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Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

Does Music Lower Preoperative Anxiety in Pelvic Reconstructive Surgery Patients?

By Chiara Ghetti, MD

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SYNOPSIS: Listening to music may lower preoperative anxiety in patients undergoing pelvic reconstructive surgery.

SOURCE: Chen YB, Barnes H, Westbay L, et al. Preoperative music listening in pelvic reconstructive surgery: A randomized trial. *Female Pelvic Med Reconstr Surg* 2021;27:469-473.

The main objective of this study was to determine the effect of music listening compared to usual care on preoperative anxiety scores in patients undergoing pelvic reconstructive surgery. This was a randomized controlled trial of women undergoing pelvic reconstructive surgery over one year at one academic center. Subjects included women 18 years of age or older scheduled for surgery within the Division of Female Pelvic Medicine and Reconstructive Surgery and who were enrolled on the day of surgery. Women scheduled with other surgical departments were excluded, as were women with hearing impairments or women who were unable to complete study questionnaires. The primary study outcome was the change in preoperative anxiety state score as measured by the State-Trait Anxiety Inventory Form Y1 (STAI-Y1). The STAI-Y1 is a self-reported measure of the patient's current state of anxiety and consists of 20 four-point Likert items. Scores range from 20 to 80, with higher scores signifying higher symptoms of anxiety. The STAI-Y1 was administered at baseline before surgery. Subjects then were assigned randomly to music listening vs. usual care. Both groups repeated the STAI-Y1 prior to proceeding to surgery. The music listening intervention consisted of having the ability to listen to music of choice, consisting of preloaded tracks of multiple music genres, via noise-canceling headphones and an MP3 player for 30 minutes prior to surgery. Subjects were able to listen for however long they wanted within the 30 minutes and were instructed to stop when necessary to speak with providers.

The secondary outcome included six-week postoperative patient satisfaction as measured by a global patient satisfaction question with a five-point scale. The authors enrolled 70 subjects. Sixty-nine were randomized, 35 to the usual care group and 34 to the music intervention group. Fifty-four percent of subjects had pelvic prolapse

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as an indication for surgery. Other indications included stress incontinence (39%), urge incontinence (7%), fistula (4%), and other (19%). Baseline STAI-Y1 scores were similar between the music and usual care groups. After 30 minutes, the decrease in STAI-Y1 scores was greater in the music group (-6.69; standard deviation [SD], 6.98) than for participants assigned to the control group (-1.32; SD, 8.03; $P = 0.01$). Postoperative satisfaction at six weeks was higher in the music group than in the usual care group. Additionally, no associations were found between changes in STAI-Y1 scores and pelvic floor symptoms at baseline.

■ COMMENTARY

Women with pelvic floor disorders experience a variety of emotional and mood states, including depression and anxiety. A recent Cochrane review reports that women with incontinence are more likely to have symptoms of depression and anxiety. Pham et al described women's anxiety at the time of initial pelvic floor evaluation.[1,2] Ai et al reported a 19% prevalence of anxiety in women with stage 2 prolapse or greater.[3] Collins et al found that 35% of women tested prior to surgery for pelvic organ prolapse had scores consistent with anxiety state.[4] Often, patients preparing for surgery experience anxiety associated with the uncertainty of surgery and its outcomes. Elevated anxiety can result in psychological effects as well as physiological effects, including increased heart rate and blood pressure. These, in turn, can have effects on immune response and wound healing. Typically, patients may receive anxiolytics or sedatives in the preoperative period to help decrease anxiety symptoms, but these can be associated with side effects. There has been increasing interest in identifying nonpharmacologic interventions to reduce preoperative anxiety symptoms. Research on the effects of music and music therapy for patients has been an area of significant growth over the last two decades.[5] Music medicine (music administered by medical healthcare professionals) and music therapy (music administered by trained music therapists) both have been shown to aid patient anxiety in the preoperative period.[5] Chen and colleagues sought to determine the effect of music listening (music medicine) on preoperative anxiety scores and found that the ability to listen to music in the 30 minutes prior to surgery decreased anxiety scores. This is one of the first studies of music medicine in women with pelvic floor disorders, and its results are similar to other studies of preoperative anxiety. Additional studies are needed to determine the short- and long-term effects of music interventions on women undergoing major vs. minor surgical pelvic reconstructive procedures. However, in the meantime, asking women at preoperative appointments about pre-procedural anxiety, checking in on the morning of surgery, and offering the opportunity to listen to music prior to surgery may improve our patients' wellbeing, outcomes, and satisfaction. ■

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ABSTRACT & COMMENTARY

Highlights from the CDC's Updated 2021 Sexually Transmitted Infections Treatment Guidelines

By Rebecca H. Allen, MD, MPH, Editor

SYNOPSIS: The Centers for Disease Control and Prevention updated their sexually transmitted infections treatment guidelines with important considerations for women's health providers, such as new recommendations for *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis*, pelvic inflammatory disease, and *Mycoplasma genitalium*.

