Journal Pre-proof

Oocyte donors and mRNA COVID-19 vaccination: Is there any impact on ovarian stimulation parameters or in IVF outcomes for recipients?

A. Bosch , S. Albero , J. Castillo , J. Ten , J. Guerrero , J.A. Ortiz , A. Bernabeu , R. Bernabeu

PII: S1472-6483(23)00001-9
DOI: https://doi.org/10.1016/j.rbmo.2023.01.002
Reference: RBMO 3152

To appear in: *Reproductive BioMedicine Online*

Received date: 19 October 2022
Revised date: 27 December 2022
Accepted date: 4 January 2023

Please cite this article as: A. Bosch , S. Albero , J. Castillo , J. Ten , J. Guerrero , J.A. Ortiz , A. Bernabeu , R. Bernabeu , Oocyte donors and mRNA COVID-19 vaccination: Is there any impact on ovarian stimulation parameters or in IVF outcomes for recipients?, *Reproductive BioMedicine Online* (2023), doi: https://doi.org/10.1016/j.rbmo.2023.01.002

Oocyte donors and mRNA COVID-19 vaccination: is there any impact on ovarian stimulation parameters or in IVF outcomes for recipients?

Bosch A[1*], Albero S[2,*], Castillo J[3], Ten J[3], Guerrero J[3], Ortiz JA[4], Bernabeu A[3], Bernabeu R[3]

[*]Shared co-first authorship

[1]Departament of Reproductive Medicine. Instituto Bernabeu. Cartagena. Spain

[2]Departament of Reproductive Medicine. ACCUNA. Alicante. Spain

[3]Departament of Reproductive Medicine. Instituto Bernabeu. Alicante. Spain

[4]IBBIOTECH. Alicante. Spain

Correspondence: Aranzazu Bosch

abosch@institutobernabeu.com

Av. Duque Severiano, 5-7, Cartagena. Spain.

ABSTRACT

Research Question: What is the effect of mRNA SARS-CoV-2 vaccination in young oocyte donors regarding ovarian response to stimulation, fertilization rate, embryo development and clinical outcomes in recipients?

Design: This retrospective, multicenter cohort study evaluated 115 oocyte donors having performed at least two controlled ovarian stimulation protocols (before and after complete SARS-CoV-2 vaccination) between November-2020/February-2022. We compared as primary outcomes days of stimulation, total dose of gonadotropins and laboratory performance in ovarian stimulation of oocyte donors before and after vaccination. A total of 136 cycles in matched recipients were analyzed as secondary outcomes and, from those, 110 received a fresh single embryo transfer being analyzed for biochemical -B-hCG levels- and clinical pregnancy rates with heartbeat.

Results: A longer stimulation was required in the post-vaccination group (10.31±1.5 vs 9.51±1.5 days, respectively; p<0.001) and a higher gonadotropin consumption (2453.4±740 vs 2235.5±615IU; p<0.001) with a similar starting dose of gonadotropins in both groups. A higher number of oocytes were retrieved in the post-vaccination group (16.6±7.1 vs 15.4±7.0; p=0.02). Nonetheless, the number of MII oocytes was similar between groups (post-vaccination 12.61±5.9 versus pre-vaccination 13.01±6.6; p=0.39) and the ratio of MII/retrieved oocytes was favorable to the pre-vaccination group (0.83±0.1 vs 0.77±0.2 post-vaccine; p=0.019).

In recipients, to a similar number of provided oocytes, the fertilization rate, the total number of obtained blastocysts, the number of top-quality blastocysts, the biochemical and clinical pregnancy rates with heartbeat were not significantly different between groups.

Conclusions: This study shows no adverse influence of mRNA SARS-CoV-2 vaccination on the ovarian response on young population.

KEYWORDS: coronavirus / COVID-19 / SARS-CoV-2 / mRNA vaccine / infertility / oocyte donation

INTRODUCTION

The severe acute respiratory syndrome Coronavirus 2 (SARS–CoV-2) infection urged scientists to develop safe and effective vaccines. During the ongoing COVID-19 pandemic, the scientific community promoted vaccination programs to reduce morbidity and mortality. A two-dose regimen of mRNA SARS-CoV-2 vaccine is shown to confer 95% protection against Covid-19 in persons 16 years of age or older (Polack *et al*. 2020). Nonetheless, in women of reproductive age, the rapid vaccine development raised mistrust and reluctance about future fertility outcomes and vaccine safety (Murewanhema 2021), particularly for the novel mRNA-based formulations. There is an important need to review the data to improve our understanding regarding the effects of COVID-19 and vaccines on the human reproductive system and pregnancy.

