Obstetric Outpatient Management During the COVID-19 Pandemic: Prevention, Treatment of Mild Disease, and Vaccination

NAIMA T. JOSEPH, MD, MPH,* and EMILY S. MILLER, MD, MPH†

*Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts; and †Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Northwestern University Feinberg School of Medicine, Chicago, Illinois

Abstract: The majority of patients with coronavirus disease 2019 will have mild or asymptomatic disease, however, obstetric patients are uniquely at risk for disease progression and adverse outcomes. Preventive strategies including masking, physical distancing, vaccination, and chemoprophylaxis have been well studied, are critical to disease mitigation, and can be used in the pregnant population. High-quality data are needed to assess safety and effectiveness of therapeutics and vaccination in pregnancy, as well as long-term data on maternal and newborn outcomes.

Key words: COVID-19, SARS-CoV-2, pregnancy, obstetrics, management, vaccination

Introduction

Coronavirus Disease 2019 or COVID-19, was declared a pandemic by the World Health Organization in March, 2020† Globally over 180,000,000 million cases, and close

*Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts; and †Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Northwestern University Feinberg School of Medicine, Chicago, Illinois

The authors declare that they have nothing to disclose.
to 4 million COVID-19-related deaths have been confirmed.\textsuperscript{2} Since March 2020, our understanding of the viral transmission, disease prevention, treatment, and implications for the obstetric population have changed rapidly. In this review, we summarize the current understanding regarding prevention, vaccination, and treatment of mild disease, with special considerations for obstetric patients, as well as discuss critical gaps in the literature.

**VIRAL TRANSMISSION AND PRIMARY PREVENTIVE STRATEGIES**

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus is the seventh coronavirus known to infect humans; SARS-CoV, MERS-CoV, and SARS-CoV-2 can cause severe disease, whereas HKU1, NL63, OC43, and 229E are associated with mild symptoms.\textsuperscript{3} The virus uses densely glycosylated spike (S) protein to enter host cells and binds with high affinity to angiotensin-converting enzyme 2 receptor in humans, which are predominantly found in alveolar epithelial and stromal cells, but have also been found in cells of male and female reproductive organs and the placenta.\textsuperscript{4,5}

The virus is primarily spread person-to-person through respiratory droplets, although fecal-oral transmission and indirect spread through aerosolized droplets and contaminated surfaces are under investigation.\textsuperscript{6} Sexual transmission has not been reported. As the SARS-CoV-2 virus has continued to spread, genetic mutations, or variants have emerged, with increasing transmissibility. The B.1.1.7 (Alpha), B.1.351 (Beta), B.1.617.2 (Delta), and P.1 (Gamma) are variants of concern in the United States.\textsuperscript{7}

There are no data that pregnancy increases susceptibility to SARS-CoV-2 viral acquisition; therefore general preventive measures are sufficient in the outpatient setting. Personal protective measures include wearing a mask, physical distancing, and frequent hand washing (or using hand sanitizer with at least 60% alcohol if soap and water is not available).\textsuperscript{8} In addition, close monitoring for symptoms of COVID-19 is important to inform the need for early isolation for the infected person and quarantine for potential contacts.

**CLINICAL PRESENTATION AND RISK FOR SEVERE DISEASE**

In the general population, roughly one in every 2 to 3 individuals infected with SARS-CoV-2 will be asymptomatic; of individuals who are asymptomatic at the time of a SARS-CoV-2 test, 3-quarters will remain asymptomatic.\textsuperscript{9} For those who have or who go on to develop symptoms, the median onset is 4 days (range of 3 to 7) after the positive test.\textsuperscript{10} The most commonly reported symptoms of COVID-19 include cough (typically dry), headache, myalgias, fever, sore throat, shortness of breath, and loss of taste or smell.\textsuperscript{11}

The prevalence of asymptomatic infection in pregnancy appears to mirror the general population.\textsuperscript{12} Pregnant women are as likely to have fever, cough, shortness of breath but are less likely to report dyspnea, anosmia or ageusia, fatigue and myalgia, upper respiratory tract symptoms or gastrointestinal symptoms.\textsuperscript{13–18} Specifically, Ellington et al\textsuperscript{13} demonstrated that symptomatic pregnant and nonpregnant women with COVID-19 reported similar frequencies of cough (> 50%) and shortness of breath (30%), but pregnant women less frequently reported headache, muscle aches, fever, chills, and diarrhea. In nonhospitalized adults, the median duration of symptoms ranges 4 to 8 days; longer duration of up to 3 weeks has been reported in older adults and those with multiple comorbidities.\textsuperscript{19} Findings from US pregnancy registry reported median symptom duration of 37 days, with 25% of participants endorsing persistent symptoms 8 or more weeks after symptom onset.\textsuperscript{17} The difference in obstetric complaints in pregnant versus nonpregnant patients with
SARS-CoV-2 infection has not been well assessed. An early report from China showed that pregnant women reported both an increase and decrease in fetal movement compared with pregnant women without infection.18

Standardized reporting from the CDC’s National Notifiable Disease Surveillance System demonstrated that of 1,300,930 laboratory confirmed cases of SARS-CoV-2 infection among reproductive age women 15 to 44, pregnant data were available for 461,825 (35.5%), of whom 409,462 were symptomatic. Among those with symptomatic infection, 23,434 (5.7%) were reported to be pregnant.20 An earlier report demonstrated that, among women with COVID-19, approximately one-third (31.5%) of pregnant women were reported to have been hospitalized compared with 5.8% of nonpregnant women.13 Zambrano found that, after adjusting for age, presence of underlying medical conditions, and race/ethnicity, pregnant women were significantly more likely to be admitted to the intensive care unit (ICU) [aRR: 3.0, 95% confidence interval (CI): 2.6-3.4], to receive mechanical ventilation (aRR: 2.9, 95% CI: 2.2-3.8), to receive extracorporeal membrane oxygenation (aRR: 2.4, 95% CI: 1.5-4.0), and to die (aRR: 1.7, 95% CI: 1.2-2.4).20 Obesity, hypertension, diabetes, asthma have been implicated in increasing risk for severe disease, but also there has been unequivocal contribution of racial bias and health disparities.

While the absolute risk for each of these severe outcomes was low (10.5, 2.9, 0.7, and 1.5 per 1000 cases, respectively), the pregnancy-specific magnitude in increase of severe morbidity and mortality raises concerns and unanswered questions. There were not enough data to estimate the pregnancy-attributable mortality risk, nor were there reported outcomes for women outside the third trimester. Nonetheless, physiological alterations in pregnancy, specifically the alterations to the immune21 and respiratory22 systems, may contribute to an increased propensity to severe illness, and emphasize the importance of unique, individualized approach to prevention and clinical care in pregnant patients.

