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

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Validation of the French *in vitro* fertilization guidelines during the Covid-19 pandemic

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KEY WORDS

Covid-19, French guidelines, IVF, follicular fluid

KEY MESSAGE:

Administration of a symptom questionnaire to patients planning IVF, at intervals recommended by the French IVF guidelines, are adequate for effectively triaging IVF patients. Triaged in this manner, no cycles were cancelled and no patient had SARS-Cov-2 RNA detectable in their follicular fluid.

ABSTRACT

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

Design: Patients planning IVF from June 2020 through February 2021 were included in the study. In compliance with French IVF guidelines, all fever-free patients on day of oocyte retrieval were screened for risk of Covid-19 by completing a symptom questionnaire after being counseled regarding importance of a Covid-19 free medical practice. Patients cycling between June and September 2020 only completed the questionnaire (Group 1), while those planning IVF after September, 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 (FF) testing for SARS-CoV-2 and an interview post-cycle completion to determine Covid-19 exposure during 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 FF samples from Group 1 were negative for SARS-CoV-2 RNA. Of 171 patients interviewed post-IVF, 16 (9.3%) developed COVID-19 symptoms or a positive RT-PCR test, but none within two months pre- or post-retrieval.

Conclusion: 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 FF sample does not negate the possibility that FF is a viral reservoir. However, the findings provide reassurance that the follicular environment in our carefully screened population was COVID-free.

INTRODUCTION

Infertility is a disease (Zegers-Hochschild et al., 2009), it is not elective, and requires treatment in a timely manner. In vitro fertilization (IVF) centers must therefore balance pressures to treat against potential risks of introducing SARS-CoV-2 virus into their practices.

All three major societies of reproductive medicine, ASRM, ESHRE and 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 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 WHO declared the Covid-19 outbreak a pandemic, the French authorities issued guidelines for the safe administration of IVF treatment. Several updates have been released. All recommend use of screening symptom questionnaires, and while none mandate testing for SARS-CoV-2, they advise testing in symptomatic patients.

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

METHODS

Patients planning IVF from June 2020 through February 2021 were stratified into two groups: Group 1 with planned IVF, June through September 2020; and Group 2 with planned IVF, October 2020 through February 2021). Both groups completed the symptom questionnaire for Covid-19 according to the mandatory prevailing French guidelines. However, Group 2 also underwent RT-PCR testing for SARS-CoV-2, 72h before the retrieval, which was not specifically recommended by the guidelines. Questionnaires were administered two weeks before stimulation, at each appointment, on the day before retrieval and two weeks after using the Wistim application, as recommended by the French biomedicine agency (French Biomedicine Agency, May 2020). Group 1 patients consented for: 1) FF testing for SARS-CoV-2, which was performed after RNA extraction from 1 ml samples (Nimbus, Seegene*) and analysis using a SARS-CoV-2 multiplex RT-PCR using CFX96 (Biorad*); and 2) participation in a comprehensive epidemiological evaluation by phone interview more than 6 months post-cycle to determine Covid-19 exposure during 6 months before and after retrieval.

Cycle cancellation rates between the two groups were compared and incidence of Covid-19 infection among IVF personnel recorded. The percentage of FF 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 comprised Group 1 and 577 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 confirming PCR positive test. Seven other patients in Group 2 were cancelled: all 7 were asymptomatic for COVID-19 but tested positive, giving an overall cancellation rate in Group 2 of 1.4% (8/577).

183 patients in Group 1 consented to donate samples for FF testing (183/214; 85.5%), none of which tested positive for SARS-CoV-2 (0/183; 0%). 171 patients were interviewed post-cycle (171/214; 93.4%), sixteen of whom (16/171; 9.3%), declared they had Covid-19 symptoms or a positive RT-PCR test, but none within 2 months pre- or post IVF.

