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Gyn-Aesthetic: the 'new normal' after COVID-19

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Abstract

In the post-COVID-19 era, it will be important to better understand the host response to severe acute respiratory syndrome related to coronaviurus-2 (SARS-CoV-2) infection and the pathology of disease in genital tissue. A better understanding of how SARS-CoV-2 causes disease and how the host responds can help direct new therapeutic targets. With the arrival of the "new normal", women who want to start or who are already undergoing treatment require cosmetic, esthetic and/or functional gynecological procedures that have been safely and ethically modified. Given that there is a possibility of the pandemic re-emerging and that we do not know how the use of different techniques can affect the virus environment, we must take the lessons learned seriously in these unprecedented times, since the virus will not completely disappear from our society once the first wave of the pandemic ends.

Gyn-Aesthetic: the 'new normal' after COVID-19

In December 2019, a new human coronavirus associated with high mortality emerged, spreading rapidly around the world. The virus was initially named 2019-nCoV but is now called severe acute respiratory syndrome related to coronavirus-2 (SARS-CoV-2), and it causes COVID-19 disease (coronavirus disease 2019). On July 17, 2020, the World Health Organization (WHO) reported more than 13,837,000 cases and more than 590,000 deaths (4.3%) worldwide and has maintained the alert to the European Union of a new pandemic outbreak, which means that the virus will prevail in society until a vaccine is available [1]. Despite many limitations, a meta-analysis [2] suggests that there are gender-related causes of the higher mortality rate in men than in women. Therefore, we will have to live with a new reality, and we will have to adapt our clinical workflow and reformulate the way we care for patients.

Because many people infected with SARS-CoV-2 are asymptomatic, professionals who perform any of the treatments/techniques of cosmetic, esthetic and functional gynecology have been asked how to proceed to avoid contagion and whether a therapeutic procedure can inhibit or stimulate the action of the virus. Knowledge of SARS-CoV-2 and COVID-19 is changing rapidly, and guidance is based on current information, however limited.

The objective of this nonsystematic but comprehensive review was to evaluate whether the different interventions commonly used in cosmetic, esthetic and functional gynecology modify the components of immunological protection in the human vulvovaginal epithelium or the possibility of contagion for health personnel.

Background on SARS-CoV-2

The new virus belongs to the *Coronaviridae* family and, therefore, shares common characteristics of this family. The first studies on SARS-CoV-2 have shown more similarities with its homonymous virus in that the spike protein uses angiotensin-converting enzyme 2 (ACE2) as a cell surface receptor [3]. ACE2 receptors are expressed in the cardiovascular, renal, and gastrointestinal tracts, as well as in many other tissues known to harbor SARS-CoV [4]. This virus infects the target cell by binding to ACE2 through its surface peak protein, modulating ACE2 expression, and causing severe injury [3,5].

Given the speed at which the COVID-19 outbreak developed, SARS-CoV-2 appears to spread easily in the human population. Many health professionals have been infected, and with each passing day, more

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groups of cases are detected. Although it has decreased dramatically, the number of breeders (R_0) for the virus reached approximately 3 [6], showing the potential for human-to-human transmission.

SARS-CoV-2 is present in respiratory secretions and other body fluids and is spread through airborne particles [7] and, possibly, by oral-fecal transmission [8], but substantial knowledge gaps remain regarding the presence of SARS-CoV-2 in breast milk [9]; SARS-CoV-2 is able to remain stable on surfaces for days [7]. There are other possible routes of transmission. Although one study was unable to detect the virus in urine samples [10], there is evidence that SARS-CoV-2 nucleic acids were detected in one urine sample in at least 1 patient in another study [11], so potentially infectious urine should also be considered. SARS-CoV-2 RNA has been detected in stool samples, raising concerns about fecal-oral transmission [12]. However, it is unclear whether the viral RNA detected in the stool is capable of causing a productive infection. Details of 3 newborns who may have been infected with SARS-CoV-2 have been reported in the womb of mothers with COVID-19 [13,14]. Furthermore, a possible case of vertical transmission has been reported on what may be the earliest positive polymerase chain reaction (PCR) for serum SARS-CoV-2 in a newborn, which occurred 16 hours after birth [15]. Although tests to detect the presence of viruses in amniotic fluid, umbilical cord blood, or placental tissue were not performed. Negative serology in the infant up to day 5 could be explained by the immaturity of adaptive immunity in the neonatal period, especially in preterm infants, resulting in impaired B cell cytokine and immunoglobulin production relative to adults. Cases of the presence of coronavirus in the breast milk of women infected with COVID-19 have begun to appear [16].

