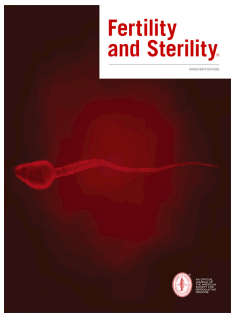

COVID-19 Vaccination and Infertility Treatment Outcomes

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COVID-19 Vaccination and Infertility Treatment Outcomes

Running title: COVID-19 Vaccination and Infertility

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Capsule:

This study demonstrated no effect of COVID-19 mRNA vaccine on the ovarian response or pregnancy rates in IVF treatment among 200 vaccinated women in comparison to 200 unvaccinated matched controls.

Abstract

Objective: To assess the influence of mRNA COVID-19 vaccine on ovarian response and IVF treatment outcomes.

Design: A retrospective cohort study.

Setting: A tertiary university-affiliated medical center and a private medical center.

Subjects: The study included a total of 400 patients, 200 vaccinated women and 200 age-matched unvaccinated women, undergoing IVF during January-April 2021.

Intervention (s): None.

Main Outcome measure (s): Mean number of oocytes retrieved and clinical pregnancy rates in vaccinated vs. unvaccinated patients.

Result(s): Two hundred patients underwent oocyte retrieval 14-68 days after receiving COVID-19 vaccination. No difference was found between vaccinated and unvaccinated patients in mean number of oocytes retrieved per cycle (10.63 vs. 10.72, p =0.93). Among 128 vaccinated patients and 133 unvaccinated patients that underwent fresh embryos transfers, no difference was demonstrated in clinical pregnancy rates (32.8% vs. 33.1%, p =0.96), with 42 and 44 clinical pregnancies, respectively. Fertilization rates and mean number of cryopreserved embryos were similar between the two groups in freeze-all cycles (55.43% vs. 54.29%, p =0.73), (3.59 vs. 3.28, p =0.80). Among vaccinated and unvaccinated patients that underwent fresh embryo transfers, no difference was demonstrated in the fertilization rate (64.81% vs. 61.98%, p=0.51), and transferred embryos' quality. Regression models applied demonstrated no effect of the vaccine on oocyte yields and pregnancy rates.

Conclusion(s): COVID-19 mRNA vaccine did not affect the ovarian response or pregnancy rates in IVF treatment. Women should be vaccinated for COVID-19 prior to attempting to conceive via IVF treatments, given the higher risk of severe illness in pregnant women.

Key words: COVID-19, mRNA vaccine, infertility treatments

Introduction

Since the discovery of the first cases in December 2019 in Hubei Province, China (1), the Corona Virus Disease-19 (COVID-19) has rapidly spread worldwide, turning into a global pandemic. Among the first COVID-19 vaccines available was the messenger RNA(mRNA) vaccine BNT162b2(Pfizer-BioNTech), that was granted Emergency Use Authorization (EUA) by the Food and Drug Administration (FDA) in December 2020 (2). On December 20, 2020, Israel initiated a national vaccination program against COVID-19, initially prioritizing high-risk populations and healthcare workers but rapidly expanding the program to include all adults. Since early studies demonstrated that infection with COVID-19 during pregnancy increased the risk for development of severe disease and pregnancy complications, the American Society for Reproductive Medicine (ASRM) recommended that pregnant women should be prioritized to receive vaccination, whether prior to conception or during pregnancy (3), despite the fact that the vaccine trial did not include this population. Nevertheless, a recent meta-analysis of international data (4) showed a declining tendency to be vaccinated, possibly influenced by exposure to widespread misinformation and public concerns over safety of the vaccines. Specifically, concerns were raised about a possible detrimental effect on fertility and pregnancy outcomes due to similarity between syncytin-1, a human placental fusion protein, and the SARS-CoV-2 spike protein expressed after administration of the COVID-19 vaccine. A recent study (5) concluded it was unlikely that the vaccine protein would generate an immune response that could affect fertility and pregnancy due to very low sequence similarity between the proteins. Indeed, preliminary data on vaccinated pregnant women (2) have shown reassuring safety results, and a prospective study on vaccinated men suggested no effect on sperm parameters (6). A retrospective analysis on 36 infertility patients has assessed the influence of COVID-19 vaccination on in vitro fertilization (IVF) treatment outcomes, and found no differences in the stimulation characteristics and embryological variables compared to treatment before vaccination (7).In addition, a very recent prospective study demonstrated no association to fecundability among vaccinated participants trying to conceive spontaneously. The study was limited by internet-based questioners, lack of possible infertility assessment and lack of timed pregnancy test which could lead to missed documentation of early pregnancy loss (8)

The lack of safety data in this vulnerable population prompted us to conduct this study, aiming to evaluate the effect of COVID-19 vaccination on the results of IVF treatments, ovarian responses, embryo quality and pregnancy rates. No significant effect on fertility treatments outcomes would allow to recommend vaccination prior to treatments in order to lower the risk of severe illness during pregnancy.

