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Considerations on the restriction of Assisted Reproductive Technology (ART) due to COVID-19

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ABSTRACT

The rapid rise of novel coronavirus disease 2019 (COVID-19) cases led the American Society for Reproductive Medicine (ASRM) to recommend immediate cessation of all new fertility treatment cycles on March 17, 2020. Controversial from the start, providers and patients expressed their opposition through online petitions, surveys, and other forums. While the impact of a delay in access to reproductive care is unknown, previous studies are reassuring that a delay in the timespan of months may not affect clinical outcomes. However, dropout from care during this pandemic remains a serious concern. Effective therapies against the virus and a vaccine are not on the immediate horizon. Accepting COVID-19 will likely be a part of our lives for the near future necessitates the modification of fertility protocols to keep patients, providers, and staff as safe as possible. We believe fertility treatment is an urgent, essential service that can be performed safely and responsibly during this pandemic.

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Impact of COVID-19 on ART care in the United States

On March 17th, 2020, the American Society for Reproductive Medicine (ASRM) issued recommendations developed by an expert Task Force meant to protect patients and providers from the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for coronavirus disease 2019 (COVID-19), help "flatten the curve,"1 and preserve personal protective equipment (PPE) that was limited at the beginning of the pandemic. The recommendations included the abrupt suspension of all new, non-urgent treatments including ovulation inductions, intrauterine inseminations (IUIs), and in vitro fertilization (IVF) indefinitely.2 Clinics were strongly encouraged to cancel all embryo transfers and suspend elective surgeries and non-urgent diagnostic procedures. Only those patients currently “in-cycle” or requiring urgent stimulation and cryopreservation were suggested to continue care.

While some reproductive epidemiologists applauded the ASRM’s guidance,3 the newly formed Fertility Providers Alliance (FPA) representing hundreds of fertility specialists around the country criticized the Task Force for not seeking more input from active providers and failing to recognize the measures clinics could take to reduce disease transmission risk. Perhaps the most fervent opposition came from an online petition stating the ASRM’s COVID-19 recommendations violate the principles of justice, autonomy, and non-maleficence, quickly gaining over 20,000 signatures.4 A survey of over 500 fertility patients at our academic practice in New...
York City, the epicenter of the COVID-19 pandemic, was notable for 85% of patients reporting moderate to extreme upset regarding the ASRM’s recommendations, with 22% rating it equal to the upset they would feel if they lost a child. Additionally, 82% would have preferred the option to start a treatment cycle during the pandemic in consultation with their reproductive endocrinologist.²

Impact of a delay in ART care during COVID-19

Despite the controversy over the ASRM’s recommendations, surveys from national webinars indicated most providers around the country were suspending new cycle starts in accordance with ASRM guidance. The clinical impact, if any, of delayed cycles is unknown. It is well accepted that patients who undergo alkylating chemotherapy or pelvic radiation for cancer indications have diminished ovarian reserve and reduced IVF success after therapy,⁶,⁷ thereby prompting the recommendation for urgent cryopreservation of gametes, embryos, or ovarian tissue prior to gonadotoxic cancer therapies.⁸ The significance of a delay in fertility treatment for those with diminished ovarian reserve is less clear. Female fecundity decreases with age due to a decrease in the number of primordial follicles and an increase in aneuploidy rates in oocytes and embryos.⁹ Historical data from married women in populations not routinely using birth control suggest a significant decline in fecundity after age 35, with a reduction of 31% in women age 35 to 39 years compared to women age 20 to 24 years.¹⁰ ART cannot fully overcome this age-related decline in fertility, with decreased cumulative live birth rates with increasing age.¹¹

