Questions and answers for professionals

The COVID-19 Working group has addressed the questions that were asked during the webinar of 11 May 2020. Some questions have been combined or reformulated. Questions and answers are listed below per topic.

- GENERAL
- RESTART ACTIVITY and ADAPTATION OF SERVICES
- STAFF – testing and protection
- CODE OF CONDUCT - preventing infection during treatment
- TRIAGE AND TESTING
- LAB PROCEDURES
- CLINICAL PROCEDURES

There were a number of remaining questions that were not considered as they were comments outside our scope or questions related to costs and reimbursements. For questions on general IVF laboratory issues unrelated to COVID-19, we recommend consulting the Revised guidelines for good practice in IVF laboratories (2015) (https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Revised-guidelines-for-good-practice-in-IVF-laboratories-(2015))

GENERAL

1. Why has ESHRE made a statement to stop all fertility treatments?

In an event such as the COVID-19 pandemic, a scientific society as ESHRE will be in the best position to formulate advice to centres and ART professionals on how to handle the situation. Taking into account all available information, to support the necessary reallocation of healthcare resources, and to observe the current recommendations of social distancing, a group of experts weighing all benefits and risks of such a statement concluded that a temporary stop of non-urgent fertility treatments is appropriate to ensure the safety of all patients and professionals. Meanwhile ESHRE has prepared a document 'guidance for recommencing ART treatments" to support centres restarting their activities.

2. Why did ESHRE not advise to refrain from spontaneous / natural pregnancies?

A pregnancy resulting from fertility treatment is the outcome of a controlled medical procedure, whereas a pregnancy resulting from natural conception is not. An IVF pregnancy can be suspended or deferred, even after treatment has started; a non-IVF pregnancy cannot. Moreover, the method of conception of a natural pregnancy does not infringe social distancing from a community standpoint or does not consume medical resources. As such, we did not see a strong rationale for avoiding natural conceptions, as long as a couple desires pregnancy under current circumstances.

In addition, the ESHRE COVID-19 Working group refrains from making statements on issues outside of their field of expertise, i.e. obstetric follow-up of pregnancy.

3. Why did ESHRE make an exception for fertility preservation for oncology patients?

Fertility preservation for cancer patients is considered an urgent procedure, as these patients have to undergo treatments which usually cannot be postponed.

4. Is there really no evidence of vertical transmission?

So far, there is no convincing evidence of vertical transmission, i.e. transmission of the virus to the embryo/foetus during pregnancy, for SARS-CoV-2, and for other Coronaviridae, i.e. SARS and MERS. The reported cases of neonatal infection seem to be explained by postnatal infection, perhaps except for IgM (+) but PCR negative new-borns. However, it should be noted that cross reactions with other antibodies is a limitation of serologic tests, potentially leading to false positivity.

5. I have the impression to have more early miscarriages since 3 months with no evidence of covid-19, is there any evidence of vertical transmission or miscarriage?

So far, there is no convincing evidence of vertical transmission, i.e. transmission of the virus to the embryo/foetus during pregnancy, for SARS-CoV-2, and for other Coronaviridae, i.e. SARS and MERS. However, there are two case reports of placental infection, which may or may not be associated with increased miscarriage risk. Since our knowledge is mostly limited to second and third trimester pregnancies, uncertainty remains regarding risk of miscarriage associated with SARS-CoV-2 infection.

6. Are we already assured that first trimester pregnancy with COVID 19 infection is safe?

Since our knowledge is mostly limited to second and third trimester pregnancies, uncertainty remains regarding risks associated with SARS-CoV-2 infection during the first trimester.

RESTART ACTIVITY and ADAPTATION OF SERVICES

7. When will centres be able to restart ART treatments?

Of course, any decision on restarting treatments will need to take into consideration the national recommendations on non-urgent medical procedures, the impact on the clinic's organization.

Based on the specific reasons mentioned in the statement on our website, we recommend a temporary cessation of ART practices and expect that IVF treatments will be restarted as soon as the COVID-19 pandemic is under control and the risk of infection reduced to a minimum. Safety is the major concern, both for patients and professionals.

8. What precautionary measures should be considered when ART centres restart their activities?

It is of major importance that, when activities and treatments are being reinitiated, the safety for patients and professionals can be maximized. The COVID-19 working group has prepared a specific guidance document on how activity should be re-started (see https://www.eshre.eu/Press-Room/ESHRE-News#COVID19P2.)

