



Rates of COVID-19 infection among in vitro fertilization patients undergoing treatment at a university reproductive health center

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Abstract

Background The coronavirus disease 2019 (COVID-19) caused an unprecedented challenge for in-vitro fertilization (IVF) patients. The incidence of COVID-19 infection among this population is a fundamental knowledge gap.

Objective The purpose of this study was to determine the rate of COVID-19 infection among IVF patients compared to other gynecologic surgery patients.

Materials and methods This retrospective study evaluated the incidence of COVID-19 infection among patients undergoing IVF, female fertility-related surgeries (FRS) and other gynecologic surgeries at a single academic institution in Los Angeles, California. All patients underwent routine COVID-19 polymerase chain reaction (PCR) screening prior to treatment.

Result A total of 2742 patients underwent asymptomatic COVID-19 screening before a surgical procedure or IVF between March 1, 2020, and April 5, 2021. The rate of COVID-19 infection among patients who underwent preoperative testing for a non-fertility-related gynecologic procedure was 1.74% (28/1612). In comparison, the positive test results for those who underwent either FRS or IVF were 0.56% (1/180) and 0.34% (1/290), respectively, representing 6.70% (2/30) of positive tests for the whole cohort. The infertility patients had a significantly lower positivity rate compared to the other gynecologic patients during preoperative COVID-19 testing (0.43% vs 1.74%, $p=0.03$).

Conclusion(s).

Our study demonstrated that there was a significantly lower incidence of COVID-19 infections in infertility patients undergoing IVF or FRS compared to other gynecologic surgery patients. Future studies should evaluate the cost-effectiveness of routine screening in both the gynecology and infertility patient population, especially in the setting of different variant surges and vaccination rates.

Keywords COVID-19 · Infertility · Gynecology · Surgery

Introduction

The emergence of coronavirus disease 2019 (COVID-19) caused an unprecedented challenge for many patients, including those undergoing infertility treatment. Stresses on the capacity of the US healthcare system led to suspension of elective procedures [1]. The World Health Organization (WHO) declared COVID-19 a global pandemic on March 11, 2020. Thus, the American Society for Reproductive Medicine (ASRM), the European Society of Human Reproduction and Embryology (ESHRE), and the International Federation of Fertility Societies (IFFS) recommended suspension of new infertility treatment, postponement of embryo transfers, elective surgeries, and non-urgent diagnostic procedures [2, 3]. However, for patients and providers,

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infertility remains a time-sensitive disease [4]. One survey study reported that the majority of patients classified infertility as their number one stressor even during the pandemic [5]. For both patients and providers, the question remains: how safe is proceeding with infertility treatment during a pandemic?

In April 2020, the ASRM COVID-19 Task Force declared that with proper safety protocols, infertility treatment could return [6]. These now-familiar protocols include wearing personal protective equipment (PPE) and implementation of preprocedural COVID-19 testing [7]. After a 2-month delay in care for patients, most infertility clinics reopened in May 2020, despite a lack of specific guidelines advising clinicians how to resume operations [8]. Clinics established their own COVID-19 testing protocols for infertility patients undergoing various treatments [9].

The incidence of COVID infections among infertility patients compared to other groups of patients is unknown. A small New York City study during early limited COVID-19 testing demonstrated a <2% COVID-19 positivity rate in asymptomatic infertility patients even as city-wide positivity rates approached 40% [10]. This disparity merits further research. The purpose of this study was to determine the rate of COVID-19 infection among infertility patients compared to other gynecologic surgery patients.

Materials and methods

This was a retrospective study that evaluated the incidence of COVID-19 infection among patients undergoing in vitro fertilization (IVF), female fertility-related surgeries (FRS), and other gynecologic surgeries at a single academic institution in Los Angeles, California, from March 2020 to April 2021. The University of California at Los Angeles (UCLA) instituted routine universal polymerase chain reaction (PCR) screening of COVID-19 for patients undergoing any surgical procedure or IVF. All IVF cycles as well as surgeries across all gynecologic specialties from March 1, 2020, to April 5, 2021, were included. Institutional Review Board (IRB #20–001,133) approval was obtained at UCLA. The inclusion criteria were patients who had a COVID-19 test result prior to gynecologic surgery or IVF treatment. All surgical cases within the gynecology department, whether scheduled, urgent or emergent, were included. IVF patients included female patients who underwent COVID-19 screening prior to controlled ovarian stimulation start and within 5 days of embryo transfer. The male partners of IVF patients were excluded from our analysis. Only reproductive age patients, 18–46 years old, were included. Patients were categorized into six groups: IVF, FRS, gynecologic oncology surgery, urogynecology surgery, family planning surgery, and general gynecology surgery. FRS was defined as any

