Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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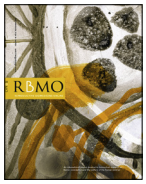

ARTICLE

Pfizer SARS-CoV-2 BNT162b2 mRNA vaccination (BNT162b2) has no adverse effect on elective oocyte cryopreservation outcomes

BIOGRAPHY

Dr Gilad Karavani graduated from the Hebrew University of Jerusalem, Israel, and recently completed his residency training in obstetrics and gynaecology at Hadassah-Hebrew University Medical Center. His major areas of interest are fertility preservation and in-vitro maturation, as well as male infertility.

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KEY MESSAGE

Analysis of data from women undergoing elective fertility preservation up to 13 months after the Pfizer SARS-CoV-2 BNT162b2 mRNA vaccine shows no negative effect on oocyte cryopreservation cycle outcomes compared to unvaccinated women.

ABSTRACT

Research question: Do elective oocyte cryopreservation outcomes in women 1–13 months after SARS-CoV-2 vaccination alter compared with unvaccinated women and do different time intervals between vaccination and ovarian stimulation impact these outcomes?

Design: This retrospective cohort study, conducted in a university-affiliated IVF centre, included 232 elective oocyte cryopreservation cycles of vaccinated and unvaccinated patients, without previous infection with the SARS-CoV-2 virus, between December 2020 and January 2022. Two control groups – pre-pandemic (January 2019 to February 2020) and intra-pandemic (December 2020 to January 2022) unvaccinated groups – were compared with the vaccinated group, further divided into four subgroups (under 3, 3–6, 6–9 and 9–13 months). The primary outcome was the elective oocyte cryopreservation cycle outcomes – number of retrieved and number of mature oocytes.

Results: The vaccinated group demonstrated comparable outcomes with regards to number of retrieved and mature oocytes compared with the pre-pandemic and intra-pandemic unvaccinated groups (12.6 ± 8.0 versus 13.0 ± 8.2 and 12.5 ± 7.4 retrieved and 10.1 ± 6.9 versus 9.5 ± 6.4 and 10.1 ± 6.3 mature oocytes, respectively; not significant for both). Similar results were noted in a comparison between the intra-pandemic unvaccinated group and the four vaccinated subgroups. No correlation was found between the parameter of days from vaccination and cycle outcomes. Similarly, analysis of covariance showed no association between vaccination status and timing and number of mature oocytes.

Conclusions: The SARS-CoV-2 vaccination does not alter the outcomes of elective oocyte cryopreservation procedures. This is true even in a relatively long time interval of 9 to 13 months from vaccination.

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KEYWORDS

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INTRODUCTION

Over the past 2 years, the COVID-19 pandemic has been a major concern and focus of interest for the medical community worldwide (*Andrews et al., 2022*). In addition to leaving behind millions of casualties, it has disrupted standard medical care, overwhelming medical systems on a global scale.

The SARS-CoV-2 vaccine was introduced in late 2020, dramatically decreasing morbidity and mortality from the disease within the general population (*Abu Jabal et al., 2021*). Several studies have reported vaccine safety in women of reproductive age, with no adverse effects on fertility and reproductive function (*Bentov et al., 2021*; *Hillson et al., 2021*; *Mohr-Sasson et al., 2022*; *Wainstock et al., 2021*). Likewise, IVF outcomes such as implantation rates and clinical and ongoing pregnancy rates have not been negatively affected by vaccination (*Aharon et al., 2022*; *Aizer et al., 2022*; *Orvieto et al., 2021*). One recent study evaluating the effect of SARS-CoV-2 vaccination on IVF outcomes found number of oocytes retrieved and rate of good-quality embryos were comparable between vaccinated and unvaccinated groups (*Huang et al., 2022*).

Despite the current burden on the healthcare system, fertility preservation by oocyte cryopreservation during the COVID-19 pandemic has continued (*Trawick et al., 2022*). More specifically, women interested in elective oocyte cryopreservation (EOC) have also continued to seek medical care. This group is unique in the absence of an underlying infertility pathology for which IVF treatment is indicated. Hence, safety is paramount when recommending such elective procedures during a global pandemic.

Previous available data focuses on short-term (up to 6 months) outcomes, while data on longer intervals between vaccination and IVF treatment remain scarce. Furthermore, the studies mentioned included a heterogenous population with a wide array of indications for IVF treatment.

The aim of this study was to assess outcomes of EOC in women receiving the SARS-CoV-2 vaccine up to 13 months prior to their procedure. The study specifically sought to evaluate how different time intervals between vaccination and ovarian stimulation may impact these outcomes.

