

ORIGINAL ARTICLE

Does mRNA SARS-CoV-2 vaccine in the follicular fluid impact follicle and oocyte performance in IVF treatments?

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Abstract

Problem: The COVID-19 pandemic has many clinical manifestations. Rapid vaccine development raised concerns and speculations about future fertility outcomes and vaccine safety. We evaluated the effect of Pfizer-BioNTech mRNA SARS-CoV-2 vaccine on IVF treatment, oocyte and embryo quality, and pregnancy outcomes.

Method of study: This prospective, observational cohort study was conducted in a referral IVF Unit, 3/2021-5/2021. We aimed to recruit all women undergoing IVF/ICSI cycles from 3/1-4/30/2021, 2-8 weeks after the second vaccination, and to analyze 50-60 samples in the 2-month period. Patients were categorized according to serum antibody levels: positive for spike (S), positive for nucleotide (N), or negative for both. On the day of ovum pick-up, follicular fluid and blood samples were analyzed for anti-nucleotide (anti-N) antibodies, and anti-spike (anti-S) antibodies, hormonal profile, C-reactive protein (CRP) and other metabolic parameters.

Results: Of 59 women enrolled, 37 reported being vaccinated and 22 were not. We found 97% correlation between anti-S and anti-N in the blood and the follicular fluid. Follicular fluid was analyzed based on antibody categorization. All IVF treatment parameters in the follicular fluids and serum were comparable, except CRP was significantly elevated among patients with anti-N antibodies (2.29 [1.42-6.08] vs. 4.11 [1.62-5.75] vs. 1.44 [.36-8.33]; $p < .001$). Pregnancy outcomes were comparable (44% vs. 33% vs. 50%; $p = .97$).

Conclusion: mRNA SARS-CoV-2 vaccine did not appear to affect treatment outcomes or ovarian reserves in the subsequent IVF cycle.

KEYWORDS

Covid-19, C-reactive protein level, follicular fluid, mRNA SARS-CoV-2 vaccine, pregnancy rate

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1 | INTRODUCTION

Near the end of 2019, in Wuhan, China, Coronavirus disease was identified to be the cause of many cases of severe pneumonia, eventually spreading worldwide. In March 2020, the World Health Organization declared COVID-19 to be a global pandemic, with a wide spectrum of clinical manifestations, ranging from asymptomatic to severely ill patients, with the major symptom of acute respiratory failure and possible death.^{1,2}

This declaration caused many changes in almost all aspects of life worldwide. One of these changes was the suspension of ART services, which had major psychological effects on couples with infertility seeking to become pregnant, where time is a decisive factor.

The rapid development of the vaccine raised many questions from the public and from healthcare professionals. Speculations and rumors about COVID-19 and its vaccine were further accelerated by the relatively new technology that was used to generate the vaccine.³⁻⁵ Among the most common claims that circulated on social media, was the scientifically unproven concern that the mRNA vaccine for Covid-19 causes female infertility. This issue was also one of the main concerns among healthcare workers and staff.^{6,7}

Misconceptions influencing public perceptions and decision-making were especially worrisome to women planning to conceive, since compared to their peers, pregnancy puts them at higher risk for severe illness associated with COVID-19, and increased risk of pre-term birth, along with coping with the after-effects of fetal prematurity.⁸⁻¹¹

Previous studies demonstrated the presence of antibodies in the ovarian follicular fluid, such as anti-thyroid antibodies, antiphospholipid antibodies, anti-toxoplasma antibodies, with potential effects on female fertility, implantation failure and oocyte quality, respectively.^{12,13} Whether mRNA SARS-CoV-2 vaccine antibodies would be found in follicular fluid, and if so, would they alter the treatment's results, remained to be evaluated.

In this study, we tested follicular fluid for anti-nucleotide (anti-N) antibodies, which are related to infection with Covid-19 and anti-spike (anti-S) antibodies which appear in the serum after mRNA SARS-CoV-2 vaccine, for all patients undergoing an ovum pick-up procedure. The objective was to determine the differences in ovarian response, embryo quality and hormonal profile of follicular fluid between women who had been infected and/or vaccinated, or neither.

2 | MATERIAL AND METHODS

2.1 | Study design

This prospective, observational cohort study compared the IVF treatment parameters and outcomes of patients based on their vaccination status. Patients who were vaccinated had received two doses of the Pfizer-BioNTech vaccine 21 days apart, patients who were infected and sick, and a control group were patients with non-clinical COVID-19 infection. Patients were enrolled from March 2021 to May 2021.

