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Original Research

COVID-19 Vaccination, Adverse Effect, and SARS-CoV-2 Infection among Couples in Infertility Clinic: A Prospective Study

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Abstract

Background: Although periconception vaccination is important for maternal and neonatal health, vaccine hesitancy could pose a challenge to achieving a healthy pregnancy in infertile women. We assessed the prevalence of coronavirus disease 2019 (COVID-19) booster vaccination, associated factors, adverse event after vaccination, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection among women seeking fertility treatment. **Methods**: We used the data from participants of the Pregnancy and Urban Environment study (PRUNE study), which is a prospective observational study designed to explore the association between pregnancy and the urban environment in infertile couples. From October 2019 to September 2021, a total of 534 patients provided informed consent and participated in the first and second rounds of a mobile survey conducted at six-month intervals. In the second and third rounds of the survey, we included questions about COVID-19 vaccination and SARS-CoV-2 infection. Adjusted risk ratios (aRR) were calculated for COVID-19 booster vaccination and SARS-CoV-2 infection. **Results**: All the women participating in the survey had completed the primary series of COVID-19 vaccination. The booster vaccination rate was 38.5%, and the prevalence of SARS-CoV-2 infection was 34.4%. The likelihood of receiving a booster vaccination was higher when women reported alcohol consumption (aRR = 1.90, 95% confidence interval (CI): 1.03–3.51, $p = 0.041$). SARS-CoV-2 infection was inversely associated with nulliparity (aRR = 0.44, 95% CI: 0.17–1.09, $p = 0.077$). Among the women vaccinated against COVID-19, 44.3% of respondents reported at least one adverse reaction after receiving the vaccine. **Conclusions**: All the women participating in the survey had completed primary series of COVID-19 vaccination. The booster vaccination rate was 38.5%, and the prevalence of SARS-CoV-2 infection was 34.4%. Among the vaccinated women, 44.3% reported experiencing at least one adverse reaction after receiving the COVID-19 vaccine. Fever/chilling was the most common (61.8%), followed by abnormal vaginal bleeding/menstrual irregularity (41.8%). A targeted education program by health professionals is needed to promote the benefits of periconception vaccination and reduce the resistance to the COVID-19 vaccine among infertile couples. **Clinical Trial Registration:** The study was registered at Clinical Research Information Service (https://cris.nih.go.kr/cris/info/dataset.do), registration number: KCT0003560.

Keywords: COVID-19; booster vaccination; infertility; vaccine hesitancy; adverse effect; SARS-CoV-2

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic has had a profound impact on the entire world, causing significant health and economic consequences. The development of effective vaccines against the virus has been a major milestone in the fight against the disease. The first COVID-19 vaccine to receive Emergency Use Authorization from the U.S. Food and Drug Administration (FDA) in December 2020 was developed by Pfizer-BioNTech, followed subsequently by others such as Moderna, AstraZeneca, and Johnson & Johnson/Janssen. These COVID-19 vaccines have demonstrated high efficacy in reducing the risk of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and COVID-19-related morbidity [1,2]. Globally, as of Oct 3, 2022, 69.7% of the world's population has received their initial doses of COVID-19 vaccine [3]. Despite the ongoing emergence of omicron variants, the worldwide coverage of booster doses stands at 31.9%.

Safety concerns regarding possible side effects are the primary reasons reported for skipping booster vaccinations [4]. There is particular concern about the potential impact of vaccination on fertility [5]. Given the effective protection offered by booster doses and the potential risks associated with antenatal SARS-CoV-2 infection, vaccine hesitancy regarding booster shots presents a challenge in achieving healthy pregnancies for infertile couples. Misin-

Table 1. Distribution of female baseline characteristics by third dose of coronavirus disease 2019 vaccination status and history of infection with severe acute respiratory syndrome coronavirus 2, Pregnancy and Urban Environment study, June 2022–August 2022.