A recent publication suggests no measurable detrimental effect on the function of the ovarian follicle after mRNA SARS-CoV-2 vaccination (Bentov *et al.,* 2021). Moreover, anti-Müllerian hormone (AMH) levels does not seem to be affected following mRNA SARS-CoV-2 vaccination (Mohr-Sasson *et al*., 2021). However, the impact of COVID-19 vaccination in the IVF laboratory outcomes warrants further investigation. The available medical evidence seems encouraging. Orvieto *et al*., 2021 showed no detrimental effects in patients undergoing IVF regarding stimulation characteristics, oocyte yield, fertilization, or top-quality embryos rate, after receiving mRNA SARS-CoV-2 vaccine compared to their IVF cycles prior to vaccination. Furthermore, a recent retrospective cohort study including 200 vaccinated women and 200 age-matched unvaccinated women undergoing IVF showed that mRNA SARS-CoV-2 vaccine did not affect the mean number of oocytes retrieved and clinical pregnancy rates with heartbeat in vaccinated versus unvaccinated patients (Avraham *et al.,* 2022). Of note, the mean age of patients included in the aforementioned trials were > 36 years old, thus, there is a paucity of medical evidence about the impact of the COVID-19 messenger ribonucleic acid vaccine in younger population undergoing ovarian stimulation.

The aim of our observational study was to investigate, in ovarian stimulation cycles of oocyte donors before and after vaccination, the influence of mRNA SARS-CoV-2 vaccination on cycle characteristics and laboratory outcomes. Primary objective: number of cumulus-oocyte complexes (COCs) retrieved, mean number of metaphase II (MII) oocytes, mature/total

oocyte rate, length of stimulation (days) and dose of gonadotropins (IU). Secondary endpoints were fertilization rate, blastocyst formation rate, high-quality blastocysts rate, biochemical and clinical pregnancy rate with heartbeat in matched recipients.

MATERIALS AND METHODS

This study was approved by the Ethics Institutional Committee of Instituto Bernabeu in October 2021 (reference MR38).

Trial design

This retrospective multicenter cohort study enrolled oocyte donor participants who completed two doses of mRNA vaccine at least 7 days before starting the ovarian stimulation cycle (post-vaccination group). The study group was matched by prior stimulations in the same oocyte donor (pre-vaccination group). The ovarian stimulations prior to vaccination were performed employing the same type of stimulation protocol as those used after the vaccination schedule as within a period of one year. Donors were included only once in the data analysis.

Participants

We conducted the trial between November 2021 and February 2022, at Accuna Medical Center and Instituto Bernabeu Medical Center (Alicante, Spain). Eligible oocyte donors were included according to the Spanish Fertility Legislation, in brief, age 18 - 33, have a negative family history for genetically transmitted diseases, have a normal karyotype, negative screening for genetic diseases, negative study for diseases of sexual transmission (HIV, Hepatitis B and C, Syphilis), normality of the reproductive system, physical and mental health, previous fertility history and/or adequate response to treatment ovarian stimulation and an adequate body mass index (BMI).

Ovarian stimulation in oocyte donors

At least 7 days after of receiving the last dose of mRNA SARS-CoV-2 vaccine, donors started stimulation in a random protocol during the follicular phase with an initial dose of 100-300 UI/day of FSHr (Bemfola®, Gedeon Richter, Madrid, Spain) according to antral follicular count

(AFC) and BMI. We considered AFC includes follicles with a mean diameter ranging from 2 to 10 mm performed using a transvaginal ultrasound probe with frequency ≥ 7 MHz. In addition, the donors received a dose of 200mg of natural micronized progesterone/night (Utrogestan®, SEID S.A., Barcelona; Spain) oral route from the first day of stimulation until the day before trigger for prevention of premature LH-peak (Castillo *et al.* 2019). Donors were monitored from day 5-6 of stimulation by transvaginal ultrasounds scans every 2-3 days. A GnRH agonist (triptorelin [Decapeptyl®, Ipsen Pharma, Spain], 0.2 mg) bolus was used to induce final oocyte maturation when at least 3 follicles were ≥18 mm in diameter. Oocyte aspiration was performed 36 hours later by transvaginal ultrasound-guided needle-aspiration.

IVF laboratory and clinical outcomes

Our oocyte donation program guarantees a minimum of eight metaphase II oocytes to be provided for recipients, hence, the COCs were decumulated and all eggs were fertilized by intracytoplasmic sperm injection (ICSI). The oocyte donor cycles without recipients in both stimulations, pre and post vaccination, were excluded from the IVF laboratory analysis. According to this, there are 68 recipients for the 115 pre vaccination donor stimulation and 68 recipients for the 115 post vaccination stimulation, in order to avoid statistical bias. Additionally, each recipient had contributed to the study with one cycle. In matched recipients, the fertilization and blastocyst formation rates were compared between groups (ASEBIR categories, 2015).

All embryo transfer procedures were performed at the blastocyst stage. Biochemical and clinical pregnancy rates with heartbeat were additionally compared between recipients´ groups receiving only a fresh single embryo transfer.

