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REVIEW ARTICLE

The impact of COVID-19 in pregnancy: Part II. Vaccination to pregnant women

Peng-Hui Wang[a,b,c,d,*], Wen-Ling Lee[b,e], Szu-Ting Yang[a,b], Kuan-Hao Tsui[b,f,g,h], Cheng-Chang Chang[i], Fa-Kung Lee[j]

[a]Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [b]Institute of Clinical Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; [c]Department of Medical Research, China Medical University Hospital, Taichung, Taiwan, ROC; [d]Female Cancer Foundation, Taipei, Taiwan, ROC; [e]Department of Medicine, Cheng-Hsin General Hospital, Taipei, Taiwan, ROC; [f]Department of Obstetrics and Gynaecology, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, ROC; [g]Institute of BioPharmaceutical Sciences, National Sun Yat-Sen University, Kaohsiung, Taiwan, ROC; [h]Department of Pharmacy and Master Program, College of Pharmacy and Health Care, Tajen University, Pingtung, Taiwan, ROC; [i]Department of Obstetrics and Gynecology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC; [j]Department of Obstetrics and Gynecology, Cathy General Hospital, Taipei, Taiwan, ROC

Abstract: Effective strategies are urgently needed to decrease the risk of untoward outcomes of pregnant women with severe acute respiratory syndrome coronavirus 2 (coronavirus disease 2019 [COVID-19]) infection. Pregnant women are a vulnerable population to infectious disease pandemics with dramatically increased infectious diseases-related serious complications, such as the need of hospitalizations, the need of admission to intensive care unit, and the final disease-related death compared with those nonpregnant counterparts or those pregnant women without infection. Several studies have shown that vaccinations in pregnancy are a safe and highly effective strategy, not only for pregnant women but also for fetus and/or newborn because of the passive transplacental transfer of antibodies to the offspring. Active and passive prevention of infectious diseases is approved as effective strategies for women who attempt to become pregnant or during pregnancy. Despite the large and proven scientific evidence, pregnant women still puzzle over whether they should get vaccinated. The question therefore arises: Why are pregnant women so reluctant to receive vaccination? The explanation is more likely in the way that the benefits of vaccination have been communicated "confusedly." In fact, like virtually all clinical trials, all the COVID-19 vaccine trials have excluded pregnant and lactating women from participating, contributing to uncertainty of safety and efficacy in COVID-19 vaccines that have been well prepared and available for the general adult population worldwide. Moreover, messenger RNA vaccine is a relatively brand-new vaccine, and experience with this type of vaccine is still scarce. It is hard to overcome this innovation deadlock. The knowledge and awareness of pregnant women who are at risk, and full information on the knowledge of vaccines and related preventable diseases in pregnant women may avoid hesitancy and increase vaccine acceptance. The current review is a part two addressing the impact of COVID-19 on pregnant women. We focus on the up-to-date information about the application of vaccination on pregnant women, especially during this COVID-19 pandemic.

Keywords: Coronavirus disease 2019; COVID-19; Pregnancy; Pregnant; SARS-CoV-2; Severe acute respiratory syndrome coronavirus 2; Vaccination; Vaccine

1. INTRODUCTION

Because severe acute respiratory syndrome coronavirus 2, SARS-CoV-2 (coronavirus disease 2019 [COVID-19]), is rapidly and widely disseminating to the world and evidence-based knowledge about COVID-19 in pregnant is limited,[1–5] a better understanding of knowledge about COVID-19-related impact on pregnant women, who are a vulnerable population to infectious disease pandemics, is of paramount importance.[6–8] Therefore, we have conducted a series of review addressing the impact of COVID-19 on pregnant women. The first part (which focused on the clinical presentations and untoward outcomes of pregnant women with COVID-19) has been published in the September issue of the *Journal of the Chinese Medical Association*.[9] We found pregnant women have less frequency to present symptoms or signs when they get SARS-CoV-2 infection compared with non-pregnant women did. Additionally, if they have COVID-19-related symptoms, their symptoms tend to be mild than those of non-pregnant women with COVID-19.[9] Unpredictably, these pregnant women with COVID-19 are more likely to progress to severe diseases, needing admission to intensive care unit (ICU, risk ratio [RR] 2.1-3.0), mechanical ventilation (RR 2.6-2.9), and extracorporeal membrane oxygenation (ECMO, RR 2.0-2.4), and finally result in more COVID-19-related deaths (RR 1.1-1.7)