OBSTETRIC AND FETAL RISKS OF COVID-19

SARS-CoV-2 infection has been associated with an increased risk of adverse perinatal outcomes. There is not enough data to inform risk to pregnancy in the first or early second trimester, however, symptomatic infection in the late second and third trimester have been associated with increased risk for hypertensive disorders, preterm birth, cesarean delivery, and possibly stillbirth.23-25 The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Maternal Fetal Medicine Units (MFMU) Network conducted an observation prospective cohort study of 1219 persons with a positive SARS-CoV-2 test and singleton pregnancies.25 Severe-critical disease was associated for increased risk of hypertensive disorder of pregnancy (aRR: 1.61, 95% CI: 1.18-2.20), cesarean birth (aRR: 1.57, 95% CI: 1.30-1.90), and preterm birth (aRR: 3.53, 95% CI: 2.42-5.14) compared with asymptomatic infection.

The effect on perinatal death and stillbirth remains uncertain. In the MFMU cohort, a higher proportion of fetal loss occurred in the severe-critical group (4.3%) compared with the asymptomatic group (1.9%) although the sample was underpowered. The United Kingdom and Global Pregnancy and Neonatal outcomes in COVID-19 (PAN-COVID) and the American Academy of Pediatrics (AAP) Section on Neonatal-perinatal medicine (SONPM) National Perinatal COVID-19 Registry identified incidences of small for gestational age deliveries to pregnant individuals with SARS-CoV-2 infection of 9.7% of 1606 and 9.6% of 2466 infants born to SARS-CoV-2 positive pregnancies, respectively, compared with an estimated representative incidence of 10% before the pandemic.26
# Characteristics, Diagnosis, and Management of COVID-19 According to Disease Severity in Pregnancy

| Clinical Features | Asymptomatic/Presymptomatic | Mild | Moderate | Severe | Critical |
|-------------------|-------------------------------|------|----------|--------|---------|
| **Clinical Features** | Positive SARS-CoV-2 Test, no symptoms | Fever, cough, change in taste or smell, mild dyspnea, no clinical/radiographic evidence of lower respiratory tract disease | Fever, cough, change in taste or smell, dyspnea and clinical evidence of lower respiratory tract disease | Oxygen saturation <95%, Respiratory rate > 30, breaths/min | Respiratory failure, shock, multisystem organ failure |
| **Diagnostic Testing** | Positive SARS-CoV-2 NAAT | Positive SARS-CoV-2 NAAT or Antigen Test | Positive SARS-CoV-2 NAAT or Antigen Test | Positive SARS-CoV-2 NAAT or Antigen Test | Positive SARS-CoV-2 NAAT or Antigen Test |
| **Underlying Pathology** | Viral Replication | Viral Replication | Viral Replication | Inflammation | Inflammation |
| **Management** | Isolation Monitoring for symptoms | Isolation Outpatient management Supportive care | Isolation Outpatient management based on risk factors Supportive Care | Inpatient management Supportive care | Inpatient management Supportive care |
| **Obstetric Considerations** | Consider growth ultrasound after period of isolation | Consider growth ultrasound after period of isolation | Antenatal testing and growth ultrasound during period of acute illness; Consider follow up growth ultrasound after acute illness | Steroid dosing for fetal lung maturity | Steroid dosing for fetal lung maturity |

www.clinicalobgyn.com

Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.
Neither registry reported any neonatal deaths. Similarly the INTERCOVID-19 Study compared 706 women with COVID-19 to 1424 women without COVID-19 diagnosis and found increased risk for low birth weight (<2500 g) (aRR: 1.58, 95% CI: 1.29-1.94) and composite severe perinatal morbidity (aRR: 2.14, 95% CI: 1.66-2.75) but differences in neonatal or fetal mortality were not reported.

Further studies assessing the implications of in utero exposure and perinatal transmission are lacking. In utero transmission does occur, although its incidence is relatively uncommon.\textsuperscript{27–29} How risk of in utero transmission is modulated by maternal disease severity, gestational age at infection, latency period from infection to delivery, and mode/timing of delivery remains unknown. Long-term fetal and neonatal outcomes data are also still needed.

There is biological plausibility that COVID-19 disease may mediate adverse perinatal outcomes. SARS-CoV-2 infection in pregnancy has been associated with direct placental injury such as decidual arteriopathy and chronic deciduitis.\textsuperscript{30} Histopathologic evaluation in the placentas of women with coronavirus have also demonstrated increased burden of lymphohistiocytic villitis and intervillous thrombi, features of maternal vascular malperfusion, compared with uninfected controls.\textsuperscript{30,31} These lesions, in turn, can be associated with fetal growth restriction, preterm birth, and stillbirth, although the epidemiologic data are not definitive. Need for further studies investigating mechanism of transplacental infection and placental role in mitigating transmission.

**TABLE 1. (Continued)**

| Asymptomatic/Presymptomatic Mild | Moderate | Severe | Critical |
|----------------------------------|---------|--------|---------|
| Potential Treatments             | Supportive care | Bamlanivimab 700 mg plus etesevimab 1400 mg or Casirivimab 1200 mg plus imdevimab 1200 mg | Remdesivir Dexamethasone plus Remdesivir | Dexamethasone plus Tocilizumab |
|                                 | *Bamlanivimab 700 mg plus etesevimab 1400 mg or Casirivimab 1200 mg plus imdevimab 1200 mg | Bamlanivimab 700 mg plus etesevimab 1400 mg or Casirivimab 1200 mg plus imdevimab 1200 mg | Remdesivir Dexamethasone plus Remdesivir | Dexamethasone plus Tocilizumab |

COVID-19 indicates coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

**APPRAOCH TO EVALUATION OF THE OUTPATIENT PREGNANT PERSON**

**Clinical Evaluation**

Clinical evaluation in pregnant patients should not differ from nonpregnant counterparts and includes a careful history and physical exam to assess for presence of sepsis, respiratory distress, multiorgan failure, and fetal compromise (Table 1). In addition, testing for other pathogens (eg, influenza, depending on season) should be performed if available, and radiographic imaging should be done in persons with tachypnea and/or hypoxemia. Maternal Early Warning Criteria can be used to guide and interpret physical exam and laboratory findings.\textsuperscript{32}

**Diagnostic Testing**

Nucleic acid amplification test (NAAT), most often using reverse transcription polymerase chain reaction-based SARS-CoV-2 RNA detection (RT-PCR) from respiratory samples is the standard for diagnosis and has high sensitivity and specificity. It is unlikely that pregnancy affects test sensitivity and specificity. In general, a positive test confirms the diagnosis and one negative test is suffi-
cient to exclude diagnosis, considering clinical context. Antigen testing allows for diagnosis of current infection with a rapid turn-around time. While the sensitivity and specificity are highly variable, the highest sensitivity is in symptomatic individuals within 5 to 7 days from symptom onset. Antibody testing allows for diagnosis of prior infection within 3 to 4 weeks. Immunoglobulin G is detectable in ~14 days; maternal immunity, neutralizing potency, and immune response following natural infection has been well characterized and mimics the nonpregnant cohort. For instance, one report found that there was no difference in maternal neutralizing potency and Immunoglobulin G response in those with symptomatic and asymptomatic infection and no clinically significant difference in antibody titers less than or greater than 14 days from infection.

