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COMMENTARY

Managing the IVF laboratory during a pandemic: international perspectives from laboratory managers

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ABSTRACT

Fertility societies worldwide responded to the COVID-19 pandemic by recommending that fertility clinics close, or sharply reduce, the clinical operation, leading to a shift in the management of IVF laboratories in three phases: shutdown preparation; maintenance during shutdown; and restart. Each of these phases carries distinct risks that need identification and mitigation, forcing laboratory managers to rethink and adapt their procedures in response to the pandemic. The sudden and unprecedented nature of the pandemic forced laboratory managers from around the world to base decisions on opinion and experience when evidence-based response options were unavailable. These perspectives on pandemic response were presented during a virtual international symposium on COVID-19, held on 3 April 2020, and organized by the London Laboratory Managers' Group. Laboratory managers from seven different countries at different stages of the pandemic (China, Italy, Spain, France, UK, Brazil and Australia) presented their personal experiences to a select audience of experienced laboratory managers from 19 different countries. The intention of this paper is to collect the learnings and considerations from this group of laboratory managers who collaborated to share personal experiences to contribute to the debate surrounding what constitutes good IVF laboratory practice in extraordinary circumstances, such as the COVID-19 pandemic.

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INTRODUCTION

On 12 March 2020, the World Health Organization declared the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (COVID-19) outbreak a pandemic. Several fertility societies worldwide (*ESHRE, 2020a*; *2020b*; *ASRM, 2020a*; *2020b*; *BFS and ARCS, 2020*; *Agence de la Biomédecine, 2020*; *De Santis et al., 2020*; *SIFES, 2020*; *Fertility Society of Australia COVID Response Committee Statement 2020*, *ASEBIR, 2020*) responded by recommending that fertility clinics cease IVF treatment, with the exception of essential medical fertility preservation, to protect staff and patients from unnecessary exposure to the virus (particularly given the unknown risk during pregnancy) while also allowing resources to be redeployed to frontline medical staff treating COVID-19 patients. The decision to close, or sharply reduce, the clinical operation of IVF clinics, led to a shift in the management of IVF laboratories in three phases: shutdown preparation; shutdown maintenance; and restart.

Each of these phases carries distinct risks that need identification and mitigation, forcing laboratory managers and directors to rethink and adapt their procedures in response to the pandemic.

The sudden and unprecedented nature of the pandemic forced laboratory managers from around the world to base decisions on local society and government advice, as well as personal opinion and experience when evidence-based responses were unavailable. These perspectives on how to respond to a pandemic were presented during a virtual international symposium on COVID-19, held on 3 April 2020, and organized by the *London Laboratory Managers' Group (2020)*. Laboratory managers from seven different countries at different stages of the pandemic (China in phase 3, Italy, Spain and France in phase 2, UK transitioning into phase 2, and Brazil and Australia in phase 1 (TABLE 1) presented their personal experiences to a select audience of experienced laboratory managers from 19 different countries (Australia, Austria, Belgium, Brazil, China, Denmark, France, Germany, Greece, Italy, Japan, Malaysia, Mexico, New Zealand, Saudi Arabia, Spain, Sweden, UK and USA), with attendees sharing how they personally responded to the COVID-19 pandemic.

The intention of this paper is to collect the learnings and considerations (TABLE 2) from this geographically diverse group of laboratory managers who collaborated to share personal experiences within the context of the guidelines provided by their local professional societies and governments. The proceedings reflect similarities as well as variations of opinion and practice, and can add to the debate about what constitutes good IVF laboratory practice in extraordinary circumstances, such as the current COVID-19 pandemic.

SHUTDOWN PREPARATION

In establishing processes for a planned shutdown due to COVID-19, the laboratory managers adopted standard protocols routinely carried out for short-term laboratory closures. These established routines were expanded to include elements of emergency and disaster recovery procedures (*ASRM, 2016*) and allowed the laboratory team to prepare to cease activity. The main difference to a 'standard emergency' was building in factors to mitigate the possibility of harm caused by an infectious agent that could potentially enter the laboratory either via patients or staff.

Maintaining staff morale and security through the formulation of a business continuity plan

Leadership and communication are key to maintaining staff morale, as is establishing a cohesive approach throughout the clinic. The clinic management team, the laboratory and medical director may consider establishing a themed action plan. The 'business/clinical contingency plan' sets out to:

- help manage patients, staff and others who are associated with the clinic, including suppliers and governmental bodies; and
- ensures compliance with guidelines provided by local governments and national or international professional societies.