Address correspondence. Dr. Peng-Hui Wang, Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail addresses: phwang@vghtpe.gov.tw; pongpongwang@gmail.com (P.-H. Wang).

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compared with non-pregnant women.[1,9–12] Moreover, these pregnant women with COVID-19 not only have the higher risk of severe diseases and death compared with non-pregnant women, but also have a continuously higher risk of morbidity and mortality compared with pregnant women without SARS-CoV-2 infection. These dramatically increased risks include the development of severe diseases, needing ICU administration (RR 3.6-18.6), mechanical ventilation (RR 12.7), preterm birth before 37 gestational weeks (GWs) (RR 1.5-1.6) and cesarean section (RR 1.1-1.3), and disease-related maternal death (RR 2.9-22.3), than pregnant women without COVID-19.[1,9–14] Besides the significantly increased risk of maternal morbidity and mortality, the perinatal and neonatal outcomes of children born to pregnant women with COVID-19 are significantly worse, such as the need to be admitted to the neonatal ICU (RR 4.9), as well as an increased risk of intrauterine fetal death (RR 2.8) and perinatal death (RR 2.8) than those born to pregnant women without COVID-19.[1,9–14] All emphasize an urgent need of national or international recommendations and guidelines to optimize prevention and management strategies for COVID-19 in pregnancy.[9,13,14] The healthcare team should help pregnant women to minimize the risk of SARS-CoV-2 infection and provide an adequate counseling and optimal medical service for those pregnant women, regardless of whether they have SARS-CoV-2 infection or not.[13,14]

Several studies have shown that vaccinations in pregnancy are a safe and highly effective strategy that is not only good for pregnant women themselves but also beneficial for fetus and newborn mediated through passive transplacental transfer of antibodies (Abs).[1,4,6] Active and passive prevention of infectious diseases is approved effective strategies for women who attempt to be pregnant or during pregnancy. Despite the large and proven scientific evidence, pregnant women still puzzle over whether they should get vaccinated. The real reason is unknown, but we are wondering why vaccination of the pregnant women faces impasse? The explanation is more likely in the way that these benefits of vaccination have been communicated "confusedly". Like virtually all clinical trials, all the COVID-19 vaccine trials have excluded pregnant and lactating women from participating, contributing to uncertainty of safety and efficacy in COVID-19 vaccines that have been well prepared and available for the general adult population worldwide. Furthermore, messenger RNA (mRNA) vaccine is a relatively brand-new vaccine because the idea of using RNA in vaccines has been around for nearly three decades.[8,15–17] Moreover, two vaccines made using mRNA technology (Pfizer/BioNTech Comirnaty [BNT162b2] vaccine and Moderna COVID-19 vaccine, focusing the SARS-CoV-2's spike protein, a surface protein used to enter cells) proved effective at warding off COVID-19, but they are expensive and must be stored at −70°C to maintain the integrity of the RNA, and most importantly, both vaccines cannot be stored for a reasonable period.[17] Finally, RNA vaccines tested for human use against COVID-19 have generally required a double dose to be effective (an initial prime dose followed by a boost to stimulate the immune system's memory cells and amplify the immune response). The adverse events (AEs, reactogenicity) are substantially and dramatically increased, which became greater after the second shot (greater with Moderna than with Pfizer vaccine and greater in younger than in older subjects).[17–20] All are associated with poor compliance of the acceptance of the second shot. In real-world clinical practice, many people who get the first shot probably won't get the second shot. Taken together, it is hard to overcome this innovation deadlock. With the knowledge and awareness of pregnant women who are at risk, and full information about knowledge of vaccines and related preventable diseases in pregnant women may avoid hesitancy and increase vaccine acceptance. The current review is a part II addressing the impact of COVID-19 on pregnant women. We focus on the up-to-date information about the application of vaccination to pregnant women, and use the experience of common and wide-accepted vaccines as examples to introduce the COVID-19 vaccination in pregnant women.