However, all these data are debatable since any contact in person results in a substantial risk of disease transmission due to the stability of the virus on common surfaces and the propensity to spread in the oropharynx and respiratory tract [17]. Infected people have the potential to spread secretions on their skin and personal items, through which the virus can be transmitted to another person. The genitals are a critical gateway for most sexually transmitted infections (STIs) and may be a critical gateway for SARS-CoV-2 transmission.

SARS-CoV-2 in the lower genital organs

In the Human Protein Atlas, the presence of ACE2 has been confirmed in the vagina (and in the uterus). ACE2 mRNA is more abundant in epithelial cells than in stromal cells and higher in the secretory phase than in the proliferative phase [18].

To date, no damage to the female reproductive system has been reported in patients with COVID-19. Two small studies of people infected with SARS-CoV-2 did not detect viruses in semen or vaginal secretions [19,20]. Another study found no SARS-CoV-2 in vaginal fluid and exfoliated cervicovaginal cells in 10 women with confirmed severe COVID-19 pneumonia [21]. However, it is plausible that any type of sexual contact is likely to carry a risk of transmission of SARS-CoV-2. The immune mechanism that works in the vagina is still not well understood. Little is known about the distribution and cellular composition of intraepithelial immune cells in normal human vaginal epithelium, and even less is known about the influence of different regenerative techniques for the genitalia on these parameters.

Vulvovaginal microbiota and COVID-19

The vaginal microbiota, mainly dominated by *Lactobacillus* spp., plays a key role in defending the female genital tract against numerous urogenital pathogens [22], possibly including COVID-19. The protective mechanisms of *Lactobacillus*-mediated vaginal cells are virus inactivation through acidification of the vagina at pH ≤ 4.5, capture of virions through bacterial membrane lectins, stimulation of anti-virus immune responses and inhibition of the growth of pathogens responsible for bacterial vaginosis, which increase the risk of viral infection [23]. Furthermore, we now know that *Lactobacilli* release extracellular vesicles (EVs) [24], which are involved in cell-cell communication in various biological systems. The protective effect of *Lactobacilli* against viruses may, in part, be mediated by EVs released by these symbiotic bacteria [25].

SARS-CoV-2 RNA has been detected in the stool of some COVID-19 patients [26]. The gut microbiota affects lung health through vital crosstalk between the gut microbiota and the lungs, known as the "gut-lung axis" [27]. In the intestine, Bacteroidetes and Firmicutes predominate, while Bacteroidetes, Firmicutes and Proteobacteria predominate in the lung [7]. The fact that some patients with this disease have diarrhea points to a clear possibility of involvement of the intestine-lung axis [28]. On the other hand, several bacterial species colonize both the gastrointestinal and reproductive tracts (the "intestine-vagina" axis) [29], and the rectum could play an important role as a source of organisms that colonize the vagina [30], functioning as a reservoir for vaginal colonization by lactobacilli in the maintenance of normal vaginal microflora. This raises an interesting possibility that the new SARS-CoV-2 could also have an impact on the vaginal microbiota [31].

Energy-based treatment for gynecologic conditions & COVID-19

The energy-releasing systems developed for vulvovaginal use stimulate neocollagenesis and neoelastogenesis after the tissue surface temperature reaches 40-45°C [32]. Four decades of observation allows us to safely argue that there is no risk of neoplastic growth or DNA mutation.

Given the possibility of a new outbreak of COVID-19, the safety of energy-based devices should be emphasized, focusing on the potential biological risks of different surgical techniques/methods to reduce the potential risks of airborne contaminants, especially with the use of lasers [33].

Pollutants in the air are associated with certain wavelengths and the application of energy-based devices. Thermal disruption of viable human cells has been shown to cause the release of carbon particles, viruses, bacteria, deoxyribonucleic acid (DNA), and toxic gases. These dangerous particles are found in all surgical plumes, regardless of the energy source, and in all types of surgical procedures except the use of low-power devices [34]. This means that aerosolized blood, bloodborne pathogens, and pathogens found in the blood or other secretions can be forcefully expelled when the cell is disrupted and transported into the air. These organic materials, including human immunodeficiency virus (HIV), human papilloma virus (HPV), and hepatitis B virus (HBV), as well as other biological particles, are released from human tissue during vaporization [35,36].

We consider that these pollutants are strictly related to the wavelength used, as well as to the amount of energy, and the virolytic effect of lasers is widely known in the literature. Remember that a carbon dioxide (CO2) laser reaches temperatures of up to 100 degrees Celsius during the time of biophysical interaction with tissues, usually on the order of 1000 microseconds. This temperature is responsible for the virolytic effect, which is why we consider the possibility of

contamination by aerosols generated by their interaction with tissues to be extremely rare [37]. There is no specific description in the literature about the generation of aerosols and viral particles of equipment, such as erbium Yag, (2940 nm), ND-YAG (1064 nM), and diode (980-1470 Nm) lasers, operating in a subablative or nonablative mode or about their virolytic properties.

