79 (51.97%)	6 (46.15%)	213 (53.29%)	0.925
Clinical pregnancy rate, *n* (%)	99 (41.77%)	70 (46.05%)	6 (46.15%)	176 (43.94%)	0.943
Early miscarriage rate, *n* (%)	6 (6.06%)	7 (10.0%)	1 (16.67%)	20 (11.02%)	0.958
Live birth rate, *n* (%)	87 (36.70%)	62 (40.79%)	5 (38.46%)	156 (39.10%)	0.959
Pregnancy complications	**($n = 167$)**	**($n = 105$)**	**($n = 11$)**	**($n = 289$)**	
Hypertension, *n* (%)	4 (2.40%)	4 (3.81%)	0 (0.00%)	8 (2.77%)	0.861
Gestational diabetes, *n* (%)	9 (5.39%)	4 (3.81%)	0 (0.00%)	28 (9.69%)	0.175
Fetal growth restriction, *n* (%)	1 (0.60%)	0 (0.00%)	0 (0.00%)	3 (1.04%)	0.847
Premature rupture of membranes, *n* (%)	5 (2.99%)	4 (3.81%)	0 (0.00%)	3 (1.04%)	0.325
Placenta previa, *n* (%)	1 (0.60%)	1 (0.95%)	0 (0.00%)	3 (1.04%)	0.97
Preterm birth rates, *n* (%)	4 (2.40%)	5 (4.76%)	0 (0.00%)	13 (4.50%)	0.58

Data are expressed as mean ± standard deviation or number (percentage). One-way ANOVA followed by the Fisher's least significant (LSD) post hoc tests was used to assess continuous variables. Categorical variables were expressed as a percentage and analyzed by chi-squared tests or Fisher's exact tests (SPSS V22.0, SPSS Inc., Chicago, IL, USA). Group A: both partners vaccinated; Group B: only man vaccinated; Group C: only woman vaccinated; and Group D: neither partner vaccinated.

Abbreviations: ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization.

oocyte rates, cleavage rate, blastocyst formation rate, number of embryos transferred, as well as biochemical pregnancy rates and clinical pregnancy rates (Table 1). COVID-19 vaccination does not increase early miscarriage rates; however, the miscarriage rate in Group A, where both partners vaccinated, was still the lowest among all. Moreover, there was no difference in the live birth rate among the four groups (Table 1). Although there was no statistical significance in the incidence of pregnancy complications, the gestational diabetes rate in Group D (none vaccinated couple) nearly doubled the risk in Group A (both partners vaccinated); while the premature birth rate was the smallest in Group A (Table 1). No complications were recorded in Group C, due to the small sample size.

Here, we observed unaffected IVF/ICSI outcomes, which can promote future inactivated COVID-19 vaccine uptake in this special patient population. The success of assisted reproductive technology cannot be achieved without high-quality embryos and the well receptivity of the endometrium. Ovarian function is one of the important factors affecting the success rate of IVF/ICSI, which directly determines the quantity and quality of oocytes retrieved, and thereafter the quality of the embryos. The total duration and dosage of gonadotropin during ovarian induction can indirectly reflect ovarian function.[12] The strength of our study is that we used the same IVF/ICSI treatment protocol among all participants. COVID-19 vaccine did not change the need for gonadotropin, suggesting a minimum impact on ovarian function compared with nonvaccinated patients. COVID-19 vaccination did not affect the embryo quality and implantation success rate expected for the early follicular phase long-acting GnRH-agonist protocol either. High-quality sperm is also an essential precondition for high-quality embryos. Our study also included the status of male partners, whose vaccination status did not affect the IVF/ICSI outcome, consistent with findings in previous studies in China.[9,13] However, these early studies used different IVF protocols from ours. Our protocol can give full rest to the ovaries, improve the pelvic environment and endometrium receptivity, and thus increase the rate of successful pregnancy and live birth, which thus has been well adopted in southern China. In addition, the major limitation of the previous study is the inclusion of vaccines that are not recognized internationally,[9] whereas the other one did not include groups with only one partner vaccinated.[13] Therefore, our study provided more comprehensive information on the safety profiles of inactivated COVID-19 vaccination.

The evidence of vaccination on endometrial receptivity remains scarce. Endometrial receptivity is essential to embryo implantation, reflected by endometrial thickness on HCG days. Here, we found no significant difference in endometrial thickness and characteristics on HCG days among the four groups. Previous studies used continuous implantation rate and clinical pregnancy rate as surrogates to confirm the safety of mRNA vaccines in the first trimester without any evidence of the impact on live birth rate.[14] In the current study, endometrial thickness, biochemical and clinical pregnancy rates, miscarriage rate, intrauterine growth, and live birth rate were not affected in the vaccinated participants, which provides robust evidence of the safety of inactivated COVID-19 vaccine for endometrial receptivity and placental function to sustain a successful pregnancy.

Another strength of our study is the evaluation of pregnancy outcomes and complications, which have not been published in previous studies. Here, the biochemical pregnancy rates, clinical pregnancy rates and early miscarriage rates were not affected by the vaccination status. Beyond that, live birth is the ultimate and most important goal of IVF/ICSI. This study provides evidence to suggest that inactivated COVID-19 vaccination does not compromise the live birth rate. The risk of gestational complications was not affected by vaccination status among the couples either. However, we did notice somewhat reduced gestational diabetes risk in women with vaccination in Group A. A recent study has reported cases of acute hyperglycemia crisis in males due to COVID-19 vaccination in the United Kingdom, which was speculated as a cross-reaction with ACE2 in the pancreas.[15] Here, we show no impact of vaccination itself on glucose homeostasis during pregnancy.

The limitations of our study are the small sample size, especially in the group where only females were vaccinated, which may affect statistical analysis and some related conclusions. In addition, this study was only performed in a single location where the population diversity can be limited. Future studies need to increase the sample size and follow-up time, and include more perinatal outcomes data and additional birth centers to verify the findings on the safety of inactivated COVID-19 vaccine on IVF/ICSI-ET outcomes in this study.

In conclusion, we recommend patients consider inactivated COVID-19 vaccination before commencing IVF/ICSI treatments to reduce the risk of SARS-CoV-2 infection and severe symptoms during pregnancy that may threaten the well-being of both pregnant mothers and their unborn children.

ACKNOWLEDGMENTS

The authors would like to thank all staff at the Center for Reproductive Medicine for their active involvement and collaboration in this study. In addition, the authors are sincerely grateful to the infertile couples who participated in this study.

Open access publishing facilitated by University of Technology Sydney, as part of the Wiley - University of Technology Sydney agreement via the Council of Australian University Librarians.

CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest.

FUNDING INFORMATION

This study was supported by a research grant from the Health Commission of Zhejiang Province (2022KY897) and the Natural Science Foundation Committee of Zhejiang Province (LGF22H160053).

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