DISCUSSION

Upon resumption of activities after the first lock-down early in 2020, French IVF centers 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 centers, including ours, have set up a systematic RT-PCR test for SARS-CoV-2, performed 72 hours preceding the retrieval. However, 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 of patient status (La Marca and Nelson, 2020). The test is also expensive, not all IVF centers have access to testing, and during a peak epidemic, testing can add complexity to the routine of a laboratory. We therefore considered it 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. We therefore conclude 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 we interviewed post-IVF in Group 1 developed pathognomonic symptoms of Covid-19 or had a positive PCR test in the two months before or after their retrieval, which is once again reassuring about our practices without testing.

That none of the 183 FF samples from Group 1 were positive for SARS-CoV-2 gave us reassurance that despite not having a PCR test before retrieval, the safety of our patients' oocytes was ensured. Recently, Rajput et al (2021) also reported absence of SARS-CoV-2 viral RNA in FF, although their patients had tested negative for Covid-19, 3-4 days prior to the procedure. While neither observation negates FF being a viral reservoir, a single case report failing to detect viral RNA in FF of a SARS-CoV-2 positive woman suggests that viral transmission in FF may not occur (Demirel et al., 2021).

In summary, our 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.

REFERENCES

Demirel, C., Tulek, F., Celik, H.G., Donmez, E., Tuysuz, G., Gokcan, B. Failure to detect viral RNA in follicular fluid aspirates from a SARS-CoV-2-positive woman. Reprod Sci 2021. Published Feb 22, 2021. https://doi.org/10.1007/s43032-021-00502-9.

https://www.agence-biomedecine.fr/Recommandations-sur-les-modalites-de-prise-en-charge-des-couples-dans-le

La Marca, A., Nelson, S.M., SARS-CoV-2 testing in infertile patients: Different recommendations in Europe and America, J Assist Reprod Genet 2020; 37(8):1823-1828.

Rajput, A.K., Khan, S.A., Goheen, B.B., Engelhorn, H. J., Logsdon, D.M., Grimm, C.K., Kile, R.A., West, R.C., Yuan, Y., Schoolcraft, W.B., McCormick, S., Krisher, R.L., Swain, J.E. Absence of SARS-CoV-2 (COVID-19) virus within an active IVF laboratory using strict patient screening and safety criteria. Published: March 06, 2021 https://doi.org/10.1016/j.rbmo.2021.03.005.