9. What are recommendations for frozen vs fresh embryo transfers post-COVID?

From the clinical point of view, if you assess your patient to be of very low risk of infection, based on triage and testing, you can go ahead with any treatment including fresh embryo transfer. It is important to consider though that one would still want to prevent COVID-19 infection during pregnancy, and hence if the patient lives in area with an infection number1

[1] The infection number or reproduction number represents the number of new infections estimated to stem from a single case.

(reproduction number) of over 1, the risk of the patient becoming infected during pregnancy is relatively large and pregnancy could be advised against.

10. Do we need special consent for ART procedure in this time ?

Patients need to be informed, and the information in the consent form must be specific for the current situation. We recommend that standard consent forms to be updated with available information on SARS-CoV-2, including the risk, but also the aspects of care where risks are currently unknown and cannot be estimated. As stated in our guidance document; all patients should be offered a choice to proceed with or postpone their ART treatment.

11. Is it recommended to reduce IVF centre activity at the beginning?

In our Guidance for recommencing ART treatment, we suggest a number of adaptations to the ART services. Depending on the local situation and for instance the size of the clinic, applying all suggested adaptations will likely result in a reduction of treatment cycles performed. Each centre should adapt its activity to the physical capacity and staff availability aiming to ensure social distancing and respect for national guidance on reducing risk of COVID 19. Starting small and increasing the numbers as the service becomes confident that measures in place are working is recommended.

12. If the clinic will be closed for quarantine, the patient, which must be go for the puncture - what will be doing with them? Also closed for quarantine.

In our Guidance for recommencing ART treatment, we suggest emergency agreements are made between ART centres to guarantee continuity of treatment provision (see https://www.eshre.eu/Press-Room/ESHRE-News#COVID19P2.).

13. Can donor cycles be restarted, can thawed embryos be replaced?

As long as treatments can be performed according to the suggested safety precautions, the ART centre should decide which treatments are to be performed and whether or not certain patients or treatments need to be prioritized, taking into consideration national and local regulations and recommendations.

In any case, patients must be comprehensively informed and clearly understand the risks related to COVID-19 disease. Patients should be offered a choice to proceed with or postpone their ART treatment.

14. Should we stop doing baseline scans before starting ovarian stimulation and see patients directly on day 8?

While this is reasonable for most patients on a long GnRH agonist or fixed GnRH antagonist protocol, each woman varies in her response to ovarian stimulation and clinical decisions should be case based.

15. Which rotation type do you recommend for mini teams? 1 team per week? 1 team per day rotating? Is there any recommendation?

The size of the team and the timetable (daily, three daily or weekly rotation) is dependant on the number of cases that are allowed to pursue treatment and the number of staff in the service. Each centre must do due diligence by involving all staff in this decision process. The principle is that only the minimum needed staff should be present at any one time.

16. Given all these uncertainties should we prepare patients for possibility of regular clinic closures?

All IVF laboratories should develop and implement an emergency plan with specific procedures (De los Santos, 2015). During the current COVID-19 pandemic, the emergency plan should be re-evaluated and available in case a centre needs to close for instance due to insufficient staff to guarantee its activity or in case of a major COVID-19 outbreak in the area.

17. Do we quarantine IVF lab or clinic if an ongoing patient turns out to be positive?

If a patient undergoing treatment becomes SARS-COV-2 positive, it is a clinical decision whether and when her treatment can be stopped. An oncology patient ideally will continue treatment as it is her only chance to cryopreserve fertility. Other patients should be advised to discontinue treatment. All contacts should be traced and managed according to local and national protocols.

18. If you perform pick up to a COVID+ because of OHSS risk and you freeze the oocytes, would you thaw them for use just after recovery of the patient or you would wait until there will be enough evidence of safety of using those oocytes?

Any subsequent treatment should only be considered after full recovery of the patient and provided she has no secondary health issues related to the COVID 19 episode. To date there is no scientific evidence that oocytes are affected by the virus. The advice for patients will need to take into consideration the evidence at the time of return for subsequent therapy.

STAFF – testing and protection

19. How frequent do we need to test our staff?

The ideal approach is to test staff whenever they have symptoms or no later than every 2 weeks, but this depends on test availability. At present, the swab/RT-PCR tests are not 100% accurate and false positive or false negative results occur. Therefore, it remains important to primarily monitor staff symptoms on daily basis and act accordingly.