2.2 | Participants

Women undergoing IVF or ICSI at the Hillel Yaffe Medical Center were eligible to participate. Criteria for study inclusion were women undergoing IVF/ICSI cycles. No exclusion criteria were applied.

2.3 | Data collection

Patient data collected from electronic medical records, included baseline parameters (age, parity, BMI, number of previous IVF/ICSI cycles, basal FSH), cycle characteristics (length of follicular phase, amount of gonadotropins used, endometrial thickness and estradiol levels on day of hCG administration), clinical outcomes (number of oocytes and mature oocytes, fertilization rate, cleavage rate, blastulation rate, number of transferred embryos and number of frozen embryos) and pregnancy outcomes (chemical pregnancy rate and clinical pregnancy).

2.4 | Treatment protocol

Treatment protocols were prescribed according to the physician's judgment, based on each patient's characteristics, to prevent compromising the treatment relative to the study goals. Physicians were blinded to the patient's vaccination status, at the point of prescribing the protocol. The protocols used in this study reflect the normal variety of treatments available in the IVF clinic, as previously described.¹⁴ Ovarian stimulation was performed using 150–300 IU of either recombinant FSH (rFSH) (Gonal-Fw, Merck-Serono, Darmstadt, Germany), or hMG (Menopur, Ferring Pharmaceuticals, Lausanne, Switzerland), with adjustments according to age, basal hormone values, antral follicular count at ultrasound and BMI. Estrogen (E2) and progesterone (P) levels were evaluated at every follow-up visit, including the day of hCG (Ovitrelle, Merck-Serono, Darmstadt, Germany) administration. Ovulation was induced when at least two leading follicles with mean diameter of at least 17 mm were seen. The oocyte was extracted 36 h later.

After oocyte retrieval, IVF or ICSI was performed as clinically indicated. Following ICSI or insemination, the oocytes were placed on EmbryoSlides and incubated in the EmbryoScope™ (Unisense Fertil-iTech, Aarhus, Denmark) up to five days at 37°C in 5.8% CO₂ and 5% O₂. Fertilization was determined based on the presence of two pronucleus 16 h after fertilization. Images of each embryo were acquired every 10 min in seven focal planes, starting from the second polar body extraction up to 120 h after fertilization, to determine the exact timing of cell divisions.¹⁵ Embryos were scored based on Known Implantation Data (KID) score and Alfa ESHRE score, as well as on common morphology.¹⁶ The quality of all available embryos was evaluated and no more than two were transferred on day 3 or one on day 5 of embryonic development. Embryo quality was also evaluated on the day of transfer according to number of cells, symmetry, granularity, type, percentage of fragmentation, presence of multinucleate blastomeres and degree of compaction, as previously described. A top-quality embryo

was defined as one with four to five cells on day 2 or >6 equal-size blastomeres on day 3, $\leq 20\%$ fragmentation and no multinucleate cells.¹⁷ If no pregnancy was achieved in the fresh cycle, the remaining top-quality embryos were vitrified and used in the next frozen embryo transfer. Fertilization rate was calculated as the total 2PN divided to M2 and cleavage rate as the number of day 3 embryos divided by the total 2PN.

2.5 | Collection of follicular fluid and blood samples

On the day of oocyte retrieval, oocytes were separated from the follicular fluid. Only pure follicular fluid samples that were not mixed with blood were examined for the presence of antibodies. Blood samples from patients scheduled for oocyte pick-up were collected. The level of COVID-19 antibodies, hormonal profile, lipid profile (including cholesterol and triglycerides) as substrate of steroidogenesis and C-reactive protein (CRP) as an acute phase biomarker were measured in serum and follicular fluid.

2.6 | COVID-19 serology test

2.6.1 | Anti-spike levels

Antispike levels were measured using the LIAISON SARS-CoV-2 S1/S2 IgG (DiaSorin, Saluggia, Italy) quantitative assay; a test with high sensitivity and specificity (97.9% and 99%, respectively). These antibodies are targeted to S1 and S2 subunits of the Spike protein and correlate with neutralizing antibodies. Results are presented in AU/ml.

2.6.2 | Anti-nucleotide levels

Specimens were obtained from patients and analyzed the same day using the commercial immunoassay LIAISON SARS-CoV-2S1/S2 IgG, performed on LIAISON-XL analyzer platform (DiaSorin). The detection is based on chemiluminescence immunoassay (CLIA) technology and detects IgG against S1/S2 epitopes of the viral spike proteins. The result is quantitative (up to 400 AU/ml) with positive threshold value of 15 AU/ml. Results are interpreted as negative (< 12 AU/ml, intermediate ($12.0 < x < 15.0$) or positive (≥ 15.0).