Some proponents of a pause in fertility treatments have proposed that a delay on the time-scale of months does not have a clinical impact. The FORT-T trial was a randomized controlled trial (RCT) including 154 couples with female partners aged 38 to 42 who were initially treated with two cycles of either clomiphene citrate (CC) and IUI or injectable follicle stimulating hormone (FSH) and IUI or immediate IVF. Those randomized to IUI had diminished pregnancy rates and live births compared to couples randomized to IVF. However, at the end of the study, all couples were offered IVF and clinical pregnancy rates and number of live births did not differ significantly between the three groups despite the delay.¹² Caution should be applied when extrapolating the results of this RCT to the current COVID-19 pandemic. Namely, this RCT took place in a state with mandated infertility insurance coverage and had a low dropout rate. It is an unfortunate reality in reproductive medicine that a large percentage of patients discontinue fertility treatment due to a multitude of reasons, including psychological, emotional, and financial concerns.¹³ A German study reported an increase in dropout from 39.3% after the first failed cycle of IVF to 62.2% after the fourth failed cycle. The significant psychological stress and frustration associated with unsuccessful fertility treatment partially explains this dropout from care.¹⁴

Current public health efforts to slow the spread of COVID-19 have led to millions of American citizens losing their jobs and subsequently their health insurance.¹⁵ The impact of these measures on patients’ ability to fund fertility treatments is unknown, but may further increase dropout rates. On webinars during the pandemic, clinics that remained open during this pandemic reported a significant decrease in the volume of treatment cycles and new patients. Additionally, limited data suggest public catastrophes may negatively affect IVF outcomes. A small study out of a New York City fertility center after the terrorist attacks on the morning of September 11th reported worse IVF outcomes with a significant increase in pregnancy loss for patients with a positive pregnancy test after September 11th compared to before.¹⁶

Changes in infertility evaluation and treatment due to COVID-19 in New York

For a period, New York was the epicenter of the COVID-19 pandemic in the United States and worldwide.¹⁷ The first case was confirmed on March 1st and a state of emergency was declared shortly thereafter. The first confirmed death occurred in mid-March, with over 327,000 confirmed cases and over 20,000 fatalities reported by May 8th.¹⁸ Timely research on obstetric patients presenting for delivery at New York Presbyterian/Columbia University Irving Medical Center revealed the vast majority of patients with positive nasopharyngeal swabs for SARS CoV-2 PCR were asymptomatic, leading to questions about incubation periods and how to keep providers, other staff members, and patients safe. At Columbia University Fertility Center (CUFC), policies were implemented in an effort to maintain social distancing and limit the spread of the virus. Visits were converted to telemedicine visit where possible. Critical staff was divided into teams that would rotate days when they would be at the fertility center in order to minimize exposure to the entire team. Staff members were encouraged to work from home when possible. PPE was provided to all safe members traveling to and from the fertility clinic.

To highlight how our practice adapted at the beginning of the pandemic, we present two cases of couples undergoing fertility treatment whose care was complicated by COVID-19 during the initial days of the pandemic. The first case involves a 28-year-old married woman gravida zero whose husband had severe male factor infertility. She underwent an uncomplicated single blastocyst transfer less than a week before the release of ASRM’s recommendations. Shortly thereafter, both her and her husband developed symptoms concerning for COVID-19 and both tested positive for the virus 4 days prior to her planned pregnancy test in the office. She was advised to take a home pregnancy test, which was positive. She was encouraged to stay at home until she was afebrile and asymptomatic for more than 7 days. After that time, she returned to the Fertility Center and an intrauterine pregnancy with fetal cardiac activity was confirmed by ultrasound. All staff members interacting with this patient wore appropriate PPE. A follow-up ultrasound confirmed a viable 8-week intrauterine pregnancy.