female infertility enhancing surgery (i.e., operative hysteroscopy, salpingectomy, laparoscopy for endometriosis), any surgeries as a direct result of infertility treatment (i.e., dilation and curettage after failed pregnancy), or any other surgeries performed by a Reproductive Endocrinology and Infertility (REI) physician (Appendix). Surgical cases were rescheduled, and IVF cycles were cancelled for patients with positive COVID-19 tests. Our primary objective was to compare the overall rate of COVID-19 infection among patients undergoing fertility treatments or FRS with the rate among patients undergoing gynecologic surgery for other indications during our study period. We further stratified the COVID-19 positivity rate by county to explore regional differences. Additionally, we calculated the positivity rate per month for each of the six groups to examine temporal trends during the COVID-19 pandemic. Finally, we used the LA County COVID-19 Surveillance Dashboard from the LA County Department of Public Health to compare monthly positivity rates of gynecology patients at UCLA to that of greater Los Angeles County.

Laboratory tests

All COVID-19 tests were nasopharyngeal PCR tests, which were processed and interpreted within the UCLA Health System (Roche Cobas 6800). The overall sensitivity and specificity of this PCR test's results at UCLA are 95.5% and 100%, respectively. Each oocyte retrieval patient had two COVID-19 tests per cycle, once prior to starting ovarian stimulation and again prior to oocyte retrieval. Each frozen embryo transfer cycle patient had one COVID-19 test prior to transfer. The analysis was limited to one test per patient.

COVID-19 preoperative plan

There were two waves of COVID-19 safety measures at UCLA in response to the two COVID-19 surges in Los Angeles County. UCLA cancelled all elective cases twice during the study period between March 13, 2020, and May 3, 2020, and December 9, 2020, and February 5, 2021. However, IVF cycles were not cancelled during the second period. Preoperative COVID-19 testing started during the first wave on April 13, 2020. COVID-19 vaccines were offered beginning on January 27, 2021, to UCLA patients who were residents of skilled assisted living facilities or those with high-risk occupational tiers, including healthcare, education, childcare workers, agriculture workers, and emergency services workers. COVID-19 vaccine eligibility was extended to all individuals 50 years or older starting April 1, 2021, in California and then further expanded to those over age 16 on April 15, 2021 [11].

Analyses

Overall COVID-19 infection rate was calculated over the duration of the study period. We also compared COVID-19 test results by patient groups and county (within Los Angeles County vs outside Los Angeles County) with a chi-square test (or Fisher's exact). All statistical tests were two-sided with an alpha at 0.05 for significance. All analyses were performed in SAS 9.4 (SAS Institute Inc, Cary, NC).

Results

A total of 3433 COVID-19 screening tests were performed before a surgical procedure or before and during an IVF cycle between March 21, 2020, and April 5, 2021. Of these screening tests, 691 were excluded due to patient age, resulting in 2742 tests for analysis. This included patients who underwent IVF ($n = 685$), FRS ($n = 442$), or a non-fertility-related gynecologic surgical procedure ($n = 1615$). The analysis was further limited to the first test per patient, resulting in 2082 unique female patients with the following patient cohorts: IVF ($n = 290$), FRS ($n = 180$), or a non-fertility-related gynecologic surgical procedure ($n = 1612$).

The overall asymptomatic COVID-19 positivity rate in this cohort was 1.44%, with 30 positive tests out of 2082 unique patients (Table 1). The rate of COVID-19 infection among patients who underwent preoperative testing for a non-FRS was 1.74% (28/1612). In comparison, the positive test results for those who underwent either IVF or FRS were 0.34% (1/290) and 0.56% (1/180), respectively, which represented only 6.70% (2/30) of positive tests for the whole cohort. The infertility patients had a significantly lower positivity rate compared to the other gynecologic patients during routine preoperative COVID-19 testing (0.43% vs 1.74%, $p = 0.03$) (Table 1). There was a total of four indeterminate test results. The general gynecology patients trended toward a higher COVID-19 positivity rate of 2.02% (21/1040) compared to patients undergoing surgery related to family planning, urogynecology, gynecologic oncology, or infertility ($p = 0.47$). The preoperative COVID-19 positivity rates from highest to lowest among the groups were as follows: general gynecology, gynecologic oncology, family planning,

urogynecology, FRS, and IVF patients (Supplemental Table 1).

The highest monthly positivity rate was 10.4% in January 2021 among the general gynecology group (Fig. 1). This corresponded with the highest general Los Angeles County test rate, which was 20.8%, in January 2021 [12]. This serves to validate the utility of our preoperative screening protocol. The asymptomatic COVID-19 positivity rate for all UCLA preoperative gynecology patients whose home address was Los Angeles County was not significantly different than those patients who lived outside Los Angeles County (1.54% vs 1.43%, $p = 0.87$).