20. What kind of personal protective equipment PPE should be used during ART procedures (in the clinic and the lab)?

With regards to Personal protective equipment, ESHRE does not have any specific guidance on how and when to use personal protective equipment (gloves, masks, etc). If there are no local of national guides in your country, you can find detailed information on how and when to use personal protective equipment from the World Health Organisation (WHO) on their website https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public/when-and-how-to-use-masks

21. What is the advice for staff if they had Covid-19 symptoms, did not have the test at the time, and have recovered clinically ?

For staff that had symptoms, but recovered, a return to the clinic can be considered when the staff members is symptom free for 48h.

CODE OF CONDUCT - preventing infection during treatment

22. Would it be advisable for the patient and her partner to be isolated at home during the period of ovarian stimulation to minimize social exposure?

This question fits with the philosophy of the code of conduct. Reducing the risk of infection to a minimum is important, and patients could adapt their lifestyle to do so by for instance not going to the shops every few days or refraining from attending big gatherings. However, patients can still attend their job. Home isolation would be too strict but being extra cautious and meticulous in social distancing and hand hygiene is certainly advised during therapy.

23. Can ESHRE provide a template for the Code of Conduct?

The Code of Conduct is a matter for each centre to agree with their staff and their patients. It should detail what the services recommend as good measures to reduce risk of infection and what the services advises against. Such document would need to be in line with national recommendations (for instance in relation to protective measures) and local habits, and proportionate to the impact of COVID-19 in a certain country. Therefore, we consider that the Code of Conduct should be written within the context of the centre, the patients, the staff and the country.

TRIAGE AND TESTING

24. What kind of test are you recommending?

Each ART centre should discuss with the laboratory testing service which SARS-CoV-2 tests are available. The laboratory specialists should offer advice and guidance in interpreting the results, acknowledging that no test has 100% accuracy. COVID-19 data are emerging continuously, and both the testing tools and the advice given must be adjusted accordingly.

Repeating the tests or verifying the test result with another test can be relevant in case of unclear results. For instance, the rapid test can be useful but should if the result is doubtful, it should be repeated or followed up with a RT-PCR test.

25. Do we have to test both male and female for Covid-19, before starting stimulation?

As outline in our Guidance for recommencing ART treatments, a preliminary triage of both partners should be performed two weeks before starting the ART treatment and a further triage of both partners should be performed during ovarian stimulation. Both partners should undergo triage and if triage suggests a high risk of COVID-19 infection, the patient should not be admitted for treatment until further testing has been performed.

26. Do asymptomatic patients need to be tested? If yes, how frequently & when?

Asymptomatic patients will probably be negative on the triage questionnaire and in absence of any further risk factors for COVID-19 infection, routine testing should not be performed.

27. At what stages of the treatment pathway should tests be repeated?

Our guidance for recommencing ART treatments suggests triage (where needed combined with testing) to be performed 2 weeks prior to initiation of treatments, at the start of ovarian stimulation, before oocyte retrieval and before embryo transfer

28. How soon after a patient was SARS-CoV-2 infected will s/he be allowed to continue treatment.?

Our guidance for recommencing ART treatments reads "Patients who have recovered from a previous COVID-19 infection, proven by certified medical evidence of clearance, should have SARS-CoV-2 IgM/IgG testing prior to starting treatment". These patients can start ART treatment as soon as they can provide a negative test result showing clearance of the infection.

29. What is the option with Triage if testing is not available?

If testing is not available, one could use the Triage questionnaire to identify patients at possible risk of being SARS-CoV-2 infected. Patients at low risk can start ART treatments, while patients at high risk (for instance with specific symptoms) should be excluded from starting treatment. Without the availability of further testing, patients with moderate risk of being SARS-CoV-2 infected can be excluded from further treatments, although it is clear that this strategy would delay treatments in some healthy, i.e. SARS-COV-2-negative, patients.

30. If someone is already IgG positive, or has previously recovered from COVID-19, should we still keep checking them?

Whether re-infection with SARS-COV-2 is feasible has not been fully established, so as a precaution, triage could be performed in IgG positive patients or patients that recovered from COVID-19, similar to other patients. If the patient shows symptoms (positive triage), an RT-PCR test is recommended to exclude or confirm re-infection.

