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Review article

International Society for Gynecologic Endoscopy (ISGE) guidelines and recommendations on gynecological endoscopy during the evolutionary phases of the SARS-CoV-2 pandemic

Viju Thomas[a], Charlotte Maillard[a,b,*], Annelize Barnard[a], Leon Snyman[c], Andreas Chrysostomou[d], Lusandolwethu Shimange-Matsose[d], Bruno Van Herendael[e,f]

[a] Department of Obstetrics and Gynecology, Tygerberg Hospital, University of Stellenbosch, Cape Town, South Africa
[b] Department of Gynecology-Andrology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain (UCL), 1200 Brussels, Belgium
[c] Department of Obstetrics and Gynecology, Kalafong Tertiary Hospital, University of Pretoria, Pretoria, South Africa
[d] Department of Obstetrics and Gynecology, Charlotte Maxeke Hospital, University of Witwatersrand, Johannesburg, South Africa
[e] Stuivenberg General Hospital, Ziekenhuis Netwerk Antwerpen (ZNA), Antwerp, Belgium
[f] Università degli Studi dell'Insubria, Varese, Italy

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ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has raised some important interrogations on minimally invasive gynaecological surgery. The International Society for Gynecologic Endoscopy (ISGE) has taken upon itself the task of providing guidance and best practice policies for all practicing gynaecological endoscopists. Factors affecting decision making processes in minimal invasive surgery (MIS) vary depending on factors such as the phase of the pandemic, policies on control and prevention, expertise and existing infrastructure. Our responsibility remains ensuring the safety of all health care providers, ancillary staff and patients during this unusual period. We reviewed the current literature related to gynecological and endoscopic surgery during the Coronavirus Disease 19 (COVID-19) crisis. Regarding elective surgery, universal testing for SARS-CoV-2 infection should be carried out wherever possible 40 h prior to surgery. In case of confirmed positive case of SARS-CoV-2, surgery should be delayed. Priority should be given to relatively urgent cases such as malignancies. ISGE supports medical optimization and delaying surgery for benign non-life-threatening surgeries. When possible, we recommend to perform cases by laparoscopy and to allow early discharges. Any procedure with risk of bowel involvement should be performed by open surgery as studies have found a high amount of viral RNA (ribonucleic acid) in stool. Regarding urgent surgery, each unit should create a risk assessment flow chart based on capacity. Patients should be screened for symptoms and symptomatic patients must be tested. In the event that a confirmed case of SARS-CoV-2 is found, every attempt should be made to optimize medical management and defer surgery until the patient has recovered and only emergency or life-threatening surgery should be performed in these cases. We recommend to avoid intubation and ventilation in SARS-CoV-2 positive patients and if at all possible local or regional anesthesia should be utilized. Patients who screen or test negative may have general anesthesia and laparoscopic surgery while strict protocols of infection control are upheld. Surgery in screen-positive as well as SARS-CoV-2 positive patients that cannot be safely postponed should be undertaken with full PPE with ensuring that only essential personnel are exposed. If available, negative pressure theatres should be used for patients who are positive or screen high risk. During open and vaginal procedures, suction can be used to minimize droplet and bioaerosol spread. In a patient who screens low risk or tests negative, although carrier and false negatives cannot be excluded, laparoscopy should be strongly considered. We

Abbreviations: AAGL, American Association of Gynecologic Laparoscopists; ACE2, Angiotensin Converting Enzyme 2; ACOG, American College of Obstetricians and Gynecologists; BiPAP, Bilevel Positive Airway pressure; BSGE, British Society for Gynaecological Endoscopy; COVID-19, Coronavirus Disease 19; CPAP, Continuous Positive Airway Pressure; CT, Computed Tomography; ERAS, early recovery after surgery; ESGE, European Society for Gynaecological Endoscopy; GIT, Gastrointestinal Tract; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; HPV, Human Papillomavirus; ICU, Intensive Care Unit; IPC, Infection, Prevention and Control; ISGE, International Society of Gynecologic Endoscopy; LAVH, laparoscopic assisted vaginal hysterectomy; LLETZ, Large Loop Excision of the Transformation Zone; MIS, Minimal Invasive Surgery; PCR, Polymerase Chain Reaction; PPE, Personal Protective Equipment; RNA, Ribonucleic Acid; SARS-CoV-2, Severe Acute Respiratory Syndrome CoronaVirus-2; SASGE, South-African Society for Gynaecological Endoscopy; SOP, Standard Operative procedure; WHO, World Health Organization.