Characteristic	Third dose of COVID-19 vaccination (column %)		SARS-CoV-2 infection (column %)	
	Yes (n = 62)	No (n = 99)	Yes (n = 55)	No (n = 105)
Age (years)				
≥35	72.58	66.32	72.2	65.7
Body mass index (kg/m^2)				
<18.5	4.92	6.25	5.6	5.9
18.5–25	60.66	71.88	64.8	69.6
≥25	34.43	21.88	29.6	24.5
Alcohol drinking	64.52	42.71	60	46.08
Occupation				
Not employed, student	24.59	27.08	22.22	26.47
Manager, business owners and professionals	21.31	26.04	22.22	26.47
Clerical, service and sales	45.9	43.75	53.7	40.2
Industrial, manual, elementary, others	8.2	3.13	1.85	6.86
Monthly household income (KRW)				
Less than 4 million	64.71	54.29	58.7	59.2
Nulliparity	91.94	89.58	85.5	94.1
Self-rated poor health	16.13	19.39	18.2	18.3

1 USD = 1351 KRW. COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

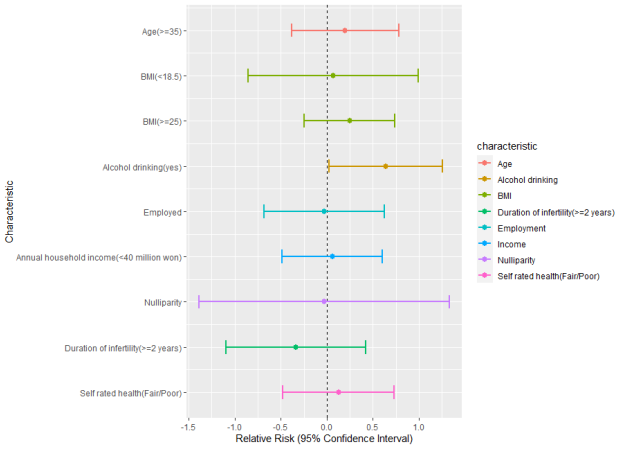

Fig. 1. Log-transformed adjusted RR 95% confidence interval of female baseline characteristics by third doses of COVID-19 vaccination. BMI, body mass index; RR, risk ratios.

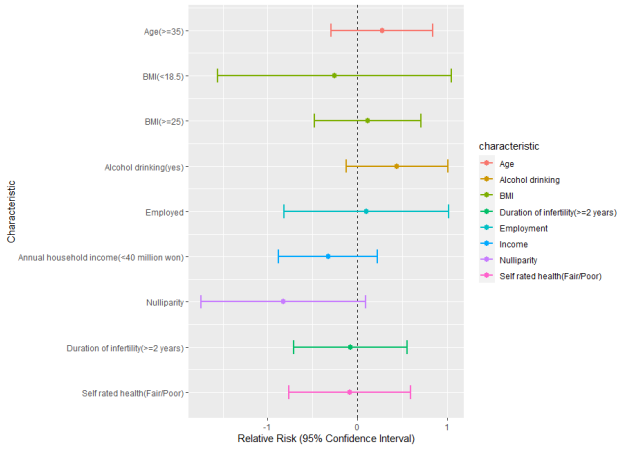

Fig. 2. Log-transformed adjusted RR 95% confidence interval of female baseline characteristics by SARS-CoV-2 infection.

formation and conspiracy claims linking COVID-19 vaccines to infertility or adverse reproductive outcomes are widespread on social media, leading to vaccine hesitancy among couples of reproductive age, especially those facing infertility [6].

This study aimed to assess the prevalence of COVID-19 booster vaccination, associated factors, adverse events after vaccination, and SARS-CoV-2 infection among women seeking fertility treatment. This information will be valuable for healthcare providers, policymakers, and women facing infertility.

2. Materials and Methods

2.1 Study Population

We utilized data from participants in the Pregnancy and Urban Environment study (PRUNE study), a prospective observational study designed to investigate the association between pregnancy and the urban environment in infertile couples (Clinical Research Information Service (CRIS) registration No.: KCT0003560). The inclusion criteria included individuals aged 20 and above who were part of heterosexual couples cohabiting and willing to provide informed consent for both baseline and follow-up surveys. Exclusion criteria applied to individuals with known genetic disorders or severe chronic conditions that could im-

Table 2. Adjusted relative risk of female baseline characteristics by coronavirus disease 2019 vaccination status and history of infection with severe acute respiratory syndrome coronavirus 2, Pregnancy and Urban Environment study, June 2022–August 2022.