Materials & Methods

Study design

A retrospective age-matched cohort study.

Study population

All vaccinated women aged 20-42 who underwent IVF treatment cycles between January 1, 2021 and April 31 2021 at Shamir Medical Center and Herzliya Medical Center, both in Israel, were included. All participants completed two doses of the BNT162b2 (Pfizer-BioNTech) vaccine at least two weeks before starting ovarian stimulation. The study group was matched by age to unvaccinated patients who underwent IVF treatments during the same period. Patients with a positive COVID 19 test in the past were excluded. Stimulation protocols and fertilization methods were chosen by the treating physician and embryologist according to the infertility cause or past cycles' performance. The study was approved by the Institutional Review Boards of both participating medical centers (ASF-0094-21 and HMC-0010-21).

Embryo and blastocyst scoring

The grading of embryos and blastocysts was based on the Istanbul consensus workshop (9), and adjusted to the local laboratory, resulting in three quality grading groups.

General characteristics and outcomes measured

We recorded demographic and baseline characteristics (including age, partner's age, smoking status, previous pregnancies and deliveries, previous IVF treatments, infertility cause), as well as treatment protocol and cycle characteristics (total gonadotropins (GT) administered, estradiol levels on the day of ovulation-triggering (maximal E2) and fertilization method). Combined protocol referred to an ultrashort flare protocol combined with an antagonist (10).

The main outcome measures were mean number of retrieved oocytes per cycle and clinical pregnancy (1 or more intrauterine gestational sacs detected on ultrasound) rates. Secondary outcomes included oocyte maturation rate (MII (mature oocytes)/oocytes retrieved), fertilization rate (2PN (pronuclei)/oocytes retrieved), mean number of embryos frozen per cycle, and chemical pregnancy rate (elevated hCG (human chorionic gonadotropin) levels without a clinical pregnancy).

Cycles were further stratified and analyzed by the presence of fresh embryo transfer or "freeze-all" cycles. Freeze-all cycles referred to cycles in which all embryos were cryopreserved for various reasons, such as ovarian hyperstimulation, need for genetic analysis and surrogacy.

Statistical methods

Shapiro & Wilk test was used to test for normal distribution of continuous variables.
Continuous variables were summarized with mean and 95% confidence intervals (CI) and compared between groups using the Mann-Whitney test. Categorical variables were summarized using frequency and percentages. Fisher's Exact Test or Chi-square test were used to compare differences between groups.
A logistic regression model was applied to identify factors related to clinical pregnancies and to adjust for confounding variables. The following variables were included in the preliminary model: age, smoking, previous retrievals and transfers, body mass index (BMI), gravidity (G), parity (P), stimulation protocol, final embryo ranking and vaccination status. The forward elimination method was applied to select the optimal model with a threshold of $p<0.05$ for inclusion and $p>0.15$ for exclusion. Vaccination status was forced to be included in the model. The final model included vaccination status, age, previous transfers and final embryo rank.
A linear regression model was applied to identify factors related to the total number of oocytes retrieved. The following variables were included in the preliminary model: age, smoking, previous retrievals and transfers, BMI, G, P, protocol and vaccination status. The forward elimination method

was applied to select the optimal model with a threshold of $p<0.05$ for inclusion and $p>0.15$ for exclusion. Vaccination status was forced to be included in the model. The final model included vaccination status, age, previous transfers and previous retrievals.
No imputations for missing data were applied, and each measure was reported based on the existing valid data. The logistic regression was based on 86% of cases (224/261), and the linear regression was based on 87% of cases (349/400).