31. Why to exclude from ART based on IgM+IgG positivity? Infectiousness ends much earlier, IgM lasts much longer than actual infection, it shows only that she met the virus once. More and more not sick people will fall out

Based on the uncertainties regarding SARS-COV-2 and the lack of knowledge in most IVF centres, we suggest a cautious approach. An IgM negative/IgG positive test could be a sign of previous disease and immunity, but such interpretation should better be made by experts. We therefore suggest referring patients/staff that are IgM and/or IgG positive for further assessment by experts in virology and where needed additional testing. Off course, when confirmed that IgG is a sign of immunity due to previous disease, and the patient/staff is no longer contagious, they can off course restart treatment/professional activity.

32. Is it reasonable to ask patients who resulted negative at the triage to report any later change of status?

Patients can be requested to inform the clinic in case of any symptoms of SARS-COV-2, or for instance diagnosis of COVID-19 in someone from the same household. This request can be included in the Code of Conduct,

33. Can you specify details of the IgM and IgG test for Covid-19 . This is different to RNA PCR test?

Each ART centre should discuss with the laboratory testing service which SARS-CoV-2 tests are available. The laboratory specialists should offer advice and guidance in interpreting the results, acknowledging that no test has 100% accuracy. COVID-19 data are emerging continuously and both the testing tools and the advice given must be adjusted accordingly

LAB PROCEDURES

34. Should any specific precautions be taken when freezing oocytes or sperm? Should patients be tested for SARS-CoV-2, should samples be stored in separate tanks?

We consider any risk of viral contamination to gametes and embryos in the IVF laboratory likely to be minimal (if at all) because the repeated washing steps required for the culture and freezing protocols will result in a high dilution of any possible contaminants.

There have been no published reports on SARS-CoV-2 and cryopreservation and storage of gametes, tissues or embryos or presence of the virus in liquid nitrogen. Therefore, no specific recommendations on cryopreservation and storage can be given, except for the general recommendation to follow good clinical and laboratory practice to guarantee safety for processed tissues and cells, professionals and patients (see also https://academic.oup.com/humrep/article/31/4/685/2380139 and https://www.eshre.eu/Europe/European-Union/Legislation-EUTCD).

Applying culture and freezing protocols for samples infected with other viruses (HIV, HepC) could be considered for storing samples from SARS-CoV-2 infected patients. .

35. What about IVF methods? ICSI or conventional IVF?

Our guidance for recommencing ART treatments outlines a strategy of triage and testing aimed at detecting all patients that have a high risk of SARS-COV-2 infection. For patients with a low risk, the selected procedure, IVF or ICSI can be the same as in other circumstances, mainly decided by the semen parameters.

36. Are there any recommendations for the laboratory IVF protocols for handling and storing cells and tissues if a COVID+ patient is treated?

Our guidance for recommencing ART treatments outlines a strategy of triage and testing aimed at detecting all patients that have a high risk of SARS-COV-2 infection. For patients with a low risk, protocols similar to the pre-COVID-19 situation can be applied,
If it is considered necessary to treat a patient having ongoing COVID-19 symptoms (for instance in cases of urgent fertility preservation), applying similar culture and freezing protocols as for samples infected with other viruses (HIV, HepC) could be considered.

37. How should gametes and embryos from SARS-CoV-2 infected patients be stored?

The reports published on the presence of the virus in the ejaculate are controversial. Very limited information has been published on whether embryos have SARS-CoV-2 receptors and the necessary machinery for virus replication. High security straws and preferably vapor liquid nitrogen are recommended for freezing and storage of gametes and embryos from COVID-19 positive patients. Similar procedures to the ones used for other viruses (HIV, Hep C) can be used.

38. Can positive and negative samples be stored together? Is there a risk of contamination within the tank?

Samples from patients with an ongoing virus infection are always recommended to be stored separately, either in separate tanks, or in a tank with vapour gas phase.

39. Do you recommend testing (PCR) before storage of gametes/embryos?

Our guidance for recommencing ART treatments reads "the key principle in restarting activity in an ART centre is that patients, staff and anyone attending the centre is triage-negative. From a patient perspective, it means that only triage-negative patients are

commencing and continuing treatments". This means that all patients attending the clinic, including donors, should be triaged. If triage-negative, treatments/collection can be continued, if triage positive, further testing is recommended to exclude or confirm a SARS-CoV-2 infection, and appropriate actions are required.

