IVF and Early Pregnancy Outcome in Recent COVID 19 Recoverees.

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Research Article

Keywords: Covid-19, SARS-COV-2, in vitro fertilization, reproduction, infertility, pregnancy outcome.

Posted Date: November 30th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1055952/v1

Abstract

Background: COVID-19 global pandemic has affected more than 250 million people so far. Data regarding potential effects on reproduction are still limited.

Our aim was to examine the effect of COVID-19 on post exposure IVF cycle parameters and obstetric outcomes of IVF-achieved pregnancies.

The study contained two arms: a retrospective arm comparing IVF outcome parameters among patients exposed to COVID-19 having an IVF cycle within 3 months of exposure. Post COVID-19 cycle parameters were compared to previous cycles of the same individual, performed within one year of exposure. If not available, parameters were compared to non-exposed matched patients. Sperm parameters were compared before and after exposure. The second arm was prospective comparing pregnancy outcomes among IVF patients who contracted COVID-19 during pregnancy, vs. those who did not.

Results: The first arm included 120 cycle of which 60 were in exposed female patients and another 60 in either the same patients prior to exposure or matched non exposed patients. Generally, total FSH dose, cycle length, and ovarian response did not significantly differ across exposure groups: including peak serum estradiol, number of oocytes and endometrial thickness, fertilization rate and number of top-quality embryos, were similar between exposed and non-exposed cycles. In 11 of the cycles in which the female partner was exposed the male partner had been recently exposed as well. In these couples, sperm quality showed a significantly lower post-exposure concentration: 6.27million/ml vs. 16.5 (p= 0.008). Interviews conducted in 189 patients with IVF-achieved pregnancies: pregnancy loss was as well as other pregnancy related complications and hospital admissions did not differ between groups.

Conclusion: IVF treatment parameters and IVF-achieved pregnancies appear to be unaffected by SARS-CoV-2 exposure and do not involve an excess risk. Sperm concentration seems to be compromised.

Introduction

Since its emergence at the end of 2019 the corona-virus disease-19 (COVID-19) global pandemic has affected more than 250 million people and resulted in over 5 million fatalities. The multisystemic disease has short- and long-term effects that may involve any organ system [1, 2]. As recently described[3] data on potential effects on male and female reproduction are still lacking [3]. However, information on the physiology of the virus and the common symptoms associated with the acute infection, such as fever and hypercoagulability, may potentially affect both male and female reproduction. In addition, viral proteins show similarity to placental proteins and could potentially interfere with placenta formation [4, 5]. It has also been reported that pregnant women are more susceptible to a severe form of acute infection and are more likely to require intensive care admission, mechanical ventilation, and extracorporeal membrane oxygenation (ECMO), as well as suffering increased mortality rates[6]. Some of the reported risk factors among pregnant women for severe COVID-19 related complications were: age over 25 years, pre-pregnancy obesity, chronic hypertension, and pre-pregnancy diabetes [7]. All of these

risk factors are significantly more common among patients conceiving following In Vitro Fertilization (IVF) treatment as opposed to spontaneous conceptions, suggesting that pregnant women following IVF may be at a particularly elevated risk for COVID-19 related complications [8].

In Israel, other than a short interruption at the beginning of the pandemic, IVF treatment cycles were conducted following exclusion of a current infection. Under these circumstances, couples undergoing IVF treatments need to cope with the added uncertainty of the potential risk posed by COVID-19 to the safety and success of treatment and the possible implications in case of a pregnancy [9]. The aim of this double armed cohort study was to compare the outcome of IVF treatment and IVF-achieved early pregnancy outcomes between post-COVID-19 infection, recovered patients and non-exposed patients, in order to provide evidence-based consultation to our fertility patients.

Methods

The study contained two arms:

1. **a retrospective cohort analysis in which we compared IVF outcome parameters among female patients exposed to COVID-19 and performed an IVF cycle within 3 months of exposure**

The retrospective cohort included all patients who underwent IVF treatment at Hadassah Medical Center IVF units during the COVID-19 pandemic (March 2020-April 2021) and were <3 months post RT-PCR-confirmed COVID-19 disease. The study was approved by our institutional ethics committee (approval number HMO-0038-21).