Recipients and endometrial preparation

Recipients were infertile patients undergoing their first/second oocyte donation cycle. Eligible patients were aged <50 years, BMI < 30 kg/m2 and had no systemic diseases. We excluded cases with concomitant severe male factor (<1x106 spermatozoa/ml), uterine diseases (*e.g.* fibroids, polyps, Ashermans´s, previously diagnosed Müllerian abnormalities) or presence of hydrosalpinx. In patients with regular ovarian function a GnRH analogue

(Gonapeptyl 3,75, Ipsen-Pharma, Barcelona, Spain) was administered in the midluteal phase of the immediate previous cycle for pituitary desensitization; this step was omitted in patients with inactive ovaries. Subsequently, for endometrial preparation they were subjected to standard substitutive hormonal therapy with transdermal estrogen (Evopad 50, Janssen-Pharmaceutica, Belgium) or oral estradiol valerate (Progynova, Delpharm, Lille, France) at increasing doses for at least 12 days. Endometrial thickness ≥7 mm and trilaminar appearance at ultrasound were confirmed prior to embryo transfer. Micronized progesterone supplementation started with intravaginal capsules 400 mg/12 h (Cyclogest®, Gedeon Richter Ibérica, S.A., Barcelona, Spain). In pregnant patients, the hormonal treatment was sustained for 12 weeks.

Vaccination status in recipients

Most of the cycles included foreign patients, thus, inconsistent, and heterogeneous information was recorded about the vaccination status in recipients and male partners mainly due to variations in the vaccination programs among different countries. Supplementary Table S1.

Outcomes

Primary outcomes were number of COCs retrieved, mean number of MII oocytes, oocyte maturity ratio (calculated as the ratio of MII oocytes to total oocytes retrieved) length of stimulation (days) and dose of gonadotropins (IU). Secondary endpoints included fertilization rate, blastocyst formation rate, high-quality blastocysts rate. Other outcomes included biochemical pregnancy (serum levels of β-hCG > 5 IU/ml 10 days after ET) and clinical pregnancy rate with heartbeat (diagnosed by ultrasonographic visualization of a gestational sac) in matched recipients (Zegers-Hochschild *et al.,* 2017).

Statistical Analysis

Statistical analysis was performed with R Statistical Software, version 4.1.2 and the Software Statistical Product and Service Solutions, version 20.0 (SPSS, Chicago, IL, EE.UU.). For categorical variables, descriptive analysis was done using the frequency and percentage. Numerical variables were presented as number of cases, mean and 95% confidence interval. For evaluation of normal distributions, the Shapiro–Wilk's test was performed. Depending

on whether the variable has a normal distribution, the comparison between means was carried out using Paired Student's t test or Wilcoxon signed-rank test.

For the statistical analysis of qualitative variables, the McNemar test was used. Values of $p < 0.05$ will be considered statistically significant.

RESULTS

A total of 115 egg donation cycles with ovarian stimulation before vaccination and 115 after complete vaccination were included in the analysis (Figure I). Overall, the mean age of the oocyte donors was 24.32 (95%CI: 21,25), BMI was 23.19 (95%CI: 23,24) and AFC was 17.93 (95%CI: 17,19).

Baseline characteristics between groups are presented in Table I. Mean age was similar [pre-vaccination group 25.82 (95%CI: 25,27) vs post-vaccination 26.35 (95%CI: 26,27), p=0.3]. BMI was identical between groups [pre-vaccination group 23.19 (95%CI: 23,24) vs post-vaccination 23.19 (95%CI:23,24). However, baseline AFC differed significantly between groups [pre-vaccination group 15.85 (95%CI: 15.17) vs post-vaccination 20.02 (95%CI: 18.22), p<0.001] (Figure 2). There were not statistically significant differences in the starting day of ovarian stimulation between groups; mean starting day of stimulation pre-vaccination group 6.54±2.58 (95%CI: 2,12) vs post-vaccination 6.87±2.21 (95%CI: 1,12), p=0.18. The starting dose of gonadotropins was similar between both groups [post-vaccination 244.35±55.61 (95%CI: 100,300) versus pre-vaccination 240.87±53.02 (95%CI: 100,300); mean difference 3.48±29.60 (95%CI: -100,300), p=0.254]. In addition, we changed the starting dose in 24 of 115 egg donors post-vaccination group (20,9%) that's means the starting dose was increased in 15 egg donors (13.0%); the mean increased starting dose was 60.00 IU (95%CI: 42.8,77.20) and the starting dose was decreased in 9 egg donors (7,8%); the mean decreased starting dose was 55.56 IU (95%CI: 34.55,76.56).