* Corresponding author at: Department of Gynecology-Andrology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain (UCL), 1200 Brussels, Belgium.
E-mail address: maillardcv@gmail.com (C. Maillard).

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recommend, during minimal access surgeries, to use strategies to reduce production of bioaerosols (such as minimal use of energy, experienced surgeon), to reduce leakage of smoke aerosols (for example, minimizing the number of ports used and size of incisions, as well as reducing the operating pressures) and to promote safe elimination of smoke during surgery and during the ports' closure (such as using gas filters and smoke evacuation systems). During the post-peak period of pandemic, debriefing and mental health screening for staff is recommended. Psychological support should be provided as needed. In conclusion, based on the existent evidence, ISGE largely supports the current international trends favoring laparoscopy over laparotomy on a case by case risk evaluation basis, recognizing the different levels of skill and access to minimally invasive procedures across various countries.

Contents

Introduction

The International Society for Gynecologic Endoscopy (ISGE) is privileged to enjoy patronage of members from around the globe. Countries affiliated with the ISGE are experiencing different stages of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, for example, South Africa is slowly reaching its peak while other countries such as China and Italy have passed their first peak and plateau phases and others USA, Brazil are still in the midst of the pandemic. Factors affecting decision making processes in minimal invasive surgery (MIS) vary depending on factors such as the phase of the pandemic, policies on control and prevention, expertise and existing infrastructure. Given the uncertainty of immunity and new emerging strains, caution must be practiced to ensure the safety of all health care providers, ancillary staff and patients during this unusual period. The ISGE is proud to be a global leader in this regard. We reviewed the current literature related to gynecological and endoscopic surgery during the Coronavirus Disease 19 (COVID-19) crisis.

This paper provides guidelines and recommendations on practicing MIS, elective and urgent gynecological surgeries, surgery in SARS-CoV-2 positive patients, operations rooms considerations and hysteroscopic perspectives during this dynamic time and in the period of evolving back to normality.

Background

SARS-CoV-2 pandemic

The outbreak of SARS-CoV-2 (Coronavirus Disease 19 −COVID 19) which originated in Hubei was declared a pandemic in March 2020 by the World Health Organization (WHO) [1,2] and now poses a massive health and economic burden internationally [3,4]. This pandemic is further complicated by the substantial risk of viral spread posed by asymptomatic carriers [5].

Endoscopic procedures potentially and theoretically put all involved at risk of inhalation and conjunctival exposure from bioaerosol (endoscopically generated and otherwise), direct contact and contact with fecal matter [6–10]. As gynecological endoscopists, it is imperative to review current practices by evaluating and mitigating risks, to ourselves, colleagues, staff and above all, to patients.

Infection risk with SARS-CoV-2 in endoscopy/laparoscopy

The theoretical risk of infection from endoscopically generated bioaerosols may potentially be increased due to three main factors peculiar to laparoscopy [11,12]:

1 The use of gas insufflation, both during entry and intra-operatively.
2 Creation of bioaerosols from electrosurgery, a cornerstone of endoscopy.
3 A possibility of gas leaks which can potentially result in higher viral counts in the air.

In a recent article, Mallick et al. reviewed the evidence surrounding aerosolization. The authors highlight a paucity of evidence [13]. Studies on human papillomavirus (HPV), Corynebacterium, hepatitis B virus (HBV) and human immunodeficiency virus (HIV) have identified pathogens in surgical smoke, notably 40 % of HPV during large loop excision of the transformation zone (LLETZ) procedures and 90 % during laparoscopies in HBV infected patients. The high presence of pathogens in smoke plumes translates to very few actual documented cases of transmission, with four documented cases of HPV and none of HBV or HIV. Despite the reassuring nature of these findings, caution should be maintained, especially when extrapolating to potentially more virulent pathogens such as SARS-CoV-2 [6–10].