2.6.3 | Pregnancy determination

A β -hCG test was performed 12 days after embryo transfer and clinical pregnancy and implantation rates were confirmed when a gestational sac with fetal heartbeat was visible by ultrasound examination after 7 weeks of gestation. Demographic data, treatment information and results, and pregnancy outcomes were recorded and followed until delivery.

2.7 | Statistical analysis

Statistical analysis was performed using the SPSS software package version 27 (SPSS Inc., IBM Corp., Armonk, NY). Shapiro–Wilk test was used to evaluate the distribution of quantitative data. Groups were compared using Student's *t*-test or Mann–Whitney *U*-test, when appropriate. Proportions were compared using chi-square test or Fisher exact test. *p*-Values $< .05$ were considered significant. As this was a prospective cohort study, we aimed to recruit all IVF patients from March 1 to April 30, 2021, who were 2 weeks to 2 months after the second vaccination and to analyze 50–60 samples in the 2-month period.

3 | RESULTS

A total of 59 women were enrolled; 37 reported being vaccinated and 22 were not. Among them, eight patients who claimed not to be infected by COVID-19 had measurable levels of anti-N antibodies in their blood. The status of their antibodies was: (S+N-) = 29, (S+N+) = 8, (S-N-) = 18, and (S-N+) = 4, for a total of 59. We categorized the cohort of patients according to their serum antibody levels (positive for S, positive for N, or negative for both) and found a very high correlation (97%) between anti-S and anti-N in the blood and follicular fluid. Treatment outcomes were comparable between the 3 groups, including hormonal levels, number of oocytes retrieved (10.05 ± 7.6 vs. 12.3 ± 9.11 vs. 11.89 ± 9.67 ; $p = .63$), fertilization rates (49% vs. 60% vs. 58%; $p = .43$), and cleavage rates (57% vs. 51% vs. 49%; $p = .86$) (Table 1). Analyzing the follicular fluid based on this categorization, we found that except for CRP, which was significantly elevated in patients with anti-N antibodies (Table 2), all parameters evaluated in the follicular fluids were comparable.

4 | DISCUSSION

4.1 | Principal findings

This study followed IVF patients who underwent ovum pick-up and correlated the outcomes with their vaccination status. We found no statistical differences between patients who were vaccinated, infected or neither, or according to the presence of anti-N or anti-S antibodies in the serum and the follicular fluid. Moreover, IVF treatment outcomes were comparable between groups. The follicular fluid profile and all treatment parameters were comparable, except CRP levels were significantly higher among patients who had been infected with Covid-19.

Several studies have reported reassuring results regarding pregnancy outcomes after mRNA SARS-CoV-2 vaccine.^{18–21} There is no evidence that antibodies formed by Covid-19 vaccine caused pregnancy complications, placental complications or fetal abnormalities.²²

In contrast, there is little information regarding patients undergoing IVF treatment. Reports in the media regarding the possibility that the vaccine may cause infertility were based on the immunological

TABLE 1 Patient characteristics and treatment outcomes according to presence of serum antibodies

Variable	Positive anti-S* (n = 37)	Positive anti-N* (n = 9)	Negative anti S, N (n = 18)	p-Value
Age (years)	33.3 ± 6.1	31.9 ± 6.4	35.7 ± 7.03	.27
Infertility diagnosis				
Male factor	13 (35%)	1 (11%)	5 (28%)	.36
Unexplained	20 (54%)	6 (67%) ^a	8 (44%) ^a	.02
Other	4 (11%)	2 (22%)	5 (28%)	.27
Duration of infertility	2.73 ± 3.26	3.5 ± 2.35	2.23 ± 3.26	.46
% patients with previous parity	5 (13.5%)	3 (33%)	1 (5.5%)	.15
BMI (kg/m ²)	26.04 ± 7.5	29.61 ± 8.13	25.12 ± 6.36	.32
Estradiol (pg/l) in blood [range]	2070 [921–2919]	1430 [803–2513]	1637 [1028–2682]	.38
Progesterone (ng/dl) in blood	.70 ± .42	.78 ± .59	.63 ± .32	.67
Endometrial thickness (mm)	9.29 ± 1.97	9.72 ± 1.30	10.1 ± 2.18	.34
No. of follicles >14 mm	7.45 ± 4.44	7.67 ± 4.89	7.28 ± 4.57	.97
No. of oocytes collected	10.05 ± 7.6	12.3 ± 9.11	11.89 ± 9.67	.63
No. of mature oocytes (M2)	6.13 ± 4.66	4.66 ± 3.70	8.2 ± 6.5	.23
No. of 2pn [range]	3 [1–7]	5 [2.5–6.5]	3 [3–6]	.53
Fertilization rate (2PN/M2) (%)	49	60	58	.43
Cleavage rate (day3/2PN) (%)	57	51	49	.86
Pregnancy rate (%)	44	33	50	.87

^aEight patients were positive for both anti-N and anti-S.