MATERIALS AND METHODS

Study population

This was a retrospective cohort study including women who underwent EOC at a university-affiliated medical centre during two time periods: January 2019 to February 2020 and December 2020 to January 2022, without a prior or current COVID-19 infection. In accordance with the national Israeli guidelines for elective, non-medical fertility preservation, EOC is performed only in patients aged 30 years or older. Therefore, only patients aged 30–39 years were included in the study. The first period was the pre-COVID-19 pandemic period (between January 2019 and February 2020). The second period was from the introduction of the Pfizer-BioNTech (BNT162b2) COVID-19 Vaccine in December 2020, and the outbreak caused by the SARS-CoV-2 Omicron variant in January 2022.

EOC cycles performed after January 2022 were not included in the study. Exclusion of this group was driven by the high infection rate of the Omicron variant during this time period and lack of mandatory SARS-CoV-2 polymerase chain reaction (PCR) testing prior to oocyte retrieval procedures. Therefore, it was not possible to ensure lack of active COVID-19 infection within this group.

In order to explore the possible effect of the SARS-CoV-2 mRNA vaccination on fertility, the study focused on three groups of women not previously infected with the SARS-CoV-2 virus who electively chose to preserve oocytes for future fertility. The two control groups were of SARS-CoV-2 unexposed, unvaccinated women. The first group included women who underwent EOC prior to the COVID-19 pandemic outbreak (pre-pandemic group) between January 2019 and February 2020 and for which data were previously collected. This group was added to the study to establish a control group that avoided possible confounders related to the COVID-19 pandemic era itself (stress, anxiety, depression, etc.) and their possible effect on EOC outcomes. The second control group included unexposed, unvaccinated women with an EOC performed after initiation of the Pfizer-BioNTech COVID-19 Vaccine (BNT162b2) from December 2020 until January 2022 (intra-pandemic unvaccinated group). Women who received at least two doses of the Pfizer-BioNTech COVID-19 Vaccine (BNT162b2) and who underwent an EOC cycle up to 13 months after the first vaccination were included in the study group (vaccinated group). The vaccinated group was additionally divided into four subgroups according to time interval from the first vaccination to the EOC cycle: under 3 months, 3–6 months, 6–9 months and 9–13 months.

Before the oocyte aspiration procedure, patients were asked to report on data regarding previous COVID-19 infection and vaccination status. Patients who reported being previously infected with the SARS-CoV-2 virus or having been vaccinated were asked to provide documentation, including formal approval of infection diagnosis or specific dates of each vaccination. Patients who did not provide this documentation or refused vaccination were asked to undergo a PCR test 24–48 h prior to the procedure or present vaccination data upon arrival to the IVF unit on the day of the EOC procedure.

Exclusion criteria were prior or current COVID-19 infection, fertility preservation by oocyte freezing for medical indications such as high-risk premature ovarian insufficiency cases (fragile X carriers, Turner syndrome, etc.), cancer patients facing chemo/radiotherapy and patients with planned surgery in both ovaries with increased risk for ovarian reserve decline. Women 40 years or older or younger than 30 years were also excluded from the study. Women with past documentation of COVID-19 infection by positive SARS-CoV-2 PCR test or symptomatic women with a positive antigen test at any timepoint were regarded as COVID-19 exposed and excluded from this study.

Data collection

General and gynaecological medical histories were collected for all patients. Chronic medical conditions (such as hypothyroidism, inflammatory bowel disease or other autoimmune disease, hypertension or diabetes) and regular medical treatments were recorded. Reproductive data of the study population were gathered from the electronic medical records of the IVF unit and included age at cycle

initiation, body mass index (BMI), anti-Müllerian hormone concentrations (ng/ml), menstrual cycle day 3 FSH (IU/l) and oestradiol concentrations (pmol/l), number of previous EOC cycles, type of ovarian stimulation protocol (antagonist or short agonist), type of gonadotrophin given (human menopausal gonadotrophin [Menopur], recombinant human FSH [follitropin alfa, r-hFSH] and recombinant human LH [lutropin alfa, r-hLH; Pergoveris] or recombinant human FSH [follitropin alfa; Gonal-F or follitropin beta [Puregon]). Additional data included the outcomes of the ovarian stimulation cycles – maximal oestradiol concentrations at trigger day or the day before, number of oocytes retrieved, number of mature oocytes cryopreserved and the percentage of mature oocytes.

Ovarian stimulation protocols and oocyte retrieval

Ovarian stimulation was routinely initiated by gonadotrophin-releasing hormone (GnRH) antagonist protocols and in a few select cases by a short GnRH agonist protocol. The GnRH antagonist protocol included daily administration of gonadotrophins starting on cycle day 2–3 followed by a subcutaneous administration of GnRH antagonist when follicle size reached 14 mm or on the 6th day of gonadotrophin treatment.