Univariate analyses were conducted using Ethan Heinzen, Jason Sinnwell, Elizabeth Atkinson, Tina Gunderson and Gregory Dougherty (2021). Arsenal: An Arsenal of 'R' Functions for Large-Scale Statistical Summaries. R package version 3.6.3. https://CRAN.R-project.org/package=arsenal, Multivariate analyses were conducted using SPSS-27 software, IBM, Armonk, NY, USA.

Sample size calculation

Based on an assumed pregnancy rate of 30% in the control group, a sample size of 200 patients per group would be needed to detect a reduction to a pregnancy rate of 19% using a chi-square test with a one-sided type 1 error of 5% and 80% power, and a reduction of 1.4 oocytes assuming an SD of 5.5 with a one-sided type 1 error of 5% and 80% power, applying an independent t-test. In order to detect a reduction to a 25% pregnancy rate, 985 patients per group would be needed. Our study was powered to detect only a major reduction in pregnancy rate. However, the study demonstrated similar pregnancy rates among vaccinated and unvaccinated patients (32.8% vs. 33.1%). To enable confirmation of our results that show no harmful effect on the clinical pregnancy rate with a lesser reduction, a larger group would be needed. Our study was powered to detect a difference of 1.4 oocytes retrieved, and demonstrated negligible differences between groups in all comparisons.

Results

Two hundred patients met the inclusion criteria and were matched to 200 control patients of similar age that were not vaccinated or previously infected with COVID-19. Mean (range) time from second vaccination to oocyte retrieval was 30.63 (14-68) days. Mean participant's age was similar between the study and control groups (36.04 vs. 36.11 respectively, p=0.92), as were mean partner's age (37.51 vs. 37.38, p=0.54), smoking rates (13.3% vs. 15.2%, p=0.61) and mean BMI (24.48 vs. 24.36, p =0.87). No differences were observed regarding obstetrical history, infertility cause and number of prior IVF treatments.

The groups had similar treatment protocols, ovulation triggering and fertilization methods. Patients in the study and control groups had similar cycle characteristics in terms of total GT use (2938.04IU vs. 2780.14IU, p =0.14), days of stimulation (9.90 vs. 10.25, p =0.62), maximal E2 levels (7388 pmol/l vs. 8070 pmol/l, p =0.24), and endometrial thickness on the day of ovulation triggering (9.60mm vs. 9.72mm, p =0.58), respectively.

Mean number of oocytes retrieved per cycle (10.63 vs. 10.72, p=0.93) and the maturation rate in ICSI (intracytoplasmic sperm injection) cycles (83.82% vs.79.56%, p=0.17) were similar between groups. Data are presented in Table 1.

Freeze-all cycles

A total of 113 patients (66 in the study group and 47 in the control group) underwent freeze-all cycles due to fertility preservation (medical or social), need for genetic analysis, surrogacy or ovarian

hyperstimulation. There were no differences in age (34.61 vs. 35.36, p =0.28), partner's age (35.21 vs. 36.89, p =0.13), smoking rates (11.3%, 14.0%, p =0.69), or mean BMI (24.0 vs. 23.51, p =0.70) between groups, nor in obstetrical histories, infertility cause, and prior number of IVF treatments. Number of previous transfers was significantly higher in the control group, but was not felt to be clinically relevant. Data are shown in Supplemental Table 1.

Mean (range) number of days from vaccination to oocyte retrieval was 29.44 (14-62). There were no differences in the type of protocol, ovulation trigger, and fertilization method between both groups.

Patients in the study and control groups were administered similar GT dosages during stimulation (2857.72IU vs. 3103.24IU, p =0.27), reached similar maximal E2 levels (11249 pmol/l vs. 10157 pmol/l, p =0.82), and had comparable endometrial thickness on the day of ovulation triggering (9.39mm vs. 9.49mm, p =0.67).

Mean number of oocytes retrieved per cycle was 14.88 in the study group compared to 13.62 in the control group (p=0.95), with similar maturation and fertilization rates (86.01% vs. 77.66%, p =0.06 and 55.43% vs. 54.29%, p =0.73, respectively). Mean number of frozen embryos per cycle was similar both overall (3.59 vs. 3.28, p =0.80), as well as for cleavage embryos or day 5 blastocysts individually. Significantly more day 6 blastocysts were frozen per cycle in the study group (1.92 vs. 0.58, p =0.02), Table 2.

