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ARTICLE

COVID-19 mRNA vaccines have no effect on endometrial receptivity after euploid embryo transfer

BIOGRAPHY

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KEY MESSAGE

Sustained implantation rate of euploid embryos remains constant regardless of COVID-19 vaccination and doses applied. It is negatively influenced by short intervals between vaccination and embryo transfer. Data on the potential effect of vaccination on endometrial receptivity and reproductive outcomes are reassuring. COVID-19 vaccination should not delay attempts to conceive.

ABSTRACT

Research question: Does the COVID-19 vaccination affect endometrial receptivity after single euploid embryo transfer, measured by sustained implantation rate?

Design: A retrospective cohort study analysing two groups of single euploid embryo transfers using own oocytes: one historical cohort of 3272 transfers 1 year before the pandemic; and one comprising 890 transfers in women previously vaccinated with mRNA vaccines against severe acute respiratory syndrome coronavirus 2. The main outcomes were clinical pregnancy rate (CPR) and sustained implantation rate (SIR) per embryo transfer. These outcomes were compared between non-vaccinated and vaccinated women, and women who had received one and two doses. Lastly, vaccinated women were divided into quartiles according to the time from last dose to embryo transfer.

Results: Similar CPR and SIR were found between non-vaccinated and vaccinated women, and the odds ratio for both outcomes was not statistically significant after being controlled for potential confounders (OR 0.937, 95% CI 0.695 to 1.265 and OR 0.910, 95% CI 0.648 to 1.227 respectively). Within the vaccinated group, women who had received one or two doses also had similar outcomes. In addition, no differences were found according to the time interval from vaccination to embryo transfer.

Conclusion: The administration of mRNA vaccines against COVID-19 had no effect on endometrial receptivity and embryo implantation, regardless of the number of doses and time interval from vaccination to embryo transfer. The potential negative effect of the vaccine on endometrial receptivity and reproductive outcomes is reassuring for patients in the process of undergoing assisted reproductive treatment.

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KEYWORDS

COVID-19 vaccines, embryo implantation, clinical pregnancy rate, assisted reproductive techniques
SARS-CoV-2
Single embryo transfer

INTRODUCTION

In December 2019, a new coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), spread rapidly worldwide, resulting in one of the deadliest pandemics in human history. The virus predominantly affected the respiratory tract, and was highly contagious via respiratory droplets, causing the coronavirus disease 2019 (COVID-19), characterized by a severe acute respiratory syndrome. Despite the predilection for the respiratory system, the virus has been detected in various body fluids, such as saliva, urine, faeces and semen (*Johnson et al., 2021*).

Some enzymes, such as the angiotensin-converting enzyme 2 (ACE2), transmembrane protease serine subtype 2 and the spike protein of ADAM metallopeptidase domain 17 are important for the virus to infect human cells (*Shirbhate et al., 2021*). These enzymes are present in most of the human body tissues, including the reproductive tract, which could explain why the reproductive health of infected individuals may be affected by COVID-19 (*Beyerstedt et al., 2021*; *Rajak et al., 2021*).

The rapid spread of the infection worldwide, and the almost unprecedented effect of the COVID-19 pandemic, prompted an urgent need to produce a vaccine. Two main groups of vaccines have been produced: mRNA and vector vaccines. These vaccines induce high serum levels of anti-spike protein antibodies (*European Medicines Agency*).

Studies on oocytes, follicular fluid and cumulus cells suggest that neither the virus nor its vaccine affects the human ovary (*Barragan et al., 2021*; *Bentov et al., 2021*; *Demirel et al., 2021*). In addition, neither the anti-Müllerian hormone serum levels nor the course of ovarian stimulation seem to be affected (*Mohr-Sasson et al., 2021*). The same is true for human embryos, which do not seem to be infected at least during pre-implantation stages (*Colaco et al., 2021*; *Rajput et al., 2021*).