The short GnRH agonist protocol included administration of 0.1 mg GnRH agonist on cycle day 1, followed by daily administration of gonadotrophins starting on cycle day 2–3. Ovulation induction was achieved by a GnRH agonist injection given when two follicles or more reached 16–18 mm in size. Oocyte retrieval was performed under general anaesthesia using transvaginal ultrasound guidance 34–36 h after ovulation induction.

Outcomes

The primary outcome was the number of mature oocytes cryopreserved. Additional outcomes investigated were the number of oocytes retrieved and the percentage of mature oocytes (out of the total number of retrieved oocytes).

These outcomes were compared between the pre-COVID-19 control group, the unexposed unvaccinated group, and the vaccinated group.

Additional analyses compared these outcomes between the intra-pandemic unvaccinated group and the vaccinated subgroups according to months from first vaccination to the EOC cycle: under 3 months, 3–6 months, 6–9 months and 9–13 months.

The correlations between the parameter of days from first vaccination to EOC cycle and the outcomes of number of oocytes retrieved, number of mature oocytes and percentage of mature oocytes were also tested. The study also assessed the association between other basic parameters and the vaccination groups with number of mature oocytes using a generalized linear regression analysis.

Ethical approval

This study was approved by the Committee on Research Involving Human Subjects of The Hebrew University- Hadassah Medical School, Jerusalem, Israel in March 2021 (IRB 0054-21-HMO) and conforms to the provisions of the Declaration of Helsinki.

Statistical analysis

For quantitative variables, the comparison between independent variables of the study groups was performed using one-way analysis of variance (ANOVA) followed by the post-hoc test for multiple comparisons with the additional Kruskal–Wallis test and reported it in parameters with unequal distribution.

Post-hoc Scheffe or post-hoc Tukey honest significant difference test were used to identify the coupled groups differences for equal variance.

Testing the association between two categorical variables was carried out using either the chi-squared or Fisher's exact test, as indicated. The Fisher's exact test was applied in analyses of small samples, when more than 20% of cells have expected frequencies of less than five. Cross-sectional association of the days from first vaccination to the EOC cycle and the cycle outcomes: number of oocytes retrieved, number of mature oocytes and the percentage of mature oocytes were tested using linear regression models and the Pearson correlation coefficient (r).

A post-hoc power analysis was conducted for the main outcome of mature oocytes cryopreserved.

Analysis of covariance (ANCOVA) was used to evaluate the association between several basic and cycle-related parameters (including the vaccination status and timing) and the main outcome (number of mature oocytes) while adjusting for other variables. Due to the doubling of women between groups, mixed models including one or more cycles per woman were used to allow for non-independent observations and evaluate the association between basic and cycle-related parameters and the main outcome. A P-value of <0.05 was considered statistically significant for all comparisons.

RESULTS

Study population

From the introduction of the SARS-CoV-2 BNT162b2 mRNA vaccine in December 2020 until January 2022, 271 EOC cycles were performed in women aged 30–39 years in the study IVF unit. Thirty-nine patients with documented previous COVID-19 infection were excluded from the study. Out of the 232 EOC cycles of unexposed patients, 94 patients who did not provide specific vaccination date documentation prior to EOC were also excluded. A total of 138 EOC cycles were included in the final analysis – 55 cycles of 52 unvaccinated women and 83 EOC cycles performed within 13 months post-vaccination in 69 women. The additional control group of pre-pandemic (January 2019 to February 2020) EOC cycles included 133 cycles of 103 women (FIGURE 1). The entire cohort included an overall number of 271 EOC cycles (mean age at cycle of 35.5 ± 2.1 years).

Post-hoc power analysis showed that this study has 70% power to find a significant difference of three oocytes between the groups.

