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Journal of the American Pharmacists Association

journal homepage: [www.japha.org](http://www.japha.org)

## COMMENTARY

## The impact of COVID-19 on select considerations in patients of reproductive age: Brief talking points for pharmacists



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## ARTICLE INFO

*Article history:*

Received 15 September 2022

Accepted 5 January 2023

Available online 11 January 2023

## ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic has elicited many health concerns, including the impact of the infection and vaccine on reproductive health. Although robust evidence demonstrates the safety of all available COVID-19 vaccines, misinformation and disinformation related to the vaccine continue to circulate. As accessible and essential health care workers, it is crucial that pharmacists are informed of the evidence related to effects of the COVID-19 infection and vaccinations on reproductive health care. Menstrual cycle changes have been noted owing to COVID-19 infection, pandemic stress, and COVID-19 vaccination. COVID-19 infection and vaccination have not been shown to influence female fertility, pregnancy rates, and lactation. The use of exogenous estrogen may further contribute to an increased risk of thromboembolism with COVID-19 infection, and differences in the risk of cerebral venous sinus thrombosis appear to exist between the types of vaccines. The benefits of COVID-19 vaccination outweigh any risks. Shared decision-making is necessary when discussing vaccination with patients. Pharmacists play a vital role in dispelling misinformation and disinformation related to the impact of COVID-19 illness and vaccination on reproductive health care.

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## Introduction

The coronavirus disease 2019 (COVID-19) pandemic has led to fear, panic, and serious health concerns. Vaccines have proven to be safe and effective at preventing severe disease, but not all choose to be vaccinated.<sup>1</sup> As of December 2022, 77.2% of eligible individuals ages 12 years and older in the United States completed the primary COVID-19 vaccination series.<sup>2</sup> Despite strong evidence in the general population that vaccines reduce negative outcomes, patients question the reproductive impact.

Concerns related to the COVID-19 pandemic and vaccinations' impact on reproductive health have generated important questions for all health care professionals (HCPs) during

the pandemic. Changes in the menstrual cycle, effects on fertility, safety during pregnancy and lactation, and the potential for thromboembolic effects are some of the common concerns.<sup>3–12</sup> Despite available evidence providing some guidance, misinformation, disinformation, and evolving information contribute to COVID-19 vaccination hesitancy, especially during pregnancy, and for those who may desire to conceive in the future.<sup>7,13</sup> The most reported reasons for vaccine hesitancy in patients of reproductive age are safety, lack of data, and fear of adverse effects.<sup>7–11</sup> Patients have reported that more information on the vaccine, the inclusion of pregnant individuals in studies, and advice from HCPs could help alleviate potential concerns. In addition, the impact of racism and other inequities in health care delivery plays a pronounced role in vaccine hesitancy and must be addressed.<sup>9</sup>

Pharmacists, as accessible HCPs, have readily responded to the pandemic demands by providing point-of-care testing, administering vaccinations, prescribing treatment, identifying and solving medication-related problems, educating patients, and partnering with trusted community members.<sup>14–19</sup> Pharmacists are instrumental in reducing vaccine hesitancy and

**Disclosure:** The authors declare no relevant conflicts of interest or financial relationships.

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**Key Points****Background:**

- The COVID-19 pandemic has created concerns and questions over the impact of the virus and vaccines on reproductive health.
- Pharmacists should be informed of current evidence in order to educate the public and dispell misinformation and disinformation.

**Findings:**

- COVID-19 infection may impact menses, sperm quality, and the risk of severe illness during pregnancy.
- COVID-19 vaccination may impact menses, and there is a potential for an increased risk of cerebral venous sinus thrombosis with select vaccines. The benefits of COVID-19 vaccination continue to outweigh any risks.

subsequently increasing vaccination rates.<sup>15</sup> Pharmacists also play an integral role in the reproductive health care of patients.<sup>20</sup>

The purpose of this paper is to provide pharmacists with brief talking points specific to COVID-19 infection and vaccination-related reproductive health concerns to facilitate patient education to alleviate concerns and expel myths. This paper also provides counseling points and resources to help guide discussions with patients (Table 1).