The endometrium seems to have low susceptibility to SARS-CoV-2 infection based on low ACE2 and transmembrane protease serine subtype 2 expression, despite an increased expression of ACE2 during the window of implantation (*Henarejos-Castillo et al., 2020*; *Haouzi et al., 2021*; *Vilella et al., 2021*). To date, no viral RNA was detected in human endometrium (*Chandi and Jain, 2021*; *de Miguel-Gómez et al., 2021*). Interestingly, women who recovered from SARS-CoV-2 infection were found to be more likely to have decreased menstrual volume and longer cycles in the short term (*Li et al., 2021*).

The outcomes of assisted reproduction were found to be similar during the first wave of the pandemic in March 2020 compared with previous cycles (*Aharon et al., 2021b*). Similarly, patients seropositive to SARS- CoV-2 antibodies (immunoglobulin G and immunoglobulin M) where found to have similar reproductive outcomes after IVF, despite a slightly smaller blastocyst formation rate, including similar numbers of mature oocytes and high-quality embryos, as well as biochemical pregnancy, clinical pregnancy, early miscarriage and implantation rates (*Wang et al., 2021*).

The effect of any of COVID-19 vaccines on the reproductive system and outcomes of assisted reproduction is far from known. No research has been conducted on the effect of the vaccine on the endometrium. In addition, structural similarities between the spike protein of SARS-CoV-2 and human syncytin-I protein, which are involved in the formation of the placenta, have been described (*Chen et al., 2021*). If so, there could be a cross-reaction between the antibodies of the vaccine and this protein, which could lead to implantation failure or miscarriage. Nevertheless, this cross-reaction has not yet been proven (*Chen et al., 2021*). Similarly, data on vaccination before or during pregnancy seems reassuring. Preconception or prenatal vaccination with mRNA vaccines revealed no effect on spontaneous miscarriage rates (*Zauche et al., 2021*). In addition, current evidence suggests that the administration of mRNA vaccines before an IVF cycle has no effect on embryo quality and sustained implantation rate (SIR), including women with or without detectable anti-spike antibodies; however, the evidence is still limited to a few small studies (*Aharon et al., 2021a*; *Morris, 2021a*; *2021b*).

The aim of the present study was to evaluate the effect of prior vaccination against COVID-19 with mRNA vaccines on embryo implantation, including the effect of the number of doses and the time interval from vaccination to embryo transfer on endometrial receptivity. By including transfers of single, frozen euploid embryos only, it is possible to evaluate the effect of vaccination on endometrial receptivity reliably. Also, the inclusion of only euploid embryos is of upmost importance in evaluating sustained implantation rates because the main cause of early pregnancy loss is excluded.

MATERIALS AND METHODS

Study design

In this retrospective cohort study, reproductive outcomes after embryo transfer were compared between women with and without previous administration of mRNA COVID-19 vaccines. The study protocol was approved by the local Institutional Review Board on 14 December 2021 under the code 2105-VLC-064-JR, complying with all ethical and legal requirements.

Two cohorts were compared: one historical cohort of embryo transfers during the year preceding the onset of the pandemic, and another comprising data from women having received one or two doses of mRNA vaccines BNT162b2 or mRNA-1273 indistinctively.

Data were anonymously retrieved from electronic medical records among all IVIRMA Clinics in Spain. Variables retrieved included female age and body mass index (BMI), oocyte age, source of spermatozoa (own ejaculate, own from testicle biopsy or donor), endometrial preparation protocol (natural, stimulated or artificially prepared), endometrial thickness and oestradiol serum levels in late proliferative phase, day of embryo transfer, embryo classification (according to The Association for Reproductive Biology Research (Asociación para el Estudio de la Biología de la Reproducción classification [ASEBIR]) (*Meseguer et al., 2011*; *Cuevas Saiz et al., 2018*), the use of vitrified oocytes, number of vaccine doses, time from last administration of vaccine to embryo transfer, presence of intrauterine gestational sac on ultrasound and presence of embryo heartbeat at the eighth week of gestation.