Basic characteristics and EOC cycle data

Basic characteristics and cycle-related data were compared between the pre-pandemic group, the intra-pandemic unvaccinated group and the vaccinated group (TABLE 1). Medical background of chronic disease or medication taken and rates of patients with a previous fertility preservation cycle were lower in the intra-pandemic unvaccinated group compared to the pre-pandemic group (1.9% versus 15.5% and 9.6% versus 37.9%, $P = 0.039$ and $P = 0.001$, respectively). Additionally,

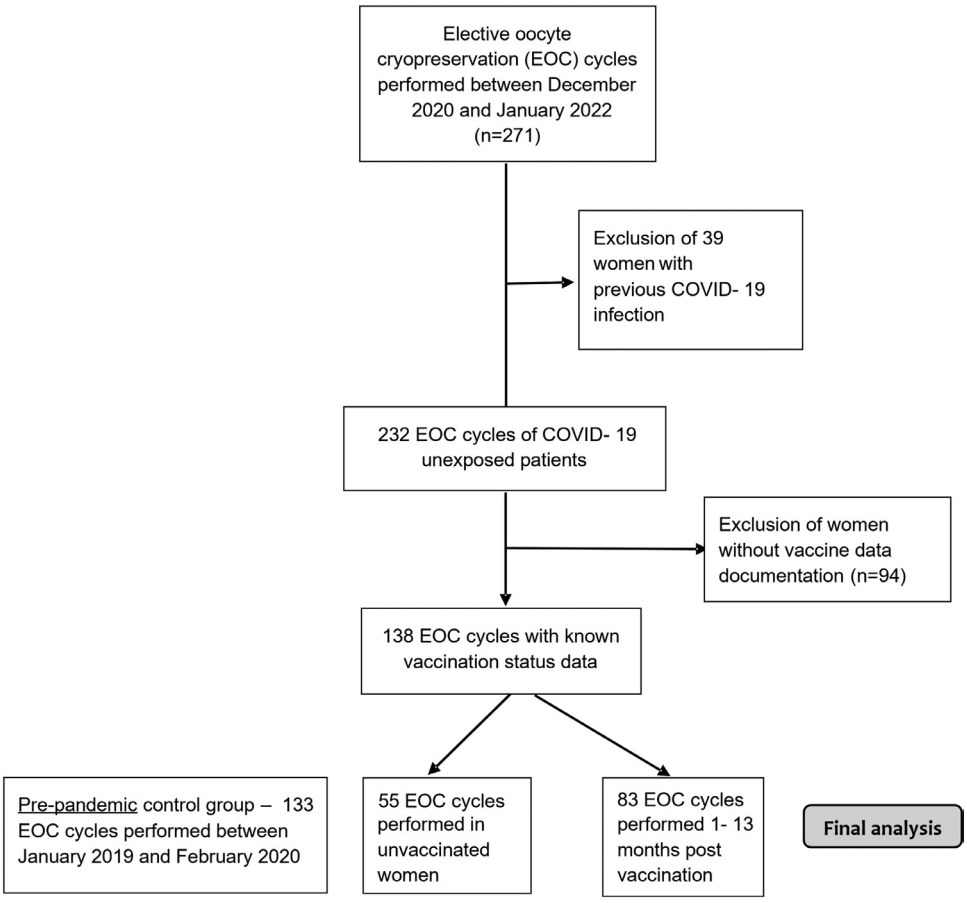

FIGURE 1 Flow chart of the study population.

the vaccinated group had 1.2 more days of gonadotrophin treatment and higher peak oestradiol concentrations compared with the pre-pandemic group (11.1 ± 2.2 versus 9.9 ± 1.8 days and 13,553.8 ± 7597.3 versus 11,246.6 ± 5760.3 pmol/l, $P < 0.001$ and $P = 0.028$, respectively).

Comparison of EOC outcomes

Comparison of EOC cycle outcomes (TABLE 2) showed similar number of retrieved oocytes and mature oocytes in the pre-pandemic, intra-pandemic unvaccinated and the vaccinated group (13.0 ± 8.2 versus 12.5 ± 7.4 versus 12.6 ± 8.0 retrieved oocytes ($P = 0.892$) and 9.5 ± 6.4 versus 10.1 ± 6.3 versus 10.1 ± 6.9 mature oocytes ($P = 0.744$), respectively). The percentage of mature oocytes (out of those retrieved) was slightly lower ($P = 0.025$) in the pre-pandemic group compared to the vaccinated group (74.2 ± 22.4 versus 80.8 ± 16.1%), while the intra-pandemic unvaccinated group had similar rates (81.0 ± 19.6%) of mature oocytes compared with the pre-pandemic and the vaccinated groups (TABLE 2).

EOC cycle data and outcomes according to months from vaccination (under 3, 3–6, 6–9 and 9–13 months)

A subgroup analysis comparing the cycles of the intra-pandemic unvaccinated group to the subgroups of vaccinated patients by time from vaccination to EOC (under 3, 3–6, 6–9 and 9–13 months) is presented in TABLE 3. These subgroups were similar in basic and EOC cycle-related characteristics, apart from the peak oestradiol concentrations prior to ovulation trigger, which were lower in the under 3 months group compared with the 3–6 and 6–9 months post-vaccination groups (9028.6 ± 9724.4 versus 16,711.4 ± 8777.9 and 16,070.3 ± 6286.3 pmol/l, respectively, $P = 0.003$).

