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SHORT COMMUNICATION



Validation of the French IVF guidelines during the COVID-19 pandemic

**BIOGRAPHY**

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ABSTRACT

Research question: Is a symptom questionnaire as per the French IVF guidelines adequate for screening patients during the COVID-19 pandemic?

Design: Patients planning IVF from June 2020 to February 2021 were included in the study. In compliance with French IVF guidelines, all patients fever-free on the day of oocyte retrieval were screened for risk of COVID-19 by completing a symptom questionnaire after being counselled regarding the importance of a COVID-19-free medical practice. Patients with IVF planned between June and September 2020 only completed the questionnaire (group 1), while those planning IVF after September 2020 also underwent the RT-PCR test for SARS-CoV-2 RNA (group 2). Cycle cancellation rates between groups were compared. Group 1 patients consented for follicular fluid testing for SARS-CoV-2 and an interview after cycle completion to determine COVID-19 exposure during the 6 months before and after retrieval.

Results: Cycle cancellation rates for groups 1 and 2 were 0% (0/214) versus 1.4% (8/577), respectively, ($P = 0.116$). All 183 follicular fluid samples from group 1 were negative for SARS-CoV-2 RNA. Of 171 patients interviewed post-IVF, 16 (9.4%) developed COVID-19 symptoms or a positive real-time PCR (RT-PCR) test, but none within 2 months pre- or post-retrieval.

Conclusions: These results provide reassurance that, consistent with the COVID-19 French IVF guidelines, use of a symptom questionnaire is effective in screening patients planning to undergo IVF. Failure to detect viral RNA in any follicular fluid sample does not negate the possibility that follicular fluid is a viral reservoir. However, the findings provide reassurance that the follicular environment in this study's carefully screened population was COVID-free.

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KEY WORDS

COVID-19
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INTRODUCTION

Infertility is a disease (Zegers-Hochschild *et al.*, 2009), it is not elective, and it requires treatment in a timely manner. IVF centres must therefore balance pressures to treat against the potential risks of introducing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus into their practices.

All three major societies of reproductive medicine – the American Society for Reproductive Medicine (ASRM), European Society for Human Reproduction and Embryology (ESHRE) and International Federation of Fertility Societies (IFFS) – have independently published recommendations for the management of patients planning to undergo IVF treatment during the pandemic. More recently, these societies published a joint statement reaffirming the importance for continued reproductive care during this unprecedented time (Veiga *et al.*, 2020). Although specific to the administration of reproductive care, each society emphasizes the importance of strict adherence to official government guidelines, given differences in national, regional and local regulations and variations in viral penetration, transmission rates and changing conditions.

Shortly after the World Health Organization declared the coronavirus disease 2019 (COVID-19) outbreak a pandemic, the French authorities issued guidelines for the safe administration of IVF treatment. Several updates have been released. All recommend the use of symptom-screening questionnaires, and while none mandates testing for SARS-CoV-2, they advise testing in symptomatic patients.

Little is known regarding whether the use of a symptom questionnaire without testing is reliable for the triage of asymptomatic patients. This question is particularly important for IVF laboratories, which must maintain the safety not only of laboratory personnel and patients, but also of the gametes and embryos in their care. Therefore, the present study was undertaken to assess the efficacy of using a symptom questionnaire for screening IVF patients for COVID-19 infection. Secondly, the prevalence of SARS-CoV-2 RNA detection in follicular fluid was investigated.