Primary outcomes measure

With regards to oocye yield, a higher number of oocytes were retrieved in the post-vaccination versus the pre-vaccination group [16.6±7.1 (95%CI: 15,18) vs 15.4±7.0 (95%CI: 14,17), respectively; mean difference -1.24±6.0 (95%CI: -2.34,-0.14), p=0.02]. Nonetheless,

the number of MII oocytes was similar between groups [post-vaccination 12.61±5.9 (95%CI: 12,14) versus pre-vaccination 13.01±6.6 (95%CI: 12,14); mean difference -0.40±4.9 (95%CI: -1.32,0.52), p=0.39]. Finally, the ratio of MII/retrieved oocytes was favorable to the pre-vaccination group [0.83±0.1 (95%CI: 0.80,0.85) pre-vaccine vs 0.77±0.2 (95%CI: 0.74,0.80) post-vaccine; mean difference 0.05±0.2 (95%CI: 0.02,0.09), p=0.019].

Secondary outcomes

Cycle parameters in oocyte donors

A longer stimulation was required in the post vs pre-vaccination group [9.51±1.5 (95%CI: 9.2,9.8) vs 10.31±1.5 (95%CI: 10,11) days, respectively; mean difference -0.804±1.74 (95%CI: -1.13,-0.48), p<0.001] together with a concomitant higher gonadotropin consumption [2235.5±615 (95%CI: 2122,2349) vs 2453.4±740 (95%CI: 2317,2590) IU, respectively; mean difference -218±472 (95%CI: -305.2,-130.6), p<0.001]. Table II.

Laboratory outcomes

A total of 136 cycles receiving donated oocytes were included in this analysis, comparing 68 cycles pre-vaccination vs 68 post vaccination. To a similar number of provided oocytes [9.46 (95%CI: 9.1,9.9) vs 9.38 (95%CI: 9.0, 9.8), pre- vs post-vaccination, respectively; p=0.79], the fertilization rate was similar between groups [82.69% (95%CI: 79.23,86.15) vs 78.84% (95%CI: 75.21,82.47), pre- vs post-vaccination, respectively; p=0.17]. Additionally, the total number of obtained blastocysts was similar between groups [4.51 (95%CI: 4.0,5.0) vs 4.34 (95%CI: 3.8,4.8), pre- vs post-vaccination, respectively; p=0.58] with day 5/6 Grade A [2.29 (95%CI: 1.9,2.7) vs 2.32 (95%CI: 2.0,2.7), pre- vs post-vaccination, respectively, p=0.90] and Grade B (2.19 (95%CI: 1.8,2.6) vs 1.90 (95%CI: 1.6,2.2), pre- vs post-vaccination, respectively, p=0.30]. Table III.

Outcomes in recipients

Overall, recipients were women under 50 years [range age 29-48;] with mean BMI of 23.38. Baseline characteristics were similar between groups regarding age [pre-vaccination oocytes group 42.51 (95%CI: 42,43) vs post-vaccination 41.69 (95%CI: 41,43), p=0.252]. The mean BMI was also similar was [pre-vaccination oocytes group 23.55 (95%CI: 23,25) vs post-vaccination 23.22 (95%CI: 22,24), p=0.758]. Table IV.

Table V shows the clinical outcomes in a total of 110 recipients who underwent a fresh single blastocyst stage embryo transfer. From those, 55 cycles transferred from the pre-vaccination group and 55 from the post-vaccination group. The biochemical [73% (95%CI: 59%,83%) vs 58% (95%CI: 44%,91%), pre- vs post-vaccination, respectively; p=0.136] and clinical pregnancy rates with heartbeat [56% (95%CI: 42%,69%) vs 45% (95%CI: 32%,59%) respectively, p=0.361] were not significantly different between groups.

DISCUSSION

In the present retrospective cohort study exploring the cycle outcomes in young oocyte donors who underwent ovarian stimulation before and after receiving the COVID-19 mRNA vaccine we confirm the findings of previous studies in own eggs cycles showing similar outcomes in terms of fertilization rates in women who underwent ovarian stimulation after vaccination in comparison with controls (Bentov *et al.* 2021; Avraham *et al.* 2022) or their prior treatment (Orvieto *et al.* 2021). Nonetheless, these earlier studies included small number of patients (Bentov *et al.* 2021) or were focussed on women >35 years old (Orvieto *et al.* 2021; Avraham *et al.* 2022). To the best of our knowledge, our study is the first in contributing with additional (reassuring) information with regards to younger vaccinated population undergoing ovarian stimulation and shows that mRNA vaccine had no detrimental effect on in vitro fertilization outcomes.

Our results observed that the fertilization, embryo development and pregnancy rates obtained in matched oocyte recipients were not jeopardized. Our findings positively contribute to the growing body of evidence regarding the safety of the mRNA SARS-CoV-2 vaccines and, in concordance with previous, does not sustain the theoretical concerns that the vaccine may induce an immune response that would affect the fertilization process (Kloc *et al.* 2021).