In line with the clinic's business contingency plan, laboratory managers considered the following:

- constructing a revised process map for the IVF laboratory;
- identifying areas within the emergency action plan that can be applied;
- outlining contingencies required for maintenance of cryo-stored material:

- liquid nitrogen delivery: maintaining communication with the suppliers of liquid nitrogen or seeking alternative suppliers, e.g. from a research facility, university or the food industry;
- training non-laboratory staff to assist with liquid nitrogen tank top-ups;
- moving material to long-term storage facilities for safety purposes.
- Formulating reciprocal support agreements with nearby clinics to ensure continuation of care, so that patient care can progress should, for instance, a clinic have to close suddenly, e.g. owing to insufficient staff.

The following issues around indemnity and liability were considered by laboratory managers:

- reviewing regulatory and legal requirements when planning to carry out treatment in a third-party laboratory under a reciprocal support agreement.
- determining the need for additional indemnity insurance coverage if patient care is transferred elsewhere and if manipulation and cryopreservation of gametes and embryos carried out in the clinic of origin by external staff or in another clinic should have to take place.

Mitigating the risk of insufficient staff

Initial stages of the pandemic may lead to insufficient staff being available to handle the clinical workload. Staff may themselves become ill (or be in a high-risk group and, therefore, be advised to stay at home), may need to care for a family member, or may need to be deployed to other services in public healthcare. To avoid potential staff shortages, several laboratory managers split their laboratory team into groups and shifts. This helped to reduce the number of embryologists present in the clinic at any one time and formed a back-up system. This decision also helped to ensure that a sufficient number of team members were available, should a need arise to quarantine particular staff members.

Organizing teams of senior and junior embryologists has been easy to achieve for larger IVF units but, for smaller

TABLE 1 COVID-19 REGULATORY AND OFFICIAL RESTRICTIONS FROM GOVERNMENT AND PROFESSIONAL BODIES FOR EACH OF THE SEVEN COUNTRIES REPRESENTED IN THIS PAPER, AS OF 3 APRIL 2020

Country	Date	Response from local government and professional bodies	Phase most clinics were in as of 3 April	Clinic shutdown	Confirmed cases on 3 April 2020	Confirmed deaths on 3 April 2020
China	31 December 2019	China first notifies WHO of multiple cases of pneumonia with an unknown virus in Wuhan.	3.Restart phase	voluntary	81,639	3326
	3 January 2020	Chinese Centre for Disease Control and Prevention complete the gene sequencing, and National Health Commission of the People's Republic of China notifies WHO and other countries and regions.				
	7 January 2020	Chinese Centre for Disease Control and Prevention isolate the genome of the virus.				
	22 February 2020	Chinese Society of Reproductive Medicine guideline on actions towards COVID-19 is first published.				
	3 April 2020	Lockdowns and restrictions on IVF practice are regional. As China is past the peak, clinics are restarting cycles.				
Italy	31 January 2020	First case reported.	2. Shutdown maintenance phase	forced	119,827	14,681
	3 March 2020	The Centro Nazionale Trapianti (National Transplant Centre) recommends criteria for the triage of donors and suggests excluding patients with symptoms of COVID-19 from undergoing IVF				
	9 March 2020	Lockdown (extended to at least 4 May 2020).				
	16 March 2020	Minister of Health restricts clinical activities only to urgent and non-deferrable ones.				
	17 March 2020	The Istituto Superiore di Sanità (Italian National Institute of Health) and Centro Nazionale Trapianti recommend postponing the start of IVF cycles, concluding ongoing ones and stopping donation cycles. Urgent treatments remain possible.				
	30 March 2020	Minister of Health notifies the shutdown of all IVF services other than emergency fertility preservation for Public Service.				
Spain	31 January 2020	First case reported.	2. Shutdown maintenance phase	forced	119,199	11,198
	3 March 2020	Spain reports its second COVID-19 death.				
	4 March 2020	228 cases. The Spanish Health Organization recommends not attending conferences and similar events.				
	13 March 2020	5232 cases. The Spanish Health Organization enforces the cessation of new stimulation cycles.				
	14 March 2020	6391 cases. State of emergency declared.				
	15 March 2020	Sociedad Española de Fertilidad (Spanish Society of Infertility) recommends not planning or starting treatments, even if they do not meet the diagnostic criteria for COVID-19 infection.				
	18 March 2020	14,796 cases. Clinics plan to shut down activity.				
	21 March 2020	Spanish clinics close and remain in shutdown maintenance phase.				
	3 April 2020	Clinics remain closed.				
France	24 January 2020	First case reported.	2.Shutdown maintenance phase	voluntary	76,460	6507
	13 March 2020	Agence de la Biomedecine recommends postponing the start of IVF cycles, donation cycles, converting ongoing cycles to freeze-all, stopping treatment for symptomatic patients, postponing collection of donor oocytes and semen and postponing non-medical fertility preservation. Recommends continuing with fertility preservation in urgent situations (oncological patients). Later in March Agences Régionales de Santé (Regional Health Agencies) imposes the cessation of all treatments related to medically assisted reproduction and fertility preservation in their region.				
	16 March 2020	Closure of schools and universities imposed by government leads to a shortage of staff in IVF laboratories, and 15 days' lockdown imposed by government makes transportation to clinics difficult for patients and staff.				
	27 March 2020	Lockdown extended to at least 15 April 2020.				
	13 April 2020	Lockdown announced to end on 11 May 2020.				
	3 April 2020	Clinics remain shut.				
United Kingdom	3 February 2020	First case reported. On the basis of British Fertility Society/Association of Reproductive and Clincal Scientists (professional body) guidelines, the Human Fertilisation and Embryology Authority (regulatory body) issues a guidance note forcing clinics to shut down all services other than emergency fertility preservation.	Transitioning between 1. shutdown preparation and 2. shutdown maintenance	forced	38,168	3605
	16 March 2020	No embryo transfers.				
	30 March 2020	Last egg collection.				
	23 March 2020	Lockdown commences for non-key workers and Schools, and is expected to continue until at least 11 of May.				
	3 April 2020	Most clinics are closed, with a few completing ongoing cycles.				

