ESHRE SIG SQART Webinar "Going through the COVID-19 transition in the IVF lab: how can quality management help?" on 08/06/2020

Questions during the webinar:

NOTE: All the responses provided below are based on currently available evidence and current expert opinions. As explained in the webinar, the aim was to explain how to use quality management (TQM) principles to develop answers to laboratory questions, rather than make didactic statements or specific recommendations. Dr David Mortimer (SIG Safety and Quality in ART) has answered below questions in writing.

- **Can the virus be transmitted during incubation? If we missed appropriate handling of asymptomatic patient embryos, is there a possibility of contaminating another embryo sharing the same incubator or cultured in the same place?**

  There is no evidence currently to support this. SARS-CoV-2 is a respiratory virus that requires particular receptors (ACE2) on the cell surface to infect cells. Also, the surface of embryonic cells is concealed by the zona pellucida until blastocyst hatching. However, I have found a non-peer-reviewed MS about this on the arXiv website (https://arxiv.org/abs/2004.04935) – but the site states that it "should not be relied upon without context to guide clinical practice or health-related behavior and should not be reported in news media as established information without consulting multiple experts in the field". While those authors recommend "that couples be advised to avoid conceiving during the pandemic and that IVF procedures be kept to a minimum to prevent any possible hazard to the developing embryos", this has not been seen as a concern in the field at large.

  While a more definitive response should therefore be sought from expert virologists, the transmission of viruses between patients through embryo culture procedures should be extremely unlikely with proper handling practices - along the same lines as the risks of transmission of other infections between cases. This should be considered via a formal risk assessment based on your own practices.

- **Do you suggest self-isolation for patients before, during and after treatment?**

  This is a matter of public health management based on the local risk of infection transmission. For example, New Zealand has just been declared COVID-19 free and is reopening without social distancing, yet other places are still in total lockdown.

- **Can we use alcohol gel to disinfect hands in the theatre/lab area?**

  This was answered during the webinar, but is a very important point: alcohol gel should not be used where there is any possibility of alcohol fumes entering the embryology lab because they are highly embryotoxic.

- **Do you advise using a dedicated tank for COVID patients?**

  This was answered during the webinar. Your risk assessment needs to consider a range of points, including:
  - information on the risk of transmission of SARS-Cov-2 via this route
  - the real world likelihood of transmission between packaging devices within the tanks (might be influenced by local regulatory requirements)
  - open vs closed vs sealed devices (I recommend using high security devices that are virus-proof)

- sanitizing devices upon removal from storage for use
- risk of tank contamination by frozen moisture (with microorganisms) from staff-exhaled air

- **Do we need to reduce carry on media volume during gamete or embryo handling to reduce chance of viral load between drops?**

  This depends on your initial risk assessment of the possible presence of virus in the culture media. If you consider this a significant risk. For example, if sperm are processed using a technique such as DGC with the ProInsert device, the carry-over of virus would be considered negligible. For embryos, a protease treatment technique such as used with bovine embryos to eliminate BVD (bovine viral diarrhoea) virus (see, for example, https://pubmed.ncbi.nlm.nih.gov/10735047/) might be considered. For human ICSI cases, this might be performed after stripping and before injection; for IVF cases, perhaps after the fertilization check denudation.

  This would seem to be an area where the SIG Embryology might provide guidance.

- **Do we need to limit number OPU procedures per day to reduce risk between patients? If yes, how many OPUs per day / per OPU procedure room?**

  This was answered during the webinar. The answer is likely to be clinic-specific and will depend on many local factors. I recommend that each centre calculates its own practical patient throughput, including:
  - current prevalence of COVID-19 in the population being served, including its R value (effective reproduction number)
  - time taken per OPU
  - time to turn around the OPU room (including sanitization procedures and number of staff available)
  - layout (open spaces, bays, etc) and capacity of the recovery area
  - time allowed in recovery
  - time needed to sanitize the recovery space (including number of staff available)

- **How do you think this will impact labs choosing to take on new staff, in particular trainees? And then what would you recommend to people trying to start their embryology career in the current climate?**

  It will certainly be more difficult to train novices, but not impossible. Consider the following: education sessions can be given while distancing. Demonstrations can be given via video link. Record the trainee performing ICSI and review afterwards, watch them performing “solo” injections using a remote monitor. General oversight of lab work can be done while distancing, or one could consider the use of a “bodycam” (or perhaps a Go-Pro camera or a re-purposed “dashcam” device that has a suitably close-up focal distance?).

  Poor performing staff probably just need practice rather than fresh instruction. Remedial practice for ICSI or biopsy could easily be handled via video recordings or oversight on a second remote monitor.

- **Decontaminating the straws?**

  This was answered during the webinar. For sperm (or slow-frozen embryo) straws, thaw them as per protocol then sanitize the outside using, e.g. Oosafe, then cut them and expel the contents into a tube or dish.

  Decontamination of open vitrification devices is problematic. For close devices see the manufacturer’s recommendations. For HSV devices it is not an issue.