2. SPECIAL FEATURES OF THE IMMUNE SYSTEM IN PREGNANCY

As shown in part I,[9] immune tolerance to the semi-allogeneic fetus by the maternal immune system is critical for a successful pregnancy, but pregnancy is an immunologically dynamic state with high levels of human chorionic gonadotropin (hCG, produced by the blastocyst and later by trophoblasts to stimulate the production of interleukin [IL]-10^{+} Breg [regulatory B 10 cells: B10] and IL-35^{+} Breg cells that function to downregulate effector cells) and the sex hormones estradiol (estriol [E3] causes thymic involution, leading to decrease in T cell development and suppresses B cell lymphopoiesis) and progesterone (inhibiting Toll-like receptor [TLR]-induced cytokine production and promoting T helper cell type 2 (Th2) immune responses while inhibiting T helper cell type 1 (Th1) immune responses and stimulating Th2 cells to release C-X-C motif cytokine ligand 10 [CXCL10] and upregulating non-classical human leukocyte antigen-G [HLA-G] expression), modifying the immune responses (driving bone marrow precursor cells to formation of cluster differentiation 11^{c+} [CD11^{c+}] dendritic cells and decrease antiviral responses in addition to augmenting Th2 responses, including interferon gamma [IFNγ] production and to expand Treg populations) and shifting the Th1/Th2 ratio toward a more tolerogenic Th2 profile, and subsequently attenuating cell-mediated immunity by comprising IL-4, IL-10, IL-13, and transforming growth factor-beta and, suboptimal to certain viral infection, contributing to the unique susceptibilities to infectious diseases pandemics and increased severity of virus-related diseases. All were experienced previously by the Spanish influenza, H1N1 (influenza A, swine flu), Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome, and more recently SARS-CoV-2 pandemics.[1,9–12,21–26] These infectious diseases predispose pregnant women to the untoward pregnancy outcomes not only presenting a dramatically increased risk of maternal and perinatal morbidities, but also resulting in both maternal and perinatal deaths.[1,9–14,21–24,27]

As strong evidence supporting the highest risk of pregnant women in this COVID-19 pandemic, the rapid development of a vaccine to protect against COVID-19 has been a historic scientific achievement in most people aged 18 years and older.[18–22,28–32] Challenges still arise in the healthcare system when COVID-19 vaccination possibly improve maternal health but brings the possibility of risk to fetal health, resulting in uncertainty of safety and efficacy for these subjects who were not included in these clinical trials.[25] Because the goal of any preventative prenatal intervention is to minimize risk to both mother and fetus, while maximizing health benefits, experience from a precedent for immunization during pregnancy, such as tetanus, diphtheria, and acellular pertussis (Tdap) vaccine between the 27th and the 36th GWs, and influenza vaccine at any stage of pregnancy, may be an acceptable and well-documented reference.[21,22,33–37]

However, past pandemics with accelerated vaccine development timelines have included pregnant women in immunization efforts, such as H1N1, but unfortunately, a few pregnant women decided to be vaccinated against H1N1 in 2009.[27] Therefore, the following section attempts to summarize the vaccines routinely administered during the pregnancy, based on primary benefits to mother against infection as well as secondary benefits to the fetus, including prevention of complications during labor and

the transmission of protective Abs (high and protective levels of immunoglobulin G [IgG]) passing through the placenta or giving through breastfeeding.[28,35,38,39] In general, immunization in pregnancy can provide a promising contribution to globally reducing neonatal and under-five childhood mortality and morbidity secondary to transmitting infections.[22,40] Additionally, maternal vaccinations may also directly provide passive immunity early in life, which is the period of vulnerability for the infant.[40]