**Menstrual cycle concerns**

Limited data suggest COVID-19 infection may contribute to a decline in menstrual blood loss and an increase in menstrual cycle length.<sup>21</sup> The exact impact of COVID-19 illness on menses has yet to be determined owing to sparse published data and impact of confounding variables, such as anxiety and social isolation owing to the pandemic. Approximately half of women in 2 studies reported heavier menstrual bleeding and changes in cycle length since the pandemic began.<sup>22,23</sup>

More data exist related to the impact of COVID-19 vaccination on the menstrual cycle. A transient, nonstatistically significant change in menstrual cycle length by approximately 1 day was noted in one observational study that compared more than 2400 vaccinated women with 1500 unvaccinated individuals.<sup>3</sup> A smaller study of more than 300 women observed menses occurred 1 to 5 days earlier postvaccination compared with prevaccination.<sup>24</sup> In addition, a short-term increase in heavier menstrual bleeding within the menstrual cycle after vaccination was reported. An observational study of more than 60,000 individuals noted that 83.6% reported alterations in menstrual cycle timing and 67% reported additional an increase in menstrual symptom severity postvaccination.<sup>25</sup>

Although menstrual cycle changes have been noted after vaccination, the benefit of vaccination does outweigh these transient changes.

**Fertility concerns**

Pregnancy rates do not differ between individuals who have had a recent COVID-19 infection or have been vaccinated against COVID-19 and those who have not.<sup>26-30</sup> Through social media, a popular concern arose that messenger ribonucleic acid (mRNA) vaccines (Pfizer-BioNTech, Moderna) would induce autoreactive antibodies against Syncytin-1, a protein involved in placenta formation in early pregnancy, given that it resembles the spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).<sup>31</sup> Syncytin-1 facilitates the fusion of trophoblast cells to form syncytiotrophoblasts, which are crucial for placenta development. No cross-reactivity or anti-Syncytin-1 antibodies were detected in the plasma of vaccinated individuals. This has strengthened the body of research suggesting that there is little to no impact of COVID-19 vaccination on placenta formation and, thus, fertility.

Embryo quality and pregnancy rates did not differ based on vaccination status, type of vaccine used, and timing between complete vaccination and in vitro treatment among 735 couples.<sup>32</sup> There are no data on the optimal interval after COVID-19 infection recovery and initiation or assisted reproductive technology.<sup>30</sup> In addition, there has been no demonstrated influence of COVID-19 vaccination on success during assisted reproductive technology cycles.

Infection with COVID-19 may affect the quality of sperm, although the full impact is not well known.<sup>33</sup> Some studies have indicated that patients with COVID-19 infection have lower sperm concentrations than those without infection ( $P < 0.001$ ).<sup>34</sup> Long-term studies assessing this impact are lacking. In small studies of sperm parameters after COVID-19 vaccination, there was no statistically significant decrease in any sperm parameters in healthy men, such as sperm concentration and motility, after vaccination.<sup>35,36</sup> Men with oligospermia also do not seem to experience a decline in sperm parameters.<sup>36</sup> Vaccination has the potential to minimize or eliminate the impact of COVID-19 infection on sperm.

COVID-19 vaccination is indicated for those trying to conceive, and it does not need to be delayed. COVID-19 infection may have a small impact on male fertility; recent infection may inform the need for further analysis in male partners.

**Pregnancy and lactation concerns**

Randomized clinical trials (RCTs) evaluating the impact of COVID-19 infection and the safety and efficacy of COVID-19 vaccines in pregnant and lactating individuals are lacking; however, several observational studies are described in this section. In scenarios when RCTs are unlikely, observational studies are considered reliable and valid.<sup>37</sup> Whether pregnancy increases the susceptibility of infection remains unknown, owing to variability in exposures and the lack of similar control groups.<sup>38</sup> Several studies demonstrate more severe outcomes in pregnant versus nonpregnant patients, such as increased rates of hospital admissions, intensive care unit admissions, ventilation use, intubation, oxygen use, and death.<sup>39-41</sup> Adverse pregnancy outcomes such as preeclampsia, preterm birth, and stillbirth are higher among pregnant persons with COVID-19 than pregnant persons without COVID-19.<sup>42</sup> Intrauterine transmission of COVID-19 has been