Characteristic	Third doses of COVID-19 vaccination		SARS-CoV-2 infection	
	RR (95% CI)	*p*-value	RR (95% CI)	*p*-value
Age				
20–34	1.00 (reference)		1.00 (reference)	
≥35	1.22 (0.68–2.18)	0.503	1.32 (0.74–2.32)	0.345
Body mass index				
18.5–25	1.00 (reference)		1.00 (reference)	
<18.5	1.07 (0.42–2.69)	0.887	0.77 (0.21–2.84)	0.698
≥25	1.28 (0.78–2.09)	0.325	1.12 (0.62–2.04)	0.698
Alcohol drinking				
No	1.00 (reference)		1.00 (reference)	
Yes	1.90 (1.03–3.51)	0.041	1.56 (0.88–2.75)	0.128
Employment				
Non employed	1.00 (reference)		1.00 (reference)	
Employed	0.97 (0.50–1.87)	0.926	1.10 (0.44–2.76)	0.837
Annual household income (KRW)				
More than 40 million	1.00 (reference)		1.00 (reference)	
Less than 40 million	1.06 (0.62–1.82)	0.833	0.72 (0.42–1.25)	0.242
Parity				
Primi- or multiparity	1.00 (reference)		1.00 (reference)	
Nulliparity	0.97 (0.25–3.77)	0.966	0.44 (0.17–1.09)	0.077
Duration of infertility				
Less than 2 years	1.00 (reference)		1.00 (reference)	
2 years or longer	0.71 (0.33–1.52)	0.380	0.92 (0.49–1.74)	0.807
Self rated health				
Good/very good/excellent	1.00 (reference)		1.00 (reference)	
Fair/Poor	1.13 (0.62–2.08)	0.685	0.92 (0.47–1.81)	0.805

1 USD = 1351 KRW. RR, relative risk; 95% CI, 95% confidence interval.

pact reproductive function, as well as those involved in gamete donation cycles, surrogacy, or *in vitro* fertilization (IVF) procedures utilizing frozen oocytes or sperm. From October 2019 to September 2021, a total of 534 patients provided informed consents and participated in the first and second rounds of a mobile survey, conducted at six-month intervals. In the second-round survey, we included questions about COVID-19 vaccination and SARS-CoV-2 Infection.

2.2 Survey for COVID-19 Vaccination and SARS-CoV-2 Infection

The questions regarding COVID-19 vaccination included: 'Have you received the COVID-19 vaccine?', 'How many times have you received the COVID-19 vaccine?', and 'Did you experience any adverse events after receiving the COVID-19 vaccine?'. Out of the 183 female participants who agreed to participate in the COVID-19 vaccination survey, we received 166 responses and utilized data from 161 patients, excluding those with missing information.

2.3 Statistical Analysis

Descriptive statistics were calculated for COVID-19 booster vaccination and SARS-CoV-2 infection. Age, body mass index (BMI), alcohol consumption, occupation, household income, parity, duration of infertility and self-rated health since first survey were used as covariates. Adjusted risk ratios (aRR) were calculated for booster vaccination and SARS-CoV-2 infection. The risk estimates were analyzed using log-binomial regression. All analyses were performed using R version 4.0.5 (The R Foundation, Vienna, Austria).

3. Result

Among the women participating in the survey, all the then completed the primary series of COVID-19 vaccination. The coverage for booster doses was 38.5%, and the prevalence of SARS-CoV-2 infection was 34.4%. The booster vaccination rate was higher among women aged 35 years or older, those who were overweight, currently consuming alcohol, had a low average monthly household income, had never been pregnant, and reported good sub-

Table 3. Adverse event after COVID-19 vaccination, Pregnancy and Urban Environment study.

Symptom	Frequency	Percentage
Fever/chilling	34 (55*)	61.8%
Gastrointestinal symptoms (Nausea, Vomiting, Diarrhea)	20 (55*)	36.4%
Local/general allergic reaction	11 (55*)	20.0%
Dyspnea or chest pain	13 (55*)	23.6%
Abnormal vaginal bleeding/menstrual irregularity	23 (55*)	41.8%
Spontaneous abortion or stillbirth	2 (7*)	28.6%
Preterm birth	1 (7*)	14.3%
Others	18 (54*)	33.3%

*number of respondents who reported vaccine adverse effects.

jective health. COVID-19 infection was more common in people over the age of 35, those who were overweight, currently consuming alcohol, and those who had been pregnant (Table 1).

In a multivariate-adjusted model, the risk of receiving a COVID-19 booster vaccination was higher among women who currently drink compared to women who do not drink (relative risk (RR) = 1.90, 95% confidence interval (CI): 1.03–3.51, $p = 0.041$, Table 2, Fig. 1). The risk of COVID-19 infection was lower in women who have never given birth compared to women who have had children (0.44, 95% CI: 0.17–1.09, $p = 0.077$; Table 2, Fig. 2).

Among the women who were vaccinated against COVID-19, 8.1% was pregnant at the time of vaccination. Fifty-five women (44.3% of respondents) reported experiencing at least one adverse reaction after receiving the any dose of COVID-19 vaccine (Table 3). Fever/chilling were the most common (61.8%), followed by abnormal vaginal bleeding/menstrual irregularity (41.8%).