Cycle outcomes after fresh embryo transfer

A total of 261 transfer cycles were analyzed, 128 from vaccinated women and 133 from unvaccinated women. There were no differences between groups in age (36.70 vs. 36.39, p=0.55), partner's age (38.72 vs. 37.60, p=0.64), smoking rates (13.9%, 15.5%, p=0.73), or mean BMI (24.87 vs. 24.64, p=0.73), as well as in obstetrical history, infertility cause, and number of prior IVF treatments, Supplemental Table 2.

Mean (range) number of days from vaccination to oocyte retrieval was 30.38 (14-68). No difference was demonstrated in type of protocol, ovulation trigger, and fertilization method between both groups. Patients in the study group consumed higher total dosages of gonadotropins (2980.45 IU vs. 2634.90 IU, p=0.01), needed similar periods of stimulation (9.73 vs. 9.59 days, p= 0.83), reached similar maximal E2 levels (5896 pmol/l vs. 6199 pmol/l, p=0.7), and similar endometrial thickness on the day of ovulation triggering (9.67 vs. 9.80mm, p=0.72). The number of embryos transferred per cycle and the day of transfer were similar in both groups (p=0.96, 0.07), as were the grades of transferred cleavage embryos and blastocysts (p=0.89) and mean number of surplus embryos frozen per cycle (1.53 vs. 1.22, p=0.42),

Importantly, there were no differences in the clinical pregnancy rate (32.8% vs. 33.1%, p=0.96) or chemical pregnancy rate (4.7% vs. 9.8%, p=0.11) between the study and control groups, respectively. Furthermore, no difference was observed in the number of oocytes retrieved per cycle (mean 8.47 vs. 8.32, p=0.78), with similar maturation and fertilization rates (84.63% vs. 80.07%, p=0.35; and 64.81% vs. 61.98% p=0.51, respectively), Table 3.

In a logistic regression model, variables that were related to pregnancy rates were age (p=0.02) and embryo quality (p=0.05). Vaccination status had no effect on pregnancy rates (p=0.49). A linear regression model demonstrated no effect of vaccination status on oocyte yield (p=0.84), while age remained a significant factor, reducing the number of oocytes by 0.6 for every additional year of age (p<0.001), Tables 4 and Supplemental Table 3. The same models were applied to cycles of vaccinated patients only, and found no association between the number of days from vaccination and pregnancy rates, OR=1.02 (CI 0.98, 1.05, p=0.35) or oocyte yields, slope=0.02 (CI -0.07-0.11, p=0.64).

In a sub-analysis of the main outcomes stratified by age (39 years or above), vaccination status had no effect on pregnancy rates or oocyte yield in both age groups, Supplemental Table 4.

Discussion

In this retrospective cohort study of patients undergoing IVF treatments, ovarian response and pregnancy rates were similar in patients that were vaccinated with the mRNA COVID-19 vaccine prior to IVF treatment, as compared to unvaccinated women. Concerns that the vaccine might affect fertility treatment outcomes were not supported. The theoretical concept of the supposed similarity between the SARS-CoV-2 spike protein and the syncytin protein that is speculated to take part in the fertilization process and the formation of the placenta, has led to the assumption that the vaccine might induce an immune response which would affect implantation and pregnancy (5). Our results confirm the findings of an earlier small study that showed similar treatment outcomes in terms of oocyte yield and embryo quality in 36 women who underwent ovarian stimulation after vaccination in comparison to their prior treatment (7). Moreover, despite concerns (11) (12) that the virus itself may harm steroidogenesis and folliculogenesis through the ovarian renin-angiotensin axis, or through creating a systematic cytokine storm (7), to the best of our knowledge, only one study has been published regarding the effect of COVID-19 on ovarian function, and demonstrated no detrimental effect on function of the ovarian follicle among 9 patients who recovered from COVID-19 infection. The study was limited by the small sample size and long interval from infection which might have missed short term effect on ovarian function (13). Our results demonstrate similar oocyte yields and fertilization rates among vaccinated and unvaccinated women. These results are also supported by a very recent study (14) that showed similar Anti Mullerian Hormone (AMH) levels before and 3 months after the COVID-19 vaccination. Although AMH is considered the test of choice for ovarian reserve estimation (14), it has some limitations (15), and our study's strength is that it demonstrated that the vaccine did not harm ovarian function during IVF treatments in practice. Therefore, taking into account the potential harm of the infection itself on fertility, the already proven worse pregnancy outcomes (16) among pregnant women with COVID-19 infection, and the higher risk of infection among unvaccinated pregnant women (17), it seems reasonable to reduce infection risk through vaccination.