EOC cycle outcomes were also compared in this subgroup analysis and demonstrated comparable number of retrieved oocytes, mature oocytes and percentage of mature oocytes in the intra-pandemic unvaccinated and vaccinated subgroups (data presented in TABLE 4).

When comparing the EOC cycles performed 6–13 months after vaccination ($n = 43$) with cycles of unvaccinated patients between January 2021 and January 2022 ($n = 55$), similar results of comparable cycle outcomes were found between the vaccinated and unvaccinated groups regarding number of oocytes retrieved (13.3 ± 8.7 versus 12.5 ± 7.4 oocytes, $P = 0.636$), number of mature oocytes (10.9 ± 7.6 versus 10.1 ± 6.3 oocytes, $P = 0.603$) and percentage of mature oocytes (80.8 ± 16.5 versus 81.0 ± 19.6%, $P = 0.950$).

To analyse possible biases that may affect number of mature oocytes cryopreserved (as a continuous parameter), the correlation between various parameters (basic characteristics including age, BMI, day 3 FSH concentrations, peak oestradiol concentrations, gonadotrophins and their overall dose, as well as the vaccination status and timing and the number of mature oocytes cryopreserved) was evaluated using analysis of covariance (ANCOVA). The analysis reported is

TABLE 1 CHARACTERISTICS OF THE STUDY POPULATION – WOMEN UNEXPOSED TO THE SARS-COV-2 VIRUS WHO UNDERWENT EOC PRIOR TO THE COVID-19 PANDEMIC OUTBREAK AND DURING THE COVID-19 MRNA VACCINATION INITIATIVE

Parameter	Pre-pandemic	Intra-pandemic unvaccinated	Vaccinated	*P*-value
Number of patients	103	52	69	
Age (years)	35.4 ± 2.1	35.9 ± 1.9	35.4 ± 2.3	0.308
BMI (kg/m^2)	24.0 ± 3.9	23.0 ± 4.3	24.1 ± 5.1	0.328
Chronic disease or medication taken	16/103 (15.5)[c]	1/52 (1.9)[c]	8/67 (11.9)	0.039
Previous fertility preservation cycle	39/103 (37.9)[c]	5/52 (9.6)[c]	19/69 (27.5)	0.001
Days from first vaccination to cycle	–	–	191.5 ± 103.1	
Third vaccination given	–	–	33/69 (47.8)	
Day 3 FSH concentrations[a] (mIU/ml)	7.4 ± 2.5	7.3 ± 2.4	7.2 ± 2.6	0.838
Day 3 oestradiol concentrations[a] (pmol/l)	185.3 ± 120.5	174.8 ± 93.0	192.6 ± 115.3	0.684
AMH concentrations (ng/ml)[b]	2.4 ± 2.5	3.3 ± 2.6	2.8 ± 2.3	0.344
Number of cycles	133	55	83	
Antagonist protocol	121/133 (91.0)	51/55 (92.7)	77/81 (95.1)	0.591
Gonadotrophin treatment				0.416
FSH	30/133 (22.6)	10/55 (18.2)	23/83 (27.7)	
FSH+LH	103/133 (77.4)	46/56 (82.1)	60/83 (72.3)	
Days of gonadotrophin treatment	9.9 ± 1.8[d]	10.6 ± 1.8	11.1 ± 2.2[d]	<0.001
Overall dose of gonadotrophin (IU)	2579.4 ± 1144.9	2525.6 ± 1023.0	2818.9 ± 1287.4	0.244
Peak oestradiol concentrations (pmol/l)	11,246.6 ± 5760.3[d]	12,986.4 ± 5973.4	13,553.8 ± 7597.3[d]	0.028

Data are presented as mean ± SD or *n*/*N* (%).

AMH = anti-Müllerian hormone; BMI = body mass index; EOC = elective oocyte cryopreservation.

[a] Baseline FSH and oestradiol concentrations measured in hormone panel test at day 3 of menstrual period.

[b] Data available for 32/103 patients in the pre-pandemic group, for 23/52 patients in the intra-pandemic unvaccinated group and for 41/69 patients in the vaccinated group.

[c] $P < 0.05$ when comparing the pre-pandemic and the intra-pandemic unvaccinated groups using post-hoc Tukey honest significant difference test.