- **How could we clean the microscope's lenses without damaging them?**

First read https://www.olympus-lifescience.com/en/discovery/how-to-clean-and-sterilize-your-microscope/

Basic points to consider:
a) To prolong the life of the lenses clean only as often as necessary; every time you wipe them there is a risk of scratching. So preferably clean when you have finished using the microscope rather than between cases.
b) Use highpoint eyepieces to reduce physical contact with the eyepieces.
c) Mount all sperm morphology and vitality slides before reading them to avoid contaminating the objectives (this should already be standard practice).
d) In the embryology lab wipe with H2O2 or Oosafe (and then perhaps with sterile water if Oosafe was used). In an andrology lab outside the cleanroom alcohol could be used.
e) If you have to use alcohol to remove grease (or dried-on immersion oil), do so outside the embryology lab.

- **Are any clinics that you are aware of asking patients to sign a disclaimer in relation to the risk associated with treatment at this time**

  This is a medical practice matter.

- **What are your thoughts on the efficacy of Oosafe between cases?**

  Information available from Sparmed states that Oosafe is effective against coronaviruses. Contact the company (info@sparmed.dk) or your local distributor for a copy of that document.

- **ESHRE recommends serological testing for SARS-CoV-2 before starting ART treatment. You said that serological testing is not reliable, meaning that you disagree with the recommendation?**

  This was answered during the webinar. It is also mainly a medical practice matter upon which ESHRE has provided guidance for all clinics to consider when developing their own strategies.

  The key issue behind my comment was that many of the antibody tests launched during the past few months have very high false negative rates, so caution need to be exercised based on what the local availability of testing is, and what tests are being used. PCR testing, if available, is obviously the most effective, with repeat testing during stimulation and just before OPU (and perhaps ET); this reflects many people's ideas of best practice. If only fever monitoring and antibody testing are used, then there would be a much higher risk of an infected but asymptomatic patient entering the clinic.

- **What concentration of H2O2 is used for regular cleaning in the IVF lab? What do you recommend use between one procedure and the other?**

  Usually 6% (v/v) H2O2

  It is usual for labs to wipe down between cases, often with a more rigorous cleaning if biological material was spilled.

  Also see the answers to related questions on H2O2 later in this list.

- **What should be the strategy for sterilizing LN2 tanks with embryos stored inside? What should be the usual duration to sterilize?**

  The specimens have to be moved into a spare tank before cleaning.
  I suggest reading the review by Schiewe et al., J Assist Reprod Genet 36:5-14, 2019. doi: 10.1007/s10815-018-1310-6
  Also see http://lentilab.unige.ch/liquidn2tanksdecontamination.html

- **But there is still the possibility of transferring contamination already present in LN2 around canisters?**

  This is why all specimens should be considered as contaminated on their outside when removed from cryostorage (even if vapour storage is used), and should be sanitized after thawing before opening the packaging. This is why I personally am not a fan of open vitrification devices.

  Also refer to my earlier answer to a similar question.

- **If the whole culture room is equipped with a proper air purification system, is it still necessary to have laminar flow running?**

  The laminar air flow (LAF) cabinet is to protect the specimens (including dishes during preparation) from possible contamination from the operator. To protect the operator, vertical (VLAF) cabinets are better than horizontal (HLAF) cabinets, but, if that is a real need, a biohazard (Class II) cabinet should be used. This is why all semen samples need to be handled in a Class II biohazard cabinet, but once the sperm are separated from the leucocyte-rich cells (i.e. after the gradient has been centrifuged) a VLAF cabinet is usually considered adequate protection.

- **In our laboratory, I found alcohol more effective than Oosafe. is alcohol preferred?**

  How do you define "more effective"? It would be good if you'd share your evidence, i.e. data (and methodology) – and better still if you could publish it.

  Alcohol should not be used inside the embryology lab (or anywhere within the contiguous cleanroom space) due to its embryotoxicity. See the Cairo Consensus on the IVF lab environment and air quality (open access: Reprod Biomed Online 36:658-674, 2018; https://doi.org/10.1016/j.rbmo.2018.02.005)

- **What is your suggestion time between processing two semen samples?**

  This would be very much influenced by your infection control practices, especially if the lab is located in a hospital environment. I have seen a wide range of "accepted" practices, ranging from quite broad in terms of allowing multiple samples to be processed within the lab at the same time to highly restrictive, allowing only one at a time.

  Usual risk analysis allows only one specimen within the active work area at a time, but often allows more than one to be processed in parallel for efficiency. It is better to have two separate 3-ft cabinets rather than to have two people working in a 5- or 6-ft cabinet.

  What is acceptable in one lab might not be allowed in another, so I recommend a local formal risk assessment by a group whose members cover all the relevant areas of expertise, remembering that specimen identity verification and the safety of the sperm are paramount.

- **is it necessary to wear N95 masks when we treat the embryos?**

  There is no evidence of infection of people from embryos, so they are not the risk here. The real risk is your colleagues, and mask wearing is about protecting your co-workers, not yourself. If you believe you are infected with SARS-CoV-2 then you should not be at work.

  The question about operators infecting embryos in culture was answered already in this list. If your are working in VLAF cabinets or IVF chamber workstations using proper handling practices, the transmission of viruses through embryo culture practices seems extremely unlikely, similar to the risks of transmission of other infections between cases.