40. What is the best protocol for semen analysis in IVF clinic during the pandemic?

One should assume that any patient can be contagious. Based on a recent study detecting SARS-COV-2 in sperm samples, precautions should be taken, as always. Semen preparation for COVID-19 negative patients can be performed applying standard procedures in the lab, although additional washing steps can be added. The general recommendation is to follow good clinical and laboratory practice to guarantee safety for processed tissues and cells, professionals and patients (see also https://academic.oup.com/humrep/article/31/4/685/2380139 and https://www.eshre.eu/Europe/European-Union/Legislation-EUTCD). This being said, the most important thing is still to try to identify possible SARS-COV-2 infected patients before they enter treatment, by applying the triage and performing tests where needed.

For handling SARS-COV-2 positive samples, for instance in cases of urgent fertility preservation, applying culture and freezing protocols for samples infected with other viruses (HIV, HepC) could be considered.

41. How long does the virus survive in culture media?

No information is available on this issue, but the methodologies used in the IVF lab (repeated washings that lead to high dilution levels) should minimize virus presence in culture media.

42. Would be a PCR testing of the embryo medium culture necessary to know if there are virus particles affecting it? Is there someone studying it?

No information is available on this issue, but the methodologies used in the IVF lab (repeated washings that lead to high dilution levels) should minimize virus presence in culture media. If you would want to confirm the presence of the virus in the culture medium, you would indeed need to perform a PCR test.

43. How should ART labs be disinfected?

ESHRE does not provide guidance on which disinfectants need to be used in IVF laboratories, except for mentioning "Disinfectants with proven compatibility and efficacy for an IVF laboratory should be used." (see https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Revised-guidelines-for-good-practice-in-IVF-laboratories-(2015))

A recently published paper (https://pubmed.ncbi.nlm.nih.gov/32275260/) has presented the following data:

Table 1 - Inactivation of SARS coronavirus Strain FFM1 by different types of biocidal agents.

Virus	*Biocidal agent*	*Reduction of viral infectivity (log_{10})*	*Exposure time*	*Ref*
SARS coronavirus Strain FFM1	Ethanol 95%	≥ 5.5	30s	[21]
	Ethanol 78%	≥ 5.0	30s	[21]
	2-Propanol 75%	≥ 4.0	30s	[22]
	2-Propanol 70%	≥ 3.3	30s	[23]
	Formaldehyde 1%	>3.0	2min	[23]
	Glutardialdehyde 0.5%	>3.0	2min	[23]
	Povidone iodine 0.23%	≥4.4	15s	[24]

We suggest to check your current disinfectants, compatible with an IVF laboratory, against this table.

44. Do you recommend testing embryos for virus before embryo transfer?

Very limited information has been published on whether embryos have SARS-CoV2 receptors and the necessary machinery for virus replication. The methodology used in the IVF lab (repeated washings that lead to high dilution levels) should minimize virus presence in culture media and potential attachment to the embryo. Furthermore, it is probably more efficient to test the patient rather than the embryo.

45. Is aliquoting of media safe?

There are no indications of any risks related to aliquoting of media. General guidance can be found in the Revised guidelines for good practice in IVF laboratories (2015) (https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Revised-guidelines-for-good-practice-in-IVF-laboratories-(2015))

CLINICAL PROCEDURES

46. Are there any recommendations concerning ovarian stimulation protocols in the Covid-19 era? Should antagonist only protocol be used to reduce OHSS in all patients?

Our guidance for recommencing ART treatments outlines a strategy of triage and testing aimed at detecting all patients that have a high risk of SARS-COV-2 infection. For patients with a low risk, ovarian stimulation protocols can be applied, similar to the pre-COVID-19 situation.

With regards to the antagonist protocol, there may be 2 advantages. The first advantage is that the antagonist protocol allows you to better react to overresponse and hence can be helpful to avoid OHSS. A second advantage is that it may require less visits to the clinic. However, there may be patients however that would benefit from an agonist protocols, like endometriosis patients, so the choice of protocols should be based on experience and patient suitability.

47. How about the choice of anaesthesia for egg collection? It switching from aerosol generating general anaesthesia to local anaesthesia to be considered?

In the current situation and considering the risks of horizontal transmission, switching from aerosol generating general anaesthesia to local anaesthesia may be a reasonable approach.