SOURCE: Centers for Disease Control and Prevention. Sexually Transmitted Infections Treatment Guidelines, 2021. July 22, 2021. https://www.cdc.gov/std/treatment-guidelines/default.htm

Highlights from the Centers for Disease Control and Prevention's (CDC) Sexually Transmitted Infections (STI) Treatment Guidelines, 2021 are as follows:

• For women, *Chlamydia trachomatis* and *Neisseria gonorrhoeae* urogenital infection can be diagnosed by vaginal or cervical swabs or first-void urine with nucleic acid amplification tests (NAATs). NAATs that are Food and Drug Administration (FDA)-approved for use with vaginal swab specimens can be collected by a provider or patient in the clinic. Patient-collected vaginal swab specimens are equivalent in sensitivity and specificity to those collected by a provider. Vaginal swabs are more sensitive than first-void urine testing and, therefore, are the optimal route of sample collection. Annual screening of all sexually active women younger than 25 years of age is recommended, as is screening of older women at increased risk for infection (e.g., women 25 years of age or older) who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has an STI).

• The recommended regimen for the treatment of *C. trachomatis* in women has changed to doxycycline 100 mg orally twice a day for seven days. Alternative regimens are azithromycin 1 g orally once or levofloxacin 500 mg once daily for seven days. However, pregnant women still can be treated with azithromycin preferentially.

• The recommended regimen for the treatment of *N. gonorrhoeae* urogenital infection in women is ceftriaxone 500 mg intramuscularly (IM) in a single dose for patients weighing < 150 kg and, for those weighing more, 1 g of ceftriaxone should be administered. Alternative regimens are gentamicin 240 mg IM in a single dose with azithromycin 2 g orally in a single dose or cefixime 800 mg orally in a single dose. For pregnant women who are allergic to cephalosporins, because gentamicin cannot be given, consultation with an infectious disease expert is recommended.

• *Mycoplasma genitalium* is increasingly being recognized as a pathogen. There is one NAAT approved for use by the FDA for testing. However, screening of asymptomatic *M. genitalium* infection among women is not recommended. Nevertheless, women with recurrent cervicitis should be tested for *M. genitalium*, and testing should be considered among women with pelvic inflammatory disease (PID). Testing should be accompanied with resistance testing, if available. In clinical practice, if testing is unavailable, *M. genitalium* should be suspected in cases of persistent or recurrent cervicitis and considered for PID.

• The recommended treatment for trichomoniasis among women has changed to metronidazole 500 mg orally twice a day for seven days. Two grams of metronidazole is no longer recommended. Tinidazole 2 grams orally in a single dose is an alternative option but is more expensive. Topical metronidazole vaginal gel is not recommended because it does not reach therapeutic levels in the urethra and perivaginal glands. Importantly, we no longer need to counsel patients to avoid alcohol consumption while taking metronidazole, since a review found there was no convincing evidence of a disulfiram-like reaction.

• Whereas before, the addition of metronidazole to the treatment regimens for PID was recommended in the case of tuboovarian abcess, the guidelines now recommend routine use of metronidazole with both intravenous and oral therapy for all cases of PID. The recommended outpatient IM/oral treatment regimens for PID now are ceftriaxone 500 mg IM in a single dose with doxycycline 100 mg orally twice a day and metronidazole 500 mg orally twice a day for 14 days.

Alternative regimens include cefoxitin 2 g IM in a single dose and probenecid 1 g orally administered concurrently in a single dose with doxycycline 100 mg orally twice a day and metronidazole 500 mg orally twice a day for 14 days or other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime) with doxycycline 100 mg orally twice a day and metronidazole 500 mg orally twice a day for 14 days. The CDC also endorsed the recommendation from the United States Selected Practice Recommendations for Contraceptive Use that intrauterine devices (IUDs) do not automatically need to be removed during treatment of PID, stating that "if no clinical improvement occurs within 48 to 72 hours of initiating treatment, providers should consider removing the IUD."