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Table 1 – (continued)

Country	Date	Response from local government and professional bodies	Phase most clinics were in as of 3 April	Clinic shutdown	Confirmed cases on 3 April 2020	Confirmed deaths on 3 April 2020
Australia	25 January 2020	First case reported.	1.Shutdown prepa-	voluntary	5454	28
	17 March 2020	The Australian Health Protection Principal Committee issues an ethical framework statement that the health sector must continue its core functions.	ration phase			
	19 March 2020	The Fertility Society of Australia supports this statement, recognizing the importance of providing its members and the public with appropriate and timely guidance on best practices in reproductive care.				
		The COVID-19 FSA Response Committee is established.				
	25 March 2020	The Prime Minister announces that all elective surgery, other than urgent, is suspended until further notice. The Fertility Society of Australia recognizes some medical circumstances for which delaying treatment is not advisable and recommends that treating specialists should advise their patients on medical grounds for commencing treatment.				
	April 2020	The Fertility Society of Australia guidance remains in effect.				
Brazil	25 February 2020	First case reported	1.Shutdown prepa-	voluntary	9194	363
	March 2020	Agência Nacional de Vigilância Sanitária (ANVISA) (regulatory body) outlines guidelines for donors who have been contaminated, who have symptoms or have been in contact with someone who has. Later in March Brazilian professional societies (Sociedade Brasileira de Reprodução Assistida, Sociedade Brasileira de Reprodução Humana, and Pronucleo) and ANVISA recommend following international standards set by ESHRE and ASRM. Regional lockdowns are instated in some states, including Sao Paulo, where most IVF clinics are located.	ration phase			
	3 April	Clinics have a plan to wind down and are still operational				
Worldwide	11 March 2020	COVID-19 declared a pandemic by WHO.			1,117,272	61,465
	March 2020	ESHRE publish guidelines recommending only urgent cases of fertility treatment to proceed.				
	March 2020	ASRM public guidelines in line with ESHRE				

ASRM, American Society for Reproductive Medicine; EHSRE, European Society of Human Reproduction and Embryology, WHO, World Health Organization.

groups, this is a challenge, especially when satisfying the requirements of local legislation. It seems that fluid and informal arrangements to provide emergency cover have been forged by, and between, laboratory managers in different regions, designed to help ensure that support is available when necessary. These arrangements need to be formalized to ensure that suitable staffing and orientation programmes can be organized, highlighting how competency can be demonstrated in the host laboratory and the processes supervised. This can be carried out during the shutdown period and therefore on short notice. In retrospect, some of the larger programmes operating multiple clinics in more than one city may consider whether centralizing activities will be sufficient to scale-down services.

Reassuring patients

In clinics in which laboratory staff were involved with direct patient communication, laboratory staff supported patients through discussion of infection risk and current evidence to clarify areas in which information was unknown. Patients who were disappointed that treatment had to cease for an indefinite period were referred for implication counselling.

Laboratory managers considered modifying standard protocols for patient communication, their visits to the clinic, culture procedures and vitrifying all embryos in culture, at an appropriate stage. Several local fertility societies encouraged clinics to advise couples to avoid embryo transfer in their attempt to achieve a pregnancy (*ESHRE, 2020a*; *2020b*; *ASRM, 2020b*; *BFS and ARCS, 2020*; *Agence de la Biomédecine, 2020*; *De Santis et al., 2020*; *Vaiarelli et al., 2020*; *ASEBIR, 2020*).

Mitigating risk of contamination by patients

IVF laboratory managers considered:

- using teleconferencing, email and telephone calls for all patient communication;
- ensuring staff were available to answer patient queries;
- ensuring counselling staff were aware of clinic closure plans and available to provide patient support, where necessary.

