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•LETTER TO THE EDITOR•

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Receipt of inactivated COVID-19 vaccine had no adverse influence on embryo implantation, clinical pregnancy and miscarriage in early pregnancy

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Dear Editor,

Pregnant women are at high risk of COVID-19 infection. During pregnancy, COVID-19 infection increases the risk of preterm delivery and the probability of intensive care unit care for the parturient and neonate (Allotey et al., 2020; Lu et al., 2020). Several women have altered their pregnancy plans due to the COVID-19 pandemic (Flynn et al., 2021). In China, the inactivated COVID-19 vaccine has been widely promoted, and third booster shots have been started (Yue et al., 2021; Yue et al., 2022). However, data are currently lacking regarding the effects of the inactivated COVID-19 vaccine on embryo implantation and maternal safety. In addition, concerns about the impact of vaccination on maternal health are a barrier to vaccination before pregnancy.

We retrospectively collected and analyzed the data on embryo implantation, clinical pregnancy, and spontaneous abortion to investigate the effect of inactivated COVID-19 vaccine on early pregnancy and in vitro fertilization (IVF). All participants had completed gamete retrieval and embryo cryopreservation before getting vaccinated with inactivated COVID-19 vaccine at the reproductive medicine center of Peking University Third Hospital. After completing two doses of inactivated COVID-19 vaccine, the patients underwent embryo thawing and transplantation. By the end of our statistics, all patients, whether vaccinated or unvaccinated, who were pregnant after transplantation had reached the second or third trimester of pregnancy. The data in this study were adjusted and analyzed by Statistical Package for Social Sciences version 18.

Overall, 460 patients vaccinated with inactivated COVID-19 vaccine were included in this study. Of these, 192 patients (Group 1) were transferred with cleavage embryos, 268 patients (Group 2) with blastocysts, and patients unvaccinated in the same period served as controls. The basic characteristics showed no statistical differences between the vaccinated and the control groups (Table 1). The average vaccinated female ages were 33.20±4.74 and 33.95±4.47 years (Group 1 and Group 2, respectively), and the control groups were 32.56±4.20 and 33.69±4.03 years. More than half of the participants had primary infertility (Group 1: 67.19% and Group 2: 54.10%). After receiving two doses of inactivated COVID-19 vaccine, the patients underwent an embryo warming-transplantation cycle. The outcomes of embryo implantation, clinical pregnancy, and miscarriage

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Table 1 Baseline clinical characteristics and embryo warming-transferred cycle outcomes of patients

Variable	Group 1 (*n*=192)	Control (*n*=451)	*P* value (adjusted)	Group 2 (*n*=268)	Control (*n*=585)	*P* value (adjusted)
Female age (year)	33.20±4.74	32.56±4.20	0.159	33.95±4.47	33.69±4.03	0.615
Male age (year)	34.47±6.43	33.88±4.83	0.088	34.95±5.29	35.04±5.22	0.658
Female BMI	22.34±3.71	22.70±3.70	0.608	22.46±3.11	22.41±3.32	0.062
Male BMI	25.04±3.67	25.76±4.02	0.327	25.23±4.62	25.36±3.90	0.692
Type of infertility			0.829			0.884
Primary	129/192 (67.19)	295/451 (65.41)		145/268 (54.10)	330/585 (56.41)	
Secondary	63/192 (32.81)	156/451 (33.59)		123/268 (45.90)	255/585 (43.59)	
Duration of infertility	4.66±3.11	4.42±3.19	0.320	5.51±4.02	4.90±3.52	0.651
Etiology of infertility			0.333			0.703
Tubal	55/192 (28.65)	116/451 (25.72)		61/268 (22.76)	142/585 (24.27)	
Male factor	31/192 (16.15)	96/451 (21.29)		49/268 (18.28)	107/585 (18.29)	
Endometriosis	7/192 (3.65)	38/451 (8.43)		13/268 (4.85)	28/585 (4.79)	
Ovulatory disorder	45/192 (23.44)	109/451 (24.17)		62/268 (23.13)	141/585 (24.10)	
Uterine factor		4/451 (0.89)		4/268 (1.49)	7/585 (1.20)	
Unexplained infertility	9/192 (4.69)	44/451 (9.76)		11/268 (4.10)	46/585 (7.86)	
Others	45/192 (23.44)	44/451 (9.76)		68/268 (25.37)	114/585 (19.49)	
Endometrial thickness on transfer day (mm)	10.23±1.65	9.87±1.76	0.181	9.77±1.68	9.96±1.61	0.494
Number of transferred embryo	1.92±1.65	1.90±0.29	0.402	1.02±0.14	105±0.03	0.877
Implantation rate (%)	25.00 (92/368)	28.47 (244/857)	0.663	38.46 (105/273)	39.22 (242/617)	0.692
Clinical pregnancy rate (%)	39.58 (76/192)	43.43 (196/451)	0.088	38.43 (103/268)	40.00 (234/585)	0.797
Miscarriage rate (%)	6.58 (5/76)	7.65 (15/196)	0.543	13.59 (14/103)	10.68 (25/234)	0.477
Ectopic pregnancy rate (*n*)	2	1	NS	0	1	NS

showed no statistical differences from the noninjected group (Table 1). The clinical pregnancy rates of Group 1 and Group 2 were 39.58% and 38.43%, and the embryo implantation rates were 25.00% and 38.46%, respectively, which showed no statistical differences from the noninjected group. All pregnant participants had reached the second or third trimester of pregnancy. In addition, 6.58% (5/76) of vaccinated participants transferred with the cleavage stage embryos reported a miscarriage. All the miscarriages occurred during early pregnancy (within 10 weeks), including four cases of fetal suspension and one case of spontaneous abortion. In addition, 13.59% (14/103) of vaccinated participants transferred with blastocysts had a miscarriage; except two cases of spontaneous abortion, all the others were fetal suspension.

Several women have postponed or changed pregnancy plans during the COVID-19 pandemic (Flynn et al., 2021). Important reasons might be the concerns about the COVID-19 pandemic and doubts about vaccine safety. In this study, our results showed that receiving two doses of inactivated COVID-19 vaccine had no influence on embryo implantation, clinical pregnancy, and miscarriage during the embryo warming-transplantation cycle. Rouse et al. (2017) reported that spontaneous abortion is a primary indicator of female vaccine safety. Our study demonstrated no adverse influence on the miscarriage rate in vaccinated patients compared with unvaccinated patients. Studies reported that COVID-19 might have reproductive toxicities for the ubiquitous expression of ACE2 (Jing et al., 2020), and infection with COVID-19 reduced the proportion of "top quality embryos" in IVF treatment (Orvieto et al., 2021). Vaccination with inactivated COVID-19 vaccine could avoid more than 50% chance of infection (Li et al., 2021). Our study further confirmed that vaccination had no adverse influence on embryo implantation and early pregnancy. The major limitations of our research were the small sample size and the short follow-up time. However, these results are still helpful in vaccine promotion and patient consultation.

Compliance and ethics *This study was approved by the Reproductive Medicine Ethics Committee of Peking University Third Hospital (2022SZ-005). The author(s) declare that they have no conflict of interest.*

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