MATERIALS AND METHODS

Patients planning IVF from June 2020 to February 2021 were stratified into two groups: group 1 with planned IVF, June to September 2020; and group 2 with planned IVF, October 2020 to February 2021. Both groups completed the symptom questionnaire for COVID-19 according to the mandatory prevailing French guidelines. However, group 2 also underwent real-time polymerase chain reaction (RT-PCR) RT-PCR testing for SARS-CoV-2, 72 h before the retrieval, which was not specifically recommended by the guidelines. Questionnaires were administered 2 weeks before stimulation, at each appointment, on the day before retrieval and 2 weeks after using the Wistim application, as recommended by the French Biomedicine Agency (French Biomedicine Agency, May 2020). Group 1 patients consented to: (i) follicular fluid testing for SARS-CoV-2, which was performed after RNA extraction from 1 ml samples (Nimbus; Seegene, Eurobio, France) and analysis by SARS-CoV-2 multiplex RT-PCR using a CFX96 system (Bio-Rad, France); and (ii) participation in a comprehensive epidemiological evaluation by phone interview more than 6 months after the cycle to determine COVID-19 exposure during 6 months before and after retrieval. Foch Hospital Ethical Committee approved the study on 17 February 2021 (reference number: IRB00012437).

Cycle cancellation rates were compared between the two groups and the incidence of COVID-19 infection among IVF personnel was recorded. The percentage of follicular fluid samples positive for SARS-CoV-2 was determined, as was the proportion of group 1 patients interviewed post-IVF who had COVID-19 symptoms (anosmia and ageusia) or a positive RT-PCR test after their IVF cycle.

RESULTS

The results are shown in **FIGURE 1**. Of the 791 patients who planned IVF during the study period, 214 were in group 1 and 577 in group 2. Cycle cancellation rates based on questionnaire responses were 0% (0/214) and 0.2% (1/577) in groups 1 and 2, respectively ($P = 1.000$; Fisher's exact test); the one patient in group 2 had a fever and a confirmatory positive PCR test. Seven other patients in group 2 were cancelled: all seven were asymptomatic for COVID-19 but tested

positive, giving an overall cancellation rate in group 2 of 1.4% (8/577).

A total of 183 patients in group 1 consented to donate samples for follicular fluid testing (183/214; 85.5%), none of which tested positive for SARS-CoV-2 (0/183; 0%). Of these, 171 patients were interviewed post-cycle (171/183; 93.4%), and 16 of these (16/171; 9.3%) declared that they had had COVID-19 symptoms or a positive RT-PCR test, but not within 2 months pre- or post-IVF.

DISCUSSION

Upon the resumption of activities after the first lockdown early in 2020, French IVF centres set up a triage system using a symptom questionnaire based on the recommendations of the French Biomedicine Agency, ESHRE and the prevailing literature. Subsequently, some centres, including the authors', set up a systematic RT-PCR test for SARS-CoV-2, performed 72 h before the retrieval. However, the accuracy of this test is limited by viral load, specimen handling and the patient's window of positivity, which together may lead to unreliable results in terms of patient status (La Marca and Nelson, 2020). The test is also expensive, not all IVF centres have access to testing, and during a peak in the epidemic, testing can add complexity to the routine of a laboratory. It was therefore considered important to study the relevance of such testing in the setting of clinical IVF.

In the present study, the cycle cancellation rate of patients who complied with the guidelines by answering a symptom questionnaire was insignificantly different from those who also had a RT-PCR test for SARS-CoV-2 (0% versus 1.4%; $P = 0.116$). Moreover, no IVF personnel developed COVID-19 during the study period. It was therefore concluded that use of a symptom questionnaire is effective in screening patients planning to undergo IVF and that adding a PCR test does not improve patient triage. Finally, none of the patients interviewed post-IVF in group 1 developed pathognomonic symptoms of COVID-19 or had a positive PCR test in the 2 months before or after retrieval, which is once again reassuring in relation to the use of the practice without testing.