Mitigating risk of equipment damage, malfunction or loss of power

Procedures to temporarily decommission equipment to reduce unnecessary running costs during an extended shutdown were verified with the equipment manufacturers, distributors, or both, to ascertain the best practice for short- or long-term equipment inactivity, taking into account:

- potential for contamination in humidified incubators;
- the age of equipment and whether keeping the item on a 'low running' mode would be beneficial at startup;
- use of high-efficiency particulate air filtration or air purifications systems during shutdown;
- time required to restart the equipment.

TABLE 2 CHECKLIST WITH CONSIDERATIONS FOR PREPARING AN IVF LABORATORY FOR THE THREE PHASES OF A RESPONSE TO A PANDEMIC: SHUTDOWN PREPARATION; SHUTDOWN MAINTENANCE; RE-START

Phase	Risk	Mitigators considered by laboratory managers
Shutdown Preparation	Unsatisfied patients	❑ Patient support and advice ❑ Identify the need to provide formal and informal counselling ❑ Make fertility society and government advice available on patient portals and clinic websites
	Insufficient staff	❑ Clinic closure, centralized activity ❑ Formalize support agreements with local clinics, in accordance with regulation
	Equipment damage[a]	❑ Ensure manufacturer's advice is sought and followed ❑ Risk assessment for shutdown preparation actions
	Unnecessary cost of running equipment	❑ Run equipment in low operation mode or modify to reduce gas (incubators) or electricity (air handling) use, or both ❑ Switch off if possible and ensure not a risk during restart
	Low staff morale and security	❑ Set one-to-one as well as team-wide meetings to ensure staff feel supported and individual needs are addressed ❑ Maintain regular communication with staff (email updates, video conference calls, social virtual catchups) ❑ Set tasks for team members that can be carried out at home, i.e QMS, research, training, CPD, brainstorming improvements) ❑ Provide regular reassurance, information and updates
Shutdown maintenance Restart	Non-compliance with local guidelines	❑ Assess what changes are required to comply with local guidelines. Compile into the laboratory continuity plan ❑ Update laboratory continuity plan as the guidelines evolve ❑ Ensure all relevant staff are informed of latest guidelines and changes to the laboratory continuity plan
	Equipment malfunction during lockdown	❑ Follow manufacturer's instructions regarding use of equipment. Request specific advice regarding shutdown maintenance ❑ Contact equipment suppliers for support, and possibly discuss loan items for restart. Update laboratory continuity plan ❑ Enact reciprocal support agreements to use alternative equipment; not every clinic will restart at the same time or with the same demand. Short period loans could be a possibility until service/replacement is possible
	Liquid nitrogen disruption	❑ Ensure that the liquid nitrogen supplier is aware that your facility is preserving gamete and embryos. Be considered as a 'priority customer' ❑ Consider external specialized biorepository
	Liquid nitrogen levels unchecked	❑ Consider all efforts to ensure levels can be checked. Arrange for storage vessels or frozen material to be moved to an off site storage facility ❑ Consider automation where possible, with external monitoring
	Safe liquid nitrogen levels not maintained	❑ Ensure alarm/monitoring system functions, configured with early warning thresholds (not just critical) ❑ Ensure staff are able to access the clinic within appropriate time-frame if alarm is triggered ❑ Consider increasing backup liquid nitrogen levels ❑ Consider increasing dewar/vessel liquid nitrogen depth, if possible ❑ Attempt to make links with alternative liquid nitrogen providers. ❑ Establish contact with other companies that use liquid nitrogen, i.e. contacting different companies to identify a supply, e.g. frozen food producers ❑ Consider automation where possible, with external monitoring
	Cryostorage alarm malfunction	❑ If possible, physical checks should be carried out alongside the alarm monitoring system ❑ Periodic physical storage vessels checks and measuring nitrogen levels
	Low staff morale and permanent loss of staff	❑ Maintain regular communication with staff (email updates, video conference calls, social virtual catchups) ❑ Set tasks to team members that can be carried out at home, i.e. QMS, research, training, CPD, brainstorming improvements ❑ Provide regular reassurance, information and updates.
	Risk of patients as a potential source of contamination	❑ Consider a patient 'code of conduct' (which patients must agree to) to avoid unnecessary exposure to risk of becoming infected during treatment, i.e. restricting social life and interactions and using tracing apps ❑ Consider triage questionnaire for all patients to assess health status, symptoms, lifestyle of patients and those living in their household ❑ Test all patients (immunoglobulin G and immunoglobulin M, if available). Ensure necessary diagnostic test volumes can be delivered ❑ Irrespective of negative test results, treat all as 'infected or infectious' ❑ Social distancing policies to be reinforced. Non-essential clinic visit banned ❑ Ensure clinical procedures are punctual to avoid patients waiting in clinic longer than necessary ❑ Teleconsultation, online information videos and instructions should be used instead of face-to-face interactions, where possible
	Risk of biological samples as potential source of contamination	❑ Insufficient evidence at the moment but prudent to consider: ❑ Disinfecting incubator after cases ❑ Increasing culture media washing steps in gamete and embryo handling procedures. ❑ Vapour phase storage over liquid nitrogen storage ❑ Closed system for cryopreservation, although only when thawing and warming results are demonstrated to be comparable to open systems ❑ Washing samples in sterile nitrogen at warming, although there is no evidence to suggest that this is necessary. ❑ Using category III containment cabinets not feasible in most circumstances