- **What do you think about ozone air cleaning?**

  Ozone is harmful to embryos (and human beings) so I'd not recommend it except under very strictly controlled conditions where there is no risk of exposure.

- **Is there any risk of COVID-19 infection during semen analysis?**

  Assuming that SARS-CoV-2 is present in semen (published evidence is equivocal and based on low case numbers, but the precautionary principle would assume its presence) then there is some risk, but probably only via hand contamination followed by face touching, or inhalation of aerosol droplets. Standard safe handling practices would seem adequate to cover this risk, and be enhanced if a face mask (better, a face shield) is worn. In general, I would be far more worried about hepatitis C or HIV infection from semen than SARS-CoV-2.

  I recommend a collaborative formal risk assessment if staff are overly concerned about this matter.

- **As a quality measure, what is your suggestion about microbial testing. Should frequency be reduced?**

  Microbial testing is usually only for bacteria, not viruses, so I'm not sure this would be helpful. If you are concerned about validating your sanitization procedures, appropriate protocols should be developed in consultation with an infectious diseases expert.

- **Do you suggest fumigation in a patient room/embryo transfer room or installation of a UV lamp?**

  All infection control / public health recommendations that I have seen consider surface cleaning and ventilation more important. Outside the cleanroom this is a medical practice issue and strategies need expert development. But remember that fumigation typically requires a clearance period afterwards, so it will greatly influence the throughput of patients.

  Inside the cleanroom I have recommended the use of photocatalytic oxidation systems to remove VOCs, and their integral UV light kills airborne bacteria and fungal spores and also destroys viruses.

  Units such as the Zandair PCOC3 can be retro-fitted into the HVAC ducts, and the Zandair 100C floor-standing units can be used inside the lab, as well as in semen collection rooms.

- **What is the risk of transmission to the embryologist if proper PPE are not provided?**

  This was answered during the webinar. The extent of the risk will depend on local conditions in terms of the likelihood of patients – and, more importantly, co-workers – being infectious. So, for example, right now in New Zealand the risk would be seen as essentially zero, but in many parts of the world it would be judged as quite high based on the likely prevalence of asymptomatic infected people.

  All COVID-19 public health regulations require the use of appropriate PPE, and this has to be provided by employers. Worker safety regulations would typically allow a worker to refuse to work in unsafe conditions without prejudice to their employment.

- **What is your reference for using h2o2 as disinfectant?**

  Cairo Consensus on the IVF lab environment and air quality (open access: Reprod Biomed Online 36:658-674, 2018; https://doi.org/10.1016/j.rbmo.2018.02.005)

- **H2O2: for how long must it be left on the surface?**

  The longer the better. Many authorities recommend at least 1 minute. But since H2O2 breaks down to water and oxygen there is no need to wipe it off, so use it as a disinfecting agent and not as a cleaner – or use it twice, the first time to clean off the surface, and then a second time to act as a disinfectant. I'm not aware of any authoritative or consensus protocols for this in an IVF lab setting, so some well-designed studies would be very useful.

- **Sperm collection at home: how strict would you be concerning the containers that patients use. sometimes we get a container that is probably not sperm toxic tested. What to do?**

Simple answer here: always provide the patient with a known non-spermotoxic container to use (we've been doing this since the 1980s).

- **Can we use UVC to clean infected semen or is UVC safe for semen? Can it cleanse semen without damage?**

  I cannot see how this might work since UVC damages cells.
  I also do not see why this would be a new major concern since all semen samples are already treated as being potentially infectious anyway.
  Protocols to avoiding carry-over of viruses into the washed prep are already available, e.g. for HIV-positive cases, see my response to an earlier question in this list.

- **In countries like Nepal, its very expensive to suggest PCR testing before treatment cycle and before a procedure. So what can we do here?**

  This is a question that needs to be answered by your physicians in consultation with local infection control and public health officials.

- **How safe is hydrogen peroxide in the embryology lab?**

  Please refer to the other questions on H2O2 already answered in this list.

- **Don't you have to leave the tank to air dry after cleaning? And what about the warranty of the tank; isn't that compromised by cleaning the tank?**

  Certainly, the tank must be allowed to dry before refilling, otherwise you'd have a layer of ice inside. See http://lentilab.unige.ch/liquidn2tanksdecontamination.html

- **Do you use cryotanks separately?**

  I assume you're asking about separate storage for known infectious samples, so this is a much larger question about safe cryobanking. My preferred solution for the past 20+ years has been to use high security devices whenever possible as they are accepted by many regulatory authorities as constituting "separate storage" (e.g. as per the EUTCD) and thereby eliminate the need for using separate tanks (and quarantine tanks too); see my review in Reprod Biomed Online (9:134-151, 2004).

- **If so, can we use 6% hydrogen peroxide in the OT room for cleaning and sterilization if the lab does not have a separated ventilation system?**

  Sanitization of disinfection using H2O2 can be used throughout the contiguous cleanroom space, which includes the embryology lab. The oxygen released is obviously not an issue.

  Please also see my comment on sanitization versus sterilization elsewhere in this list.