[d] $P < 0.05$ when comparing the pre-pandemic and the vaccinated groups using post-hoc Tukey honest significant test.

a mixed model including one or more cycles per woman in order to correct for the doubling of women between groups to allow for non-independent observations. This analysis demonstrated that the parameters significantly associated with number of mature oocytes were age ($P = 0.001$), BMI ($P = 0.004$), day 3 FSH concentrations ($P = 0.025$), treatment with FSH only ($P = 0.008$), overall gonadotrophin dose ($P = 0.038$) and peak oestradiol concentrations ($P < 0.001$). However, vaccination status and timing (months) were not associated with this outcome (TABLE 5). A similar analysis performed for the sub-population of patients with an anti-Müllerian hormone (AMH) measurement found that AMH, BMI and peak oestradiol concentrations were associated with number of mature oocytes (data available upon request).

Correlation between days from first vaccination and cycle outcomes

The linear correlation between the quantitative parameter of days from first vaccination and cycle outcomes was assessed by calculation of the Pearson's correlation coefficient (r). This analysis demonstrated lack of correlation between the days passed from vaccination and number of retrieved and mature oocytes, as well as the percentage of mature oocytes out of total oocytes retrieved (data available upon request).

DISCUSSION

This study focuses on EOC outcomes in women inoculated with the Pfizer-BioNTech (BNT162b2) COVID-19

TABLE 2 OUTCOMES OF EOC PRIOR TO THE COVID-19 PANDEMIC OUTBREAK AND DURING THE COVID-19 MRNA VACCINATION INITIATIVE IN WOMEN UNEXPOSED TO THE SARS-COV-2 VIRUS

Parameter	Pre-pandemic	Intra-pandemic unvaccinated	Vaccinated	*P*-value
Number of cycles	133	55	83	
Number of oocytes retrieved	13.0 ± 8.2	12.5 ± 7.4	12.6 ± 8.0	0.892
Number of mature (MII) oocytes	9.5 ± 6.4	10.1 ± 6.3	10.1 ± 6.9	0.744
Mature oocytes (%)	74.2 ± 22.4[a]	81.0 ± 19.6	80.8 ± 16.1[a]	0.025

Data are presented as mean ± SD.

EOC = elective oocyte cryopreservation; MII = metaphase II.

[a] $P < 0.05$ when comparing the pre-pandemic and the vaccinated groups using post-hoc Tukey honest significant difference test.

TABLE 3 CHARACTERISTICS OF WOMEN UNEXPOSED TO THE SARS-COV-2 VIRUS WHO UNDERWENT EOC FOR FERTILITY PRESERVATION DURING THE COVID-19 MRNA VACCINATION INITIATIVE – ACCORDING TO VACCINATION STATUS AND TIMING

Parameter	Intra-pandemic unvaccinated	Vaccinated less than 3 months prior to cycle	Vaccinated 3–6 months prior to cycle	Vaccinated 6–9 months prior to cycle	Vaccinated 9–13 months prior to cycle	*P*-value
Number of women	52	15	23	17	25	
Age (years)	35.9 ± 1.9	35.6 ± 2.4	36.1 ± 1.6	35.3 ± 2.7	34.8 ± 2.3	0.156
BMI (kg/m^2)	23.0 ± 4.3	22.7 ± 3.9	24.1 ± 5.7	23.6 ± 4.7	25.1 ± 5.5	0.425
Chronic disease or medication taken	1/52 (1.9)[b]	2/14 (14.3)	1/23 (4.3)	3/17 (17.7)	3/25 (12.0)	0.151
Previous fertility preservation cycle	5/52 (9.6)	4/14 (28.6)	6/23 (26.1)	5/17 (29.4)	7/25 (28.0)	0.168
Days from first vaccination to cycle	N/A	48.6 ± 20.2	133.7 ± 25.3	226.0 ± 34.1	314.0 ± 28.9	<0.001
Third vaccination given	N/A	N/A	N/A	9/17 (52.9)	24/25 (96.0)	
Day 3 FSH concentration[a] (mIU/ml)	7.3 ± 2.4	6.7 ± 2.9	6.8 ± 1.9	6.7 ± 1.4	8.0 ± 3.3	0.379
Day 3 oestradiol concentration[a] (pmol/l)	174.8 ± 93.0	221.9 ± 168.9	226.2 ± 112.4	177.2 ± 117.9	157.6 ± 74.4	0.121
AMH concentrations (ng/ml)	3.3 ± 2.6	3.2 ± 3.9	3.1 ± 1.8	2.1 ± 0.8	2.8 ± 2.1	0.766
Number of cycles	55	16	24	17	26	
Antagonist protocol	51/55 (92.7)	13/14 (92.9)	22/24 (91.7)	17/17 (100.0)	25/26 (96.2)	0.782
Gonadotrophin treatment						0.269
FSH	10/55 (18.2)	5/16 (31.3)	4/24 (16.7)	4/17 (23.5)	10/26 (38.5)	
FSH+LH	45/55 (81.8)	11/16 (68.8)	20/24 (83.3)	13/17 (76.5)	16/26 (61.5)	
Days of gonadotrophin treatment	10.6 ± 1.9	10.6 ± 1.5	11.0 ± 1.5	11.2 ± 2.5	11.3 ± 2.8	0.564
Overall dose of gonadotrophin (IU)	2525.6 ± 1023.0	2627.2 ± 1215.1	2943.0 ± 1237.8	2369.4 ± 1061.9	3116.2 ± 1466.7	0.152
Peak oestradiol concentrations (pmol/l)	12,986.4 ± 5973.4	9028.6 ± 9724.4[b]	16,711.4 ± 8777.9[b]	16,070.3 ± 6286.3[b]	11,551.9 ± 5735.7	0.003