The main route of transmission is via droplet spread and via contact transmission from contaminated surfaces to mucosal surfaces [14–16]. The virus may also become aerosolized during certain airway interventions and cardiopulmonary resuscitation [17]. Additionally, Wang et al. reported of SARS-CoV-2 viral ribonucleic acid (RNA) particles in stool in 29 % of cases and detected live virus in few cases. SARS-CoV-2 uses angiotensin converting enzyme 2 (ACE2) receptors in the gastrointestinal tract to gain entry into the cell, and this receptor seems well expressed in the gastrointestinal tract (GIT), however, a lower presence of 1–15 % of RNA particles are found in the blood [18].

This is supported by a study in children where they tested negative for nasopharyngeal swabs but positive for rectal swabs and further highlights the false negative rates of nasopharyngeal swabs [19].

The above information is mostly anecdotal evidence and highlights a severe paucity of academic ammunition available for decision making and we must attempt to apply it with care and caution to clinical practice]. It must also be noted that the risk of open surgery with regards to the spread of COVID-19 disease is also not known, and open surgery also produces electrocautery fumes that can potentially spread the virus.

Considerations for elective surgery

Early phase of pandemic

It is important to take advantage of governmental strategies in the early phase of an outbreak which would be to create capacity by anticipating the exponential nature of infection. For example, the Australian and New Zealand Hepatic, Pancreatic and Biliary association categorized three phases [20]:

(1) Semi-urgent setting where there are few SARS-CoV-2 patients, good hospital and intensive care unit (ICU) capacity

(2) Urgent setting: many SARS-CoV-2 patients and limited capacity

(3) Where all resources are re-routed to the SARS-CoV-2 cause.

It would be prudent in the early phase to fast track “time sensitive diseases” during this time, such as certain oncological cases, as failure to do this might worsen patients’ outcomes. Once the exponential phase overruns capacity, surgeons will find themselves with inadequate operating time and safe recovery facilities for their urgent cases and left with uncertainty as to when these cases can be performed.

- Priority should be given to urgent cases such as early stage endometrial and cervical cancer.
- Perform urgent cases by laparoscopy and discharge early while the pandemic and the cancer are in their early phases.
- It would be prudent to prospectively stratify and prioritize the urgency of each cancelled case.
- Universal testing for SARS-CoV-2 infection should be carried out wherever possible 40 h prior to surgery for all patients booked for semi-urgent surgery such as endometrial cancer cases to be performed laparoscopically. This will allow identification of most asymptomatic carriers and will allow appropriate management of those who test positive, including postponement of surgery where possible.

Peak phase of pandemic

In the acute phase of the COVID-19 pandemic, all elective surgical procedures should be postponed where it is possible to safely to so without harm to patients [21–23]. It is prudent to ensure that postponement is balanced against the patient’s outcome and quality of life.

- Decisions regarding the management of malignancies should be undertaken in conjunction with an oncologist.
- ISGE supports medical optimization and delaying surgery for prolapse and incontinence.
- Where a delay in surgery will influence the reproductive prognosis of a patient, the case should be managed with a reproductive medicine specialist with the aim of optimizing medical management and consideration given to fertility preservation options.
- Surgery for endometriosis should be deferred as it is not life threatening and when bowel involvement is present, the risk of viral exposure is increased during excision [22].
- Any procedure where there is a risk of bowel involvement including conditions (such as pelvi-abdominal sepsis, or tubo-ovarian abscesses) should be performed by open surgery as studies have found a high amount of viral RNA in stool [18].

Post-peak period of pandemic

In countries where the peaks have been reached, there is ongoing uncertainty as to when elective surgeries can begin. This period should start with addressing the needs of the health care workers and an inventory of available capacity / resources. These need to be balanced against the backlog of the elective cases.

- Debriefing and mental health screening for staff is recommended.
- Psychological support should be provided as needed.
- Human inventory must be balanced with hospital capacity.
- Reconciliation of the burden of backlogged cases can be made on an individual case basis.

The SARS-CoV-2 pandemic should be considered a harbinger of new surgical practices. The long-term risk of viral epidemics / pandemics is uncertain but very real. Predictions of mutations, new strains and novel new viruses should make us change our practice.