3. TYPES OF VACCINATION AVAILABLE DURING PREGNANCY

To provide the protection of vaccination-preventable infectious disease for pregnant women and their offspring, timely administration of the standard vaccines from birth and avoidance of gaps in the vaccination status of women of childbearing potential are recommended.[21,34,41,42] One of the best examples is vaccination of live viral and bacterial vaccines (live attenuated vaccines [LAIV]) that are attenuated before being used in a vaccine, such as Rota virus, chickenpox (varicella), measles, mumps, rubella (MMR), Bacillus Calmette–Gue´rin (BCG), live herpes zoster (shingles) vaccine, live attenuated influenza vaccine, oral live polio vaccine, and typhoid live oral vaccine, and some of them are highly recommended as standard vaccination of women during their infancy, finishing preconceptional vaccination of women of childbearing potential with gaps in the vaccination status.[21,22,43] These infectious diseases are associated with risk of severe maternal infection as well as congenital viral syndrome, resulting in severe congenital fetal abnormalities; when pregnant women get infected during the pregnancy period, the risk is highest in the first 12 GWs.[21,22,43] As shown in Special Features of the Immune System in Pregnancy, administration of these LAIV to the pregnant women is not encouraged; however, no evidence shows that inadvertent vaccinations to the pregnant women will increase clinically significant AEs to both mother and fetus in a real-world scenario.[21,42] Moreover, it is sometimes suggested that the vaccinations can be given under special circumstances based on the significant benefits over their potential risks, when exposure of the disease threatens the global health of both mother and/or fetus, and cannot be avoided.[40] Infectious disease outbreak is a typical example, in which it is hard to escape from the disease exposure.[44] Of the utmost importance is that the potential benefits of the vaccine outweighing its potential risk to the mother and the fetus should be thoroughly discussed and consulted.[45]

LAIV are generally avoided in pregnancy because the vaccine virus can spread to the fetus and theoretically, put the fetus at risk.[21,22,28,41,42] A maximum risk, in theory, for congenital rubella syndrome (CRS) is 0.2% based on the detection rate of antirubella IgM in the cord blood following inadvertent vaccination with rubella vaccination during the early pregnancy.[21,42] It is often recommended that conception should be delayed at least one month after LAIV.[21] However, the above-mentioned comment is not based on evidence. For example, the data are not obtained from the clinical trial. The description "the overstatement of an increased risk in pregnant women with inadvertent LAIV vaccination" should be interpreted with caution. No data from the well-designed clinical trials (evidence) supported the safety of inadvertent LAIV vaccination in pregnant women, and clinical trials demonstrating AEs of pregnant women treated with LAIV are also absent. In a real-world scenario, pregnant women, regardless of which trimester their pregnancy belong to, may be vaccinated by LAIV inadvertently. So far, no cases of CRS or congenital varicella syndrome had been reported among more than 3500 susceptible women who have received rubella vaccinations or varicella vaccinations shortly before or in the early trimester of pregnancy.[21,41,42] Furthermore, even though vertical transmission of rubella vaccination to the fetus had been reported before, no clinical significance had been demonstrated in these infants.[21,42] Similar to rubella vaccine, other LAIV, such as measles, mumps, or combination, yellow fever, and oral poliovirus, are also not recommended for pregnant women.[21,41,42] The contraindication of LAIV to the pregnant women may be a purely precautionary measure, and inadvertent vaccination of pregnant women with LAIV cannot be used as an indication for termination of the pregnancy.[21,42] Basically, if any concern of safety of these vaccinations by LAIV should not be underestimated, but it is not worthy of overemphasis. All we can do is providing adequate knowledge or information to the women in the reproductive age, regardless of who plans to get conceived or who are pregnant. Table 1 is a summary of the vaccines that may not be suitable for pregnant women.