The second case involves a 35-year-old woman with recurrent pregnancy loss planning IVF who called our practice with a positive home pregnancy test on March 17th. She additionally reported classic symptoms of COVID-19 (fever, cough, loss of smell/taste for 5 days). Empiric vaginal progesterone
Table 1 – IVF protocol modifications pre- and post-COVID-19.

| IVF Protocol Modifications                  | Post-COVID-19                                      |
|---------------------------------------------|---------------------------------------------------|
| In-person consultations                     | Telemedicine consultations                        |
| In-person meetings with nurses, coordinators| Virtual meetings with nurses, coordinators         |
| Unrestricted travel with no personal protective equipment | All staff were issued and encouraged to wear masks on their way to and from the center, all patients were issued masks to wear at the center if they didn’t already have one |
| Hepatitis B, C, HIV, and syphilis tests prior to stimulation | Consider addition of SARS CoV-2 testing prior to start of stimulation (if positive, do not start) |
| Multiple visits during stimulation (typically 5-7 visits before egg retrieval) | Space out visits during stimulation where appropriate (3-4 visits before egg retrieval). Temperature checks at each visit (patients and staff). |
| Crowded waiting rooms                       | Patients immediately roomed after checking in. Vital signs and blood draw done while in the exam room. Seating and location of staff were changed to maintain >6 foot distancing wherever possible. |
| Rapid turn-over of ultrasound examination room | Empty waiting room, thoroughly wipe down surfaces, longer interval between procedures |
| Partner encouraged to accompany patient at visits, egg retrieval, and transfer | No partners or visitors (encourage use of video-telephone products) |
| Sperm production on site in small collection room | Off-site sperm production |
| Signed consent forms – common pens          | Electronic consent forms – clean pens available if need to sign forms |

Resuming treatment, path towards safe and responsible fertility care during pandemic

By the beginning of April 2020, New York had past the peak of the outbreak with declining hospital admissions, number of patients on ventilators, and reported deaths. ASRM had revised its initial statement granting more autonomy to fertility providers and reaffirming that fertility care is an essential and timely health service. Furthermore, the Task Force recognized regional differences in coronavirus incidence and overall risk mitigation upon the resumption of fertility services.\(^{19}\) Until a vaccine or effective therapy is created, COVID-19 will remain part of our reality. Therefore, fertility protocols must be modified to protect patients and providers during this vulnerable time. Table 1 outlines potential IVF protocol modifications pre- and post-COVID 19.

Resuming treatment is not without risks. Due to our limited knowledge of the virus, uncertainly exists regarding the impact on pregnancy outcomes. Pregnancy can be postponed with freeze-all approaches; however, it is reassuring that no major organizations including the American College of Obstetricians and Gynecologists (ACOG) or the World Health Organization (WHO) has recommended against pregnancy. Additionally, we have known for years that the risk of cross contamination of viruses in liquid nitrogen appears negligible\(^{20}\) and washing with sterile liquid nitrogen can further reduce the risk.\(^{21}\) It is common practice that specimens from patients positive for human immunodeficiency virus (HIV) or hepatitis are cryopreserved in separate tanks. We do not typically quarantine respiratory viruses or other viruses such as cytomegalovirus (CMV). Nonetheless, laboratory practice may need adjustment during the COVID-19 pandemic. The Society for Assisted Reproductive Technology (SART), the College of Reproductive Biology (CRB), and the Society for Reproductive Biologists and Technologists (SRBT) recently published a consensus document with recommendations to help laboratories implement policies to attenuate the risks posed by COVID-19. Recommendations included ensuring only symptom-free technicians be present in the clinic, changing scrubs upon entrance to the laboratory, consistently using PPE, discouraging sharing pipettes and pens, dividing laboratory staff into non-overlapping teams, disinfecting all surfaces at the beginning of the shift, considering remote options for non-bench activity, and reviewing precautions and labeling practices in individual laboratories to minimize risk of cross-contamination.\(^{22}\)

Conclusions

In summary, the COVID-19 pandemic has had a major impact on New York and will likely shape the way we practice reproductive medicine in the future. Fertility treatment is an urgent, essential service that can be performed safely and responsibly. Telemedicine visits and social distancing are the new normal. Fertility clinics must adjust to the new reality with novel protocols to minimize risk to patients and staff.
Disclosures

The authors report no disclosures.

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