Study population

Eligible patients were women aged 50 years or younger undergoing an embryo

transfer after intracytoplasmic sperm injection and preimplantation genetic testing for aneuploidy. Only transfers of a single euploid frozen blastocyst using own oocytes were included. Ovarian stimulation, oocyte retrieval, intracytoplasmic sperm injection, embryo culture, embryo biopsy, genetic study and embryo vitrification and warming were carried out according to standard protocols, as previously described (*Bellver et al., 2021*; *Cozzolino et al., 2021*).

Fresh embryo transfers after ovarian stimulation, cryopreserved embryo transfers in natural cycles and cryopreserved embryo transfers after artificial endometrial preparation according to the protocol described by *Labarta et al. (2017)* were included. After embryo transfer, patients were routinely prescribed vaginal progesterone twice a day (200 mg until 8 weeks of gestation for natural and stimulated cycles and 400 mg until 12 weeks of gestation for artificially prepared cycles).

Serum beta-HCG levels were measured 11 days after embryo transfer to confirm pregnancy, and ultrasound scans were carried out around the sixth and eighth week of gestation.

End points

The main outcomes were clinical pregnancy (presence of at least one intrauterine gestational sac on ultrasound) and sustained implantation rate (number of embryos with heartbeat per number of embryos transferred).

Statistical analysis

All variables relating to patient and cycle characteristics assessed in the descriptive analysis, as well as reproductive outcomes, were expressed with means and their 95% confidence intervals for continuous variables and compared using paired Student's t-test. Proportions and their 95% confidence interval together with the odds ratios and their 95% confidence interval were calculated for categorical variables.

Chi-squared test was used for univariate comparisons, as the main outcomes were categorical variables. Multivariate logistic regression was used to adjust for potential confounding variables, including female age and BMI, oocyte age, source of spermatozoa (own ejaculate, own spermatozoa from testicle biopsy or donor), the use of vitrified oocytes, day of embryo transfer, embryo classification, endometrial preparation protocol, endometrial thickness and oestradiol levels. Both crude odds ratio and adjusted for the same potential confounders were calculated, the latter with generalized estimating equation (GEE) analysis to control repeated measures and non-independent data (patients repeating cycles and different centres involved).

The time from last administration of vaccine and embryo transfer was recoded in quartiles (Q): defined as Q1 (if less than 1.8 months), Q2 if 1.8 to 3.1 months, Q3 if 3.2 to 4.5 months and Q4 if 4.5 months or more. The analysis was carried out using the Q1 as reference.

Missing data were excluded. A significance level of 0.05 was used. Statistical package SPSS 25.0 (IBM Corp., Armonk, New York) was used for all statistical analyses.

RESULTS

A total of 4162 embryo transfers were included: 3272 for the control non-vaccinated group and 890 from women already vaccinated with at least one dose at the time of embryo transfer.

Mean age of our study sample was 38.3 years (95% CI 38.2 to 38.4); mean BMI was 23.2 kg/m^2 (95% CI 23.1 to 23.4); and mean age at oocyte retrieval was 37.6 years (95% CI 37.5 to 37.7). The endometrium was prepared with stimulated cycles in 0.9%, natural cycles in 20.6% and hormonal replacement therapy in 78.5%. The mean oestradiol level (last measurement during proliferative phase) was 226.7 pg/ml (95% CI 226.6 to 226.8) and endometrial thickness was 8.4 mm (95% CI 8.34 to 8.46). Baseline characteristics stratified according to the two groups are presented in TABLE 1.