Data on treatment outcome parameters were retrieved from patients' treatment summaries and embryology reports (gonadotropin consumption, duration of stimulation, peak serum estradiol, number of retrieved oocytes, maximal endometrial thickness, fertilization rate, total number of cleavage stage embryos, and number of top quality embryos). The definition of top-quality embryos was defined at 72 hours of development with 6-8 cells, with either grade A or B used for eligibility. These parameters were compared to a previous cycle performed in the same patient within 1 year of index cycle. In cases for which no previous cycle was available, the comparison group included non-exposed patients matched by *age, indication for IVF, and treatment protocol*. Pregnancy outcome was not included since patients underwent the post exposure treatment because conception was not successful in a previous cycle; we therefore chose to concentrate on the cycle parameters and embryological outcomes. Male exposure status was also documented. Sperm concentration and motility were compared in couples in which a male partner was also recovering from COVID19. The following variables were assembled: age, background morbidities, parity, BMI, smoking status, indication for IVF treatment, cycle type, and cycle number, as well as time from COVID-19 recovery for both partners.

It was recently reported that COVID-19 patients and recent recoverees are at higher risk for thromboembolism [10]. Since IVF treatments are often associated with markedly elevated serum estradiol, which may pose an increased risk for thromboembolism, we recommended serum D-Dimer

measurement to all COVID-19 recoverees starting treatment within the first 3 months post recovery. Results of 0.5 µg/mL were defined as a cut-off mandating either postponement of the treatment or addition of low molecular weight heparin to the treatment protocol.

2. A prospective cohort analysis of pregnancy outcomes among IVF-achieved conceptions, comparing patients who contracted COVID-19 immediately before or in early pregnancy vs. those who did not.

The prospective cohort study arm assessed pregnancy outcomes following an IVF cycle achieving a viable pregnancy (approval number HMO-0924-20). The primary outcome measure was early pregnancy loss, defined as a miscarriage or missed abortion diagnosed after discharge from the unit with an intrauterine pregnancy demonstrating fetal cardiac activity (6-7 weeks), and until 14 weeks of pregnancy. Power analysis was conducted with the assumption of two-fold increase in early pregnancy loss among exposed patients while the background early pregnancy loss was defined as 25%, with a statistical power of 80% and 5% level of significance. Accordingly, the minimum sample size was determined to be a total of 58 patients in this arm of the study.

We had also compared the rate of pregnancy loss among patients that conceived following a recent recovery from COVID 19 to unexposed IVF pregnancies.

Data were collected via telephone questionnaire. All patients included in this arm of the study tested negative for SARS-CoV-2 by PCR, at the time of IVF treatment completion and confirmation of viable pregnancy. The telephone questionnaire queried confirmed diagnosis of COVID-19, pregnancy viability, pregnancy complications, and hospital admissions.

Statistical analysis:

Data were extracted from the patients' electronic medical records (EMR). Missing information was retrieved directly from the patients via telephone interview.

All analyses were conducted using IBM SPSS Statistics for Windows, Version 23.0 (Armonk, NY: IBM Corp). Normally distributed continuous variables are reported as means and standard deviations. Matched data were compared using a generalized estimating equation model with interchangeable correlation matrix. A t-test was used where data was normally distributed and by matched nonparametric test (Wilcoxon) in case of a non-normally distributed data. Pregnancy complication rates and proportions were compared using the Chi-squared or Fisher's exact test for small numbers, as appropriate. A logistic regression model adjusting for age was used for the analysis of pregnancy loss rate.

Sperm parameters were compared for each patient's samples, analyzed before and after exposure to COVID-19, using matched t test when the data were normally distributed, and Wilcoxon signed rank test in case of non-normally distributed data.

All p-values were tested as two-tailed and considered significant at <0.05.