**Diagnostic Evaluation**

Laboratory findings appear similar to nonpregnant persons, with the caveat that laboratory data must be interpreted within the context of pregnancy. For instance, Cheng et al published a retrospective study of 30 pregnant compared with 81 nonpregnant females aged 22 to 41 in Renmin Hospital, Wuhan, China, and found higher white blood cell counts in pregnant women, although need for ICU admission and mechanical ventilation was not different between groups, suggesting their findings were because of physiological leukocytosis in pregnancy. The majority of patients with COVID-19 severe or critical disease will demonstrate alterations in renal and hepatic function, lymphopenia or leukocytosis, and demonstrate laboratory evidence of coagulopathy. Although radiographic differences have been demonstrated in pregnant compared with nonpregnant women, findings do not correlate with disease severity and clinical outcomes.

**Assigning Disease Severity**

The NIH has published a classification scheme for categorization of the clinical spectrum of SARS-CoV-2 infection. Mild illness is defined as any symptom of COVID-19 but the absence of shortness of breath or abnormal pulmonary imaging. Moderate illness is defined as lower respiratory disease but not requiring supplemental oxygen. Severe illness is defined as requiring supplemental oxygen (ie, oxygen saturation <94% at room air), marked tachypnea (respiratory rate > 30 breaths per minute), or lung infiltrates that occupy > 50% of the lung fields. Critical illness is defined by organ dysfunction. Importantly, the threshold for clinical interventions may diverge for pregnant people to mitigate pregnancy risks and ensure oxygen support for the developing fetus and so some have suggested using slight modifications to the classification scheme.

In symptomatic adults, ~81% classify as mild, 14% as severe, and 5% as critical; the case fatality is ~2.3% which occurs primarily in severe and critical patients. In contrast, among symptomatic pregnant women, a larger proportion appear to meet criteria for severe and critical disease. The American College of Obstetricians and Gynecologists with the Society for Maternal Fetal Medicine developed an algorithm to support clinicians in the evaluation and treatment of pregnant people with possible COVID-19. Importantly, many comorbidities have been associated with an increased risk of severe disease, and thus individuals with a history of health conditions such as hypertension, diabetes, or other chronic diseases are advised to be evaluated in person. Most pregnant individuals with SARS-CoV-2 infection can be managed as outpatients. However, those with respiratory compromise or without the infrastructure needed to self-manage and follow up with worsening symptoms...
should be managed as an inpatient. Close symptom surveillance for those patients deemed safe for outpatient management, can be facilitated using hospital or clinic specific algorithms, such as California’s COVID-19 self-assessment tool for determination of medical advice: https://covidassessment.org.

Fetal Evaluation
Fetal testing during initial evaluation should not deviate from standard hospital protocols, is dependent on gestational age, and can include assessment of fetal growth. Fetal nonstress tests or biophysical profiles for a history of SARS-CoV-2 infection are not recommended in the outpatient setting for the general population, although this should be individualized.

TREATMENT FOR SARS-COV-2 PREGNANT PERSONS DEEMED SAFE FOR OUTPATIENT MANAGEMENT

Supportive Care
Treatment considerations for those being managed as an outpatient include isolation, supportive care, and anti-SARS-CoV-2 monoclonal antibodies. The majority of SARS-CoV-2 infections in pregnancy individuals are asymptomatic or mild and can be managed through home-based monitoring, with a 14-day self-quarantine. Supportive care includes rest and hydration, and pregnant people can be advised on the use of over-the-counter therapies such as acetaminophen, decongestants, or cough suppressants. Telehealth visits may be utilized to mitigate community exposure, although evidence of its effectiveness and the optimized modality (eg, telephone vs. video-based) are not established.

Monoclonal Antibodies
Antibody-based therapies, such as monoclonal antibodies, have been evaluated as possible treatments to prevent hospitalization in high-risk patients. Recognizing the correlation between viral neutralization and the magnitude of antibody responses, monoclonal antibodies targeting the spike protein were initially evaluated to prevent severe disease early in the course of infection. Two anti-SARS-CoV-2 combination products—bamlanivimab plus etesevimab and casirivimab plus imdevimab—have received Emergency Use Authorization (EUAs) from the Food and Drug Administration (FDA) for the treatment of outpatients with mild to moderate COVID-19 who are at high risk for disease progression and initiated either as soon as patient has a positive result of a SARS-CoV-2 antigen or NAAT or within 10 days of symptom onset. The BLAZE-1 Trial was a randomized trial that included 1035 high-risk participants, with primary endpoint as the proportion of participants who had a COVID-19-related hospitalization (defined as ≥ 24 h of acute care) or who died from any cause by day 29 with participants randomized to placebo or bamlanivimab 2800 mg plus etesevimab 2800 mg; treatment was associated with an expedited decrease in viral load and reduction in the severity of symptoms, as well as a 5% absolute reduction and a 70% relative reduction in COVID-19-related hospitalizations or death from any cause. High-risk patients were those age above 65, BMI > 35, hypertension, underlying chronic medical condition. Similarly, REGN-COV2 was a randomized trial of 2 doses of combination monoclonal antibodies, casirivimab plus imdevimab, versus placebo in patients who presented within 7 days of symptom onset and within 72 hours after a positive nasopharyngeal RT-PCR; they found a reduced viral load and 9% reduction in medically attended visits in the treatment arm. The limitations of these trials include the exclusion of pregnant persons, data conducted before widespread circulation of variants of concern, and the
absence of proven benefit in outpatients who are not at high risk for disease progression.

Currently, the NIH COVID-19 treatment guidelines panel and the Infectious Disease Society of America recommend the use of bamlanivimab-etesevimab or casirivimab-imdevimab in high-risk patients (including those with obesity, chronic kidney disease, diabetes, immunosuppression, or advanced age) for those presenting within 10 days of symptom onset or as soon as possible from positive SARS-CoV-2 antigen or nucleic acid test. Because of reports of resistance related to SARS-CoV-2 variants, bamlanivimab alone is not recommended. While the efficacy of monoclonal antibodies in pregnancy people has not been evaluated, the NIH treatment guidelines panel recommends that treatments should not be empirically withheld from pregnant people. SMFM recommends providers engage in discussion regarding risks and benefit of their use compared with disease progression in pregnant patients.

**Anticoagulation**

COVID-19 has been associated with hypercoagulability in a pattern that has been termed “thromboinflammation”. Data from early cases of COVID-19 infection demonstrated a marked increase in venous thromboembolism (VTE), although the risk was seen primarily in patients with severe-critical disease. Although pregnancy and postpartum pose additional risk for thrombosis, there are no data to guide the use of VTE prophylaxis in the outpatient setting, and therefore the use of VTE prophylaxis for patients with mild or asymptomatic COVID-19 is not currently recommended. Postpartum prophylaxis may be considered in those patients who are already at high risk for VTE, as per the ACOG and the American College of Chest Physicians Evidence-based Clinical Practice Guidelines for VTE, thrombophilia, antithrombotic therapy, and pregnancy.