■ COMMENTARY

The last update of the CDC sexually transmitted disease treatment guidelines occurred in 2015. One important change this time around is the title. The CDC changed "disease" to "infection" to reduce the stigma associated with sexually transmitted infections and recognize that "disease" refers to the condition that results from an infection in some, but not all, cases. This round of updates contains important changes for women's health providers.

The rationale for the change in chlamydia treatment from a single dose of azithromycin to a seven-day course of doxycycline stems from the fact that studies show doxycycline is more effective for rectal chlamydia in both men and women.[1] However, the CDC acknowledges that adherence to this regimen is more difficult than with a single dose. Nevertheless, they state that concomitant rectal chlamydia infection can occur in women and place them at risk for repeat urogenital infection through autoinoculation from the rectal site. Interestingly, in one study, *C. trachomatis* was detected at the anorectal site among 33% to 83% of women who had urogenital *C. trachomatis* infection. Its detection was not associated with a report of receptive anorectal sexual activity.[2] The CDC states that "when nonadherence to doxycycline regimen is a substantial concern, azithromycin 1 g regimen is an alternative treatment option but might require posttreatment evaluation and testing because it has demonstrated lower treatment efficacy among persons with rectal infection."

For gonorrhea treatment, the dose of ceftriaxone was increased from 250 mg to 500 mg (this had been released previously by the CDC) to maximize efficacy against any

isolates with elevated minimal inhibitory concentrations. For trichomoniasis treatment, the single 2-g dose of metronidazole was eliminated after trials found it was inferior to the seven-day regimen.[3]

Currently, the CDC thinks that *M. genitalium* can cause cervicitis and may contribute to PID, but routine screening of asymptomatic women is not warranted. Rather, the organism should be suspected in cases of recurrent cervicitis and possibly should be considered in PID. The treatment of *M. genitalium* is difficult, and while the CDC recommends resistance testing, this may not be routinely available.

Treatment without resistance testing involves doxycycline 100 mg orally twice a day for seven days, followed by moxifloxacin 400 mg orally once daily for seven days. The doxycycline reduces the load of the organism and the moxifloxacin eradicates it. Although current PID treatment regimens do not cover *M. genitalium*, the CDC does not recommend routinely adding moxifloxacin, rather it recommends only treating the organism if it happens to be detected. They state, "No data have been published that assess the benefits of testing women with PID for *M. genitalium*, and the importance of directing treatment against this organism is unknown."

Finally, the CDC now recommends the routine addition of metronidazole to PID treatment regimens because this regimen eradicates anaerobic organisms more effectively from the upper genital tract.[4]

There are other important changes to the guidelines regarding novel treatments for bacterial vaginosis, human papillomavirus vaccine recommendations and counseling messages, expanded risk factors for syphilis testing among pregnant women, and two-step testing for serologic diagnosis of genital herpes simplex virus that are relevant to women's health providers. All of these should be incorporated into clinical practice as needed. The app for the 2021 guidelines for iOS or Android is not yet available from the CDC; however, there are posters and pocket guides that can be downloaded from the website. ■

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ABSTRACT & COMMENTARY

Vaginal Misoprostol vs. Prostaglandin E2 Pessary for Induction of Labor at Term

By Ahizechukwu C. Eke, MD, PhD, MPH

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SYNOPSIS: In this randomized, noninferiority, clinical trial of pregnant women who underwent induction of labor with misoprostol compared to dinoprostone, the rate of vaginal delivery within 24 hours was higher in the misoprostol group. Maternal satisfaction, assessed by a visual analog scale, also was higher. Although the noninferiority of dinoprostone to misoprostol could not be demonstrated, the clinical risk-to-benefit ratio justifies the use of both drugs.

SOURCE: Gaudineau A, Senat MV, Ehlinger V, et al. Induction of labor at term with vaginal misoprostol or a prostaglandin E2 pessary: A non-inferiority randomized controlled trial. *Am J Obstet Gynecol* 2021; Apr 19. doi: 10.1016/j.ajog.2021.04.226. [Online ahead of print].