Results

1. ***IVF Treatment outcome:***

The cohort included 120 cycles of which 60 were exposed patients meeting the inclusion criteria matched to 60 non-exposed ones (either the same patient prior to exposure, or age, treatment and indication matched non-exposed patients): 41 underwent fresh controlled ovarian hyperstimulation (COH) cycles (13 with a self-comparison, 28 with matched controls) and 19 underwent frozen-thawed cycles (13 with a self-comparison, 6 with matched controls). Five of the patients undergoing COH cycles were oocyte cryopreservation treatments, all serving as their own controls. The patient characteristics as well as their treatment outcomes comparing exposed to non-exposed patients are detailed in Table 1. Age, BMI, and smoking were similar for the exposed and unexposed patients among self-comparison patients and those with matched controls: mean age 34.76 vs. 31.94, p=0.06; BMI 23.85 vs. 25.43, p=0.261, for the self-comparison and matched patients, respectively. Smoking rates were 12.8% vs. 12.5% respectively (p=1). Generally, total FSH dose, cycle length and ovarian response did not differ significantly across exposure groups (Table 1). Importantly, quantitative measures such as peak serum estradiol, number of oocytes and endometrial thickness, as well as qualitative measures such as fertilization rate and number of top-quality embryos, were similar between exposed and non-exposed cycles (Table 1).

Among this cohort ,38 were going through an embryo transfer and 17 conceived. 6 experienced a pregnancy loss (35.3%). As compared to the post discharge pregnancy loss of non-exposed patients, the difference was not statistically significant (P value 0.5). Serum D-Dimer was measured in 15 of the exposed patients. The mean serum concentration was 0.35 ±0.08 (range 0.19-0.44 µg/mL). No thromboembolic complications were recorded in any of the exposed patients.

Sperm quality

Eleven male partners were also exposed to COVID 19 and within 3 months of recovery. Their sperm analysis during the fertilization process, as compared to pre-COVID parameters, are detailed in Table 2; the sperm demonstrated a significant decline in concentration following COVID-19 recovery (P value **0.008)**, however no significant change in sperm motility was apparent.

IVF outcome parameters in fresh cycles involving fertilization were also compared according to the male partner's exposure: fertilization, number of embryos and top quality embryos were no affected by the male exposure status (P values 0.74,0.68, 0.65 respectively).

2. IVF early pregnancy outcome

Obstetric outcomes of IVF-achieved pregnancies were compared among exposed and unexposed pregnant women (Table 3). A total of 189 IVF COVID naïve patients, who were discharged from the clinic following demonstration of a clinical pregnancy, were contacted. The rate of post-discharge exposure in this group of patients was 15.9%. None of the patients included in this group developed severe

symptomatic COVID-19 disease requiring hospitalization. Mean and median age of exposed and non-exposed patients were similar at 32.9 and 32 years, respectively.Table 3 summarizes a comparison of outcome measures among exposed and non-exposed patients. The rates of hospitalizations, pregnancy loss, or any other clinically significant complications did not differ between the two groups. Emergency room visits were more frequent among exposed patients (23.3% vs. 15.1%), but this did not reach statistical significance. We performed a logistic regression analysis for pregnancy loss, adjusting for maternal age. According to this model, COVID-19 exposure was not associated with pregnancy loss (p=0.84, OR 1.11, 95% CI 0.41-2.9 for exposed vs. non-exposed), while maternal age was, as expected (p=0.02, OR 1.06, 95% CI 1.007-1.112 for each additional year).

Discussion

Since the emergence of SARS-CoV-2 and the COVID-19 pandemic, a plethora of data has accumulated on the virus and its clinical effects on different organ systems, age groups, and special clinical conditions. This information allowed for a rapid development of a currently widely available vaccine and identification of susceptible groups of patients, among them pregnant women, especially those with comorbidities [7, 6].

Although the acute infection causes mainly respiratory related symptoms, a systemic inflammation as well as thromboembolic events and acute cardiac injury have been described [11, 12]. Studies have shown that the main mechanism by which the virus invades cells is through binding to the angiotensin-converting enzyme 2 (ACE2) receptor and via transmembrane serine protease 2 (TMPRSS2) [13, 3, 14].

Since co-expression of ACE2 and TMPRSS2 has not been detected in the human male or female reproductive tract, it was presumed that human reproductive organs were less susceptible to the virus[3, 14]. However, acute COVID-19 is often associated with fever for several days and even weeks. Since fever may affect spermatogenesis, acute infection with SARS-CoV-2 may indirectly impact spermatogenesis [15].