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Table 2 – (continued)

Phase	Risk	Mitigators considered by laboratory managers
	Risk of staff as potential source of contamination	❑ Consider a staff 'code of conduct' (which staff must agree to) to avoid unnecessary exposure to risk of becoming infected ❑ Consider triage questionnaire for all patients to assess health status, symptoms, lifestyle of staff and those living in their household at least 2 weeks before beginning clinical activities ❑ Consider testing all staff (immunoglobulin G and immunoglobulin M, if available). Consider isolating staff with symptoms until test results are available. ❑ Consider contact tracing and testing when staff are diagnosed with COVID-19 ❑ Reinforce social distancing policies in the laboratory (ideally, 2 m distancing between staff at all times. Consider decommisssioning work stations) ❑ Calculate and implement maximum laboratory occupancy (minimum 4 m^2 per staff member) ❑ Restrict laboratory staff from entering general patient areas. ❑ Increase glove wearing and change over when handling equipment. ❑ Consider eye protection when it does not impair equipment use, i.e. difficulty in using eye protection during microscopy. ❑ Consider visualizing microscope images through a screen rather than through microscope binoculars, where appropriate ❑ Use embryo safe hand washes before and after applying gloves. ❑ Mask and goggle use mandatory when handling liquid nitrogen.
	Risk of staff becoming contaminated by laboratory environment	❑ Insufficient evidence at the moment but prudent to consider: ❑ Additional PPE as described above ❑ Increasing number of air change overs ❑ A deep clean before restarting ❑ Increasing cleaning requirements when operational in terms of procedure and frequency ❑ Using ultraviolet sterilization during periods of inactivity or no gamete or embryo handling ❑ Retaining minimal worker and rotational split teams' procedure ❑ Using disposable scrubs or considering how the scrubs are laundered
	Critical equipment non-conforming	❑ Assess monitoring data for critical equipment during shutdown. Quarantine non-confirming equipment ❑ Re-validate equipment that was temporarily decommissioned during shutdown before re-use ❑ Ensure all laboratory team is aware which equipment is cleared for use ❑ Use reciprocal support agreements
	Disinfectant toxic to gametes or embryos	❑ Use ammonia-based, embryo-safe disinfectants and ultraviolet light where possible. ❑ Consider periodic treatment with pauses in between cases to allow for deep clean decontamination and removing toxic fumes
	Insufficient consumable stock	❑ Use reciprocal support agreements and create support agreements with clinics that operate in different regions to avoid stock availability issues in a particular country ❑ Liaise with suppliers to ensure consumable distribution chain can support planned patient volume
	Insufficient staff[b]	❑ Ensure the projected work volume matches the projected available staff ❑ Have contingency plans for sudden insufficient staff levels ❑ Use reciprocal support agreements (locum staff, other clinics, or both)
	Staff not competent of, aware of, or compliant with revised processes and procedures	❑ Detail orientation and competency assessment before agreeing cover. ❑ Ensure a senior staff member is present to accompany new or junior staff. Attendance or supervision can be carried out via teleconferencing, remote logging on to computer terminals or face-to-face mobile telephone calls during procedures
	Low staff morale	❑ Set one-to-one as well as team wide meetings to ensure staff feel supported and individual needs are addressed ❑ Create and communicate the laboratory continuity plan ❑ Keep the plan up to date as the pandemic cycle evolves

[a] Owing to incorrect shutdown.

[b] Owing to sickness and governmental guidance of who can leave lockdown.CPD, continuing professional development; QMS, quality management system.

To prepare for an extended shutdown for an undetermined period, IVF laboratory managers considered:

- increasing their back-up power supply, particularly when using inline uninterruptible power source;
- only connecting critical equipment to the uninterruptible power source;
- setting up daily alarm tests and verifying the callout function; and
- identifying suppliers' delivery contingency plans, sourcing alternative options for essential items such as liquid nitrogen and medical gases.

SHUTDOWN MAINTENANCE

During shutdown, the IVF laboratory is responsible for maintaining the equipment and the cryostorage inventory with limited staff and resources. The laboratory managers considered preparing for a worst-case scenario, in which liquid nitrogen may not be available for delivery or after a distribution failure. By identifying these risks in advance, the clinic can prepare contingencies to mitigate the identified risks.