Our study examined pregnancy rates that have not been previously published in a controlled study, and found similar chemical and clinical pregnancy rates. Preliminary reports on vaccine safety in pregnant women found similar miscarriage rates among vaccinated women, as compared to historical data from the literature. However, concern has been raised with regard to the proportion of miscarriages in the vaccinated group since it might not reflect true post-vaccination occurrence. It is possible that early pregnancy losses were not recognized (2) since they were not followed-up from menstruation, as were the pregnancies followed in our study, and as a consequence, early placentation failures may have been missed. The results of our study strengthen the notion that it is unlikely that the vaccine would generate a response that might interfere with placentation. Further studies are needed to evaluate the safety of the vaccine beyond the 8th week of pregnancy, as long-term pregnancy outcomes were beyond the scope of this study and require further follow-up.

Limitations of our study include its retrospective nature and the different treatment protocols used. However, our sample size was sufficient to control for this variable, and vaccination status was found to have no effect on pregnancy rates and oocyte yield when regression models were applied. Thus, our interpretation of treatment outcomes should be valid regardless of treatment protocol. An additional limitation is the lack of information about vaccination or past-infection status of the male partners. One would assume that if unbalanced, the proportion of vaccinated males would be higher in the study group since partners tend to make similar choices with regard to vaccine administration, thus only strengthening our conclusion that the vaccine had no detrimental effect on fertility (18).

Furthermore, though more research is needed, preliminary data have shown that vaccination has no effect on sperm parameters (6). Some studies have suggested that the infection itself can have an impact on sperm parameters (19), but data are still lacking regarding the severity and infection status at the time of semen collection.

The wide range of time from vaccination to oocyte retrieval (14-68 days), the similar number of oocytes retrieved and the increased risk for complications when infected with COVID-19 during pregnancy, strengthen the recommendation to administer the vaccine prior to IVF treatments. The similar outcomes in vaccinated and unvaccinated women above age 39 are reassuring inasmuch as the vaccine had no influence on treatment outcomes even in a population with reduced ovarian reserve.

The results from the current study add valuable information to the ongoing debate concerning timing of vaccination (20) during the fertility treatment process. Delaying vaccination until conception may lead to missed opportunities to receive the vaccine, as its availability may change over time (18).

In conclusion, this study found no effect of COVID-19 mRNA vaccine on oocyte yield during hormonal stimulation or on pregnancy rates during IVF treatments. Thus, we recommend considering COVID-19 vaccination prior to commencing IVF treatments in order to reduce the risk of SARS-CoV-2 infection during pregnancy.

Authors' roles

S.A, A.H, A.K and E.M were involved in contemplation and study design. Acquisition and analysis of data: S.A, I. G, G.Y, Y. G, H.Z, O.Y, M. Y. G.M was responsible for the statistical analysis. Drafting of the manuscript by S.A and E.M. A.H. Revision of manuscript: M.Y, M.B, E. M, A.H, A.K, A.H. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that they have no competing interests

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Table 1. Baseline characteristics and treatment outcomes of vaccinated vs. unvaccinated women.

	Unvaccinated (N=200)	Vaccinated (N=200)	P- value
Mean age (years)	36.11 (35.49, 36.73)	36.04 (35.41, 36.67)	0.92
Mean partner age (years)	37.38 (36.48, 38.27)	37.51 (36.38, 38.64)	0.54
Smoking (%)	27 (15.2%)	23 (13.3%)	0.61
Previous retrievals	1.73 (1.44, 2.01)	1.83 (1.49, 2.16)	0.78
Previous transfers	1.82 (1.46, 2.17)	1.78 (1.43, 2.13)	0.48
BMI	24.36 (23.58, 25.15)	24.48 (23.68, 25.27)	0.87
Infertility cause Male factor Fertility preservation Mechanical Unexplained infertility Age related infertility Other	 34 (18.8%) 26 (14.4%) 14 (7.7%) 42 (23.2%) 49 (27.1%) 16 (8.8%)	 35 (19.6%) 14 (7.8%) 12 (6.7%) 35 (19.6%) 55 (30.7%) 28 (15.6%)	0.15
G 0 1 2+	 84 (51.2%) 46 (28.0%) 34 (20.7%)	 77 (48.4%) 37 (23.3%) 45 (28.3%)	0.26
P 0 1 2+	 105 (62.1%) 48 (28.4%) 16 (9.5%)	 93 (58.1%) 43 (26.9%) 24 (15.0%)	0.21
Days from vaccination to retrieval Range	-	30.63 (28.81, 32.45) 14.00 - 68.00	
Protocol MNC	8 (4.0%)	4 (2%)	0.17