Donor spermatozoa was used in 12.8% of treatments and surgically retrieved testicular spermatozoa in 2.5% of treatments. Fresh oocytes were used in 80%, mixed in 16.4% and vitrified in 3.6% of the cases. Embryos were transferred on day 5 of development in 71.3% of the cases and day 6 in 28.6% of cases; 12.2% were classified as A, 63.2% as B and 24.0% as C. These baseline characteristics stratified according to the two groups are presented in TABLE 2.

A comparison of the main outcomes between groups is shown in FIGURE 1. The crude odds ratio between the vaccinated and non-vaccinated group for clinical pregnancy was 0.994 (95% CI 0.849 to 1.163); for sustained implantation rate,

TABLE 1 BASELINE PATIENT AND CYCLE CHARACTERISTICS

Characteristics	Non-vaccinated (*n* = 3272 embryo transfers)	Vaccinated (*n* = 890 embryo transfers)	*P*-value
Female age, mean (95% CI)	38.2 (38.1 to 38.3)	38.7 (38.5 to 38.9)	<0.001
Female BMI, mean (95% CI)	23.2 (23.1 to 23.3)	23.4 (23.1 to 23.7)	0.16
Female age at the time of oocyte retrieval, mean (95% CI)	37.5 (37.4 to 37.6)	38.0 (37.7 to 38.2)	<0.001
Type of cycle, %			
Stimulated	0.9	0.6	<0.001
Natural	19.3	27.3	
Artificial	79.8	72.3	
Endometrial preparation			
Serum oestradiol level,[a] pmol/ml, mean (95% CI)	227 (218 to 237)	222 (203 to 242)	>0.99
Endometrial thickness,[a] mm, mean (95% CI)	8.4 (8.2 to 8.5)	8.4 (8.2 to 8.5)	>0.99

[a] Last measurement during the proliferative phase.

TABLE 2 BASELINE GAMETE AND EMBRYO CHARACTERISTICS

Characteristics	Non-vaccinated (*n* = 3272 embryo transfers)	Vaccinated (*n* = 890 embryo transfers)	*P*-value
Source of own spermatozoa, %			
Own ejaculate	97.4	98	0.52
Own from testicle biopsy	2.6	2	
Donated semen, %	12	16.9	<0.001
Status of oocytes, %			
Fresh	80	80.3	0.97
Vitrified	3.6	3.6	
Both	16.4	16.1	
Day of embryo transfer, %			
5	70.6	74.4	<0.001
6	29.3	25.4	
7	0.1	0.2	
Embryo classification: inner cell mass (ASEBIR), %			
a	17.4	23.7	<0.001
b	73.4	67.3	
c	9.2	9.0	
Embryo classification: trophectoderm (ASEBIR), %			
a	14.9	16.4	0.08
b	63.4	63.9	
c	21.7	19.7	
Embryo classification: overall classification (ASEBIR), %			
A	12.9	11.7	0.34
B	63.0	64.0	
C	24.1	24.3	

ASEBIR, Asociación para el Estudio de la Biología de la Reproducción classification (The Association for Reproductive Biology Research).

the crude odds ratio was 0.929 (95% CI 0.777 to 1.110).

Analysis of the number of vaccines received by the time of embryo transfer showed that patients that received only one dose showed a clinical pregnancy rate (CPR) of 65.2% (95% CI 59.0 to 71.5) and those receiving two doses 72.5% (95% CI 69.0 to 76.0, *P* = 0.034), with a crude odds ratio between one and two doses for CPR of 1.408 (95% CI 1.031 to 1.923) and for sustained implantation rate (SIR) 1.380 (95% CI 0.965 to 1.972).

Q1 was used as reference in determining the time from last administration of the vaccine to embryo transfer. Crude odds ratios for CPR were as follow: Q1–Q2 was 1.125 (95% CI 0.748 to 1.692), Q1–Q3 was 1.009 (95% CI 0.672–1.517) and Q1–Q4 was 0.683 (95% CI 0.454 to 1.027). Similarly, the same odds ratio for SIR between Q1–Q2 was 1.073 (95% CI 0.680 to 1.693), Q1–Q3 was 0.869 (95% CI 0.545 to 1.385) and Q1–Q4 0.512 (95% CI 0.321 to 0.818). The odds ratio adjusted for confounders and accounting for repeated measurements per patient by GEE for CPR and SIR, are shown in FIGURE 2 and FIGURE 3, respectively.