**Follow up of Obstetric Patients with Asymptomatic or Mild Disease Management**

For patients with mild or asymptomatic disease who do not progress, there does not appear to be an increased risk of adverse perinatal complications. Therefore the frequency of prenatal care and timing of delivery can occur as per usual clinical indications. Given the ongoing biological possibility of fetal growth restriction, an interval growth assessment can be considered with further follow up informed by the clinical assessment.

**Unintended Consequences of COVID-19 Prevention Measures**

During the COVID-19 pandemic, health systems underwent massive changes with a focus on emergency preparedness and response, as well as reduction in inadvertent exposures. Aligned with public health efforts, obstetric health services quickly transitioned to a clinical visit cadence that was less frequent, shorter in duration, often occurring through telemedicine, and without a support person present at clinical visits. The physical distancing, stay-at-home orders, and changes to obstetric care delivery, while all important for infection control, have come with psychosocial risks that may be magnified in pregnant and postpartum people. Several reports have indicated potentially deleterious impact on care seeking behavior, including reduced prenatal care utilization and hospitalizations which may have adverse downstream consequences, especially in relation to adverse maternal and neonatal health outcomes. Furthermore, these unintended consequences may uniquely exacerbate health disparities as well as postpartum mental health.

**Vaccination**

With the global pandemic in its second year, there is no evidence that SARS-CoV-2 spread will naturally stop before
the conservative 50% to 67% estimated threshold of community immunity needed to stop transmission. As state and federal restrictions ease, increasing domestic and international travel, relaxed individual vigilance surrounding physical distancing, mask wearing, and other public health interventions, new variants are emerging, and only 47% of the US population is fully vaccinated. Given the unique vulnerability of pregnant patients and their infants to severe COVID-19, it is imperative that physicians who take care of obstetric patients remain well informed regarding vaccination technology, safety, and effectiveness.

Vaccine Technology

The vaccine landscape can largely be divided into classic versus next generation vaccine platforms. Classic technologies rely on delivery of antigen (inactive virus, purified protein, or other) into the body to produce an immune response. Virus based vaccines consist of inactivated virus that is no longer infectious or live-attenuated virus (ie, measles-mumps-rubella vaccine). Protein-based vaccines consist of a protein purified from the virus or virus-infected cell, recombinant protein, or virus-like particles and require the addition of an adjuvant to induce a strong immune response (ie, seasonal influenza). Novel technologies work by carrying genetic information necessary to manufacture the most immunogenic portion of the virus. They use the host cell machinery to transcribe and produce the protein, and the host cell’s natural and adaptive immune system to elicit response. mRNA vaccines take advantage of modified RNA chemistry to encode the SARS-CoV-2 spike protein with stabilizing mutations added to lock the shape-shifting surface protein into a form easily recognizable to the immune system. Viral vector-based vaccines differ from most conventional vaccines in that they do not actually contain antigens, but rather use the body’s own cells to produce them. They do this by using a modified virus (the vector) to deliver genetic code for antigen, which in the case of COVID-19 is the SARS-CoV-2 spike protein found on the surface of the virus. By infecting cells and instructing them to make large amounts of antigen, triggering an immune response, the vaccine mimics what happens during natural infection, but have the advantage of inducing a stronger cellular immune response by T cells as well as the production of antibodies by B cells. The benefit of novel vaccine technologies is that new technologies facilitate rapid development and deployment of vaccines in pandemic scenarios and also induce a more potent immunity.

mRNA Vaccines

The 2 mRNA vaccines recommended by the FDA under emergency use authorization (EUA) are Pfizer-BioNTech’s BNT162b2 and Moderna’s mRNA-1273 vaccines (Table 2). The Pfizer-BioNTech BNT162b vaccine is a 2 doses, 30-µg vaccine administered intramuscularly 21 days apart. The Moderna mRNA-1273 vaccine is a 2 doses, 100-µg each vaccine administered intramuscularly, 28 days apart. Both are lipid nanoparticle-formulated, nucleoside-modified mRNA vaccines encoding the prefusion spike glycoprotein of SARS-CoV-2. Data for their use were guided by randomized, double-blind, placebo-controlled Phase II/III clinical trials. Both vaccines demonstrated high efficacy (Pfizer 95%, 95% CI: 90.3-97.6; Moderna 94.1%, 95% CI: 89.3-96.8) in preventing symptomatic laboratory confirmed COVID-19 in persons without previous SARS-CoV-2 infection by 14 days after the second dose of vaccine. In addition, both have demonstrated some efficacy against variants of concern [B1.1.7 (alpha) and B.1.617 (delta)] although specific studies targeting the variants are planned. Both vaccines have been recommended for use since

www.clinicalobgyn.com

Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.
| Vaccine                  | Technology                                                                 | Administration        | Eligibility                                                                                     | Efficacy (Including Variants)                                                                 | Pregnancy Data                                                                 |
|-------------------------|----------------------------------------------------------------------------|------------------------|------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Pfizer-BioNTech BNT162b2| Lipid nanoparticle-formulated nucleoside-modified messenger RNA (mRNA) encoding SARS-CoV-2 spike protein locked in its prefusion conformation | Two dose, 30 µg, I.M. 21 d apart | Persons age ≥12 and older without history of severe allergic reaction (eg, anaphylaxis) to a previous dose or component (ie, PEG) of the vaccine | 95% (95% CI: 90.3-97.6) in preventing symptomatic, laboratory confirmed COVID-19 in persons without previous SARS-CoV-2 infection 14 d after 2nd dose | 23 inadvertent pregnancies enrolled in trial (12 in vaccine arm) with no difference in pregnancy outcomes |
| Moderna mRNA-1273       | Lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine encoding SARS-CoV-2 spike protein locked in its prefusion conformation | Two dose, 100 µg, I.M., 28 d apart | Persons age ≥18 and older without history of severe allergic reaction (eg, anaphylaxis) to a previous dose or component (ie, PEG) of the vaccine | 94.1% (95% CI: 89.3-96.8) in preventing symptomatic, laboratory confirmed SARS-CoV-2 infection, COVI-19 hospitalization, and severe disease 7 d after 2nd dose | 13 inadvertent pregnancies (6 in vaccine arm) with no difference in pregnancy outcomes |
| Johnson & Johnson - Janssen Pharmaceuticals Ad26.COV2.S | Recombinant, replication-incompetent adenovirus serotype 16 (Ad26) vector vaccine, encoding the stabilized prefusion spike glycoprotein of the SARS-CoV-2 virus | Single dose, 5 mL, I.M. | Persons age ≥18 and older without history of severe allergic reaction (eg, anaphylaxis) to a previous dose or component (ie, polysorbate) of the vaccine | 66.3% (95% CI: 59.9-71.8) efficacy in preventing symptomatic, lab confirmed COVID-19 at 14 d from vaccination, including against B.1.351 variant | 8 inadvertent pregnancies (4 in vaccine arm) and DART studies do not show any adverse effects on female reproduction, fetal/embryonal development, or postnatal development |
|                         |                                                                           |                        |                                                                                                | 93.1% (95% CI: 71.1 – 98.4%) against COVID-19 associated                                     | 800 pregnant women enrolled in CDC VSD, no adverse pregnancy, but underpowered |

