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

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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 ≥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 (Table S1).

For vaccinated patients, the mean time interval between complete vaccination and ET was 126.5±64.0 (range 13–246) days. As demonstrated in Table S2, both laboratory and pregnancy
outcomes remained comparable when these patients were subdivided into ≤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.

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|                              | Vaccinated  | Unvaccinated | P-value |
|------------------------------|-------------|--------------|---------|
| **Age (years)**              | 31.8±4.3    | 31.0±4.4     | 0.017   |
| **Body mass index (kg/m²)**  | 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        | Unvaccinated  |
|----------------|--------------|--------------|
|                | 40 (32.3)    | 370 (29.3)   |
|                | 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)   |

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.