- Even after the peak of the pandemic, strict screening should continue and all preoperative patients should be tested until vaccines or treatment have negated their need.
- If the patient screens/tests positive or there is uncertainty of the status of the patient this case should be postponed.

- If the patient screens or tests negative and if hospital capacity allows then elective surgery may commence with standard personal protective equipment (PPE).

Considerations for urgent surgery

Testing

Although universal testing is probably ideal for all patients, this may not be practical in all settings. Screening and testing should be employed as per local protocol.

Testing includes screening for symptoms, nasopharyngeal swabs with nucleic acid amplification such as polymerase chain reaction (PCR) which has a high specificity but a low sensitivity, rapid antigen/antibody but considering the 5–10-days delay for the production of antibodies [24].

The role of chest imaging is controversial. Zhu et al. demonstrated radiological evidence of pneumonic changes in 67 % of SARS-CoV-2 patients who tested negative [25]. In contrast PCR confirmed patients had normal computed tomography (CT) scan findings in 56 % of positively tested patients [26].

The role of imaging probably lies in the "grey zone" where there is discrepancy between clinical suspicion and test results. With a high index of clinical suspicion, imaging is probably beneficial.

- Each unit/center should create a risk assessment flow chart based on capacity.
- Ideally all preoperative patients should be tested if resources allow.
- Where universal testing is not available, patients should be screened for symptoms based on the local guidelines for example the National Institute of Communicable Diseases [27].
- Symptomatic patients must be tested.
- Imaging of the chest should be performed if clinically indicated and not for screening.
- Patients who screen or test negative may have general anesthesia and laparoscopic surgery while strict protocols of infection control are upheld.
- Surgery in screen-positive as well as SARS-CoV-2 positive patients that cannot be safely postponed should be undertaken with full PPE.
- Liang et al, supported by ISGE on their website, provided guidance for donning and removing of PPE in their handbook [28].

Operating theatre considerations during the peak

- All patients requiring surgery must be screened and ideally tested preoperatively for purposes of managing the patient and protecting staff.
- Irrespective of the result of the screen or the test, during the peak, all health workers should wear full PPE.
- With a high clinical suspicion pulmonary assessment with chest X-ray or CT scan preoperatively may be of benefit.

Recommended algorithm for patients requiring surgical intervention Figure 1.

Approach to COVID positive patients

Anesthetic considerations

In addition to laparoscopically generated bioaerosols, SARS-CoV-2 is primarily a respiratory virus and the team involved in general anesthesia performing endotracheal intubation and extubation, are at the highest risk of viral transmission [17,29,30].

