It has been more than one year since the first case of COVID-19 was identified in the United States (U.S.) and the first SARS-CoV-2-related death was recorded. The largest surge of cases since the onset of the pandemic occurred following the seasonal holidays, lasting for most of January 2021, but is now on a downward trajectory in the U.S. Nevertheless, current community transmission rates continue at a substantial level.

In the current update, the ASRM Coronavirus/COVID-19 Task Force (the “Task Force”) continues to support strict adherence to its earlier recommended mitigation strategies for disease prevention, including use of Personal Protective Equipment (PPE), implementation of travel restrictions and quarantines when appropriate (see Update #3).

Even though the decreasing trend in infection rates is encouraging, and 52 million in the U.S. have been vaccinated, CDC guidelines should be strictly followed, and COVID-19 prevention should remain a top priority to reduce the likelihood of the emergence of additional, new SARS-CoV-2 variants. While COVID-19 vaccines are highly effective in preventing illness and hospitalization, their effectiveness for prevention of transmission remains unclear. Care centers should continue to maintain usage of masks and double masking, hand washing, avoidance of crowds, and social distancing.
Since the last update published on January 18, 2021, the Task Force has observed the following:

- As of February 21st, the U.S. continues to lead the world in COVID-19 cases and deaths. Documented COVID-19 cases now exceed 28 million in the U.S., though estimates suggest that up to 100 million individuals may have had the virus. Most disconcerting is that the country is now approaching the grim milestone of half a million deaths (499,000). In addition, new viral variants with higher transmissibility and possibly higher mortality, are spreading across the U.S. and pose a challenge because increased transmissibility increases the percentage of the population required to achieve “herd immunity” and with continued viral spread, more mutations and thus viral variants arise.

- On February 21st, new daily cases in the U.S. were 70,646 and falling, in contrast to the reported peak of more than 260,000 daily cases in January 2021. Despite this significant overall decrease in cases, statewide positivity and transmission rates continue to differ by region even though positivity rates have dropped dramatically with only two states above 40/100,000 (New York at 41/100,000 and South Carolina at 56/100,000). Eight states have positivity rates of 30-40/100,000 (New Jersey, Rhode Island, North Carolina, Virginia, Delaware, Kentucky, Oklahoma and Florida). Other states with leading transmission rates at the time of the last Update are now exhibiting improvements, with Arizona dropping from 126.5/100,000 to 22/100,000 and California improving from 107.9/100,000 to 21/100,000. Hawaii continues to have the lowest positivity rate at 4/100,000 (down from 20/100,000).

- In early December, the U.S. Food and Drug Administration (FDA) issued Emergency Use Authorizations (EUAs) for two SARS-CoV-2 vaccines in the U.S. (the Pfizer-BioNTech and the Moderna vaccines). As of February 21st, an EUA is pending for a third vaccine from Johnson & Johnson. EUA applications for other vaccines used in other countries (i.e., Astra Zeneca from the United Kingdom [U.K.]) have not been submitted to the FDA and are not presently approved for use in the U.S. As of mid-February, 52 million (15.7% of the U.S. population) have received at least one dose of a COVID-19 vaccine, though vaccine shortage remains an issue.

- There continues to be variation in vaccine acceptance among demographic subgroups, with a lower likelihood of acceptance among women, individuals under 50 years of age, African Americans, Native Americans, Latin Americans, and those without a college degree.

- Given the known risks and severity of COVID-19 disease during pregnancy, the Task Force continues to support vaccination of pregnant women or women attempting pregnancy. ASRM, the World Health Organization (WHO), the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) have all supported vaccination.

In addition to continuing to maintain all mitigation strategies, including wearing PPE and social distancing, the Task Force is issuing this update to assist reproductive care specialists in counseling their patients and their communities regarding the new variants of SARS-CoV-2, the effectiveness of the two available vaccines in preventing infection with the new variants and further guiding administration of the vaccine to women who are pregnant or are attempting pregnancy. Due to the systemic side effects observed in some individuals receiving the COVID-19 vaccines, a guidance as to the timing of vaccination vis a vis fertility treatments and procedures is also included in this Update.