DISCUSSION

Scientific evidence and further guidelines on vaccinating against COVID-19 in a preconception context, including assisted

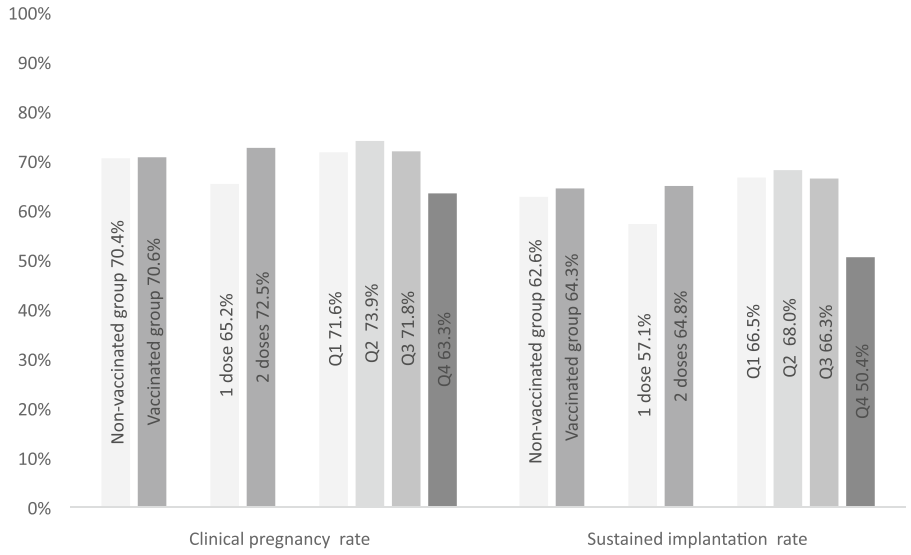
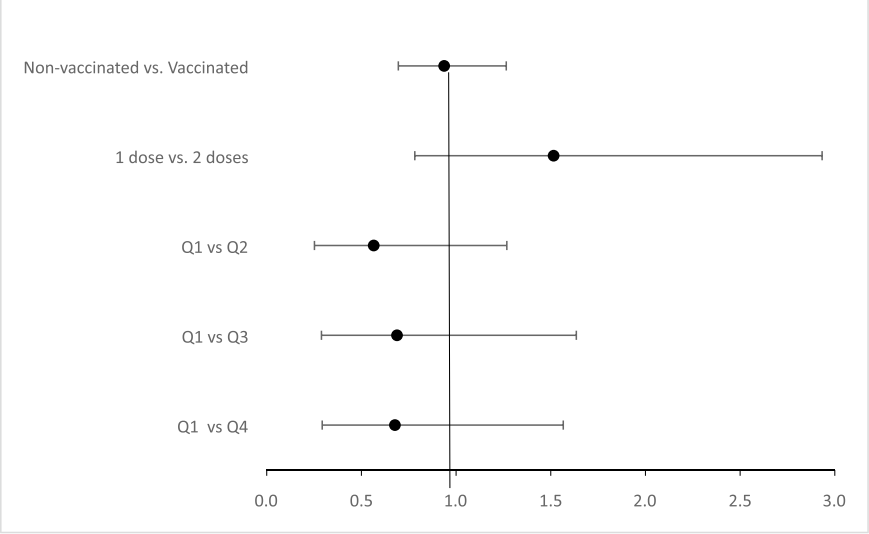