In this study, we followed 'real life' IVF cohorts: the first composed of patients recently recovered from COVID19, which were compared either to self or a strictly matched control, and a second, composed of patients with IVF-achieved pregnancies who contracted COVID-19, compared to those who did. We also looked at the outcomes of couples in which both partners had recently recovered from COVID 19. Female patients in both cohorts did not demonstrate compromised outcomes as compared to the non-exposed patients. The rate of clinical pregnancy loss did not differ between exposed and unexposed parturients (25%). Moreover, serum concentration D-dimer values were normal among tested recovering patients. In addition, no thromboembolic events or any other hematological complications were observed among the exposed patients.

On the other hand, male partners participating in a fresh IVF cycle following recent recovery from COVID-19 showed reduced sperm concentration (p=0.008). However, this compromise in sperm quality did not translate to a poorer IVF outcome. None of the patients presented with symptoms suggesting direct

infection of the testicles, however, the effect of a febrile illness on sperm production may have played a role [15]. Since all the patients provided the tested samples within the 3-month spermatogenesis cycle, it is likely that the effects of COVID on the quality of sperm relate to a transient adverse effect of the fever caused by the general illness. It is still not clear whether the decline in sperm quality remains after the effects of the general illness have subsided.

Our results coincide with recent reports on the outcome of IVF treatment and early pregnancies among COVID-19 patients. A recent study reported on the outcome of IVF treatments in the county of Lombardy, Italy [16]. Lombardy was one of the areas hardest hit in the early stages of the pandemic. The authors compared several outcome parameters of the pre-exposure cohort, comprised of all the patients undergoing both fresh and frozen IVF treatment cycles before the pandemic (November 2018 to March 2019) to the potentially exposed cohort, composed of all IVF cycles conducted during the peak of the COVID-19 outbreak (November 2019 to March 2020). Although asymptomatic patients were not tested for SARS-CoV-2, 28% of blood donor samples from that period tested positive for anti SARS-CoV-2 IgG, suggesting that a similar number of patients undergoing IVF were exposed to the virus. The authors found similar rates of clinical pregnancy, early pregnancy loss, and extrauterine pregnancies[16].

A study by Calvo et al [17] reported on the perinatal outcome of 1,347 pregnant women, among them 74 who conceived following IVF, who were infected with SARS-CoV-2 during pregnancy. This multicenter study compared the rate of early pregnancy loss, pregnancy complications, and mode of delivery according to exposure status. They were only able to show a significant increase in the rate of cesarean sections among exposed patients[17].

Another small study from Israel examined the effect of COVID-19 on IVF treatment outcomes [18]. The study included 9 couples, of which 7 women and 2 men were exposed. They reported a lack of any significant difference in IVF cycle outcomes between the exposed and non-exposed groups, other than a significant decrease in top quality embryo rate among exposed couples[18]. In our study neither patients conceiving immediately following recovery from COVID -19, nor those that contracted the infection during the first trimester showed an increased rate of early pregnancy loss. Furthermore, we did not observe a decline in embryo quality in the exposed group, however further larger studies are required to determine the effects of COVID-19 on embryo quality and rate of aneuploidy.

Further reassurance is found in a recently published systematic review and meta-analysis that examined the risk of intrauterine fetal demise (20 weeks of gestation or later) and neonatal death in exposed and non-exposed patients on admission to delivery [19]. No significant difference was found between the groups. The authors reported on the lack of any statistically significant increase in the risk for preterm birth or maternal death. However, other studies have shown an adverse effect of the virus on the course of pregnancy and perinatal outcomes[19].

There is presently a dearth of published evidence regarding resumption of reproduction system function post-COVID-19, since long term follow up data are still being gathered. Whether COVID-19 has prolonged effects on reproductive function remains an open question [20]. To the best of our knowledge, our study

is the first to examine both IVF treatment and pregnancy outcomes in recovered COVID-19 patients, or who contracted the virus in pregnancy. Study patients either served as their own controls or were compared to carefully matched controls, in the retrospective arm. The pregnancy outcome study arm was prospective and included a relatively large group of patients. The study did however include a mixed comparison, self, and control group. Sample size calculations were based on the best estimates of exposure effect available at the time of study design. Among the patients included in the study, the time between recovery and the onset of the treatment cycle ranged from two weeks to three months (mean=1.75 months). Thus, our results only address the early post-exposure period.