Besides the relatively controversial issue about LAIV vaccination in pregnancy, other vaccines have been frequently mentioned in pregnancy. These vaccines can simply be classified as vector vaccines and non-vector vaccines. Conventionally,

Table 1

Summary of vaccines that are not recommended in pregnancy

Vaccines	Comments	Real-world experience
MMR	LAIV: Not recommended in pregnancy. Recommended from birth as well as avoidance of gaps in the vaccination status of women of childbearing potential.	No congenital rubella syndrome is reported in pregnant women with inadvertent vaccination.
Varicella	LAIV: Not recommended in pregnancy.	No congenital varicella syndrome is reported in pregnant women with inadvertent vaccination.
BCG	LAIV: Not recommended in pregnancy.	
Shingles (HZ)	Both LAIV (ZVL) and RZV (a liposome-based adjuvant system) are not recommended in pregnancy.	
Influenza	LAIV: Not recommended in pregnancy.	
OPV	LAIV: Not recommended in pregnancy. Inactivated vaccine is acceptable.	No association between vaccination and poor pregnancy outcome, but vaccine-associated paralytic polio in the general population.
Oral live typhoid	LAIV: Not recommended in pregnancy. Inactivated vaccine is acceptable.	
Smallpox	Preexposure vaccination is contraindicated in any trimester of pregnancy	No congenital smallpox syndrome is reported in pregnant women with inadvertent vaccination
HPV	No need in pregnancy.	No risk is reported to both mother and fetus in pregnant women with inadvertent vaccination.

BCG = Bacillus Calmette–Gue´rin; HPV = human papilloma virus; HZ = Shingles (Herpes zoster); LAIV = live attenuated vaccines; MMR = measles-mumps-rubella; OPV = a live attenuated oral poliovirus types 1,2, and 3 (Sabin vaccine); RZV = recombinant zoster vaccine; ZVL = live zoster vaccine.

one or more types of live microorganisms (bacteria or viruses, such as large DNA viruses as adenoviruses, vaccinia, and poxviruses) that are non- or low-pathogenic to the targeted species (eg, human beings) are used as vectors in which one or more genes or RNA (subunit vaccines) that encode antigens have been inserted, usually surface proteins of pathogens.[22] These subunit vaccines include toxoid vaccines, polysaccharide vaccines, conjugate vaccines, DNA vaccines, and RNA vaccines.[22] Different components of vaccines may affect the potential efficacy of the neonate, since different subclasses of IgG have a different efficiency to pass through the placenta to the fetus.[22] In terms of efficient transferring to the fetus, the most effective IgG is IgG 1, which can reach the highest concentration to the fetus, and the other order of efficiency is IgG4, IgG3, and IgG2.[22] Therefore, the content of vaccinations is a key factor to determine the efficacy of passive immunization of the fetus and newborns. Furthermore, IgG transfer from the mother to the fetus can occur from the 13th GWs, with the largest amount of transfer occurring during the third trimester of pregnancy.[46]

Because polysaccharide vaccine often elicits predominately IgG2 response, and in contrast, protein or protein-conjugated vaccines elicit IgG1 and IgG3 response,[22] it is easily understood that for achieving maximal protection of neonates, protein-conjugated vaccination to pregnant women is a better choice. Furthermore, vaccination can be delayed to the second or third trimesters if the safety issue is still under the consideration (concerns of safety).[47]

Table 2 provides a summary of the vaccines that are often recommended in all women during the reproductive age, regardless of whether they are pregnant or not.[41,42,46–51] Table 3 lists the vaccinations that are indicated for medical needs during pregnancy.[41,42,46,47]