None of the 183 follicular fluid samples from group 1 was positive for SARS-

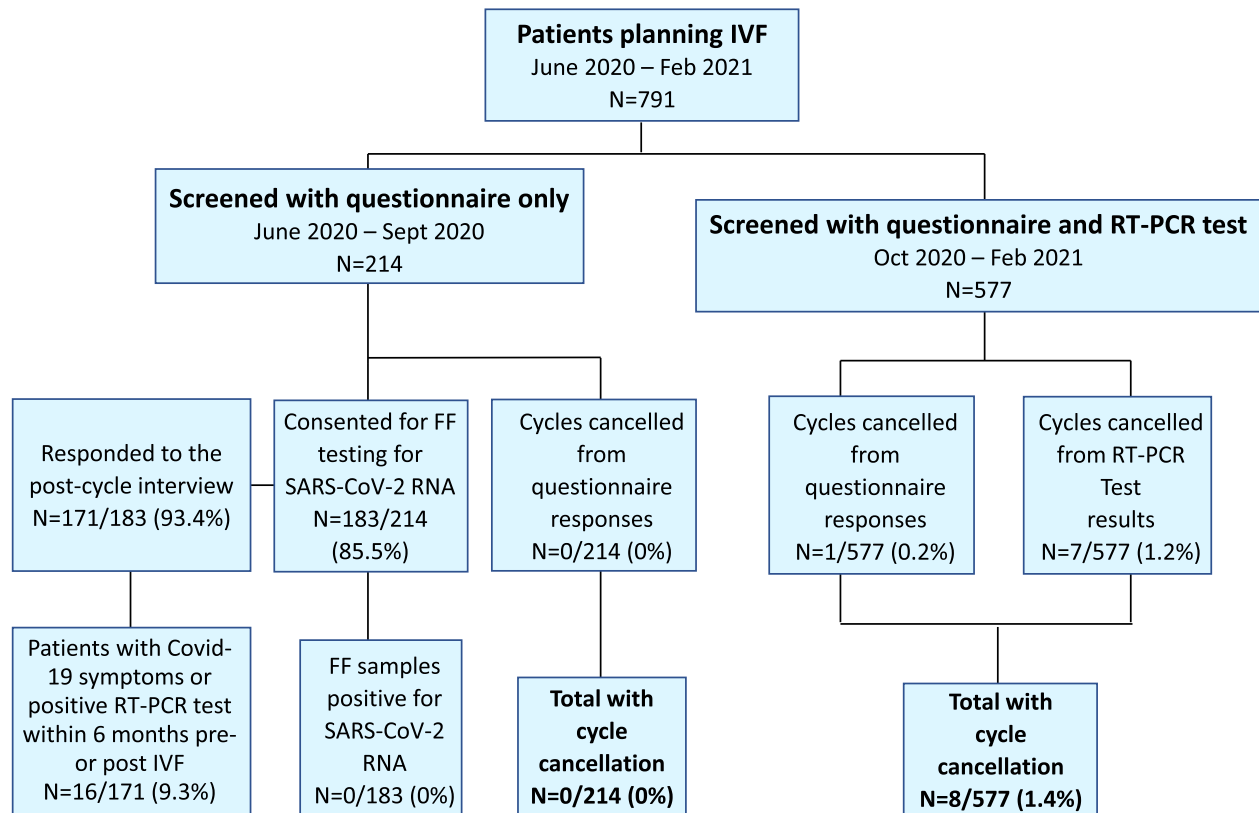


FIGURE 1 The design and results of the study, assessing the efficacy of using a symptom questionnaire for triaging IVF patients. RT-PCR, real-time-PCR.

CoV-2, which provided reassurance that despite the fact that patients had not had a PCR test before retrieval, the safety of their oocytes had been ensured. Recently, Rajput and colleagues (*Rajput et al., 2021*) also reported the absence of SARS-CoV-2 viral RNA from follicular fluid, although their patients had tested negative for COVID-19 at 3–4 days prior to the procedure. While neither observation negates follicular fluid being a viral reservoir, a single case report failing to detect viral RNA in follicular fluid from a SARS-CoV-2-positive woman suggests that viral transmission in follicular fluid may not occur (*Demirel et al., 2021*).

In summary, these results provide reassurance that a symptom questionnaire completed by patients at the intervals recommended by the French guidelines is adequate for effectively triaging IVF patients.

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