Mitigating risk of liquid nitrogen or electrical supply disruption and minimizing liquid nitrogen loss

Because of the nature of cryogens and the risks of storage of liquid over a long period of time, the suggested focus of the IVF laboratory was on reducing liquid nitrogen supply interruption. The following were identified as important in minimizing interruption risk:

- understanding how the gas supplier manages the laboratory's account and whether they prioritize medical accounts and can provide assurance that supplies will not be interrupted;
- sourcing a secondary supplier in case the main supplier is unable to meet the demand. It is advisable to source a secondary supplier who sources their liquid nitrogen from a different gas generator company;
- contacting state or local departments of health and local police (perhaps in certain more remote localities or those with strict traffic restrictions) to make them aware that the IVF clinic is a medical facility and will be receiving gas or emergency supplies. This may also be important if laboratory staff are travelling to and from the IVF clinic to avoid travel delays.

To minimize liquid nitrogen loss and other risks during a shutdown period, the managers discussed the following:

- avoiding unnecessary opening of the units to reduce evaporation;
- calculating normal evaporation rate for each dewar and monitoring for unusual loss, particularly for units older than 5 years. The evaporation rate can be used to guide storage of samples if consolidation is a possibility, and to be aware of which dewars may have a higher risk of failure;
- limiting physical measurement of nitrogen levels in dewars to once a week, while topping up the dewar with liquid nitrogen on the other daily checks;
- Stockpiling large amounts of liquid nitrogen is not advisable owing to continuous evaporation and loss of product. Maintaining dewars as full as possible is advisable over stockpiling supply tanks;
- avoiding or limiting moving of dewars to reduce liquid nitrogen splashing into the collar and the resulting loss. Laboratory managers considered placing dewars in areas in which movement was minimized;
- recording and maintaining a filling schedule to avoid opening the dewars for unnecessary activities:

- this will also make it easier to identify signs of distress or sweating or any of the other aspects of dewar failure, based on when the dewar was last filled;
- have a positive confirmation when a dewar is filled through the check sheet.

Mitigating risk of equipment malfunction during shutdown

The following were considered important by the managers:

- ensuring all laboratory staff are aware of, and understand, the emergency response plan;
- ensuring the alarm call schedule is up to date and that the first responder is always within 1 travel hour from the clinic;
- testing alarms and back-up power facilities;
- monitoring equipment quality-control parameters to ensure satisfactory performance during shutdown;
- assessing environmental conditions in the laboratory, including room temperature, humidity and air handling unit function.

Minimizing risks for staff

It was the opinion of the managers that on-site staffing should be limited to:

- supporting essential treatment, such as fertility preservation for oncological patients;
- supporting cryostorage management, dewar maintenance and liquid nitrogen top-up;
- checking expiry date of consumables and media, removing expired items and receiving essential items that may be delivered;
- maintaining laboratory equipment;
- enabling all other staff to work from home, taking the opportunity to update the quality management system with reviewed standard operating procedures, and other tasks that can be conducted remotely.

To maintain staff morale, some clinics held virtual meetings in which staff could still see each other and discuss non-work-related matters to maintain team camaraderie, and to support the emotional wellbeing of staff. It was also an opportunity to check on the mental health of the team during the pandemic. Other clinics set up daily or weekly update meetings, aimed at reducing anxiety among staff members.

RE-STARTING THE IVF LABORATORY

Communication and documenting the laboratory re-starting plan

Following the major interruption to operations, laboratory managers focused on making the laboratory team aware of the clinic's re-starting plans (part of the business/clinical contingency plans) through direct communication with other departments and the clinic's management. The re-starting part of the plan anticipated the volume of patients to be treated over time from which the laboratory's complimentary re-starting plan was devised and agreed by the clinical team. The laboratory re-starting plan included a process map to ensure the following:

- staffing is sufficient for the anticipated volume of patients;
- equipment is decontaminated and validated before first use;
- supplies of consumables are adequate;
- risk assessments specific to viral contamination are completed;
- laboratory procedures are reviewed in line with risk assessment mitigations;
- staff competencies are re-evaluated for revised procedures.

Pandemics have a lifespan, so that the risk to the laboratory will diminish over time past the peak and will eventually be eliminated. Therefore, it is important that plans are reviewed and evolve regularly, in line with the pandemic cycle stage, and any changes are communicated to the rest of the clinic and laboratory teams.

Viral contamination risk

In a pandemic involving a virus, the risk assessment must consider the nature of transmission to correctly identify the laboratory procedures that need to be adapted to protect patients, staff, gametes and embryos. A respiratory virus transmitted via aerosol requires different process adaptations than viruses transmitted via other bodily fluids.