DART studies show no adverse effects on female reproduction, fetal/embryonal development, or postnatal development outcomes. 118,292 pregnant patients enrolled in CDC VSD, no adverse pregnancy effects.
| Vaccine Brand        | Delivery Method                                                                 | Efficacy Data                                                                 | Comment                                                                 |
|----------------------|---------------------------------------------------------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------|
| AstraZeneca—University of Oxford ChAdOx1 nCOV-19, AZD1222 | Two dose, 0/5 mL, I.M., 28 d apart | 70.4% (95.8% CI: 54.8-80.6) in the US arm; Does not protect against B.1.351, unknown against other variants | Data on unintended pregnancy in trials not yet available; Previously tested in clinical trials for HIV and Ebola with no significant safety concerns; Unknown efficacy against B.1.617 (delta) variant |
| Novavax             | Two dose, 5-µg, I.M., 21 d apart                                               | 89.7% (95% CI: 80.2-94.6) in preventing virologically confirmed, symptomatic mild, moderate, or severe COVID-19 within 7 d after second dose. Vaccine efficacy after 14 d from first dose was 83.4% (95% CI: 73.6-89.5), and 86.3% (95% CI: 71.3-93.5) against B.1.17 variant and 49% against B.1.351 variant | Data on unintended pregnancy in trials not yet available; Similar to HPV vaccine |

CI indicates confidence interval; COVID-19, coronavirus disease 2019; I.M., intramuscularly; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
December 2020 by the CDC’s Advisory Committee on Immunization Practices (ACIP). Pregnant patients should not be excluded from eligibility.\textsuperscript{75-77}

**Adenoviral Vector Vaccines**

The Johnson & Johnson/Janssen COVID-19 (Ad.26.COV2.S) vaccine is the only viral vector vaccine available in the United States under an EUA. US trials for the University of Oxford/AstraZeneca’s (ChAdOx1 nCOV-19 or AZD.1222) are said to be completed by the end of 2021. Ad.26.COV2.S is a single dose vaccine administered intramuscularly. The vaccine uses a recombinant, replication-competent adenovirus serotype 16 (Ad26) vector vaccine, encoding the stabilized prefusion spike glycoprotein of the SARS-CoV-2 virus. Data for use were informed by an international Phase III clinical trial that in which 44,325 participants were randomized to vaccine or placebo in which vaccine was associated with 66.3\% (95\% CI: 59.9-71.8) efficacy in preventing symptomatic, laboratory confirmed COVID-19 at 14 days from vaccination.\textsuperscript{78} Efficacy was geographically highest in the United States (74.4\%, 95\% CI: 65.0\%-81.6\%). Moreover, vaccination was also 93.1\% (95\% CI: 71.1\%-98.4\%) efficacious against COVID-19 associated hospitalization at 14 days after vaccination and 100\% (95\% CI: 74.3-100.0) at 28 days after vaccination. Data also showed clinical efficacy against the B.1.351 variant.\textsuperscript{78,79} however, it has reduced neutralizing response against other variants.\textsuperscript{80} ACIP issued interim recommendations for use of Ad.26.COV2.S COVID-19 vaccine to persons age 18 or older for the prevention of COVID-19.\textsuperscript{81} yet on April 13, 2021, the CDC and FDA recommended pausing the use of Ad.26.COV2.S COVID-19 vaccine after reports of thrombosis with thrombocytopenia syndrome (TTS) among vaccine recipients.\textsuperscript{82} The CDC reported a total of 29 cases of TTS of 9 million persons vaccinated, which included 23 females. After population level risk-benefit analysis of available data, in which resumption of Janssen COVID-19 vaccine in persons age 18 or above at 50\% prepause administration rate could prevent 3926 to 9395 COVID-19-related hospital admissions, 928 to 2236 ICU admissions, and 586 to 1435 deaths compared with 26 expected cases of TTS per 9 million doses, the CDC recommended resumption of Janssen COVID-19 vaccination.\textsuperscript{82} Along with resumption of vaccination, providers are advised to maintain heightened alert for TTS in any patient who has received the Janssen vaccine and reporting new neurological symptoms, abdominal pain, and new thrombocytopenia.

The AstraZeneca/University of Oxford (ChAdOx1 nCOV-19 or AZD.1222) is a replication-deficient chimpanzee adenoviral vector ChAdOx1, encoding stabilized prefusion SARS-COV-2 spike glycoprotein. An interim analysis of international, placebo-controlled, randomized trial on 11,636 participants demonstrated confusing results.\textsuperscript{83} In participants who received two standard doses, vaccine efficacy at 21 days after vaccination was 62.1\% (95\% CI: 41.0-75.7) and in participants who received a low dose followed by a standard dose, efficacy was 90.0\% (67.4-97.0). Overall vaccine efficacy across both groups was 70.4\% (95\% CI: 54.8-80.6). The efficacy in the US arm was \sim 70\%. Concerns regarding TTS also caused the European Medicines Agency to briefly pause vaccine distribution. The FDA is expected to review an application by end of 2021.

**Protein-based, Virus-like Particle Vaccines**

The Novavax NVX-CoV2373 is the most recent vaccine with published Phase III findings.\textsuperscript{84} NVX-CoV2373 is a baculovirus encoded recombinant severe acute respiratory syndrome coronavirus 2 (rSARS-CoV-2) nanoparticle vaccine composed of
trimeric full-length SARS-CoV-2 spike glycoproteins and Matrix-M1 adjuvant, administered in 2 doses, 21 days apart to volunteers age 18 and older. This is an example of a protein-based vaccine using virus-like particles to stimulate the immune response, in a manner similar to the human papillomavirus vaccine. Vaccine efficacy was 89.7% (95% CI: 80.2-94.6) in preventing virologically confirmed, symptomatic mild, moderate, or severe COVID-19 within 7 days after second dose and 86.3% (95% CI: 71.3-93.5) against B.1.17 variant.

What is Known Regarding COVID-19 Vaccines in Pregnancy

The Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies (PREVENT) working group, a multidisciplinary, international team of 17 experts developed guidance including 22 recommendations for ethically responsible, socially just, and respectful inclusion of the interests of pregnant persons in the development and deployment of vaccines against emerging pathogens. Recommendations included (1) suitability for use in pregnancy was included as a strong consideration in vaccine development, (2) early initiation of nonclinical studies, such as developmental toxicity studies that can inform the inclusion of pregnant persons in efficacy trials, (3) the inclusion of pregnant women in vaccine studies conducted during outbreaks and epidemics, especially when the prospect of benefit outweighs the risks to pregnant women, their offspring, or both, and (4) that when a pregnant women of legal standing to consent is judged eligible to enroll or continue in a vaccine trial, her voluntary and informed consent should be sufficient to authorize her participation. Despite providing a framework for the inclusion of pregnant women in vaccine trials, pregnant persons were excluded in all completed clinical trials of COVID19 vaccines available to date.