Antagonist Long luteal Short Combined	160 (80.4%) 14 (7.0%) 7 (3.5%) 10 (5.0%)	172 (87.3%) 14 (7.1%) 4 (2.0%) 3 (1.5%)	
Ovulation triggering Dual HCG GnRH agonist	83 (42.6%) 51 (26.2%) 61 (31.3%)	98 (52.4%) 42 (22.5%) 47 (25.1%)	0.15
Stimulation days	10.25 (9.42, 11.09)	9.90 (9.32, 10.47)	0.62
Total Gonadotropins dose (IU)	2780.14 (2589.71, 2970.57)	2938.04 (2754.47, 3121.62)	0.14
E2 on the day of ovulation triggering pmol/L	8070.20 (7046.00, 9094.40)	7388.28 (6223.16, 8553.40)	0.24
Endometrial thickness(mm)	9.72 (9.42, 10.02)	9.60 (9.29, 9.92)	0.58
Oocytes retrieved	10.72 (9.53, 11.91)	10.63 (9.82, 11.43)	0.93
Fertilization method ICSI IVF ICSI/IVF	99 (55.0%) 22 (12.2%) 59 (32.8%)	106 (54.6%) 26 (13.4%) 62 (32.0%)	0.94
MII /oocytes retrieved (%)-in cycles with ICSI	79.56% (75.07, 84.04)	83.82% (79.62, 88.01)	0.17

Data is presented as mean and (95% CI) or counts and (percentage).

G-gravidity, P- parity. MNC- modified natural cycle. Short protocol- agonist (flare-up protocol). Combined protocol- agonist administration for 2-3 days, replaced by an antagonist.

Mechanical factor- tubal and uterine. Age related infertility - age above 39 as primary infertility indication.

Table 2. Clinical outcomes of vaccinated vs. unvaccinated patients in Freeze-all embryo cycles.

	Unvaccinated (N=47)	Vaccinated (N=66)	P- value
Days from vaccination to retrieval **Range**		29.44 (26.68, 32.19) 14.00 - 62.00	
Protocol MNC Antagonist Long luteal Short Combined	 1 (2.1%) 39 (83.0%) 4 (8.5%) 0 (0.0%) 3 (6.4%)	 0 (0.0%) 61 (93.8%) 4 (6.2%) 0 (0.0%) 0 (0.0%)	0.10
Ovulation triggering Dual hCG GnRH agonist	 13 (28.3%) 7 (15.2%) 26 (56.5%)	 21 (34.4%) 8 (13.1%) 32 (52.5%)	0.78
Stimulation days	10.67 (9.44, 11.90)	9.80 (9.20, 10.39)	0.26
Overall Gonadotropins dose (IU)	3103.24 (2709.68, 3496.81)	2857.72 (2520.08, 3195.36)	0.27
E2 on the day of ovulation triggering pmol/L	10157.74 (7975.79, 12339.69)	11249.20 (7689.82, 14808.58)	0.82
Endometrial thickness(mm)	9.49 (8.93, 10.04)	9.39 (8.83, 9.95)	0.67
Oocytes retrieved	13.62 (10.89, 16.34)	14.88 (12.07, 17.69)	0.95
Fertilization method ICSI IVF ICSI/IVF	 32 (71.1%) 3 (6.7%) 10 (22.2%)	 38 (59.4%) 7 (10.9%) 19 (29.7%)	0.43
MII /oocytes retrieved (%)-ICSI	77.66 (70.55, 84.76)	86.01 (79.64, 92.38)	0.06

Fertilization rate (PN/total oocytes) %	54.29 (46.50, 62.08)	55.43 (48.91, 61.96)	0.73
Frozen embryos per cycle			
Total	3.28 (2.43, 4.13)	3.59 (2.77, 4.41)	0.80
Day 2/3	2.72 (1.96, 3.48)	2.68 (2.00, 3.36)	0.88
Day 5	2.61 (1.54, 3.67)	2.73 (1.98, 3.48)	0.71
Day 6	0.58 (0.08, 1.09)	1.92 (0.75, 3.08)	0.025

Data are presented as mean and (95% CI) or counts and (percentage).