Mitigating the risk of patients as potential source of contamination

A patient may infect a member of staff via aerosols if they are in close proximity. Therefore, clinics considered the following changes in laboratory practice to mitigate this risk:

- reducing face-to-face contact with patients where possible. In clinics in which embryologists normally communicate face-to-face with patients, telephone, telecommunication or patient-facing apps were considered or were implemented as an alternative form of communication;

- avoiding patients sharing tools or instruments, e.g. fingerprint identification readers, pen and clipboards, and tablets for data entry, information or entertainment;
- introducing patient and staff screening for COVID-19, including viral load, antigen testing when available or temperature checks, epidemiological survey, or both). Patient screening and triage may occur before, during and after treatment. In these cases, the laboratory will need to implement processes to receive this information;
- using PPE at all times;
- increasing hand washing routines;
- disinfecting procedure rooms, semen collection rooms and other patient areas in between patients;
- increasing air exchange in rooms used by patients to at least two air changes per hour;
- increasing time between procedures to permit sufficient air renewal;
- separating couples and patients in individual waiting rooms before procedures.

Mitigating risk of biological samples as potential source of contamination

It is standard embryology practice to assume that all biological samples may potentially be infectious. As such, semen and follicular fluid are processed using universal precautions. The laboratory manager may consider re-enforcing these standards when re-starting the laboratory.

All laboratory managers who participated agreed that all IVF procedures, including intracytoplasmic sperm injection (ICSI), oocyte denudation, vitrification and embryo transfer should be modified to include multiple dish changes or cell washes with new media to dilute any potential infective agent and, therefore, limit the risk of the virus presence in the culture environment.

Some clinics chose to continue using Laminar Air Flow Hoods for these processes, whereas others chose to exclusively use class II Hoods during the pandemic.

Preliminary and unpublished reports of detection of coronavirus in semen from COVID-19 patients, lead some laboratory managers initially to consider the following cautious adaptations to routine practice to reduce contamination risk from semen:

- taking extra care in semen handling;
- cryopreserving semen in closed systems;
- changing consumables per patient, e.g. increasing pipet usage;
- offering ICSI to all patients during the pandemic cycle;
- culturing zygotes individually after ICSI;
- avoiding touching cryopreservation straws without gloves during each phase of cryopreservation (labelling, loading and storing);
- using specified liquid nitrogen containers during the pandemic period;
- using sterile nitrogen for sample washing at warming (*Parmegiani et al., 2012*).

In one recent publication, absence of viral particles in semen or testicular biopsy specimens obtained from men recovering from COVID-19 were reported (*Pan et al., 2020*), whereas in another, semen samples positive for SARS-CoV-2 during acute infection were found; however, no proof of potential infectivity was provided (*Li et al., 2020*). Therefore, the data seem to be inconclusive. As such, it is questionable whether the protective procedures associated with HIV, hepatitis B and C and Zika are applicable to COVID-19. Hence, the suggestions above were no longer considered necessary. Several laboratory managers agreed that the use of a closed system for cryopreservation merits consideration from a contamination risk perspective, although the reported increased success rate associated with open systems meant that this opinion was not unanimous. Similarly, the need to sterilize liquid nitrogen was not considered a necessity by all.

Mitigating risk of staff as potential source of contamination

Screening staff for COVID-19 infection or immunity would be the preferred first step by laboratory managers in mitigating against staff as a source of contamination. The availability of testing is, however, currently limited. Moreover, it is not clear whether virus shedding occurs while a person is asymptomatic, or infectious before the test can diagnose COVID-19. As such, laboratories chose to treat all staff as potentially infectious and adapted their processes accordingly by engaging in social distancing with increased infection control measures. These adaptations include the following:

- using PPE at all times;
- increasing awareness of staff to reduce face and surface touching unnecessarily, sterilizing workstations, including the ocular of the microscopes before and after each use and sterilizing the external surfaces of cryopreservation tanks after each use.

Environmental disinfection

Evidence on the length of time the virus can survive in aerosol and on different surfaces is still tentative (*VanDoremalen et al., 2020*). Professional disinfection of the laboratory with detergent or sanitizer agents was considered before the staff returned. Laboratory managers considered the type and concentration of sanitizer used, and the amount of ventilation time the laboratory needed before clinical cases commenced, to ensure that the environment was safe for gametes and embryos. Therefore, it was agreed that efforts were made to verify that disinfectants were volatile organic compounds and embryo-toxin free. Some laboratory managers suggested solutions of quaternary ammonium (SIERR, 2020).

The frequency of disinfection during clinical activity varied between clinics, but all clinics opted to increase their decontamination frequency. It is not feasible to swab surfaces to determine efficacy of disinfection. Therefore, managers considered disinfecting workstations in between patients as well as in between embryologists. In effect, any area a member of staff had touched was considered to be a high-risk area.