Data are presented as mean ± SD or *n/N* (%).

AMH = anti-Müllerian hormone; BMI = body mass index; EOC = elective oocyte cryopreservation; FSH = follicle stimulating hormone; N/A = not available.

[a] Baseline FSH and oestradiol concentrations measured in hormone panel test at day 3 of menstrual period.

[b] $P < 0.05$ when comparing the under 3 months group with the 3–6 and 6–9 months groups using post-hoc Tukey honest significant difference test.

Vaccine. Vaccinated women had equivalent reproductive outcomes compared with unvaccinated women during and before the COVID-19 pandemic. Furthermore, time from vaccination to EOC had no effect on outcomes with relatively long-term (up to 13 months) outcomes showing similar reassuring findings as controls.

These findings are in agreement with current literature on this topic. *Orvieto et al. (2021)* reported on 36 women who underwent consecutive ovarian stimulation cycles for IVF before and after receiving the SARS-CoV-2 mRNA vaccine. No differences were found in ovarian stimulation or embryological variables pre- and post-vaccination. In another study, 222 vaccinated patients were compared with 983 unvaccinated patients undergoing ovarian stimulation cycles. The groups were similar with regards to fertilization rate, eggs retrieved, mature oocytes retrieved, mature oocyte ratio, blastulation rate and euploid rate (*Aharon et al., 2022*). In a third study, *Bentov et al. (2021)* examined follicular fluid in women undergoing oocyte retrieval comparing patients recovering from COVID-19 infection, vaccinated and uninfected, and unvaccinated controls. They found no differences between groups with regards to any of the surrogate parameters for ovarian follicle quality.

Most available data on IVF outcomes following COVID-19 vaccination refer to short time periods between vaccination and ovarian stimulation cycles (*Aharon et al., 2022*; *Orvieto et al., 2021*). In this study an attempt was made to focus on long-term outcomes including women with at least

TABLE 4 OUTCOMES OF EOC FOR FERTILITY PRESERVATION DURING THE COVID-19 MRNA VACCINATION INITIATIVE IN WOMEN UNEXPOSED TO THE SARS-COV-2 VIRUS – ACCORDING TO VACCINATION STATUS AND TIMING

Parameter	Intra-pandemic unvaccinated	Vaccinated less than 3 months prior to cycle	Vaccinated 3–6 months prior to cycle	Vaccinated 6–9 months prior to cycle	Vaccinated 9–13 months prior to cycle	*P*-value
Number of cycles	55	16	24	17	26	
Number of oocytes retrieved	12.5 ± 7.4	11.4 ± 8.9	12.3 ± 6.2	14.4 ± 8.6	12.6 ± 8.8	0.860
Number of mature (MII) oocytes	10.1 ± 6.3	7.7 ± 6.8	10.2 ± 5.7	11.7 ± 7.8	10.3 ± 7.5	0.597
Mature oocytes (%)	81.0 ± 19.6	76.0 ± 15.0	83.8 ± 15.9	81.7 ± 18.8	80.2 ± 15.1	0.790

EOC = elective oocyte cryopreservation; MII = metaphase II.