Induction of labor is a common practice in the United States.[1,2] Between 2012 and 2017, the rate of induction more than doubled from a rate of approximately 9% to a rate of 23% of all deliveries in the United States.[1] The rate of labor induction likely will continue to increase, especially after the findings of the ARRIVE randomized clinical trial, which demonstrated that elective induction of labor in nulliparous women with low-risk pregnancies at 39 weeks may reduce the need for cesarean deliveries when compared to expectant management.[2] Therefore, understanding the safety, efficacy, and adverse effect profiles of medications used for labor induction is important.

Labor induction can be accomplished by mechanical (e.g., Foley bulb) and non-mechanical (e.g., pharmacological methods) methods, for which misoprostol (a prostaglandin E1 analogue) and dinoprostone (a prostaglandin E2 analogue) have been used off-label for decades.[3]

Although a number of randomized clinical trials have evaluated vaginal misoprostol vs. dinoprostone, their safety profiles have not been evaluated comprehensively and satisfactorily in a prospective manner using large sample sizes.[4] Therefore, Gaudineau and colleagues designed this study — the CYTOPRO (CYTOtec vs. PROpess) trial — to test the hypothesis that a 25-mcg dose of vaginal

misoprostol administered every four hours would be noninferior to a 10-mg dose of dinoprostone pessary.[4]

The CYTOPRO trial was a randomized, noninferiority, controlled trial conducted at four hospitals in France that participate in the Groupe de Recherche en Obstétrique et Gynécologie.[4] Inclusion criteria were pregnant women ≥ 18 years of age with a viable singleton gestation in cephalic presentation undergoing induction of labor at a gestational age of ≥ 36 weeks, with an unfavorable cervix (Bishop score of ≤ 5) and three or fewer uterine contractions in 10 minutes, as recorded by a 30-minute electronic fetal monitoring (EFM) at the time of admission.[4] Women were excluded if they had a previous cesarean delivery, any known allergy or intolerance to prostaglandin agents, and any contraindications to vaginal delivery.[4]

Using computer randomization, the investigators randomized participants to either the misoprostol group or the dinoprostone group. Participants received either a 25-mcg dose of vaginal misoprostol or a 10-mg slow-release dinoprostone pessary. The primary outcome was the cesarean delivery rate following induction of labor with misoprostol or dinoprostone.[4] Secondary outcomes included fever ≥ 38.5°C during labor, use of episiotomy, third- and fourth-degree perineal lacerations, postpartum hemorrhage, uterine tachysystole, uterine rupture, vaginal delivery within 24 hours, rate of pitocin use, satisfaction with labor process, neonatal seizure, admission to the neonatal intensive care unit, arterial umbilical cord pH of < 7.05, five-minute Apgar score of < 7, meconium-stained amniotic fluid, meconium aspiration, and neonatal death.[4] A sample size of 790 women per group was sufficient to demonstrate statistically significant differences between the misoprostol and dinoprostone arms based on a baseline cesarean delivery rate of 20% in the dinoprostone group, assuming 80% power, type 1 error rate of 0.025% (one-sided test), and a noninferiority margin of ≥ 5% in absolute difference in cesarean delivery rates when induction of labor is performed with misoprostol vs. dinoprostone (if misoprostol truly is not inferior).

From September 2012 to June 2015, 790 pregnant women received misoprostol and 790 women received dinoprostone. A total of 945 women (59.8%) were nulliparous and 635 women (40.2%) were parous. The baseline characteristics were similar in both groups.[4] However, the cesarean delivery rate was 22.2% (175/790) in the misoprostol group and 19.9% (157/790) in the dinoprostone group, a difference of 2.3%, with a 95% upper-bound confidence interval (CI) limit of 5.6%, which exceeded the limit for noninferiority ($P = 0.092$). The cesarean delivery rate for non-reassuring fetal heart tones was slightly higher in the misoprostol group (risk difference [RD], 2.2; 95% CI, -0.3 to 4.6), but similar cesarean delivery rates were demonstrated for arrest of labor between the two groups (RD, -0.8; 95% CI, -0.3 to 1.6).[4] Meconium aspiration occurred in 1.0% of neonates in the misoprostol group compared with 0.3% in the dinoprostone group. Vaginal delivery within 24 hours after commencement of induction of labor was higher in the misoprostol arm compared to the dinoprostone arm (59.3% vs. 45.7%, $P < 0.001$). Conversely, labor augmentation with oxytocin was lower in the misoprostol arm when compared to the dinoprostone arm (58.7% vs. 67.2%, $P < 0.001$). Women randomized to the misoprostol arm reported a significantly higher level of maternal satisfaction (78% of women, mean visual analog scale score, 7.1 ± 2.4) compared to those in the dinoprostone arm (63% of women, mean visual analog scale score, 5.8 ± 3.1; $P < 0.001$).[4]