**VIRAL VARIANTS**

As the SARS-CoV-2 virus continues to circulate, new viral variants containing mutations in the receptor binding domain are being identified in a number of countries, and in some countries, viral variants are replacing the
previously dominant strain. The three major variants recognized at this time are B.1.1.7 (first observed in the U.K.), B.1.351 (first observed in South Africa), and P.1 (first observed in Brazil). All three variants have been reported in the U.S., and most U.S. cases with variants at this time are B.1.1.7 (1). Studies show increased transmissibility of these viral variants compared to the original circulating strain. The recent recognition of these variants strengthens the case for continued use of preventive measures and vaccination to reduce transmission rates.

VACCINES
At this time, there are 20 COVID-19 vaccines in a variety of platforms in phase three trials and two vaccines approved under EUA for use in the U.S. Currently available mRNA vaccines from Pfizer-BioNTech and Moderna have efficacy rates of 94-95%, defined as a 94-95% lower risk of contracting COVID-19 among vaccinated individuals compared with an unvaccinated control group.

Published vaccine trials used endpoints of symptomatic infection in adults with confirmed COVID-19 infection. Vaccine efficacy differs from vaccine effectiveness (2), which measures how well a vaccine works when given to people in the community outside of clinical trials. Reassuring early reports suggest that vaccine effectiveness rates mirror the efficacy rates noted in the original clinical trials. Notably, none of the vaccinated individuals in the trials developed severe disease or died. Vaccine-induced immunity for available mRNA vaccines (with a two-dose series separated by 21-28 days) develops approximately two weeks after the first dose of vaccine. The second dose of vaccine is important since it helps to ensure a long-lasting immune response.

Studies suggest that immunity after vaccination lasts for at least four months and immunity after infection lasts for at least eight months (3,4). Current data also suggest that mRNA vaccines are effective in preventing infection caused by the new viral variants (5). Johnson & Johnson recently applied for an EUA from the U.S. FDA for their single dose COVID-19 adenoviral vector vaccine. Study data will be presented at the February 26, 2021 FDA Vaccines and Related Biological Products Advisory Committee Meeting, and clinical trials data from their two-dose vaccine series is expected soon. Preliminary data for the Johnson & Johnson vaccine indicate efficacy rates of 66% for the prevention of all levels of disease, 85% for the prevention of severe disease, and 100% for the prevention of hospitalization and death. Studies focused on the safety and efficacy of COVID-19 vaccination during pregnancy have been initiated.

While mRNA vaccines are excellent at preventing severe COVID-19 infections, it is not yet clear whether vaccinated individuals can acquire asymptomatic infection or transmit infection to others. Given these unknowns, continued vigilance, and the use of effective mitigation strategies remain critical until herd immunity is achieved. Mask wearing, physical distancing and hand hygiene should continue to be practiced even after vaccination.

TIMING OF VACCINATION WITH RESPECT TO REPRODUCTIVE CARE PROCEDURES
We reaffirm our endorsement of vaccination against COVID for women of reproductive age as stated on December 16, 2020 in Update #11 – “Patients undergoing fertility treatment and pregnant patients should be encouraged to receive vaccination based on eligibility criteria. Since the vaccine is not a live virus, there is no reason to delay pregnancy attempts because of vaccination administration or to defer treatment until the second dose has been administered.”

Subsequently, ASRM, the American College of Obstetricians and Gynecologists (ACOG), and the Society for Maternal-Fetal Medicine (SMFM) issued a joint statement on 5 February 2021, assuring the public that – “As
experts in reproductive health, we continue to recommend that the vaccine be available to pregnant individuals. We also assure patients that there is no evidence that the vaccine can lead to loss of fertility. While fertility was not specifically studied in the clinical trials of the vaccine, no loss of fertility has been reported among trial participants or among the millions who have received the vaccines since their authorization, and no signs of infertility appeared in animal studies. Loss of fertility is scientifically unlikely.”