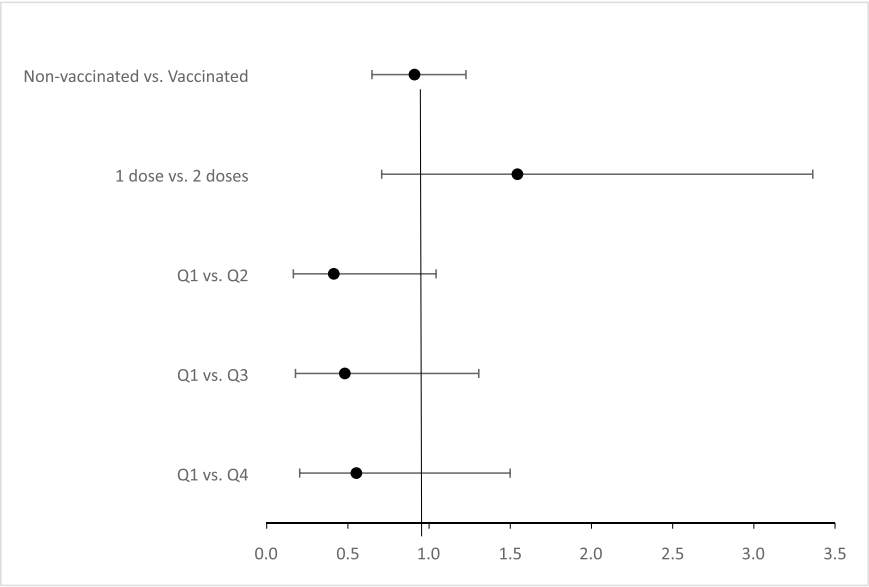
FIGURE 1 Comparison of the main outcomes between the groups. Quartiles (Q) refer to time from last administration of vaccine to embryo transfer: Q1 = less than 1.8 months, Q2 = 1.8 to 3.1 months, Q3 = 3.2 to 4.5 months and Q4 = 4.5 months or more. No statistically significant differences were found.



Non-vaccinated group §	Vaccinated group	1 dose§	2 doses	Q1§-Q2	Q1§-Q3	Q1§-Q4
0.937 (0.695-1.265)		1.515 (0.782-2.933)		0.565 (0.252-1.268)	0.688 (0.289-1.635)	0.677 (0.293-1.566)

§ - reference

FIGURE 2 Adjusted odds ratio (95% confidence interval) for clinical pregnancy rates (adjusted for type of cycle, oocyte [vitrified or fresh], origin of spermatozoa, sperm retrieval type, day of transfer, patient's age, oocyte's age, embryo quality, endometrial thickness, oestradiol and progesterone blood levels) and accounting for repeated measurements per patient by generalized estimating equation; §, reference group.



Non-vaccinated group§	Vaccinated	1 dose§	2 doses	Q1-Q2§	Q1-Q3§	Q1-Q4§
0.910 (0.648-1.227)		1.544 (0.708-3.363)		0.413 (0.164-1.043)	0.481 (0.177-1.306)	0.552 (0.203 -1.499)

§ - reference

FIGURE 3 Adjusted odds ratio (95% confidence interval) for sustained implantation rates (adjusted for type of cycle, oocyte [vitrified or fresh], origin of spermatozoa, sperm retrieval type, day of transfer, patient's age, oocyte's age, embryo quality, endometrial thickness, oestradiol and progesterone blood levels) and accounting for repeated measurements per patient by generalized estimating equation; §, reference group.

reproduction, are urgently needed. Given that insufficient time has passed since the onset of vaccination to have live birth rates, we used clinical pregnancy and sustained implantation rates as outcomes, which are considered the best predictors of live birth and are less affected by factors external to assisted reproduction (*Arce et al., 2005*).

Our results point to similar CPR and SIR between non-vaccinated and vaccinated women, and no worse outcomes with more doses or shorter time gap between administration and embryo transfer.