Interestingly, a longer stimulation (together with a concomitant higher total dose of gonadotrophins requirement) and, of note, a higher total number of oocytes were collected in cycles after receiving the COVID-19 mRNA vaccine, nonetheless, the final number of MII oocytes remained similar. The medical evidence is limited on the topic, but a previous study with a similar methodology in own eggs ovarian stimulation for IVF showed no influence of mRNA SARS-CoV-2 vaccine on patients' performance in terms of length of ovarian

stimulation, total gonadotrophin dose and total number of oocytes collected (Orvieto *et al.* 2021). Thus, these additional findings should be interpretated with caution (particularly the higher number of collected eggs after vaccination) since they could be to the individual subjects intercycle variability of the ovarian response between repeated cycles even after using the same protocol (Rombauts *et al.* 2015). To the best of our knowledge, there is no biological plausibility explaining a better performance in terms of oocyte pool / ovarian response associated to mRNA SARS-CoV-2 vaccines. Nonetheless, a recent large international cohort study found a small (and likely to be temporary) change in menstrual cycle length after covid-19 vaccination, which suggest an impact on the ovarian/uterine axis function and underscores the importance of collecting menstrual cycle data during the development of future vaccines (Edelman *et al.*, 2022). Future larger controlled trials should address this effect and other (potential) long-term effects on ovarian function as the countries continue making forward with the vaccination campaign.

The two-centre setting could also be considered as a study strength, since it allows for the generalizability of the results. As in any cohort study, data were prospectively registered.

Following oocyte assignation to matched recipients, the total number of fertilized oocytes and fertilization rate after ICSI was similar among pre-vaccination and post-vaccination cycles. Moreover, the number of top-quality embryos was optimal and not significantly different between groups. Finally, in a subset of recipients receiving a single fresh embryo transfer, we found similar biochemical and clinical pregnancy rates with heartbeat. These encouraging results reflect no detrimental effects of the vaccine on embryo development or implantation performance, with a comparable reproductive outcome in recipients and further supports the results of previous studies showing normal pregnancy rates in vaccinated women undergoing IVF cycles (Orvieto *et al.* 2021; Avraham *et al.* 2022; Aizer *et al.* 2022).

In terms of the ovarian stimulation cycle performance, our study is limited by the small sample size and those inherent to its retrospective observational nature, in which the influence of residual confounder cannot be completely excluded. On the contrary, this is the first study to examine the effect of SARS-Cov-2 vaccination on the ovarian response on

young population with the major strength of exploring IVF cycles (before and following vaccination) in the same cohort of patients which helps to mitigate multiple confounding factors or biases and to attribute the study results to the (absence of) effects of the vaccination. Our findings in the oocyte donor population might be well extrapolated to young couples with infertility due to severe male factor or tubal factor cases or ladies undergoing fertility preservation for social reasons. Nonetheless, generalizability to the general infertile population, should be made with caution.

For pregnancy outcomes in recipients, the findings should be interpretated with caution, because, again, only a limited number of transfer cycles were included in a retrospective data analysis; an additional drawback is the limited information about vaccination or past infection status of recipients and the male partners. However, in view of the efficacious vaccination campaign, it is reasonable to assume a balanced proportion of vaccinated recipients and male partners between groups, thus only strengthening our conclusion that the vaccine had no detrimental effect on fertility (Avraham *et al.* 2022, Aizer *et al.* 2022).

Our study design does not permit us to verify vaccine status or dates but this information is readily available for most individuals. Finally, although we implemented a rigorous study design and analytical method, the possibility of residual confounding and bias exists.

Conclusion

In conclusion, the present study found no detrimental influence of mRNA SARS-CoV-2 vaccines on donor oocyte cycles, reflecting no adverse effects on the assisted reproduction outcomes. The safety of SARS-CoV-2 vaccination concerning IVF cycles is encouraging for the medical community and the health of our patients.

ACKNOWLEDGEMENT

The authors would like to thank the staff at Accuna and Instituto Bernabeu in Alicante, Spain who kindly used their time to make this study possible.

Authors' roles

B. A., A. S., and J. C.: collection of data, study conception and design, analysis and interpretation of data, writing the article and critical review of the article. J. T., J. G., and J. O.: analysis and interpretation of data and critical review of the article. A. B., and R.B.: critical review of the article.

The authors agree in considering B. A. and A. S. as co-first authors of the publication.

DATA AVAILABILITY

The data underlying this article will be shared on reasonable request to the corresponding author.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

REFERENCES

Aizer A, Noach-Hirsh M, Dratviman-Storobinsky O, Nahum R, Machtinger R, Yung Y, Haas J, Orvieto R. The effect of coronavirus disease 2019 immunity on frozen-thawed embryo transfer cycles outcome. Fertil Steril. 2022 May;117(5):974-979. doi: 10.1016/j.fertnstert.2022.01.009. Epub 2022 Jan 10. PMID: 35216833; PMCID: PMC8743570.

ASEBIR. Cuadernos de embriología clínica III. Criterios de valoración morfológica de oocitos, embriones tempranos y blastocistos humanos. 3rd edition. Madrid. Gobalo; 2015.