Before the pandemic, laboratory managers considered the technical and operational requirements for assisted reproductive technology laboratory air quality as previously described in *Mortimer et al. (2018)*. In responding to the pandemic, IVF laboratories with the air-handling technology available considered disinfecting the air of the rooms used by patients using a photocatalyst air sterilizer. This will not be possible in clinics in which this technology is not available. Alternatives included ventilating the room to achieve at least two complete air changes in between patients. Limiting the number of patients that can be scheduled for egg collection, masturbation or embryo transfer to a maximum of one patient per room per hour could be sufficient.

Equipment

During the shutdown, some equipment was decommissioned. Re-commissioning the equipment requires decontamination and re-validation of the operational performance. These validations were carried out and validated as per protocol for all critical equipment.

Personal protective equipment

Advice on what personal protective equipment (PPE) should be used during routine IVF and under current pandemic conditions was inconsistent among clinics. In some IVF laboratories, surgical masks and gloves are worn at all times, whereas, in other laboratories, masks and gloves are worn only during procedures. Yet, others wear gloves only when handling semen and follicular fluid and only wear gloves and masks when handling samples for genetic analysis procedures.

Laboratory managers had a variety of views on what is considered appropriate protective equipment when carrying out procedures. With the onset of the pandemic, all laboratory managers considered increasing PPE usage requirements, in line with varied recommendations in different countries:

- all agreed that long sleeved-scrubs or surgical gowns or laboratory coats (either disposable single use or single use between high temperature wash), dedicated footwear and hair covers should be worn throughout the time in the laboratory;
- all agreed that surgical masks and gloves should be worn during procedures;
- most considered extending the use of the masks and gloves throughout the time in the IVF laboratory, maintaining the mask untouched during use, and changing masks at least every 4 hours;
- most agreed that N95 masks were not necessary in the laboratory;
- most agreed that protective face shields were not practical for microscopy and micromanipulation work;
- most agreed that goggles or eye protection could be considered throughout the time in the laboratory, when practical during microscopy and micromanipulation.

If gloves and masks were worn, these were changed regularly; masks were not touched while being worn, and the wearing of gloves did not replace the regular and thorough washing of hands for at least 20 seconds each time. These extra precautions were acknowledged to affect productivity of the embryologist and the number of cycles per day was adjusted accordingly.

Air handling

High-efficiency particulate air filters can filter 97% of 0.3 m particles from the air. Respiratory droplets, however, can vary in size from 0.01–10 μm. Therefore, the high-efficiency particulate air filters cannot block the coronavirus completely, although increased air changes with reduced air recycling settings is expected to help reduce viral contaminants in the air. Depending on the capabilities of the air handler, changing these settings may increase air temperature variation, which may, in turn, affect the incubator and heated stage performance. As such, laboratory managers considered changing the air handling settings before validating other equipment.

Automation and creating lean procedures

Social distancing in the laboratory means that the number of staff in the laboratory at any one time will need to be reduced. Technologies involving automation can help optimize the embryologists' time. Examples include:

- electronic witnessing system or telematic witnessing;
- time-lapse incubation (allowing remote embryo assessment);
- uninterrupted single-step culture;
- automated filling of the liquid nitrogen vessels;
- automated storage of samples in the storage tank;
- automated equipment monitoring and alarm systems (allowing remote quality-control evaluations).

CONCLUSION

The standards of practice laid out by the European Society of Human Reproduction and Embryology for good laboratory practice (2015) continue to be the backbone in standards of how we manage our IVF laboratories. In this paper, we have outlined additional measures used by laboratory managers around the world in response to the COVID-19 pandemic, without pandemic-specific guidelines being available. Much is still unknown about this virus and its effect on our work as we treat patients. To date, laboratory managers have had to make decisions and take action with a lack of scientific evidence, and, therefore, this paper was not meant to be a consensus of good practice, but rather a presentation of different approaches taken by laboratory managers from different countries. Initially, the approach veered on the side of caution; however, some of the mitigators implemented by laboratory managers may become less stringent once scientific evidence confirming the following become available:

- whether COVID-19 can be found in semen or follicular fluid;
- whether gametes and embryos can be infected by COVID-19;
- the size of droplets in which the virus may be transmitted;
- the amount of time that the virus can survive on different types of surfaces;
- the viral load required for infection of humans and, if relevant, gametes and embryos;
- Whether the COVID-19 virus survives in liquid nitrogen.

COVID-19 is not the first or the last emergency crisis that IVF laboratory managers will have to face. This experience will give laboratory managers a unique perspective on how to plan for and deal with future major events that lead to interruption of IVF services. The practices outlined in this paper will hopefully help formulate good practice for any IVF laboratory responding to a pandemic: be it this pandemic or the next.

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