Female Genital Cosmetic Surgery. What will elective surgery be similar to in the next phase?

At the epicenter of the COVID-19 pandemic and facing the possibility of exhausting their supply of personal protective equipment (PPE), ventilators, and intensive care unit (ICU) beds, hospitals indefinitely suspended all elective surgery [38]. Once the health crisis is over, the surgical classification systems that take into account not only the clinical emergency but also the consumption of resources will continue to be relevant.

There are numerous recommendations for safely providing surgical care during the pandemic, but it is unclear how elective surgery should be restarted in these new and uncertain conditions. It is reasonable to consider the epidemiological conditions in the community, the health of the patients, the COVID-19 status of all members of the surgical team, the facilities and resources available when making decisions about the provision of surgical care, and the provision of information to patients when obtaining consent after the peak of the outbreak.

Regarding patients, it is both epidemiologically and clinically reasonable that elective surgery candidates who may be in the incubation period or who have developed an active disease should postpone their elective procedures until full recovery [39].

Although the physiological stress induced by surgery is known, the impact that vulvovaginal surgical techniques could have on the virus and on the viral disease itself is not known. Despite all the limitations and biases, in a Spanish series, patients with COVID-19 who underwent cesarean sections had worse maternal outcomes than patients who had vaginal deliveries. After adjusting for confounding factors, cesarean delivery remained independently associated with an increased risk of clinical deterioration [40].

The resumption of female genital cosmetic surgery (FGCS) must be systematic and cautious. Ideally, surgery should be performed strictly in a COVID-free center, and the hospital stay should be as short as possible [41]. For safety reasons, the operated patients should, at first, be carefully selected according to exposure to COVID, age, the ASA physical status/risk factors classification system, the socioprofessional situation, and the surgical indication. With the slightest suspicion of COVID symptoms, elective surgery should be postponed [42]. In the event of surgery, close monitoring of COVID-19 signs and adapted PPE is recommended. The use of bipolar electrocautery, which generates less smoke, is preferable to monopolar cauterization or the harmonic scalpel.

Can stem cells improve the outcome of COVID-19?

Mesenchymal stem cells (MSCs) are known to have anti-inflammatory and regenerative effects. MSCs are found in many tissues, such as adipose tissue (adipose-derived mesenchymal stem cells, ADMSCs). ADMSCs are used in the field of regenerative medicine because they are easier to obtain in the form of body fat. ADMSCs may have regenerative and potentially therapeutic effects on postmenopausal vaginal atrophy by decreasing apoptosis (apoptosis of vaginal cells has been shown to increase atrophy) and angiogenesis [43].

Furthermore, adipose-derived stromal stem cells (ASCs) have immunomodulatory properties mediated by transforming growth factor-1 (TGF-1), hepatocyte growth factors (HGFs), and interferon-γ (INF-γ) [44]. This activity and the early establishment of new microcapillary networks, which release adequate nutrients and oxygen, could contribute to achievement of the best results during an infusion of MSCs in patients with COVID-19 [45].

Is platelet-rich plasma safe in healthy patients and in recovered patients?

Platelet-rich plasma (PRP) preparations are used in gynecology for various diseases based on their known mechanisms, which involve the wound healing process and the initiation of inflammatory reactions [46]. Tissue repair begins with platelet degranulation with the release of platelet growth factors. Autologous PRP is derived from an individual's whole blood and centrifuged to remove red blood cells. The remaining plasma has a 5- to 10-fold higher concentration (ideal 2,5) of growth factors than whole blood.

Evidence shows that convalescent plasma from patients who have recovered from viral infections can be used as a treatment without the occurrence of severe adverse events. If a patient has recovered from COVID-19 –over 7,743,000 patients (56%) have recovered worldwide as of July 17, according to the WHO–, collecting their blood for use as PRP in cosmetic gynecology is safe. In fact, recovered patients often have a relatively high level of antibodies against the pathogen in their blood. Antibodies are immunoglobulins (Igs) produced by B lymphocytes to fight pathogens and other foreign objects and recognize unique molecules in pathogens and directly neutralize them [47]. Based on this, convalescent plasma was collected from patients who recovered from COVID-19 and injected into severely ill patients. Their symptoms improved within 24 hours, accompanied by reduced inflammation and viral loads and better blood oxygen saturation.

However, despite the therapeutic effects, some disadvantages associated with plasma should be carefully considered. For example, antibodies can overstimulate the immune response and cause cytokine release syndrome, which is potentially life-threatening toxicity [48].

Can botulinum toxin attenuate COVID-19?