MNC- modified natural cycle. Short protocol- agonist (flare-up protocol). Combined protocol- agonist administration for 2-3 days, replaced by an antagonist.

Table 3. Clinical outcomes of vaccinated vs. unvaccinated patients, ET cycles.

	Unvaccinated (N=133)	Vaccinated (N=128)	P- value
Days from vaccination to retrieval Range		30.38 (28.05, 32.71) 14.00 – 68.00	
Protocol MNC Antagonist Long luteal Short Combined	7(5.3%) 109 (82.6%) 10 (7.6%) 5 (3.8%) 1 (0.8%)	4 (3.2%) 107 (84.9%) 10 (7.7%) 4 (3.2%) 1 (0.8%)	0.93
Ovulation triggering Dual hCG GnRH agonist	70 (54.3%) 42 (32.6%) 17 (13.2%)	76 (63.3%) 33 (27.5%) 11 (9.2%)	0.31
Stimulation days	9.59 (9.05, 10.12)	9.73 (8.94, 10.52)	0.83
Total Gonadotropins dose	2634.90 (2406.74, 2863.06)	2980.45 (2749.12, 3211.77)	0.01
E2 on the day of ovulation triggering pmol/L	6199.54 (5358.01, 7041.07)	5896.69 (5113.34, 6680.04)	0.70
Endometrial thickness (mm)	9.80 (9.41, 10.20)	9.67 (9.28, 10.06)	0.72
Oocytes retrieved	8.32 (7.38, 9.27)	8.47 (7.52, 9.42)	0.78
Fertilization method ICSI IVF ICSI/IVF	64 (48.5%) 19 (14.4%) 49 (37.1%)	65 (51.2%) 19 (15.0%) 43 (33.9%)	0.85
MII /oocytes retrieved (%)-ICSI	80.07 (74.09, 86.04)	84.63 (79.62, 89.65)	0.35

Table 3. Clinical outcomes of vaccinated vs. unvaccinated patients, ET cycles.

Fertilization rate (PN/total oocytes)	61.98 (57.37, 66.60)	64.81 (60.69, 68.93)	0.51
Frozen embryos per cycle Total Day 2/3 Day 5 Day 6	 1.22 (0.91, 1.53) 1.07 (0.74, 1.41) 1.07 (0.74, 1.40) 0.45 (0.14, 0.75)	 1.53 (1.16, 1.91) 1.43 (0.91, 1.95) 1.41 (1.08, 1.74) 0.48 (0.15, 0.82)	 0.42 0.51 0.11 0.75
Embryos transferred per cycle 1 2 3	73 (54.9%) 54 (40.6%) 6 (4.5%)	70 (54.7%) 53 (41.4%) 5 (3.9%)	0.96
Day of transfer /total transfers Day 2 Day 3 Day 5	 31 (25.4%) 70 (56.9%) 22 (17.9%)	 16 (13.7%) 76 (65.0%) 25(21.4%)	0.07
Top transferred embryo grade (grade/total cycles) % **A** **B** **C**	 77 (57.9%) 39 (29.3%) 17 (12.8%)	 71 (55.5%) 41 (32.0%) 16 (12.5%)	0.89
Clinical pregnancy rate (%)	44 (33.1%)	42 (32.8%)	0.96
Chemical pregnancy rate (%)	13 (9.8%)	6 (4.7%)	0.11

Data is presented as mean (95% CI) or counts (percentage).

MNC- modified natural cycle. Short protocol- agonist administered from day 1 of menstruation. Combined protocol- agonist administration for 2-3 days, replaced by an antagonist.

Table 4. Logistic regression model for pregnancy rate in fresh ET cycles.

Variable Name	OR	Lower limit	Upper limit	p value
Age (years)	0.92	0.86	0.98	0.02
Number of previous transfers	0.91	0.80	1.04	0.18
Embryo grade				0.05
C	***Reference***			
A	3.85	1.25	11.89	0.01
B	2.79	0.85	9.11	0.09
Vaccination				*0.49*
No	***Reference***			
Yes	1.22	0.68	2.19	

A- Top quality embryo, B- good quality embryo, C- impaired quality embryo
OR- Odds Ratio