A comparison of vaccinated and non-vaccinated women showed that both differences of proportions and odds ratio were not statistically significant for CPR or SIR. The odds ratio was also not significant when adjusted for potential confounders and remained statistically comparable when accounting for repeated measurements per patient by means of GEE. In addition, the number of doses did not influence the outcomes, after adjusting for confounders. We did not include women who had been given a booster dose, as only a few had been given at the time of the study.

Some investigators have postulated that the anti-spike protein antibodies could have a cross reaction to placental proteins and may be a cause of implantation failure or pregnancy loss (*Chen et al., 2021*). In addition, the serum levels of these antibodies are known to progressively decrease with time (*Doria-Rose et al., 2021*). Therefore, we took into account the time interval between the last administration of the vaccine and embryo transfer, divided in quartiles. All quartiles had similar CPR and SIR compared with Q1. Therefore, different time intervals between vaccination and embryo transfer, and therefore potentially different antibody levels, do not affect clinical outcomes.

In the present study, we included only single euploid frozen blastocyst, euploid embryos and excluded oocyte donation to avoid potential bias resulting from embryo quality or quantity, hence discerning purely endometrial factors of sustained implantation.

In view of the results of this study, the mRNA vaccines for COVID-19 seem to have no effect on either CPR or SIR. This is not dependent on the number of doses. Also, the time interval between vaccination and embryo transfer had no effect on outcomes. These findings further exclude a potential deleterious effect of the vaccine on the endometrium and embryo implantation.

The results of the few studies published to date on the effect of vaccines for COVID-19 on human embryo implantation are reassuring (*Aharon et al., 2021a*; *Morris, 2021a*; *2021b*). Current research points to similar reproductive outcomes regardless of the administration of a vaccine against COVID-19 (*Aharon et al., 2022*; *Huang et al., 2022*; *Jacobs et al., 2022*). To the best of our knowledge, this is the first study that includes thousands of embryo transfers to address the number of doses and the time between vaccination and embryo transfer.

Although this retrospective study is controlled statistically, possible biases owing to the nature of the work remain possible, and a cause–effect link cannot be purely drawn from it. We were unable to obtain data on serum levels of anti-spike antibodies. Also, we cannot assert that patients in the vaccinated group had not been infected, previously or during the reproductive treatment, compared with the control group who underwent embryo transfers before the onset of the pandemic. In any case, the results of this study are in line with current evidence, but based on a much larger sample size, including only euploid embryos and statistically controlled for potential confounders.

Ideally, cohorts in the same period should be included. To guarantee that all patients were not vaccinated in the control group, however, we chose a pre-pandemic period. To avoid the potential bias of time, we chose a period just before the beginning of the pandemic. Given the short time lag, changes in procedures or protocols during this period were minimal. Similarly, in both time periods, the overall pregnancy rates of the institutions included were similar; therefore, this factor is expected to have no effect.

Another limitation of this study is that no information on previous recurrent implantation failure or miscarriage is available for either group. The probability of being vaccinated or not is expected to be independent of these medical parameters, especially if considering the large sample size.

Further prospective studies on the potential effect of COVID-19 vaccines on reproductive outcomes are needed. In addition, no data are available on other vaccines, except for mRNA vaccines, i.e. vector-based vaccines, and further research is warranted here. Nevertheless, data concerning the use of mRNA in a preconception and assisted reproduction context is reassuring (*Aharon et al., 2021a*; *Morris, 2021a*; *2021b*)

In conclusion, the administration of mRNA vaccines against COVID-19 seems to have no effect on embryo implantation. In addition, clinical pregnancy and sustained implantation rates were similar regardless of the number of doses and time interval from vaccination to embryo transfer.

Our results are reassuring for patients who are currently undergoing assisted reproductive treatment because of the potential negative effect of the vaccine on endometrial receptivity and reproductive outcomes. These data support the recommendation of preconception or prenatal vaccination against COVID-19 made by most reproductive medicine and obstetrics societies.

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