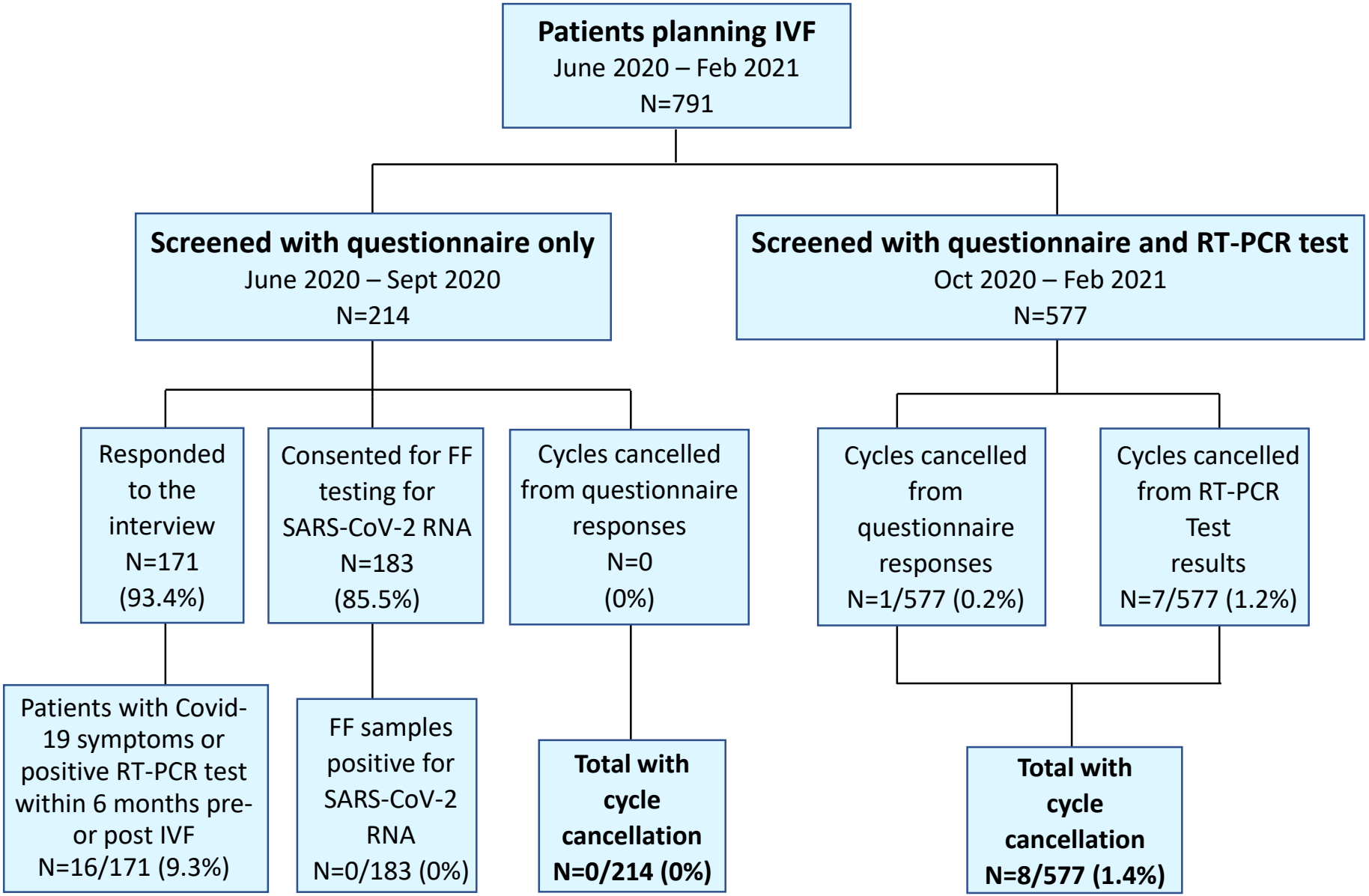
Veiga, A., Gianaroli, L., Ory, S., Horton, M., Feinberg, E., Penzias, A. Assisted reproduction and COVID-19: A joint statement of ASRM, ESHRE and IFFS. Fertil. Steril. 2020; 114(3):484-485.

Zegers-Hochschild, F., Adamson, G.D., de Mouzon, J., Ishihara, O., Mansour, R., Nygren, K., Sullivan, E., van der Poe,l S., on behalf of ICMART and WHO. The International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary on ART terminology. Hum Reprod 2009; 24(11):2683–2687.

FIGURE LEGENDS

Figure 1: Design and results of study assessing efficacy of using a symptom questionnaire for triaging IVF patients

Figure 1


Patients planning IVF
June 2020 – Feb 2021
N=791
Screened with questionnaire only
June 2020 – Sept 2020
N=214
Screened with questionnaire and RT-PCR test
Oct 2020 – Feb 2021
N=577
Responded to the interview N=171 (93.4%)
Consented for FF testing for SARS-CoV-2 RNA N=183 (85.5%)
Cycles cancelled from questionnaire responses N=0 (0%)
Cycles cancelled from questionnaire responses N=1/577 (0.2%)
Cycles cancelled from RT-PCR Test results N=7/577 (1.2%)
Patients with Covid-19 symptoms or positive RT-PCR test within 6 months pre- or post IVF N=16/171 (9.3%)
FF samples positive for SARS-CoV-2 RNA N=0/183 (0%)
Total with cycle cancellation N=0/214 (0%)
Total with cycle cancellation N=8/577 (1.4%)