Initial data regarding effects of vaccination on pregnancy were from inadvertent inclusion of pregnant persons in Pfizer, Moderna, and Janssen clinical trials. In all the trials, there was no difference in pregnancy outcomes in vaccinated individuals compared with the controls. Safety monitoring for these pregnancies are ongoing, and both Pfizer and Janssen have planned clinical trials specifically enrolling pregnant people.

Developmental and reproductive toxicology (DART) studies have not demonstrated concerning safety signals. A DART study conducted in rats according to international regulatory guidelines did not demonstrate any adverse effects of full dose BNT162b2 (> 300 times the human dose on a mg/kg basis) on fertility, ovarian function, fetal effects, postnatal survival, growth, physical or neurocognitive development. Similarly a DART to assess the effects of mRNA-1273 in pregnant and lactating rats administered 100 µg dose did not demonstrate adverse reproductive effects. A combined developmental and perinatal/postnatal reproductive toxicity study of Ad26.COV2.S in rabbits was submitted to FDA; FDA review of this study concluded that Ad26.COV.S given before mating and during gestation periods at dose of 1×10¹¹ vp (2 times the human dose) did not have any adverse effects on female reproduction, fetal/embryonal development, or postnatal development. Further, previously tested adenovirus vaccines for Ebola have been administered in pregnancy without safety concerns.

Data informing pregnancy outcomes following vaccination largely stem from the Vaccine Safety Datalink (VSD), a collaboration between CDC and 8 integrated health systems. VSD data indicate that 135,968 pregnant women have received at least 1 dose of vaccine, with 87% receiving Pfizer-BioNTech, 7.0% receiving Moderna, and 0.6% receiving Janssen. A report of 3958 participants enrolled the CDC’s Pregnancy Registry, V-safe, demonstrated pregnancy outcomes following vaccination for COVID-19 in pregnancy.
outcomes such as miscarriage, stillbirth, congenital anomalies, small for gestational age, and preterm birth did not differ significantly when compared against historic rates. The most frequently reported event was spontaneous abortion, which occurred in 15% compared with background rates of 20%. These data suggest that vaccination does not pose an increased risk to pregnancy. Placental examination in women with vaccination showed no increase in incidence of decidual arteriopathy, fetal vascular malperfusion, low-grade chronic villitis, or chronic histiocytic intervillitis compared with controls, further supporting the safety of vaccination in pregnancy. Data from the V-safe registry also showed safety, reactogenicity, and immunogenicity in vaccinated pregnant persons when compared with nonpregnant cohorts. However, data on vaccine immunogenicity from large cohorts is lacking, and has been primarily described in small case series. A prospective study enrolling 103 women, 30 of whom were pregnant and 16 lactating, showed no difference in binding, neutralizing, and functional neutralizing antibody responses as well as CD4 and CD8 T-cell responses in pregnant and lactating women compared with nonpregnant controls. Binding and neutralizing antibodies were also observed in infant cord blood and breast milk. Similar vaccine immunogenicity in pregnancy and lactating patients with antibody transfer through the placenta and/or breast milk have been observed in other cohorts. None of these studies have reported on immunogenicity of the Janssen vaccine in pregnancy, although it is not expected to differ.

Practical Considerations for Vaccination During Pregnancy
Providers caring for pregnant patients should be aware of the above data, and also aware that pregnant persons are eligible for and can receive any of the three COVID-19 vaccines available in the United States under EUA, which has been endorsed by ACOG, SMFM, and ACIP. There are no data to guide timing of administration during pregnancy, therefore pregnant patients should be encouraged to receive vaccination independent of trimester. Although theoretical risks regarding teratogenicity were discussed initially, there are no data to suggest an increased risk of birth defects in vaccinated individuals. The risks of vaccine in pregnancy remain theoretical and are mostly related to reactogenicity with fever occurring in 4% to 28% of vaccine recipients. Current guidelines recommend treatment with antipyretics, rather than prophylaxis. Balanced counseling regarding vaccination during pregnancy should include: (1) Reviewing what is known on safety of COVID19 vaccines in pregnancy; (2) Reviewing evidence for safety of other vaccines during pregnancy; (3) Reviewing risk of COVID19 complications to the pregnancy and the patient; (4) Reviewing risk of exposure and potential for mitigation; and (5) Reviewing ongoing post marketing surveillance made available through the FDA and the CDC surveillance systems.

Conclusion
Asymptomatic or mild COVID-19 in pregnancy does not appear to be associated with increased rates of adverse maternal or pregnancy outcomes. Outpatient management for low-risk pregnant patients is reasonable with safeguards in place to ensure appropriate surveillance and follow up. Nonetheless, pregnancy is an independent risk factor for severe disease and pregnant patients should be counseled on the importance of vaccination as primary prevention.

References
1. World Health Organization. WHO Timeline—COVID-19. Available at: https://www.who.int/news-room/detail/27-04-2020-who-timeline—covid-19?gclid=EAIaIQobChMI4MaewOeo6gIVyyMrCh2JRgUIEAYASAAEgLo3_D_BwE. Accessed July 1, 2021.
2. Dong E, Du H, Gardner L. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). *Lancet Inf Dis*. 2020;20:533–534.

3. Corman VM, Muth D, Niemeyer D, et al. Hosts and sources of endemic human coronaviruses. *Adv Virus Res*. 2018;100:163–188.

4. Shang J, Wan Y, Luo C, et al. Cell entry mechanisms of SARS-CoV-2. *Proc Natl Acad Sci U S A*. 2020;117:1727–1734.

5. Li M, Chen L, Zhang J, et al. The SARS-CoV-2 receptor ACE2 expression of maternal-fetal interface and fetal organs by single-cell transcriptome study. *PLoS One*. 2020;15:e0230295.

6. Wiersinga WJ, Rhodes A, Cheng AC, et al. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. *JAMA*. 2020;324:782–793.

7. Centers for Disease Control and Prevention. COVID-19 SARS-CoV-2 Variant Classifications and Definitions. 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html. Accessed July 1, 2021.

8. Centers for Disease Control and Prevention. Guidance for unvaccinated people: how to protect yourself & others. Available at: https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html. Accessed July 1, 2021.

9. Oran DP, Topol EJ. The proportion of SARS-CoV-2 infections that are asymptomatic: a systematic review. *Ann Intern Med*. 2021;174:655–662.

10. Sakurai A, Sasaki T, Kato S, et al. Natural history of asymptomatic SARS-CoV-2 infection. *N Engl J Med*. 2020;383:885–886.