As vaccines become more widely available, a practical question has arisen regarding the timing of vaccine administration with respect to certain invasive reproductive care treatments. In general, it is recommended that:

- Patients scheduled for elective surgery or outpatient procedures, including oocyte retrieval, embryo transfer, and intrauterine insemination, avoid COVID-19 vaccination at least three days prior and three days after their procedure.

This recommendation is not because being vaccinated is unsafe, but rather because known side effects of the vaccine may impact intra-operative and post-surgical monitoring. Common side effects after COVID-19 vaccination, especially after the second dose, include fever, chills, fatigue, myalgia, and headaches, which typically occur and resolve within three days. Anesthesia impairs normal thermoregulatory control and may be impacted by pre-existing fever. Additionally, these side effects would make it difficult to determine if a post-procedure fever is related to the vaccine or to a developing infection related to the procedure. Finally, many medical facilities may not allow patients into their facility or proceed with any elective procedure if a patient has COVID-like symptoms, including those that are possible side-effects of the vaccine, even if their COVID-19 test is negative.

Practices should notify and encourage their patients to communicate with their surgeons and fertility programs when they become eligible for COVID vaccination. This will help coordinate planned surgical procedures, fertility testing and treatment, and will decrease the chance of inadvertent procedure cancellation.

PREGNANCY, COVID-19, AND VACCINATION

There are emerging data that demonstrate that pregnancy is a high-risk condition for the development of severe disease associated with COVID-19. A large, multi-national cohort of pregnant women with COVID-19 showed that infection earlier in pregnancy increased the risk for complications (6). These data highlight the importance of vaccination in patients who are desiring or planning conception and/or who are pregnant, so as to prevent severe disease and add strength to the argument that the known risks of COVID-19 in pregnant women outweigh the theoretical risk of harm from COVID-19 vaccination. Risks of COVID-19 in pregnancy must be taken into consideration when counseling patients regarding COVID-19 vaccination.

Studies in pregnant women with severe disease have now shown:

- Increased need for mechanical ventilation and increased risk of death in pregnant women compared with their non-pregnant counterparts (7-9).
- Increased risk for pre-term labor (7).
- Reports of fetal death (10, 11).
There are also emerging reports of placental injury in the setting of SARS-CoV-2 infection:

- Two recent investigations of placentas from women infected with COVID-19 in the third trimester revealed prevalent placental injuries characterized by thrombotic fetal vascular malperfusion, although no evidence of acute infection (12,13).
- Additionally, a prominent inflammatory response is noted at the maternal-fetal interface (14), so that placental injury may be mediated by the maternal systemic inflammatory or hypercoagulable state.

Taken together, these studies suggest pregnancy is a time of COVID-19 vulnerability for the mother and potentially for the fetus.

In accordance with the CDC guidance stating that pregnant women are at high risk for severe disease, the Task Force recommends that pregnant women, considering guidance from their own states, should be prioritized to receive vaccination. It is recommended that patients receive vaccination at the soonest possible time, whether pre-conception or during pregnancy, while considering the timing of any surgical procedure (see section above).

PASSIVE IMMUNITY IN NEWBORNS

Pregnant women are at increased risk of COVID-19 complications. However, and importantly, studies suggest that maternal COVID-19 infection during pregnancy may confer passive immunity to newborns based on the detection of immunoglobulins in cord blood at the time of delivery and in blood samples from neonates (15); however, not all studies agree (16). Furthermore, there is emerging evidence for the presence of neutralizing antibodies in breast milk following maternal infection (17). This suggests that passive immunity to newborns is possible as a result of maternal COVID-19 infection. It remains to be seen whether vaccination might similarly confer passive immunity to neonates (18), a finding that would further support the particular importance of vaccination prior to and during pregnancy.