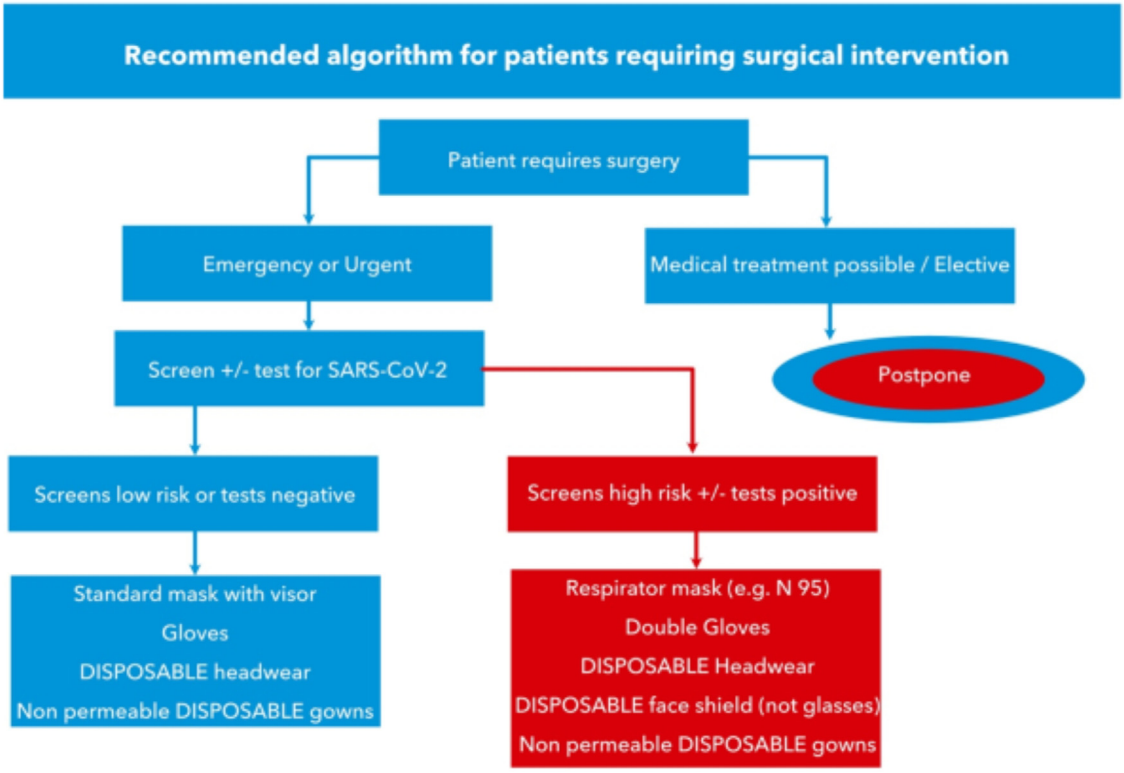

Fig. 1. Recommended algorithm for patients requiring surgical intervention.

- The patient should wear a respirator mask at all times.
- The anesthetic staff should wear full PPE.
- In the event that a confirmed case of SARS-CoV-2 is found, every attempt should be made to optimize medical management and defer surgery until the patient has recovered, and only emergency or life-threatening surgery should be performed in these cases.
- Every attempt should be made to avoid intubation and if at all possible local or regional anesthesia should be utilized.
- ISGE recommends the use of appropriate PPE for all surgical procedures - depending on the risk evaluation of the patient (refer to the flowchart).
- Minimize the operating pressures where possible to reduce gas leaks whilst optimizing ventilation.
- Avoid positive airway pressure (Continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP)).
- Trendelenburg optimization may facilitate ventilatory needs and this should be balanced between surgical and anesthetic requirements.

Open versus laparoscopic surgery

A study by Li et al. concluded that the risk of aerosol spread may be lower during laparotomies [11], however this theoretical risk must be balanced with the advantages associated with laparoscopies, including: earlier discharge, reduced nosocomial infections, reduced rates of complications (and therefore re-admissions into hospital, thus increasing the potential risk of SARS-CoV-2 infection) [31]. These advantages are robustly supported in the literature [31–38] and provide much needed capacity in terms of bed space and critical staff for health care institutions during this time.

Brücher et al. did assess the risk of open and laparoscopic surgery to be the same provided the gas/smoke was evacuated safely and water lock filters were used or if gasless laparoscopy was performed [24].

Mintz et al. demonstrated the safety of ventilator machines with “standard electrostatic filters” for HBV and hepatitis C virus (HCV) which have a diameter of 42 nm and 30−60 nm respectively and it stands to reason that the SARS-CoV-2 virus which has a wider diameter of 70−90 nm would not pass through the filter [39]. This highlights the role of filters which may be used during laparoscopy after which these filters should be discarded according to local protocols.

It must be clearly stated that there is no robust evidence of increased risk of viral transmission during laparoscopy. The current evidence is purely extrapolated from work with other, above mentioned, pathogens. While recognizing these facts, all precautions must still be taken during this time until more evidence becomes available.

Aerosols are also produced during open and vaginal surgery [6,11,13]. Unlike during laparoscopy there is no way to contain the aerosols by using filters and closed system smoke evacuators. This risk is increased with the use of any electrosurgery including monopolar, bipolar and advanced energy devices such as advanced bipolar, laser and ultrasonic devices [13,40].

- During open and vaginal procedures suction can be used to minimize droplet and bioaerosol spread.
- In a SARS-CoV-2 positive patient all attempts should be made to avoid intubation and ventilation.
- In a patient who screens low or tests negative, although carrier and false negatives cannot be excluded, laparoscopy should be strongly considered.

Currently we need to balance a hypothetical risk of aerosol spread in low risk patients to the vast array of evidence proving the benefits of laparoscopic surgery.