Conclusion

In the present study we were not able to detect any detrimental effects on IVF treatment parameters and short term pregnancy outcomes appear of exposure to the SARS-CoV-2 virus. Sperm concentration, however, seems to be compromised post-exposure, but did not affect treatment parameters.

We deduce that in the case of female partner exposure, after achieving recovery, IVF treatment should not necessarily be postponed. In the case of male partner exposure prior to a fresh treatment cycle, initiation may be delayed following discussion with the patients, in light of sperm concentration values.

This study was conducted as part of fulfilling some of the requirements for a doctorate in medicine of the Faculty of Medicine, The Hebrew University of Jerusalem.

Abbreviations

- COVID-19: Corona Virus Disease 2019
- IVF – In Vitro Fertilization
- FSH -Follicles Stimulating Hormone
- SARS-CoV-2: Severe Acute Respiratory Syndrome Corona Virus 2
- ECMO: extracorporeal membrane oxygenation
- RT-PCR: Reverse transcription polymerase chain reaction
- BMI: Body Mass Index
- EMR: electronic medical records
- COH: controlled ovarian hyperstimulation
- ACE2: angiotensin-converting enzyme 2
- TMPRSS2: transmembrane serine protease 2

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Tables

Table 1: Cycle outcomes for fresh, post COVID-19 IVF treatment as compared to non- exposed matched cycles

The table compares several outcome parameters between patients exposed or non-exposed to COVID 19 including gonadotropin dose, length of stimulation, ovarian response in number and quality of oocytes as well as endometrial thickness.

	Exposed	Non-exposed	Beta	95% CI	P value
	Mean (∓ SD), Median				
Total FSH dose (IU)	2412.63 (∓1376), 2100	2184(∓1028.1), 2025	228.6	-113.2 – 570.5	0.19
COH days	10.12 (∓ 2.3),10	9.2 (∓ 2.2), 9	0.9	0.001-1.8	0.05
Maximal Estradiol (pmol/L)	9044.24 (∓6341.8) 7273	8735.9 (∓5291.8) 7953	308.4	-1797.8-2410.6	0.7
Maximal endometrial thickness (mm)	10.8 (∓ 2.5), 0.7	10.5 (∓2.8), 10	0.04	-0.35-0.43	0.8
Number of aspirated ova	10.73 (∓ 6.9) ,9	12.22 (∓9.3) ,10	-0.13	-0.36 - 0.1	0.3
Number of fertilized ova	6.8 (∓4.5), 6	6.7 (∓5.3), 6	0.02	-0.3 -0.31	0.9
Number of cleavage stage embryos	6.56 (∓ 4.4),6	6.0 (∓ 4.4) ,5	0.09	-0.18-0.36	0.5
Number of top-quality embryos	4.57 (∓3.7), 3	3.88 (∓ 2.8), 3	0.17	-0.16 -0.5	0.3

Table 2: sperm parameters of exposed male partners: pre and post- exposure to Covid-19

The table compares sperm quality parameters in men before and shortly after contracting COVID 19.

N=11	Pre-concentration (mil/ml)	Post-concentration (mil/ml)	Pre-motility (%)	Post-motility (%)
Mean	19.4	12.7	32.3	22.5
Median	**16.5**	**6.27**	**24.5**	**25.0**
SD	18.3	16.07	29.7	23.7
P value (for ln values)	**0.008**		0.2	

Table 3: Pregnancy outcomes of COVID-19 exposed versus non-exposed IVF conceptions.

The table compares patients that conceived following IVF treatment that had were either exposed or non-exposed to COVID 19, analyzing the rate of hospitalization, emergency room visits, medical complications and early pregnancy loss.

Total pregnant patient contacted (N=189)	**Exposed to SARS–CoV-2 (N=30)**	**Not exposed to SARS–CoV-2 (N=159)**	**P-VALUE**
Hospitalizations	2/30 (6.66%)	12/159 (7.5%)	0.63
Pregnancy complications (other than pregnancy loss)	4/30 (13.3%)	18/159 (11.3%)	0.46
ER visits	7/30 (23.3%)	24/159 (15.1%)	0.18
Pregnancy loss	**7/30 (23.3%)**	**41/159 (25.8%)**	**0.48**

Supplementary Files

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