**Table 1**  
Counseling points and resources

Topic	Counseling points	Additional resources to help guide patient-centered decisions
Menstrual cycle	<ul style="list-style-type: none"> <li>• Possible menstrual cycle changes owing to COVID-19 infection-related stress in addition to the COVID-19 vaccines have been noted.</li> <li>• Changes may include modest alterations in menstrual cycle length, earlier than anticipated menses in the cycle after vaccination, and potential for heavier menses.</li> </ul>	<ul style="list-style-type: none"> <li>• ACOG. COVID-19 Vaccines: Answers from Ob-Gyns. <a href="https://www.acog.org/womens-health/faqs/covid-19-vaccines-answers-from-ob-gyns">https://www.acog.org/womens-health/faqs/covid-19-vaccines-answers-from-ob-gyns</a></li> <li>• CDC. Frequently Asked Questions about COVID-19 Vaccination. Centers for Disease Control and Prevention. <a href="https://www.cdc.gov/coronavirus/2019-ncov/vaccines/faq.html">https://www.cdc.gov/coronavirus/2019-ncov/vaccines/faq.html</a>.</li> </ul>
Fertility	<ul style="list-style-type: none"> <li>• COVID-19 vaccination has not demonstrated an impact male or female infertility.</li> <li>• COVID-19 infection may have an impact on sperm.</li> <li>• Patients trying to conceive should receive the COVID-19 vaccine as soon as possible.</li> <li>• Vaccination should not be delayed until after fertility treatments or after pregnancy.</li> </ul>	<ul style="list-style-type: none"> <li>• ACOG. COVID-19 Vaccines: Answers from Ob-Gyns. <a href="https://www.acog.org/womens-health/faqs/covid-19-vaccines-answers-from-ob-gyns">https://www.acog.org/womens-health/faqs/covid-19-vaccines-answers-from-ob-gyns</a></li> <li>• ASRM. COVID-19 FAQs for current and future fertility patients. Available at <a href="https://www.reproductivefacts.org/faqs/covid-19-faqs-for-current-and-future-fertility-patients/">https://www.reproductivefacts.org/faqs/covid-19-faqs-for-current-and-future-fertility-patients/</a></li> <li>• CDC. COVID-19 vaccines for people who would like to have a baby. <a href="https://www.cdc.gov/coronavirus/2019-ncov/vaccines/planning-for-pregnancy.html">https://www.cdc.gov/coronavirus/2019-ncov/vaccines/planning-for-pregnancy.html</a></li> </ul>
Pregnancy/lactation	<ul style="list-style-type: none"> <li>• Infection during pregnancy has been associated with increased severity of disease, adverse gestational outcomes, and increased risk of preterm birth.</li> <li>• No evidence to date demonstrates adverse effects of the vaccine on maternal, gestational, or infant health.</li> <li>• COVID-19-positive individuals should continue breast-/chestfeeding using proper PPE.</li> <li>• Pregnant and lactating patients should receive vaccinations, including a booster, against COVID-19.</li> <li>• mRNA vaccines are preferred.</li> </ul>	<ul style="list-style-type: none"> <li>• CDC. COVID-19 Vaccines While Pregnant or Breastfeeding. <a href="https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html">https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html</a>.</li> </ul>
TE	<ul style="list-style-type: none"> <li>• COVID-19 infection increases TE risk</li> <li>• Patients hospitalized for COVID-19 should discontinue estrogen products</li> <li>• Slightly increased risk of TE with AstraZeneca vaccination compared with Moderna or Pfizer-BioNTech</li> <li>• Slightly increased risk of CVST with J&amp;J vaccine</li> <li>• Benefits of receiving vaccines outweigh risks</li> <li>• Pfizer-BioNTech, Moderna, and Novavax vaccines preferred over J&amp;J and AstraZeneca</li> <li>• Counsel on TE risks and warning signs</li> </ul>	<ul style="list-style-type: none"> <li>• ACOG. COVID-19 Vaccines: Answers from Ob-Gyns. <a href="https://www.acog.org/womens-health/faqs/covid-19-vaccines-answers-from-ob-gyns">https://www.acog.org/womens-health/faqs/covid-19-vaccines-answers-from-ob-gyns</a></li> </ul>

Abbreviations used: ACOG, American College of Obstetricians and Gynecologists; ASRM, American Society for Reproductive Medicine; CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019; CVST, cerebral venous sinus thrombosis; J&J, Janssen/Johnson & Johnson; mRNA, messenger ribonucleic acid; PPE, personal protective equipment; TE, thromboembolism.

documented but appears to be rare given that most infant infections are caused by caregiver exposure.<sup>43</sup> Adverse neonatal outcomes owing to maternal infection appear to be mostly preterm birth, demonstrated in approximately 12.9% to 22% of cases.<sup>44</sup>