MENTAL HEALTH AND COVID-19

As we approach the one-year anniversary of the COVID-19 pandemic in the U.S., and as vaccination against the virus is becoming increasingly available, individuals and groups continue to struggle emotionally and mentally. Pandemic fatigue, information overload and misinformation, loneliness, fear, and confusion, and other psychological factors, are combining to threaten and undermine the pathway back to normalcy provided by following safe mitigation policies and vaccination procedures. A psychological understanding of people’s motivations, perceptions, and behaviors will help providers in fertility clinics develop successful strategies to ensure the safe delivery of reproductive care. Selected findings below may help provide some guidance.

**Increased stress:** The American Psychological Association (APA) (19) conducted an online survey within the U.S. of 2,076 U.S. adults, aged 18 and older, for their “Stress in America” project from Jan. 21 to 25, 2021. The survey’s results include:

- The highest levels of stress since April 2020, shortly after the pandemic became a significant public health crisis in the U.S.
- Of U.S. adults surveyed, 84% state the nation has serious societal issues that need to be addressed.
• Of U.S. adults surveyed, 84% reported feeling at least one emotion associated with prolonged stress. The most common emotions reported were:
  o Anxiety (47%)
  o Sadness (44%)
  o Anger (39%)
• The majority of adults reported the following significant sources of stress:
  o The future of the nation (81%)
  o The coronavirus pandemic (80%)
  o Political unrest around the country (74%)

While this survey did not assess the stress associated with the current plan to the return of children to in-school learning, it is expectable that this topic is also a source of great deal of stress for many people, including teachers and parents. In the field of fertility and reproductive medicine, this back-to-school stress, along with the increased level of stress felt by Generation Z (13-23 y.o., see Update 10, published November 17th, 2020) will no doubt greatly impact the following groups: those who are seeking to become pregnant or experiencing infertility or fertility challenges, individuals working in fertility clinics as providers and staff who are already parents, and people with secondary infertility/fertility challenges who are already parents.

**Vaccination hesitancy:** Psychologists have been tracking vaccination attitudes, hesitance, and acceptance since the spring of 2020 (20). Although the willingness to be vaccinated has increased over time, vaccination hesitancy still exists and varies across different groups (see Update 12, published January 9, 2021). Vaccination research findings include the following helpful tips to ameliorate vaccine hesitancy:

• Framing of vaccination as a beneficial apolitical decision
• Using positive emotional messages, such as altruism and hope, which are more effective than negative ones
• Tailoring messaging to different groups
• Leveraging professional organizations, such as the APA and ASRM, in communication efforts can be helpful.
• Providing opportunities for people to ask questions about vaccination
• Sharing of personal experiences by medical providers, and especially by doctors and nurses of color, is effective in building trust in vaccines.
• For anti-vaxxers, often motivated by concerns about having their freedom curtailed, the most effective messaging has to do with emphasizing that vaccination is a right and that they should strive to ensure that no one prohibits them from losing that right.
• Vaccination intent does not translate into vaccination behaviors.
• Warnings from experts early in the pandemic that vaccine development would take years have contributed to safety concerns that vaccinations have been developed too quickly.
• Other proven methods for improving vaccination rates include the use of:
  o Reminders
  o Automatically scheduled appointments
  o Strategies to make logistics for the patient as seamless as possible
  o Paid time-off for recovery from side effects
External incentives, such as airline and sports venues requiring proof of vaccination

**Resistance to mitigation practices:** Psychology research has shed light on some of the sources of risky behaviors that result in COVID-19 infection, such as not wearing masks in social situations or in gatherings of families and friends. Psychologically, the use of these mitigation strategies often depends on variables having to do with risk perception (21). Essentially, the assessment of risks is tied to interpersonal relationships – that is, people conflate friendliness and trust as risk reducers to create a false sense of security in certain situations. Therefore, while a person may feel the need to wear a mask in public, they also may feel that they do not need to wear a mask with friends or family. Consciously or not, most people are more likely to want to avoid germs from an “enemy” or “stranger” rather than from a friend or even from a stranger who seems more sociable than unsociable.