11. Gandhi RT, Lynch JB, del Rio C. Mild or moderate COVID-19. *N Engl J Med*. 2020;383:1756–66.

12. Miller ES, Grobman WA, Sakowicz A, et al. Clinical implications of universal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing in pregnancy. *Obst Gynecol*. 2020;136:232–234.

13. Ellington S, Strid P, Tong VT, et al. Characteristics of women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status—United States, January 22–October 3, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:1641–1647.

14. Aghaeepour N, Ganiyo EA, Meilwain D, et al. An immune clock of human pregnancy. *Sci Immunol*. 2017;2:eaan2946. doi: 10.1126/sciimmunol.aan2946.

15. Hegewald MJ, Crapo RO. Respiratory physiology in pregnancy. *Clin Chest Med*. 2011;32:1–13.

16. Villar J, Ariff S, Gunier RB, et al. Maternal and neonatal morbidity and mortality among pregnant women with and without COVID-19 infection: The INTERCOVID Multinational Cohort Study. *JAMA Pediatr*. 2021;e211050:1–10.

17. Norman M, Navér L, Söderling J, et al. Association of maternal SARS-CoV-2 infection in pregnancy with neonatal outcomes. *J Am Med Assoc*. 2021;325:2076–2086.

18. Metz TD, Clifton RG, Hughes BL, et al. Disease severity and perinatal outcomes of pregnant patients with coronavirus disease 2019 (COVID-19). *Obstet Gynecol*. 2021;137:571–580.

19. Mullins E, Hudak ML, Banerjee J, et al. Pregnancy and neonatal outcomes of COVID-19: coreporting of common outcomes from PAN-COVID and AAP-SONPM registries. *Ultrasound Obstet Gynecol*. 2021;57:573–581.

20. Kirtsman M, Diambomba Y, Poutanen SM, et al. Probable congenital SARS-CoV-2 infection in a neonate born to a woman with active SARS-CoV-2 infection. *Can Med Assoc J*. 2020;192:E647–E650.

21. Vivanti AJ, Vauloup-Fellous C, Prevot S, et al. Transplacental transmission of SARS-CoV-2 infection. *Nat Commun*. 2020;11:3572.

22. Alzamora MC, Paredes T, Caceres D, et al. Severe COVID-19 during pregnancy and possible vertical transmission. *Am J Perinatol*. 2020;37:861–865.

23. Shanes ED, Mithal LB, Otero S, et al. Placental pathology in COVID-19. *Am J Clin Pathol*. 2020;154:23–32.

Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.
31. Savasi VM, Mertz KD, Jiang S, et al. Placental pathology findings during and after SARS-CoV-2 infection: features of villitis and malperfusion. *Pathobiology*. 2021;88:69–77.
32. Mhyre JM, D’Oria R, Hameed AB, et al. The maternal early warning criteria: a proposal from the National Partnership for Maternal Safety. *Obstet Gynecol*. 2014;124:782–786.
33. Brodin P. Immune determinants of COVID-19 disease presentation and severity. *Nat Med*. 2021;27:28–33.
34. Liu F, Liu H, Hou L, et al. Clinico-radiological findings and disease severity in hospitalized pregnant women with coronavirus disease 2019 (COVID-19). *J Obstet Gynecol*. 2021;225:73.e1–73.e7.
35. Joseph NT, Dude CM, Verkerke HP, et al. Maternal antibody response, neutralizing potency, and placental antibody transfer after severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection. *Obstet Gynecol*. 2021;138:1–9.
36. Liu J, Liu H, Hou L, et al. Clinical-radiological features and outcomes in pregnant women with COVID-19 pneumonia compared with age-matched non-pregnant women. * Infect Drug Resist*. 2020;13:2845–2854.
37. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. 2020. Available at: www.covid19treatmentguidelines.nih.gov. Accessed July 1, 2021.
38. Society for Maternal-Fetal Medicine. Management considerations for pregnant patients with COVID-19. Available at: https://s3.amazonaws.com/cdn.smfm.org/media/2336/SMFM_COVID_Management_of_COVID_pos_preg_patients_4-30-20_final.pdf. Accessed July 1, 2021.
39. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323:1239–1242.
40. Savasi VM, Parisi F, Patane L, et al. Clinical findings and disease severity in hospitalized pregnant women with coronavirus disease 2019 (COVID-19). *Obs Gynecol*. 2020;136:252–258.
41. London V, McLaren RJ, Atallah F, et al. The relationship between status at presentation and outcomes among pregnant women with COVID-19. *Am J Perinatol*. 2020;37:991–994.
42. Andrikopoulou M, Madden N, Wen T, et al. Symptoms and critical illness among obstetric patients with coronavirus disease 2019 (COVID-19) infection. *Obstet Gynecol*. 2020;136:291–299.
43. American Journal of Obstetrics and Gynecology - Society for Maternal-Fetal Medicine ACOG-SMFM. Outpatient Assessment and Management for Pregnant Women With Suspected or Confirmed Novel Coronavirus (COVID-19). *Am J Obstet Gynecol*. 2020.
the coronavirus disease 2019 outbreak in China. Am J Obstet Gynecol. 2020;223:240.e1–240.e9.

58. Monni G, Corda V, Iuculano A. Prenatal screening diagnosis and management in the era of coronavirus: the Sardinian experience. J Perinat Med. 2020;48:943–949.

59. Oskovi-Kaplan ZA, Buyuk GN, Ozgu-Erdinc AS, et al. The effect of COVID-19 pandemic and social restrictions on depression rates and maternal attachment in immediate postpartum women: a preliminary study. Psychiatr Q. 2020. doi: 10.1007/s11126-020-09843-1.

60. Ozalp M, Demir O, Akbas H, et al. Effect of COVID-19 pandemic process on prenatal diagnostic procedures. J Matern Fetal Neonatal Med. 2021;34:3952–3957.

61. Kumari V, Mehta K, Choudhary R. COVID-19 and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2021;384:403–416.

62. Jalkanen P, Kolehmainen P, Häkkinen HK, et al. COVID-19 mRNA vaccine induced antibody responses against three SARS-CoV-2 variants. Nat Commun. 2021;12:3991.

63. Liu J, Liu Y, Xia H, et al. BNT162b2 elicited neutralization of B.1.617 and other SARS-CoV-2 variants. Nature. 2021;596:273–275.

64. Choi A, Koch M, Wu K, et al. Serum neutralizing activity of mRNA-1273 against SARS-CoV-2 variants. bioRxiv. 2021;2021.06.28.449914.

65. Van Riel D, de Wit E. Next-generation vaccine technologies: essential components of an adequate response to emerging viral diseases. Lancet Glob Heal. 2020;8:e1116–e1117.

66. Justman N, Shahak G, Gutzeit O, et al. Lockdown with a price: the impact of the COVID-19 pandemic on prenatal care and perinatal outcomes in a Tertiary Care Center. Isr Med Assoc J. 2020;9:533–537.