Discussion

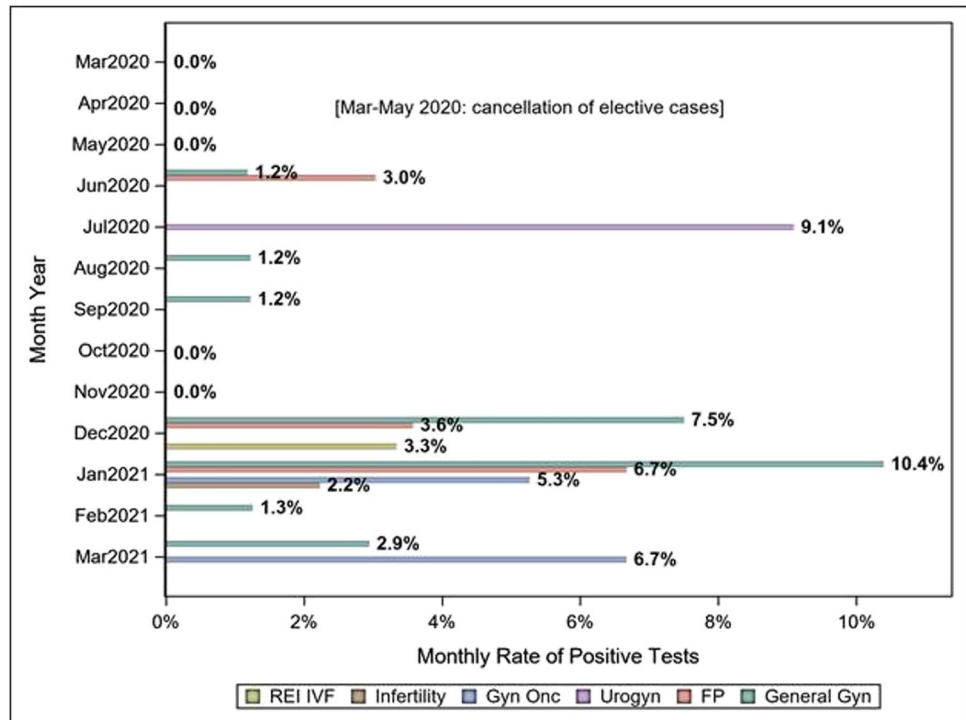
This large cross-sectional retrospective study evaluated the incidence of asymptomatic positive COVID-19 patients undergoing IVF, FRS, and other gynecologic surgeries. Our study sought to evaluate the prevalence of COVID-19 in our gynecologic patient population, and therefore the utility of universal COVID-19 preoperative testing in a major metropolitan city that underwent several surges between March 2020 and April 2021. To our knowledge, our study is the first to compare preoperative COVID-19 positivity rates among two cohorts of patients: infertility and gynecologic surgery patients.

The overall positivity rate for any patient undergoing a gynecologic procedure or IVF was low at 1.44%. Our study demonstrated that there was a significantly lower incidence of asymptomatic COVID-19 infections in infertility patients undergoing IVF or FRS compared to other gynecologic surgery patients. There are several explanations for our findings. First, the infertility patients underwent planned, elective procedures whereas other groups of patients included those who underwent time sensitive surgeries for malignancy or pregnancy termination. Second, there may be differences in health status among the distinct patient populations. The gynecology oncology patients may be more immunocompromised, dependent on caregivers, or spend more time in hospital settings. The difference in positivity rate could also be age-related with a higher prevalence of asymptomatic COVID-19 in older age groups, like in the benign

Table 1 Test results by fertility-related surgery (FRS) and IVF status ($N = 2082$)

	Total $N = 2082$ % (n)	IVF or FRS $n = 470$ % (n)	Neither IVF nor FRS $n = 1612$ % (n)	p -value
Test result				0.0274
Positive	1.44 (30)	0.43 (2)	1.74 (28)	
Negative	98.37 (2048)	99.15 (466)	98.14 (1582)	
Indeterminate	0.19 (4)	0.43 (2)	0.12 (2)	

Fig. 1 Monthly rates of positive tests each month per patient cohort



gynecology or gynecology oncology patients. Thirdly, the UCLA Reproductive Endocrinology and Infertility Clinic counseled each patient up-front that a positive COVID-19 preoperative result would cancel their cycle or scheduled surgical procedure. This was documented in each clinic encounter which may ultimately have led to lower overall positivity rates. Given the financial, emotional, and physical resources required for infertility treatments, those patients may be uniquely motivated to avoid a COVID-19 infection. Finally, while data regarding race and socioeconomic status were not available for all patients included in this study, these are possible confounders that could be responsible for the difference in COVID-19 positivity rate rather than the type of gynecologic treatment, as the prevalence of COVID-19 varies between races and socioeconomic statuses, with higher rates of infection and mortality in black and Hispanic populations [13, 14], and it has been well documented that there are racial and socioeconomic disparities between those who can afford infertility procedures and those who undergo general gynecology procedures [15, 16].