**Telepsychology/telemental health:** It is widely anticipated that the pandemic crisis will lead to a paradigm shift with many mental health providers either continuing to provide elemental health or to offer a hybrid model that includes some in-person psychotherapy and assessment treatment. Research is ongoing to investigate the effectiveness of telemental health and to compare its effectiveness with in-person treatment. However, in a recent meta-analysis, Batastini et al (22) provided preliminary evidence suggesting that the effectiveness of clinical interventions and assessments delivered via videoconferencing are comparable to those delivered in-person.

**Recommendations for reproductive care patients:** The pandemic has elevated stress levels for many individuals, and this is no different for patients struggling with infertility. The Task Force notes the following:

- Patient stress may be triggered by items that they see in the media or experience in their daily lives (e.g., national focus on children returning to school, the government considering providing additional stimulus money to those with children, the birth of babies conceived during quarantine). Patients should be encouraged to lean into their feelings and to grant themselves grace when negative feelings arise.
- Battling infertility can be isolating and the COVID-19 pandemic may exacerbate that feeling for many patients. Patients should be encouraged to utilize their support networks (e.g., partner, extended family, friends, providers) and those support networks should be proactive in supporting patients. It is recommended that patients be creative in their networking efforts (e.g., family video chats, masked walks with a friend, mailing a "thinking about you" card, at-home date night, etc.).
- Patients may be disappointed by the impact that the COVID-19 pandemic is having on their fertility treatments, including delays in treatment, additional steps such as multiple COVID-19 tests per cycle, and the inability of partner and/or intended parents to attend embryo transfers in-person. Patients can empower themselves to take control and to be creative. Examples of this may include:
  - Make embryo transfer day special: have a special meal, buy balloons or flowers, attend the transfer virtually, have intended parents be outside at the clinic for pre- and post-transfer encouragement and celebration.
  - Get mentally and physically fit for treatments: have an at-home pamper yourself day, try a new recipe, sign-up for a meditation app, attend a virtual workout class.
  - Put a positive spin on COVID-related tasks: wear your favorite mask to fertility treatments, have a treat after each COVID test.
**Recommendations for reproductive care providers:** Providers should consider the above recommendations for patients. Additionally, the Task Force suggests the following:

- Be a trusted leader and role model.
- Be personal and encourage friendly relationships and interactions within staff and providers and patients to promote trust.
- Tailor vaccination discussions appropriately with all parties.
- When possible, provide paid time-off when staff members and providers have reactions to vaccinations or problems with childcare.
- Reinforce accurate information and suggest reliable sources of information about safe mitigation and vaccination.
- Reinforce the importance of mitigation practices (masks, social distancing, etc.) and vaccination for the safety of self and others and encourage the development of social norms for these behaviors.
- Encourage the use of telemental health and support groups, and provide access to mental health resources, such as the ASRM Mental Health Professional Group for all parties (patients, providers, and staff) to decrease stress, provide support, and promote resilience.

**Recommendations for stress management for patients and providers:** The APA offers the following evidence-based advice to help people manage their stress (19):

- Give yourself permission to take a break from the news, social media, or even certain friends. Constantly exposing ourselves to negative information, images and rhetoric maintains stress at unhealthy levels.
- Practice the rule of “three good things” and ask friends and family to do the same. The rule states that at the end of each day, reflect on three good things that happened that day — large or small. This helps decrease anxiety, counter depression, and build emotional resiliency.
- Practice self-care in 15- or 30-minute increments throughout the day. This can include taking a short walk, calling a friend, or watching a funny show. Parents should encourage or help their children to do the same.
- Stay connected with friends and family. This helps build emotional resiliency so you can support one another.
- Keep things in perspective. Try to reframe your thinking to reduce negative interpretations of day-to-day experiences and events.
REFERENCES