■ COMMENTARY

Although misoprostol and dinoprostone both are prostaglandins, they have different pharmacokinetic profiles. Following insertion into the posterior vaginal fornix, vaginal misoprostol plasma concentrations gradually increase, reaching a maximum concentration after 70 to 80 minutes, before slowly being eliminated, with plasma levels still detectable six hours after administration.[5,6] In contrast, vaginal dinoprostone pessary undergoes slower absorption (absorbed at a rate of 0.3 mg per hour over 12 hours) and elimination.[5] The slower rate of absorption and time to reach maximum concentration for dinoprostone after vaginal administration may account for its longer duration of action and decreased clearance from the plasma. These differences in misoprostol and dinoprostone pharmacokinetics partly account for their differences in safety, efficacy, and adverse effect profiles.

The authors used a noninferiority, randomized trial design to study the association between misoprostol and dinoprostone and the risk of cesarean delivery.[4] They noted the difference in the absolute rate of cesarean deliveries between the two groups was 2.3%, with a 95% upper-bound CI limit of 5.6%, which was greater than the noninferiority boundary of 5% used in the study. The primary objective of noninferiority trials is to show that a new treatment is no worse (noninferior) when compared to the standard-of-care treatment, usually within a pre-specified noninferior margin with reference to a primary outcome.[7] Noninferiority randomized clinical trials of pharmacologic agents used for labor induction are critically important in obstetrics in demonstrating decreased adverse effects of using different pharmacologic doses or agents relative to an existing standard, especially because induction of labor is a common practice in the United States. Using noninferiority trials, current pharmacologic therapies used for labor induction can be compared in head-to-head randomized trials to determine if these therapies are noninferior. Although Gaudineau et al could not demonstrate noninferiority of a 25-mcg dose of vaginal misoprostol every four hours when compared to the dinoprostone pessary for cesarean delivery rates following induction of labor, the confidence limit of the difference was sufficiently close to that of misoprostol.

In conclusion, since this is a noninferiority trial, a reasonable conclusion for clinicians in practice would be that dinoprostone pessary is noninferior to misoprostol when used for induction of labor. As such, interpreting this study as "misoprostol is as 'effective' as dinoprostone" would be incorrect, since the primary aim of noninferiority trials is to

evaluate that a new therapy is "no worse" than standard therapy. Currently, the American College of Obstetricians and Gynecologists recommends low-dose (25 mcg) vaginal misoprostol as the first-line pharmacologic agent for labor induction.[8] ■

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SPECIAL FEATURE

COVID-19 Vaccination, Pregnancy, Lactation, and Fertility: What Should the OB/GYN Know?

By Katherine Rivlin, MD, MSc

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Pregnancy is independently associated with severe COVID-19 disease. Yet, with pregnant and lactating women excluded from participation in vaccine trials, the remaining information gap too often is filled with misinformation. With the increasing circulation of the Delta variant, it has become critically important for the OB/GYN to discuss COVID-19 vaccination with patients, and, specifically, to address concerns related to pregnancy, lactation, and fertility. This article will review the most recent guidance from the American College of Obstetricians and Gynecologists (ACOG), the Society of Maternal-Fetal Medicine (SMFM), and the American Society for Reproductive Medicine (ASRM) on vaccination in reproductive-age individuals.

VACCINE DEVELOPMENT, MECHANISMS OF ACTION, EFFICACY, AND SIDE EFFECTS

Given the magnitude of the COVID-19 pandemic, the effort to develop COVID-19 vaccines has been rapid. Yet, no safety standards have been relaxed in this process. Instead, additional safety monitoring systems are in place to monitor and track vaccines, including real-time assessments. Currently, the U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the following vaccines:

- Pfizer-BioNtech (Pfizer) messenger ribonucleic acid (mRNA) vaccine, for use in individuals 12 years of age and older, in a two-dose regimen, given three weeks, or 21 days, apart;
- Moderna mRNA vaccine, for use in individuals 18 years of age and older, in a two-dose regimen given one month, or 28 days, apart;
- Janssen Biotech, Inc. (Johnson & Johnson) vaccine, for use in individuals 18 years of age and older, in a single-dose regimen.