TABLE 2 Follicular fluid profile according to presence of serum antibodies

Characteristic	Positive anti-S ^a (n = 37)	Positive anti-N ^a (n = 9)	Negative anti S, N (n = 18)	p-Value
Progesterone (ng/ml)	5.03 [3.41–11.08]	6.74 [1.61–11.56]	4.29 [2.9–4.78]	.51
Estradiol (pg/ml)	955 [465–1555]	881 [503–6053]	789 [349–1765]	.88
Cholesterol (mg/dl)	163.7 ± 38.3	168.60 ± 50.5	170.99 ± 20.87	.87
Cortisol (ng/dl)	15.86 ± 6.15	11.62 ± 5.31	16.87 ± 8.39	.29
C-reactive protein (mg/l)	2.29 [1.42–6.08]	4.11 [1.62–5.75]	1.44 [.36–8.33]	<.001
Glucose (mg/dl)	80.4 ± 19.4	84.5 ± 25.18	78.79 ± 32.2	.89
High density lipids (mg/dl)	50.73 ± 9.97	50.70 ± 8.16	62.4 ± 17.55	.05
Triglycerides (mg/dl)	115.49 ± 45.58	89.6 ± 31.6	111.38 ± 44.25	.43

^aEight patients were positive for both anti-N and anti-S.

process and sowed fear among infertility patients. This concern was based on the disproven idea that one of the spike proteins in COVID-19 and the Syncytin-1 protein (which helps placental development) are the same, but they are not.¹² Other concerns regarding the immunological influence of the vaccine on female fertility were raised due to the reported observation of high titers of antigen-specific antibodies for CD8+ and Th1-type CD4+ T-cells. Fortunately, the Pfizer mRNA SARS-CoV-2 vaccine has been shown to be 95% effective in preventing Covid-19 by one week after the second dose, with a favorable safety profile.¹³

Orvieto et al. found no difference in ovarian reserves and cycle outcomes before and after COVID-19 infection. However, they found

a decrease in the number of top-quality embryos after COVID-19 infection.²³ The same group assessed patients before and after they were vaccinated and found no difference in their overall treatment outcomes.²⁴

4.2 | Clinical implications

To further assess the effect of COVID-19 infection and vaccination on IVF patients and elucidate the potential effect on oocyte performance, we examined the microenvironment that surrounds ovarian follicles and oocytes, and the follicular fluid. Follicular fluid is an ultrafiltrate of

blood, and as it is the closest product surrounding the oocyte, it reflects the influence of different materials on the oocyte.^{25,26} The fact that no differences were observed between patients who were vaccinated, infected or not exposed to COVID-19 strengthens the assumption that the vaccination did not affect fertility.

An interesting finding raised from the analysis of the follicular fluid is we found that CRP was significantly elevated in patients who were positive for anti-N. This may be explained by their recent exposure to infection. However, this did not affect treatment outcomes.

4.3 | Research implications

The results that no differences were observed in the number of oocytes collected, fertilization rate, cleavage rate and pregnancy outcomes, further support the belief that the vaccine did not alter patients' fertility potentials.

Larger studies with longer follow-up will be needed to validate our observations.

4.4 | Strengths and limitations

The limitations of this study are the small sample size and the short follow-up period. We did not evaluate serum CRP levels. However, a major strength is the evaluation of the follicular fluid profile and the comparison between patients who were infected and those who had not been exposed to the vaccine. The fact that all women who participated in our study responded similarly, with no difference in treatment parameters helps to reject the fears of any major effects on fertility potential after vaccination or infection.

5 | CONCLUSIONS

In conclusion, so far, treatment outcomes and ovarian response were not affected by the mRNA SARS-CoV-2 vaccine in the first IVF cycle after the vaccination or after COVID-19 infection. These are preliminary findings and additional studies are required.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

DATA SHARING

Data will be made available upon reasonable request to the corresponding author.

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