TABLE 5 ANALYSIS OF COVARIANCE EVALUATING THE ASSOCIATION BETWEEN PATIENT CHARACTERISTICS AND THE NUMBER OF MATURE OOCYTES CRYOPRESERVED

Parameter	Estimate	SE	*P*-value
Groups by vaccination status			0.771
Pre-pandemic control group	Referent	Referent	
Intra-pandemic unexposed unvaccinated	0.84	0.84	
Vaccination less than 3 months prior to cycle	0.45	1.38	
Vaccination 3–6 months prior to cycle	−0.99	1.14	
Vaccination 6–9 months prior to cycle	−0.03	1.23	
Vaccination 9–13 months prior to cycle	0.17	1.06	
Age (years)	−0.61	0.17	0.001
BMI (kg/m^2)	0.24	0.08	0.004
Day 3 FSH concentration (IU/l)	−0.37	0.16	0.025
Gonadotrophin stimulation			
FSH only	2.39	0.86	0.008
FSH+LH	Referent		
Overall gonadotrophin dose (IU)	−0.00	0.00	0.038
Peak oestradiol concentration (pmol/l)	<0.001	0.00	<0.001

BMI = body mass index.

3 months between vaccination and ovarian stimulation. Subgroup analysis comparing women with at least 6 months between vaccination and EOC (n = 56) and controls found no differences in reproductive outcomes. While it is recognized that the follow-up presented here is still lacking, this is an important step in establishing long-term safety of vaccination in the general female population and IVF patients.

The main long-term safety concern regarding vaccination pertains to the immune response that follows it. Following the innate phase of the immune response, the more specific adaptive phase occurs, leading to increased formation of antibodies, which in time plateaus (*Murphy and Weaver, 2016*). Previous studies focusing on premature ovarian failure have suggested formation of self-antigens as a possible aetiology (*Szeliga et al., 2021*). Several case reports have connected the quadrivalent anti-HPV vaccine to formation of anti-ovarian antibodies (*Gong et al., 2020*). While it is acknowledged that data regarding this phenomenon are anecdotal, it endorses the need for long-term data regarding vaccine safety.

Women undergoing EOC are a unique group seldom studied in the context of the COVID-19 pandemic. As opposed to most patients undergoing IVF for treatment of infertility, elective fertility preservation is usually performed on women with normal fertility. It was postulated here that any detrimental effect vaccination may have on fertility would be more prominent within this group because their potential for ovarian response is higher. The current findings showing similar outcomes between vaccinated and unvaccinated women support accumulating data in favour of vaccine safety in IVF patients.

It was found that women in the pre-pandemic group had an average of 0.7–1.2 days of gonadotrophin treatment less compared with the intra-pandemic unvaccinated and vaccinated groups, respectively, and accordingly lower mean peak oestradiol concentrations (1700–2250 pmol/l). This may be explained by the recent accumulative data on the 'freeze-all' strategy and GnRH agonist triggering (similar to the EOC protocol) safety with regards to ovarian stimulation syndrome (*Santos-Ribeiro et al., 2020*; *Zaat et al., 2021*). It is postulated that this data may have encouraged providers to adopt a more aggressive approach using longer gonadotrophin treatment with higher oestradiol concentrations to achieve more follicles in fertility preservation cycles.

In a study by *Huang et al. (2022)*, researchers compared more than 700 vaccinated and unvaccinated patients with a mean of 72 days from second vaccination to IVF cycle. They found number of oocytes retrieved (9.9 oocytes in both groups) and rate of good-quality embryos were comparable between groups. Although the current study population achieved a higher number of retrieved oocytes for all groups (12–13 oocytes), the results are in accordance with the longer time interval (average of 191 days) from vaccination results, also showing comparable number of oocytes between vaccinated and unvaccinated patients. These results support and add to current data showing long-term safety of vaccination in this clinical setting.

Apart from its retrospective construct and the relatively small size of the study population, this study has several limitations. Comparison of cycle outcomes was performed between different patients as opposed to comparing the same woman's pre- and post-vaccination EOC cycles. Moreover, AMH was not assessed pre- and post-vaccination, although the number of retrieved and mature oocytes in each cycle in otherwise fertile women is a reliable marker for ovarian reserve and reflects the actual response to stimulation. A post-hoc power analysis conducted for the main outcome of mature oocytes cryopreserved showed 70% power to find a significant difference of three oocytes between the groups. Although this study was underpowered to find small differences between the groups, it is believed to add important long-term data regarding the safety of the vaccination. Lastly, the subgroup with an interval of 9–13 months between vaccination and ovarian stimulation was relatively small, hampering the ability to reach conclusions.

In summary, it was found that women vaccinated with the Pfizer-BioNTech (BNT162b2) COVID-19 Vaccine undergoing EOC had equivalent reproductive outcomes compared with unvaccinated women during and before the COVID-19 pandemic. This was found to also be true for women who underwent EOC up to 12 months after receiving their vaccine. While this data would need to be reconfirmed in larger studies, it is hoped that these results will encourage clinicians to endorse vaccination for this patient population and so reduce patient vaccination hesitancy.

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