MRNA VACCINES (PFIZER AND MODERNA)

mRNA vaccines are a novel vaccine technology. They consist of mRNA encapsulated in lipid nanoparticles for transportation into host cells. The host cells then create coronavirus spike proteins, causing immune cells to make COVID-19 antibodies. These vaccines are not live and do not enter the host cell's nucleus or alter DNA. Their mechanism of action, the safety and efficacy data from Phase I and II trials, and the observational data collected since vaccine distribution all indicate that mRNA vaccines are safe in pregnancy. The Pfizer vaccine is 95% effective and the Moderna vaccine is 94.1% effective in clinical trials at preventing laboratory-confirmed COVID-19 illness.[1]

ADENOVIRUS-VECTOR VACCINES (J&J)

Adenovirus-vector vaccines are monovalent vaccines made of a recombinant human adenovirus. They encode a stabilized form of a coronavirus spike protein. The vaccine cannot replicate, is not live, and does not contain preservatives. Other adenovirus-vector vaccines studied in pregnancy, such as human immunodeficiency virus (HIV) and Ebola vaccines, have no known pregnancy-related safety concerns. Clinical trials indicate that the J&J vaccine is 66.9% effective at preventing moderate COVID-19 illness, 76.7% effective at preventing severe/critical COVID-19 illness, and 93.1% effective at preventing hospitalization related to COVID-19.

Side effects from all three vaccines are common and expected and indicate development of COVID-19 antibodies. Most people will experience mild flu-like symptoms, and clinicians should discuss this as part of anticipatory guidance. Allergic reactions, such as anaphylaxis, are rare. Clinicians should manage such reactions similarly in both pregnant and non-pregnant patients by notifying emergency medical services, placing the patient in the supine position, giving epinephrine, and monitoring for reoccurrence. [1]

THROMBOSIS AND THROMBOCYTOPENIA SYNDROME

The FDA has added a warning and fact sheet to the J&J vaccine about the possibility of thrombosis and thrombocytopenia syndrome (TTS) following vaccination. TTS is very rare, occurring after 8.9 per 1 million doses of the J&J vaccine. Most incidences occurred in women of reproductive age, none of whom were pregnant.

The risk of thrombosis increases in pregnancy, postpartum, and in people using estrogen-containing contraceptives. However, these factors likely do not increase the risk of TTS after using the J&J vaccine. Therefore, ACOG does not recommend stopping estrogen-containing contraceptives after the J&J vaccine. Given the high risk of serious illness from COVID-19 and the very low incidence of TTS, women of reproductive age and pregnant people still can receive the J&J vaccine.[1]

SAFETY OF THE COVID-19 VACCINE IN PREGNANCY

Despite advocacy efforts by ACOG, SMFM, and the National Academy of Medicine to include pregnant and lactating individuals in vaccine trials, none of the COVID-19 vaccines approved under EUA were tested in pregnant women. Unfortunately, the concept of "protection by exclusion" leads to experimentation on pregnant and lactating women outside of clinical trial, without the protections that clinical trials provide.[2] Although studies are underway, most of the current data come from post-marketing surveillance. One prospective cohort study showed that vaccinated pregnant and lactating patients produced comparable immune responses to nonpregnant controls.[3]

In clinical Phase II and Phase III trials some inadvertent pregnancies occurred, and are being followed for safety outcomes. The Centers for Disease Control and Prevention (CDC) is monitoring more than 100,000 pregnancies through the v-safe post-vaccination health checker. Although self-reported, these data do not indicate pregnancy-related safety concerns. To date, the CDC's v-safe pregnancy registry includes more than 5,000 pregnancies. Vaccine-related adverse events and side effects appear similar in pregnant and nonpregnant women. The post-vaccination miscarriage rate also appears consistent with the background rate, although a risk estimate is not yet available.[4]

SAFETY OF THE COVID-19 VACCINE DURING LACTATION

No biological plausibility exists to support a concern for lactating people and COVID-19 vaccination. ACOG and SMFM recommend vaccination for lactating people. Although this population was not included in most clinical trials, the potential benefits far outweigh theoretical concerns. Patients can initiate and continue breastfeeding after COVID-19 vaccination. After natural COVID-19 infection, specific antibodies are present in human milk which may offer protection to the newborn. In a prospective trial, vaccine-generated antibodies also were present in umbilical cord blood and breastmilk after maternal vaccination, which also may confer immunity.[5]