67. Lonner越来 P, Choudhary MP, et al. Health anxiety and behavioural changes of pregnant women during the COVID-19 pandemic. Eur J Obstet Gynec Reprod Biol. 2020;249:96–97.

68. Justman N, Shahak G, Gutzeit O, et al. Lockdown with a price: the impact of the COVID-19 pandemic on prenatal care and perinatal outcomes in a Tertiary Care Center. Isr Med Assoc J. 2020;9:533–537.

69. Justman N, Shahak G, Gutzeit O, et al. Lockdown with a price: the impact of the COVID-19 pandemic on prenatal care and perinatal outcomes in a Tertiary Care Center. Isr Med Assoc J. 2020;9:533–537.

70. Liu J, Liu Y, Xia H, et al. BNT162b2 elicited neutralization of B.1.617 and other SARS-CoV-2 variants. Nature. 2021;596:273–275.

71. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021;384:403–416.

72. Alter G, Yu J, Liu J, et al. Immunogenicity of mRNA-1273 against SARS-CoV-2 variants. Nature. 2021;596:273–275.

73. Oliver SE, Gargano JW, Marin M, et al. The Advisory Committee on Immunization Practices’ Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine—United States, December 2020. MMWR Morb Mortal Wkly Rep. 2020;69:1922–1924.

74. Wallace M, Woodworth KR, Gargano JW, et al. The Advisory Committee on Immunization Practices’ Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine in Adolescents Aged 12–15 years—United States, May 2021. MMWR Morb Mortal Wkly Rep. 2021;70:749–752.

75. Oliver SE, Gargano JW, Marin M, et al. The Advisory Committee on Immunization Practices’ Interim Recommendation for Use of Moderna COVID-19 Vaccine—United States, December 2020. MMWR Morb Mortal Wkly Rep. 2021;69:1653–1656.

76. Sadoff J, Le Gars M, Shukarev G, et al. Interim results of a phase 1–2a trial of Ad26.COV2.S COVID-19 vaccine. N Engl J Med. 2021;384:1824–1835.

77. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021;384:403–416.

78. Jalkanen P, Kolehmainen P, Häkkinen HK, et al. COVID-19 mRNA vaccine induced antibody responses against three SARS-CoV-2 variants. Nat Commun. 2021;12:3991.

79. Liu J, Liu Y, Xia H, et al. BNT162b2 elicited neutralization of B.1.617 and other SARS-CoV-2 variants. Nature. 2021;596:273–275.

80. Alter G, Yu J, Liu J, et al. Immunogenicity of Ad26.COV2.S vaccine against SARS-CoV-2 variants. Nature. 2021;596:268–272.

81. Oliver SE, Gargano JW, Scobie H, et al. The Advisory Committee on Immunization Practices’ Interim Recommendation for Use of Janssen COVID-19 Vaccine—United States, February 2021. MMWR Morb Mortal Wkly Rep. 2021;70:329–332.

82. MacNeil JR, Su JR, Broder KR, et al. Updated Recommendations from the Advisory Committee on Immunization Practices for Use of the Janssen COVID-19 Vaccine After Reports of Thrombosis with Thrombocytopenia Syndrome Among Vaccine Recipients—United States, April 2021. MMWR Morb Mortal Wkly Rep. 2021;70:651–656.

83. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim
analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet*. 2020;397:99–111.

84. Heath PT, Galiza EP, Baxter DN, et al. Safety and Efficacy of NVX-CoV2373 Covid-19 Vaccine. *N Engl J Med*. 2021;385:1172–1183.

85. Krubiner CB, Faden RR, Karron RA, et al. Pregnant women & vaccines against emerging epidemic threats: Ethics guidance for preparedness, research, and response. *Vaccine*. 2021;39:85–120.

86. Food and Drug Administration. Vaccines and Related Biological Products Advisory Committee Meeting December 10, 2020 Briefing Document PFIZER-BIONTECH COVID-19 Vaccine (BNT162, PF-07302048) for the Prevention of COVID-19. 2020;23:92. Available at: https://www.fda.gov/media/144246/download. Accessed July 1, 2021.

87. Food and Drug Administration. Vaccines and Related Biological Products Advisory Committee Meeting December 17, 2020 Briefing Document MODERNA MRNA-1273 Vaccine for the Prevention of COVID-19. 2020. Available at: https://www.fda.gov/media/144452/download. Accessed July 1, 2021.

88. Food and Drug Administration. Vaccines and Related Biological Products Advisory Committee Meeting February 26, 2021 FDA Briefing Document Janssen Ad26.COV2.S Vaccine for the Prevention of COVID-19. 2021;1–53. Available at: https://www.fda.gov/media/146217/download. Accessed July 1, 2021.

89. Bowman CJ, Bouressam M, Campion SN, et al. Lack of effects on female fertility and prenatal and postnatal offspring development in rats with BNT162b2, a mRNA-based COVID-19 vaccine. *Reprod Toxicol*. 2021;103:28–35.

90. Tapia MD, Sow SO, Ndiaye BP, et al. Safety, reactogenicity, and immunogenicity of a chimpanzee adenovirus vectored Ebola vaccine in adults in Africa: a randomised, observer-blind, placebo-controlled, phase 2 trial. *Lancet Infect Dis*. 2020;20:707–718.

91. Legardy-Williams J, Carter R, Goldstein S, et al. Pregnancy outcomes among women receiving rVSVA-ZEBOV-GP ebola vaccine during the sierra leone trial to introduce a vaccine against ebola. *Emerg Infect Dis*. 2020;26:541.

92. Razzaghi H, Meghani M, Pingali C, et al. COVID-19 vaccination coverage among pregnant women during pregnancy — Eight Integrated Health Care Organizations, United States, December 14, 2020–May 8, 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70:895–899.

93. Shimabukuro TT, Kim SY, Myers TR, et al. Preliminary findings of mRNA Covid-19 vaccine safety in pregnant persons. *N Engl J Med*. 2021;384:2273–2282.

94. Shanes ED, Otero S, Mithal LB, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination in pregnancy: measures of immunity and placental histopathology. *Obstet Gynecol*. 2021;138:281–283.

95. Collier AY, McMahan K, Yu J, et al. Immunogenicity of COVID-19 mRNA vaccines in pregnant and lactating women. *JAMA*. 2021;325:2370–2380.

96. Gray KJ, Bordt EA, Atyeo C, et al. COVID-19 vaccine response in pregnant and lactating women: a cohort study. *Am J Obstet Gynecol*. 2021;225:303.e1–303.e17.

97. Prabhu M, Murphy EA, Sukhu AC, et al. Antibody response to coronavirus disease 2019 (COVID-19) messenger RNA vaccination in pregnant women and transplacental passage into cord blood. *Obstet Gynecol*. 2021;138:278–280.

98. Rasmussen SA, Kelley CF, Horton JP, et al. Coronavirus disease 2019 (COVID-19) vaccines and pregnancy: what obstetricians need to know. *Obstet Gynecol*. 2021;137:408–414.