Operating room considerations

The importance of infection, prevention and control (IPC) and adequate PPE cannot be over emphasized. Whilst prioritizing patients’ needs first, it is imperative that the safety of healthcare workers is not compromised.

- Ensure that only essential personnel are exposed. For example, there is no need for the entire theatre staff to be present during intubation.
- Theatre staff including nursing staff, anesthetic staff and surgical assistants require in-service training on the infection control protocols.

Negative pressure theatres are scarce and most operating theatres have a positive pressure environment. In contrast to negative pressure theatres, this prevents air from outside the theatre from entering the operating area. Although this principle is effective for standard procedures, it may be counter effective for theatres with patients who are SARS-CoV-2 positive.

- If available, negative pressure theatres should be used for patients who are positive or screen high risk.
- Clear routes of entry, exit, donning, doffing, handling of specimens and sterilization of instruments and theatres should be established, based on institutional infrastructure and resources. These arrangements should be documented in a clear Standard Operating Procedure (SOP) document.
- Practice donning and doffing sequence for sterile procedures.
- Although disposable instruments, tubing and filters are ideal, this should be tailored to resources within the unit.

Laparoscopy

Strategies to reduce production of bioaerosols

There is no substitute for practicing sound surgical principles to ensure seamless surgery and good patient outcome. Care should be employed when choosing advanced energy sources. The theoretical risk of increased smoke and particle dispersion is associated with the high frequency oscillating mechanism of ultrasonic devices [13,40].

- Consider potential particle dispersion when choosing energy devices.
- Employ sound principles of energy to optimize tissue effect.
- Employ basic surgical principles: minimize bleeding, careful handling of tissue, minimal use of energy at the lowest but effective settings and use of atraumatic instruments.
- The most experienced, proficient and knowledgeable surgeon available should perform the procedure. This will ensure the implementation of SARS-CoV-2 protocols, shortest operating time and minimal exposure of the theatre staff to potential aerosols.

Strategies to reduce leakage of smoke aerosols

Communication and meticulous planning will result in fewer human errors. Staff should be well briefed on the surgical plan. If needed SOP and protocols can be simulated for intraoperative strategies such as avoiding leakage by not opening ports to release

smoke, use of filters, smoke evacuators, disposable tubing, use of wall suction and removal of specimens to name a few.

- Provide in service training for theatre staff and detail the surgical plan preoperatively.
- Consideration should be given to the number of ports used and size of incisions.
- Minimize the operating pressures where possible to minimize gas leaks.
- Prudent preoperative planning helps reduce gas leaks which occur during instrument changes.

Where gas leaks are anticipated, such as with specimen retrieval and removal of the uterus at total laparoscopic hysterectomy, certain strategies may be employed:

- Use of retrieval devices may minimize gas leaks.
- Ensure all colpocleiators (vaginal cuff delineators with air seal) are checked preoperatively for gas leaks.
- Once the vault has been circumcised, all the gas should be removed by suction and/or closed system evacuators, before removing the specimen vaginally.
- If one is not able to maintain colpocleisis during colpotomy, then consider an alternative strategy such as vaginal colpotomy after removing all the gas, as performed at laparoscopic assisted vaginal hysterectomy (LAVH).

Strategies to promote safe elimination of smoke

- It is advisable to use closed smoke evacuation systems intra-operatively when available.
- Filters should be used and tailored to what is available to the center.
- Wall suction connected to a central system is preferable to mobile suctioning devices.
- Suction should be generously utilized to remove the plumes of smoke generated during surgery.
- Suction should be used at the end of the procedure to remove all the gas from the abdominal cavity prior to removing the ports.
- Use closed system smoke evacuators to safely remove surgical gas at the end of the procedure.

The trough of the pandemic should not herald old practices. This must be done for two reasons: uncertainty of repeated waves of infection [41–43] and even in a post SARS-CoV-2 world, this practice will continue to keep staff from unknown toxins and bioaerosols.