In the observational and registry data available to date, the vaccines have proven to deter infection and induce antibodies in neonates.<sup>43</sup> No evidence currently demonstrates that the vaccine affects maternal, gestational, or infant health. Based on 13 observational studies of 48,000 pregnant women who received an mRNA vaccine and a retrospective cohort vaccine database study of more than 40,000 pregnant women receiving a vaccine (most women received 2 doses of a mRNA vaccine), no difference in gestational and neonatal outcomes was identified.<sup>45,46</sup> One prospective cohort study compared approximately 100 pregnant women (17–30 weeks' gestation) and neonates who received a third "booster" vaccine dose with approximately 100 pregnant women and neonates receiving 2 doses. Both maternal and neonatal antibody titers were higher in the group that had received a "third" booster vaccine dose compared with 2 doses ( $P < 0.001$ ).<sup>47</sup> Vaccine adverse effects in pregnant women are similar to the general population: mild and more common after the second dose.<sup>43</sup> The optimal timing

of the vaccine remains unclear. It should be noted that most vaccinations of pregnant women occur in the second and third trimesters with an mRNA vaccine. Data to date have been collected from the United States and Israel, which should be considered in the generalization of results.

If a lactating individual develops COVID-19, it is recommended to continue breast-/chestfeeding under conditions such as wearing a mask and washing hands frequently. There has been no evidence that the virus is transmittable via breast milk. Furthermore, newborns are considered to be at low risk of developing COVID-19, and the benefits of the nutrients gained within breast/chest milk outweigh the potential risks.<sup>48</sup>

COVID-19 vaccination is recommended for breast-feeding/chest-feeding individuals.<sup>49</sup> Although there is still minimal evidence on the effects of the vaccine on milk production, one prospective cohort study of 84 breastfeeding women who received the COVID-19 mRNA vaccine found robust secretion of SARS-CoV-2-specific immunoglobulin (Ig) A and IgG antibodies in breast milk 6 weeks after vaccination. Antibodies found in breast milk showed strong neutralizing effects, suggesting a potential protective effect against infection in the infant.<sup>50</sup>

Pregnant and breast-feeding/chest-feeding individuals are recommended to receive the COVID-19 vaccinations. The mRNA vaccines are the preferred vaccines, owing to reasons discussed in the next section.<sup>49,51</sup>

### Thromboembolism concerns

Increased risk of thromboembolism (TE) is one of the more common and widely discussed concerns associated with COVID-19 infections. Ongoing use of estrogen products while infected could theoretically further increase this risk, given that exogenous estrogen can increase the risk of TE through the activation of clotting factors.<sup>52</sup> The Society of Family Planning recommends contraceptives containing estrogen should be discontinued if a patient is hospitalized.<sup>53</sup> However, patients who are not hospitalized or using progesterone-only products can continue their regimen.

Some data suggest a slightly increased risk of TE with COVID-19 vaccination for some individuals of reproductive age. A retrospective survey consisting of 62 cases of TE reported out of 7,126,434, vaccinations showed an increased risk of cerebral venous sinus thrombosis (CVST) within 31 days of vaccination.<sup>54</sup> This event was more likely to occur with the AstraZeneca vaccine than mRNA vaccinations ( $P < 0.001$ ) and in female individuals than male individuals ( $P = 0.03$ ). Although these cases have been reported, the incidence of TE within 31 days of vaccination is 0.55 per 100,000 patients in the United States.<sup>55</sup> In another case series, within 8 days of receiving the Janssen/Johnson & Johnson (J&J) vaccine, 12 women younger than 60 years experienced CVST.<sup>56</sup> The Centers for Disease Control and Prevention and American College of Obstetricians and Gynecologists recommend the use of mRNA and protein-subunit (Novavax) vaccines over the J&J vaccine owing to the CVST concerns and longer duration of effectiveness.<sup>49,51</sup>

Current data show the benefit of getting vaccinated outweighs the risk of not being vaccinated. A shared decision-making model should be used to inform and include the patient when discussing potential risks.

### Conclusion

Data continue to emerge regarding the impact of COVID-19 illness and vaccinations on reproductive health. Patients are faced with uncertainty and conflicting information at times. Pharmacists must stay up to date on this topic to best serve their patients and dispel misinformation and disinformation. COVID-19 illness may lengthen menstrual cycle length and increase blood loss, affect sperm quality, and increase the risk of severe illness during pregnancy. Owing to the potential increased risk of TE, estrogen-containing medications should be avoided during infection. The COVID-19 vaccine may transiently increase the length of the menstrual cycle and blood loss, but the benefits outweigh any risks. Vaccination should not be delayed in those trying to conceive, pregnant, or lactating. The risk of CVST is higher with the AstraZeneca and J&J vaccines than the mRNA vaccines, but the absolute risk is small. The benefits of COVID-19 vaccination continue to outweigh any risks.

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