The low COVID-19 positivity rate in our study is consistent with prior studies examining the positivity rate among infertility centers. Shaw et al. reported an overall positivity rate of 0.4% among infertility patients undergoing treatment at a major academic institution in New York City, which is a similar positivity rate in our population [9]. Similarly, another study performed in a New York fertility practice yielded a 0.8% positivity rate in IVF patients [17]. Furthermore, a study from Israel in 2020 found that

0.54% of asymptomatic women tested positive on routine screening prior to IVF treatment [18]. Our study greatly adds to the current limited literature by expanding the timeframe and using a comparison cohort of gynecological patients.

Similar to the FDA requirement testing for sexually transmitted infections, the purpose of standard COVID-19 testing is to prevent the transmission of SARS-CoV-2 between patients, medical personnel, embryology staff, and gamete-gamete contamination. A recent international survey of fertility clinics has shown that only 53% of clinics require COVID-19 testing prior to treatment [19]. If routine testing is not implemented, it is possible that there is a risk of virus exposure and gamete contamination by treating unknown positive patients. Although prior studies have not demonstrated that SARS-CoV-2 infections impact IVF treatment outcomes thus far, the data are limited [20].

Beyond preventing COVID-19 transmission, routine patient testing is important given the concern that SARS-CoV-2 may negatively impact on male and female infertility. However, recent evidence is reassuring. Bentov et al. have shown that although anti-COVID IgG exists in follicular fluid after either vaccination or infection, follicular steroidogenesis and oocyte quality are unchanged [21]. Studies on COVID-19 and male infertility have demonstrated that spermatogenesis and testosterone production decrease with infection but are related to the disease severity and overall improve over time [22]. Ongoing studies are being performed to determine whether these effects are directly

related to the virus itself or whether they represent an inflammatory storm precipitated by the virus [15].

Although prior studies have proven the cost-efficiency of routine testing for asymptomatic healthcare workers, hospitalized patients, and college students, no data have specifically assessed gynecologic and infertility patients [23–26].

Our study has several strengths. It was performed at a single large academic institution controlling for variations in testing protocol. All patients underwent the same nasopharyngeal PCR test analyzed through one health system laboratory. Additionally, Los Angeles County has been hit with three separate COVID-19 surges in the study period thus providing a good representation for other major metropolitan cities.

Still, limitations persist. We acknowledge that the overall positivity rate in the study is quite low. One of the inherent limitations of cohort studies is having low incidence rates in rare diseases unless the follow up time is quite lengthy. Additionally, although the study patients were limited to 18–46 years old, the patient cohorts were not matched by age. Our demographic data did not include confounding variables like race/ethnicity, medical history, body mass index, socioeconomic status, history of COVID-19 infection, and vaccination status, all of which could impact COVID-19 positivity rates. Furthermore, we did not stratify by different cities within Los Angeles County which may further elucidate COVID-19 positivity findings. Finally, the surgeries were categorized by physician, which may have introduced bias. For example, a general gynecologist may have performed a surgery that revealed a malignancy and these patients were not re-categorized. Lastly, given the continually evolving nature of this pandemic, our study time frame does not address the emergence of new COVID-19 variants including the delta and omicron strains.

Conclusion

Our data showed that relative to other gynecologic patients, infertility patients displayed a lower COVID-19 incidence. Routine preoperative screening can permit infertility and gynecologic surgeries to continue during a pandemic with a low COVID-19 infection positivity rate and low probability of cancellation.

Future studies should evaluate the cost-effectiveness of routine screening in both the gynecology and infertility patient population, especially in the setting of different variant surges and vaccination rates. For now, it remains in the best interest of patients and clinicians alike to identify and isolate asymptomatic COVID-19 positive patients prior to procedures to curb viral spread and to prevent COVID-19 pregnancy complications [27, 28].

In the future, it is possible that with more reassuring long-term data regarding the risk of gamete transmission and IVF outcomes in the setting of vaccination and different variant surges, we can consider reducing screening strategies. The low positivity rates in the IVF patient population may justify a more targeted rather than routine screening approach and capitalizing on other interventions to minimize individual medical risk such as hand hygiene, personal protective equipment, questionnaires, and enhanced cleaning [24].

Appendix. List of female fertility-related surgeries

- Diagnostic hysteroscopy
- Operative hysteroscopy
- Diagnostic laparoscopy
- Laparoscopy with removal of adnexal structures
- Laparoscopy with fulguration of endometriosis
- Chromopertubation
- Dilation and curettage
- Dilation and evacuation

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s10815-022-02581-2>.

Declarations

Conflict of interest The authors declare no competing interests.

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