Avraham S, Kedem A, Zur H, Youngster M, Yaakov O, Yerushalmi GM, Gat I, Gidoni Y, Hochberg A, Baum M, Hourvitz A, Maman E. Coronavirus disease 2019 vaccination and infertility treatment outcomes. Fertil Steril. 2022 Jun;117(6):1291-1299. doi: 10.1016/j.fertnstert.2022.02.025. PMID: 35437147; PMCID: PMC8872833.

Bentov Y, Beharier O, Moav-Zafrir A, Kabessa M, Godin M, Greenfield CS, Ketzinel-Gilad M, Ash Broder E, Holzer HEG, Wolf D, Oiknine-Djian E, Barghouti I, Goldman-Wohl D, Yagel S, Walfisch A, Hersko Klement A. Ovarian follicular function is not altered by SARS-CoV-2 infection or BNT162b2 mRNA COVID-19 vaccination. Hum Reprod. 2021 Aug 18;36(9):2506-2513. doi: 10.1093/humrep/deab182. PMID: 34364311; PMCID: PMC8385874.

Castillo JC, Guerrero J, Delgado R, Moliner B, Luque L, Ten J, Fuentes A, Bernabeu A, Llácer J, Bernabeu R. O-124 Natural micronized progesterone versus a GnRH antagonist in egg-donation cycles. An extended experience. Session 38 – ART—Ovarian stimulation, Human Reproduction, Volume 21, Issue suppl_1, 1 June 2006, Pages i54–i56, https://doi.org/10.1093/oxfordjournals.humrep.a002546

Castillo JC, Guerrero J, Delgado R, Moliner B, Luque L, Ten J, Fuentes A, Herencia A, Bodri D, Cirillo P, Bernabeu A, Llácer J, Bernabeu R. Initiation of ovarian stimulation independent of the menstrual cycle (random-start) in an egg donor program: a one-year single center experience. Abstracts of the 35th Annual Meeting of the European Society of Human Reproduction and Embryology, Human Reproduction, Volume 34, Issue Supplement_1, July 2019, Pages i450–i451.

Chen F, Zhu S, Dai Z, Hao L, Luan C, Guo Q, Meng C, Zhang Y. Effects of COVID-19 and mRNA vaccines on human fertility. Hum Reprod. 2021 Dec 27;37(1):5-13. doi: 10.1093/humrep/deab238. PMID: 34734259; PMCID: PMC8689912.

Durnaoglu S, Lee SK, Ahnn J. Syncytin, envelope protein of human endogenous retrovirus (HERV): no longer 'fossil' in human genome. Anim Cells Syst (Seoul). 2022 Jan 12;25(6):358-368. doi: 10.1080/19768354.2021.2019109. PMID: 35059135; PMCID: PMC8765258.

Edelman A, Boniface ER, Benhar E, Han L, Matteson KA, Favaro C, Pearson JT, Darney BG. Association Between Menstrual Cycle Length and Coronavirus Disease 2019 (COVID-19) Vaccination: A U.S. Cohort. Obstet Gynecol. 2022 Apr 1;139(4):481-489. doi: 10.1097/AOG.0000000000004695. Epub 2022 Jan 5. PMID: 34991109; PMCID: PMC8936155.

Gonzalez DC, Nassau DE, Khodamoradi K, Ibrahim E, Blachman-Braun R, Ory J, Ramasamy R. Sperm Parameters Before and After COVID-19 mRNA Vaccination. JAMA. 2021 Jul 20;326(3):273-274. doi: 10.1001/jama.2021.9976. PMID: 34137808; PMCID: PMC8293015.

Huang J, Xia L, Lin J, Liu B, Zhao Y, Xin C, Ai X, Cao W, Zhang X, Tian L, Wu Q. No Effect of Inactivated SARS-CoV-2 Vaccination on in vitro Fertilization Outcomes: A Propensity Score-Matched Study. J Inflamm Res. 2022 Feb 9;15:839-849. doi: 10.2147/JIR.S347729. PMID: 35177919; PMCID: PMC8843422.

Jacobs E, Summers K, Sparks A, Mejia R. Fresh Embryo Transfer Cycle Characteristics and Outcomes Following In Vitro Fertilization via Intracytoplasmic Sperm Injection Among Patients With and Without COVID-19 Vaccination. JAMA Netw Open. 2022 Apr 1;5(4):e228625. doi: 10.1001/jamanetworkopen.2022.8625. PMID: 35452110; PMCID: PMC9034396.

Jing Y, Run-Qian L, Hao-Ran W, Hao-Ran C, Ya-Bin L, Yang G, Fei C. Potential influence of COVID-19/ACE2 on the female reproductive system. Mol Hum Reprod. 2020 Jun 1;26(6):367-373. doi: 10.1093/molehr/gaaa030. PMID: 32365180; PMCID: PMC7239105.