Very light doses of purified forms of botulinum toxins (BoNTs) produce therapeutic benefits against many diseases and are also used as an anti-aging cosmetic agent. Therapeutic BoNT injections appear to raise the immune cell count, including increasing the platelet count in the blood, which could help combat SARS-CoV-2 as it may improve antigen presentation and phagocytosis mediated by macrophages to eliminate virulent factors. Furthermore, it improves blood circulation and oxygen supply [49].

BoNT, at doses of 40 U to 400 U in single administration or in some cases, with repeated injection cycles, is successfully used in the treatment of symptoms of gynecological dysfunction that are refractory to conventional treatments, with few side effects and high efficacy. BoNT-A is used more frequently with good results, especially because the paralysis resulting from BoNT-B is not as efficacious as that resulting from BoNT-A [50].

Considering the nature of the spread of BoNT from the injection site to distal areas [51], a light dose of BoNT can also be expected to produce curative effects against many explained symptoms of COVID-19. Importantly, therapeutic BoNT has the ability to migrate from the intramuscular injection site to the brain and other organs

[51]. Therapeutic BoNT is relatively safe, and the beneficial effect of a single therapeutic dose of BoNT appears to be long lasting. However, the possible side effects that may arise from the use of BoNT should not be ignored [52].

Other strategies for controlling COVID-19 in Gyn-Aesthetic Offices?

One of the main challenges with the new CoVs is the high nosocomial transmission potential [53]. Healthcare settings appear to increase the risk of viral transmission due to aerosol-generating procedures [54].

When in-person encounters are limited, the use of telematic means or other nonface-to-face communication systems is in accordance with medical deontology provided that there is at least verbal consent and the consent of the patient, a responsible family member or a legal guardian, as appropriate, which must be recorded in the medical history. Telemedicine has allowed and will allow our patients to be cared for under certain conditions, facilitated their access to the health system and promoted the safety of the patient and the rest of the population, as has happened during the pandemic. Issues as essential as the privacy, confidentiality and secrecy of clinical data, which may be known, either directly or indirectly, must be guaranteed. Video consultations before surgery are already replacing face-to-face interaction, and most follow-up care is now done via conference calls. However, we need to be very vigilant in managing postoperative complications: any symptoms of pyrexia or sepsis or any signs of COVID, including postoperative fever.

It is appropriate to implement a weekly surveillance program to identify asymptomatic COVID-19–positive employees. SARS-CoV-2 tests with nasopharyngeal sampling and the use of a reverse transcriptase polymerase chain reaction (RT-PCR) assay that is 75% sensitive and at least 99% specific could be used. For mass daily detection, we continue to certify visitors and evaluate temperature of visitors and employees daily [55].

For daily mass screenings, daily attestation of visitors and daily temperature screening of visitors and all employees must be continued.

During a face-to-face consultation, the main goals are to carry out effective triage and to apply strict infection control measures, such as isolating patients and quarantine contacts as soon as possible.

Protective equipment should include waterproof gowns, disposable gloves, N95 masks and goggles or face shields. Only suction catheters and mechanical respirators with a closed loop system and viral filters should be used. In contrast, nebulizers, oxygen masks, and continuous nasal positive airway pressure systems should not be used in open rooms.

1. Strict hygiene of the hands should obviously be emphasized, and contact should be avoided or limited to an absolute minimum.
2. HCoVs persist on dry surfaces for up to 9 days [7, 56]. Persistence depends on temperature (shorter duration at 30–40°C) and humidity (longer duration at higher humidity) [57].
3. HCoVs, including new CoVs, can be inactivated by heating at 56°C for 30 minutes or using lipid solvents such as ethanol (>75%), isopropanol (>70%), formaldehyde (>0.7%), povidone-iodine (>0.23%), sodium hypochlorite (>0.21%), and hydrogen peroxide (>0.5%), but not chlorhexidine [11, 56].

Conclusions

We hope that the "new normal" will end soon, although we remain uncertain about what the next phase of the pandemic may bring. Even in the "new normal," it will take years for herd immunity to occur [58]. This disease will continue in the community for some time, so we have to continue what we have done well, such as social distancing, and the population-wide use of tests. Even in the absence of harmful data or though it "seems" positive - due to the physiological, biological or biochemical bases that support it - we must be cautious in our medical actions. This implies that the impact of COVID-19 may reverberate throughout society for the least 2 to 3 years, impacting healthcare and, of course, cosmetic, esthetic and functional gynecology and regenerative medicine in general.

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Contributors

Rafael Sánchez-Borrego conceived, designed, supervised, and drafted the article.

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Gustavo Leibashoff supervised and drafted the article.

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All authors contributed to interpreting the results and approved the final manuscript.

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