SAFETY OF THE COVID-19 VACCINE AMONG THOSE CONTEMPLATING PREGNANCY

Although fertility outcomes were not studied specifically in vaccine trials, ACOG, SMFM, and ASRM recommend COVID-19 vaccination for people actively trying to become pregnant or contemplating pregnancy. All COVID-19 vaccines available do not replicate and immediately clear from tissue following injection. Yet, misinformation around the COVID-19 vaccine and its effects on fertility is widespread on social media. The proposed mechanism of infertility relies on a presumed similarity between the SARS-CoV-2 spike protein and the syncytin-1, a protein necessary for the formation of the syncytiotrophoblast in a developing embryo. According to this theory, immune cross-reactivity could damage the trophoblast and prevent implantation. Such cross-reactivity not only would occur following vaccination, but also following natural illness. Yet, such cross-reactivity has never been demonstrated in laboratory analysis or in human clinical data, nor have effects on male fertility been shown.[6,7] Anecdotal post-vaccine menstrual disturbances have been reported, but little evidence exists. Although environmental stresses can affect menses temporarily, no prior vaccines have been associated with changes to menses. The National Institutes of Health has put out a special call for research on this issue.[1]

CLINICAL CONSIDERATIONS AND CONCLUSIONS

A clinician should understand that vaccine hesitancy exists in all populations, but that historical and current healthcare injustices play an important role. Communities of color have been affected disproportionally by COVID-19, with higher rates of severe illness and death. Yet, Black and Latinx populations generally receive vaccines at lower rates, in part as the result of differential access. Clinicians should listen to and validate patient fears and concerns, while providing accurate information and resources for accessing vaccination. Should patients decline vaccination, the clinician should continue to provide support and recommend continued protective measures, such as hand washing, social distancing, and masking. Providers then should continue to discuss vaccination with individuals in future visits if they are amenable.[1] ACOG recommends discussing and documenting vaccination status with all patients. Patients need not undergo pregnancy testing or a

conversation with the clinician before vaccination, although discussions can occur as needed. The COVID-19 vaccine can be administered simultaneously with other vaccines, including within 14 days of other vaccines. The CDC, ACOG, SMFM, and ASRM all recommend vaccination in pregnancy.[8] Yet, vaccination rates are notably low among pregnant women. Clinicians should underscore the safety of vaccination and the risks of natural infection, particularly in pregnancy and in patients with underlying comorbidities. Finally, the notable absence of pregnant and lactating women in vaccination trials and the lack of fertility outcomes all have left a notable gap in available evidence. Misinformation has filled this gap, even as we have relied on the public to accept vaccination to combat the pandemic. ■

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CME/CE QUESTIONS

1. Which of the following statements is true regarding fertility and the COVID-19 vaccine?
a. The COVID-19 vaccine has been associated with a higher miscarriage rate than the background rate.
b. Cross-reactivity between the SARS-CoV-2 spike protein and the syncytin-1 protein have been shown to affect implantation in animal models.
c. Fertility and menstrual disorder outcomes were studied specifically in vaccine trials.
d. The American College of Obstetricians and Gynecologists, the Society of Maternal-Fetal Medicine, and the American Society for Reproductive Medicine all recommend COVID-19 vaccination for people actively trying for or contemplating pregnancy.

2. Based on the study by Chen et al investigating music and preoperative anxiety, which of the following statements is correct?
a. Patients undergoing pelvic reconstructive surgery do not experience anxiety on the day of surgery.
b. Only patients with prolapse diagnoses benefited from listening to music of their choice prior to surgery.
c. Patients undergoing pelvic reconstructive surgery may benefit from listening to music of their choice prior to surgery.
d. Anxiety scores were no different for women undergoing pelvic reconstructive surgery who did and who did not listen to music.

3. According to the Centers for Disease Control and Prevention's 2021 Sexually Transmitted Infection Treatment Guidelines, the first-line treatment for urogenital chlamydia infection in nonpregnant women is which of the following?
a. Azithromycin 1 g orally once
b. Doxycycline 100 mg orally twice a day for seven days
c. Levofloxacin 500 mg orally once a day for seven days
d. Moxifloxacin 400 mg orally once a day for seven days

4. Which of the following was *not* a secondary outcome evaluated in the noninferiority, randomized clinical trial by Gaudineau and colleagues?
a. Vaginal delivery within 24 hours
b. Arterial umbilical cord pH of < 7.05
c. Ductus venosus pH of < 7.05
d. Neonatal death