Kloc M, Uosef A, Kubiak JZ, Ghobrial RM. Exaptation of Retroviral Syncytin for Development of Syncytialized Placenta, Its Limited Homology to the SARS-CoV-2 Spike Protein and Arguments against Disturbing Narrative in the Context of COVID-19 Vaccination. Biology

(Basel). 2021 Mar 19;10(3):238. doi: 10.3390/biology10030238. PMID: 33808658; PMCID: PMC8003504.

Mohr-Sasson A, Haas J, Abuhasira S, Sivan M, Doitch Amdurski H, Dadon T, Blumenfeld S, Derazne E, Hemi R, Orvieto R, Afek A, Rabinovici J. The effect of Covid-19 mRNA vaccine on serum anti-Müllerian hormone levels. Hum Reprod. 2022 Mar 1;37(3):534-541. doi: 10.1093/humrep/deab282. PMID: 34935913.

Murewanhema G. Vaccination hesitancy among women of reproductive age in resource-challenged settings: a cause for public health concern. Pan Afr Med J. 2021 Apr 7;38:336. doi: 10.11604/pamj.2021.38.336.28953. PMID: 34285758; PMCID: PMC8265245.

Nasab S, Abhari S. Coronavirus disease 2019 vaccine and in vitro fertilization outcomes: myths vs. facts. Fertil Steril. 2022 Jun;117(6):1300. doi: 10.1016/j.fertnstert.2022.04.005. Epub 2022 Apr 8. PMID: 35525817; PMCID: PMC8990686.

Odeh-Natour R, Shapira M, Estrada D, Freimann S, Tal Y, Atzmon Y, Bilgory A, Aslih N, Abu-Raya YS, Shalom-Paz E. Does mRNA SARS-CoV-2 vaccine in the follicular fluid impact follicle and oocyte performance in IVF treatments? Am J Reprod Immunol. 2022 May;87(5):e13530. doi: 10.1111/aji.13530. Epub 2022 Mar 14. PMID: 35220640; PMCID: PMC9111235.

Orvieto R, Noach-Hirsh M, Segev-Zahav A, Haas J, Nahum R, Aizer A. Does mRNA SARS-CoV-2 vaccine influence patients' performance during IVF-ET cycle? Reprod Biol Endocrinol. 2021 May 13;19(1):69. doi: 10.1186/s12958-021-00757-6. PMID: 33985514; PMCID: PMC8116639.

Orvieto R, Segev-Zahav A, Aizer A. Does COVID-19 infection influence patients' performance during IVF-ET cycle?: an observational study. Gynecol Endocrinol. 2021 Oct;37(10):895-897. doi: 10.1080/09513590.2021.1918080. Epub 2021 May 11. PMID: 33974475.

Parrella A, Irani M, Keating D, Chow S, Rosenwaks Z, Palermo GD. High proportion of immature oocytes in a cohort reduces fertilization, embryo development, pregnancy and live birth rates following ICSI. Reprod Biomed Online. 2019 Oct;39(4):580-587. doi: 10.1016/j.rbmo.2019.06.005. Epub 2019 Jun 18. PMID: 31455582.

Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, Bailey R, Swanson KA, Roychoudhury S, Koury K, Li P, Kalina WV,

Cooper D, Frenck RW Jr, Hammitt LL, Türeci Ö, Nell H, Schaefer A, Ünal S, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC; C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020 Dec 31;383(27):2603-2615. doi: 10.1056/NEJMoa2034577. Epub 2020 Dec 10. PMID: 33301246; PMCID: PMC7745181.

Rombauts L, Lambalk CB, Schultze-Mosgau A, van Kuijk J, Verweij P, Gates D, Gordon K, Griesinger G. Intercycle variability of the ovarian response in patients undergoing repeated stimulation with corifollitropin alfa in a gonadotropin-releasing hormone antagonist protocol. Fertil Steril. 2015 Oct;104(4):884-890.e2. doi: 10.1016/j.fertnstert.2015.06.027. Epub 2015 Jul 15. PMID: 26187300.

Safrai M, Herzberg S, Imbar T, Reubinoff B, Dior U, Ben-Meir A. The BNT162b2 mRNA Covid-19 vaccine does not impair sperm parameters. Reprod Biomed Online. 2022 Apr;44(4):685-688. doi: 10.1016/j.rbmo.2022.01.008. Epub 2022 Jan 31. PMID: 35279377; PMCID: PMC8801893.

Schaler L, Wingfield M. COVID-19 vaccine - can it affect fertility? Ir J Med Sci. 2021 Oct 15:1–3. doi: 10.1007/s11845-021-02807-9. Epub ahead of print. PMID: 34651258; PMCID: PMC8516490.