- Even after the peak of the disease the practice of safe elimination of smoke should continue.
- Where possible central suction should be used in all cases

Port closure

The recent article by Mallick et al. discusses the conflict between the traditional practice of port removal under vision before desufflation and the newly adopted practice of desufflating prior to removing the ports to prevent bioaerosol infection [13]. This deviation in practice marginally increases the risk of port site herniation and unrecognized port site bleeding but supports the reasoning and applied practice. Port site herniation is more likely to occur if all the gas has not been removed and the ports are not removed under direct vision. This occurs because the positive pressure in the abdomen can push structures such as omentum and small bowel through the port while the gas is trying to escape.

- ISGE supports the interim practice of desufflation prior to the removal of ports for purposes of reducing bioaerosol spread.
- Remove all ports only after all the gas has been removed to reduce port site herniation.
- At the end of the procedure, the sheath at port-sites $\geq$ 10 mm must be closed using a J needle.
- Avoid using commercial endoscopic port closure devices as they may allow for gas leaks.

Considerations after the epidemic

The new practice of safe removal of gas to avoid bioaerosols should be evaluated in studies that compare the risks of unidentified port site complications such as inadvertent bleeding and herniation against and the risk of bioaerosols. Studies have found more than 600 compounds and gasses in surgical smoke including SARS-CoV-2, HIV, HBV and HPV to name a few. An elegant study by Li et al. demonstrated that the cumulative particles numbers of 0.3 μm and 0.5 μm were higher after laparoscopic surgery when compared to open surgery supporting the need for safe smoke evacuation and well-fitting face masks [11]. The overwhelming evidence of known toxins and the fear of unknown risks of the smoke should compel us to continue safe evacuation of smoke.

- Consider the routine use of gas filters.
- Remove ports only after all the gas is removed.
- If ports are removed before gas is removed, this must be done under vision.
- The use of a protective fitting face mask is recommended.

Considerations during hysteroscopy

As with laparoscopy the evidence on hysteroscopic bioaerosol production is sparse. Electrosurgery during hysteroscopy seems to produce less smoke than laparoscopy, although there are no comparative studies to support this. In this regard mechanical hysteroscopic morcellators pose an advantage [21,35]. In the absence of evidence, it is not possible to adequately quantify the risk of bioaerosol production at hysteroscopy but the risk appears low.

- All elective cases should be postponed.
- It is plausible that hysteroscopic tissue removal systems reduce bioaerosol exposure.
- Suction device should be connected to an outflow sheath.
- Standard PPE is recommended unless SARS-CoV-2 positive/screens high risk at which time full PPE is recommended.
- ISGE recommends no anesthesia or if indicated conscious sedation, local or regional anesthesia for hysteroscopy.
- Hysteroscopic morcellators may pose anadvantage over hysteroscopic electrosurgical devices.
- Hysteroscopy is preferentially performed on a day case/outpatient basis to relieve the pressure on main theatre resources.

Post-operative strategies

The literature supports laparoscopy in allowing for same-day or early discharge [30,44]. This reduces patient exposure and enhances capacity at hospitals during this resource constrained era. Although screened, patients may not have been symptomatic at the time of surgery but may have been infected. It would be prudent to identify false negatives, their contacts (at home and at the hospital) need to be identified and appropriately managed.

- Attempt same-day or early discharge where possible to avoid nosocomial infections.
- Employing early recovery after surgery (ERAS) principles will help facilitate quicker discharge.
- It may be prudent to telephonically contact the post-operative patient to screen for symptoms after the surgery.
- A log should be kept of all staff involved in the care of any specific patient in order to aid contact tracing should a patient test positive at a later stage.

Conclusion

The position of international societies such as the American College of Obstetricians and Gynecologists (ACOG), the American Association of Gynecologic Laparoscopists (AAGL), the European Society for Gynaecological Endoscopy (ESGE), the South-African Society for Gynaecological Endoscopy (SASGE) and the British Society for Gynaecological Endoscopy (BSGE) [21–23,45,46] recommend the use of laparoscopic procedures over open procedures when appropriately evaluated. ISGE acknowledges the dynamic times we are in and based on current evidence, ISGE largely supports the current international stance favoring laparoscopy over laparotomy on a case by case risk evaluation basis. ISGE also recognizes the different levels of skill and access to minimally invasive procedures across various countries, and supports individual clinical decision making during this time with regards to surgical access. This document will be revised as more data becomes available.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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