4. Discussion

According to the World Health Organization (WHO) dashboard's vaccination data, as of May 25, 2023, South Korea had a cumulative vaccination rate of 83.81% for the primary dose and 65.62% for the booster shot. As expected, the booster vaccination rate was lower, 38.5% among women seeking infertility treatment compared to the general population. COVID-19 vaccine hesitancy was reported among women seeking fertility treatment in China, where the overall coverage rate for the primary COVID-19 vaccine was 67.68%, and none of the participants received booster vaccinations [7]. On social media, misinformation and unfounded claims linking COVID-19 vaccines to infertility were widespread, leading to vaccine skepticism [8]. Research has shown that there is no scientific evidence of any association between COVID-19 vaccines and fertility impairment in men or women [9]. However, fear of fertility-related side effects was a major reason for COVID-19 vaccine hesitancy among infertile women [10]. Therefore, it is essential to disseminate guidelines and implement targeted education programs led by health professionals to promote the benefits of periconception vaccination, and reduce resistance to COVID-19 vaccines among infertile couples.

Booster vaccination was found to be associated with alcohol consumption in this study. During the SARS-Cov-2 pandemic, the consumption of alcoholic beverages increased [11]. Lockdowns have had an impact on mental health and have contributed to a rise in global alcohol consumption. We can cautiously speculate that women experiencing the effects of lockdowns and consuming alcohol at home might be more inclined to get fully vaccinated in the hope of regaining a sense of freedom.

SARS-CoV-2 infection was inversely associated with nulliparity. The lower infection rate in nulliparous women is presumed to be due to a reduced likelihood of household transmission. Household transmission of SARS-CoV-2 is well-documented [12], and secondary transmission of SARS-CoV-2 from pediatric index cases within households has been reported to range from 0% to 75% [13].

COVID-19 vaccine can lead to various local and systemic side effects [14], including menstrual irregularities in women [15,16]. In this study, 41.8% of those who reported adverse events after vaccination (equivalent to 18.5% of the vaccinated women) experienced an abnormal uterine bleeding/menstrual irregularities. The prevalence aligns with a recent meta-analysis which reported pooled prevalence rates of menorrhagia, polymenorrhea, and oligomenorrhea at 24.2%, 16.2% and 22.7%, respectively [17]. The endocrine and immune changes following COVID-19 vaccination could potentially contribute to menstrual disturbances [18]. These vaccine-induced menstrual disturbances might raise concerns and hesitations among some women regarding receiving vaccination and booster shots. It's worth noting that menstrual irregularities after the vaccine tend to self-resolve in approximately half of the cases within two months [15]. Therefore, healthcare providers should consider informing reproductive-aged women that temporary and self-limiting menstrual cycle irregularities in the subsequent month can occur during counseling about the COVID-19 vaccine.

The strength of the study lies in its exclusive focus on infertile women seeking treatment. These women have

heightened concerns about the impact of vaccines on fertility, and given their potential role as future mothers, the necessity of vaccination becomes even more significant. However, a limitation of the study is the relatively small size of the study population, which may introduce selection bias. This study was based on an analysis of an existing database, which had some missing data. To maximize external validity, we did not include participants with missing data. Consequently, our findings rely on data collected from a restricted subset of the study population, potentially introducing selection bias.

5. Conclusions

In summary, all the women participating in the survey had completed the primary series of COVID-19 vaccination. The booster vaccination rate was 38.5%, which is lower compared to general population. The prevalence of SARS-CoV-2 infection was 34.4%. Among the vaccinated women, 44.3% reported experiencing at least one adverse reaction after receiving the COVID-19 vaccine, with fever/chilling being the most common (61.8%), followed by abnormal vaginal bleeding/menstrual irregularity (41.8%). Targeted education program led by health professionals is needed to promote the benefits of periconception vaccination and reduce resistance to the COVID-19 vaccine among infertile couples.

Availability of Data and Materials

The anonymous data used in this study are available from the corresponding author on a reasonable request.

Author Contributions

SAC and JHK designed and performed the research. EK analyzed the data. SGP and JHK drafted the manuscript. SGP, TK and YJC contributed to the interpretation of the results and critically checked the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of CHA Bundang Medical Center, CHA University School of Medicine (approval number: 2021-03-026).

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Conflict of Interest

The authors declare no conflict of interest. SK Bioscience Co., Ltd provided funding, but there was no potential conflict of interest in the preparation and publication of the manuscript.

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