Zegers-Hochschild F, Adamson GD, Dyer S, Racowsky C, de Mouzon J, Sokol R, Rienzi L, Sunde A, Schmidt L, Cooke ID, Simpson JL, van der Poel S. The International Glossary on Infertility and Fertility Care, 2017. Hum Reprod. 2017 Sep 1;32(9):1786-1801. doi: 10.1093/humrep/dex234. PMID: 29117321; PMCID: PMC5850297.

This is the first study to show no adverse influence of mRNA SARS-CoV-2 vaccination on the ovarian response on young population. The safety of SARS-CoV-2 vaccination concerning IVF cycles is encouraging for the medical community and the health of our patients.

Aránzazu Bosch Villegas is biologist and master's degree in the specialty of Biotechnology of Assisted Human Reproduction and Clinical Genetics and Genetic Counselling. With international experience as Clinical Embryologist, she currently supervises the Assisted Reproduction Laboratory of Instituto Bernabeu in Cartagena.

TABLE I. Demographics of the oocyte donnors

	N	Pre Vaccination, N = 115 [1]	95% CI[2]	Post Vaccination, N = 115 [1]	95% CI[2]	p-value[3]
Age (y)	230	25.82	25,27	26.35	26,27	0.3
BMI	230	23.19	23,24	23.19	23,24	
AFC	230	15.85	15,17	20.02	18,22	<0.001

1 Mean

2 CI = Confidence Interval

3 Welch Two Sample t-test

TABLE II. Ovarian stimulation and oocyte yield parameters

TABLE III. Laboratory outcomes

	Pre Vaccination, N = 68[1]	95% CI[2]	Post Vaccination, N = 68[1]	95% CI[2]	Difference	95% CI[2,3]	p-value
MII oocytes assigned	9.46	9.07 , 9.85	9.38	8.98 , 9.78	0.74	-0.49 , 0.64	0.79[3]
Fertilized oocytes	7.82	7.34 , 8.30	7.32	6.91 , 7.73	0.50	-0.15 , 1.15	0.13[3]
Fertilization rate (%)	82.69	79.23 , 86.15	78.84	75.21 , 82.47	3.86	-1.74 , 9.45	0.17[3]
Obtained blastocysts	4.51	4.00 , 5.02	4.34	3.82 , 4.86	0.18	-0.46 , 0.82	0.58[3]
Grade A	2.29	1.85 , 2.73	2.32	1.96 , 2.68	-0.03	-0.52 , 0.46	0.90[3]
Grade B	2.19	1.82 , 2.56	1.90	1.56 , 2.24	0.294	-0.27 , 0.86	0.30[3]

1 Mean

2 CI = Confidence Interval

3 Paired t test

	Pre Vaccination, N = 115[1]	95% CI[2]	Post Vaccination, N = 115[1]	95% CI[2]	Difference	95% CI[2,3]	p-value
Duration of stimulation (days)	9.51	9.2 , 9.8	10.31	10 , 11	-0.80	-1.13 , -0.48	<0.001[4]
Dose of gonadotrophins (IU)	2,235.54	2,122 , 2,349	2,453.48	2,317 , 2,590	-218	-305.27 , -130.60	<0.001[3]
Oocytes retrieved	15.38	14 , 17	16.62	15 , 18	-1.2	-2.34 , -0.14	0.028[3]
Metaphase II oocytes	12.61	12 , 14	13.01	12 , 14	-0.40	-1.32 , 0.52	0.39[3]
Mature/total oocyte ratio	0.82	0.80 , 0.85	0.77	0.74 , 0.80	0.05	0.02 , 0.09	0.019[4]

1 Mean

2 CI = Confidence Interval

3 Paired t test

4 Wilcoxon signed-rank test

TABLE IV. Demographics of the recipient population

	N	Pre Vaccination, N = 68 [1]	95% CI[2]	Post Vaccination, N = 68 [1]	95% CI[2]	p-value[3]
Age (y)	136	42.51	42, 43	41.69	41, 43	0.252
BMI	128	23.55	23, 25	23.22	22, 24	0.758
Infertility Cause	136					0.446
Premature ovarian failure		6/68 (8.8%)	3.6%, 19%	8/68 (12%)	5.6%, 22%	
Advanced maternal age		55/68 (81%)	69%, 89%	57/68 (84%)	72%, 91%	
Others		7/68 (10%)	4.6%, 21%	3/68 (4.4%)	1.1%, 13%	

1 Mean

2 CI = Confidence Interval

3 Paired t test; McNemar test

TABLE V. Clinical outcomes in recipients undergoing a single embryo transfer					
	Pre Vaccination, N = 55[1]	95% CI[2]	Post Vaccination, N = 55[1]	95% CI[2]	p-value
Biochemical pregnancy rate	40/55 (73%)	59% 83%	32/55 (58%)	44% 71%	0.136[3]
Clinical pregnancy rate	31/55 (56%)	42% 69%	25/55 (45%)	32% 59%	0.361[3]

1 n / N (%)

2 CI = Confidence Interval

3 McNemar test