4. ANTI-SARS-COV-2 INFECTION VACCINATION (COVID-19 VACCINATION) DURING PREGNANCY

4.1. Safety and adverse events

Before the introduction of anti-SARS-CoV-2 vaccination during pregnancy, so far, several different vaccines are in use, including Pfizer/BioNTech Comirnaty vaccine (BNT162b2, which was listed for the World Health Organization (WHO) Emergency Use Listing (EUL) or Emergency Use Authorization on December 31, 2020; SII/Covishield and AstraZeneca/AZD1222 vaccine (Oxford/AstraZeneca [AZ], listed for the WHO EUL on February 16, 2021); Janssen/Ad26.COV 2.S vaccine (Johnson & Johnson, listed for the WHO EUL on March 12, 2021); Moderna COVID-19 vaccine (mRNA 1273, listed for the WHO EUL on April 30, 2021); Sinopharm COVID-19 vaccine (Bio-Institute of Biological Products Co Ltd, listed for the WHO EUL on May 7, 2021); and Sinovac-CoronaVac vaccine (listed for the WHO EUL on June 1, 2021).[44] In general, all six different COVID-19 vaccines are safe for most people aged 18 years and older, including those with pre-existing conditions of any kind of auto-immune disorders, hypertension, diabetes, asthma, pulmonary, liver and kidney diseases, as well as chronic infections that are stable and controlled. However, the following four conditions, such as a compromised immune system, pregnancy, a history of severe allergies—particularly to a vaccine (or any of the ingredients in the vaccine)—and severe frailty should be discussed with healthcare providers if vaccinations are planned.[44]

Among the aforementioned special circumstances, pregnant women constitute one of the most important population who need more care and much communication, not only for any ethical issue but also for the safety of both the mother and fetus. In theory, either administration of drugs or vaccination to pregnant women is encouraged if the goals of "win–win" situations for both maternal and fetal interests can be achieved. However, sometimes, a challenge or a dilemma situation will occur when maternal and fetal interests are misaligned. Although it is well known that no treatment that improves fetal well-being can occur without going through the body of the pregnant woman, and most obstetrical ethicists believe that the pregnant woman is the most appropriate individual to make choices regarding if and how to proceed the treatment, pregnant patients will go to great ends to optimize the outcome of their pregnancy, and, be informed of the options and possible risk and benefits.[45]

A recent review was conducted to identify the safety concerns (including AEs during pregnancy and the neonatal period) of COVID-19 vaccines, such as their components and their technological platforms (whole virus, protein, viral vector, or nucleic acid) used in other vaccines. The review found that the most frequent exposure was to AS03 adjuvant (the oil-in-water emulsion-adjuvant AS03 system, including $AS03_A$ as 11.86 mg of tocopherol, and $AS03_B$ as 5.93 mg of tocopherol) in the context of A/H1N1 pandemic influenza vaccines (24 studies), aluminum-based

Table 2

Summary of vaccines that are recommended in pregnancy

Vaccines	Comments	Real-world experience
Tdap	Current guidelines (CDC, and ACOG) suggest that all pregnant women should get vaccinated between 27 and 36 gestational weeks. CDC recommends the administration of Tdap in very consecutive pregnancy.	Moderate: no evidence of increased risk of both mother and fetus
Tdap-IPV	UK Department of Health recommends of all previously immunized pregnant women between 16 and 32 gestational weeks.	Moderate: no evidence of increased risk of both mother and fetus
Hepatitis B		Insufficient evidence to draw a conclusion about key adverse events in pregnant women
Inactivated influenza	Evidence shows the vaccine can be given at any trimester. Global policies that recommend maternal influenza vaccination have been in place for a decade. Women planning to become pregnant should be vaccinated beforehand.	Insufficient evidence to draw a conclusion about key adverse events in pregnant women. The data supporting the benefits and safety of maternal influenza vaccination during any gestation stage. The data from population-based cohort showed that maternal influenza vaccination during pregnancy was not significantly associated with an increased risk of adverse early childhood health outcomes.

ACOG = the American College of Obstetricians and Gynecologists; CDC = the center for disease control; hepatitis B = hepatitis B vaccine, including Engerix-B, and Recombivax HB; inactivated influenza = quadrivalent inactivated influenza vaccines or quadrivalent recombinant influenza vaccine; Tdap = tetanus–diphtheria–acellular pertussis; Tdap-IPV = tetanus–diphtheria–acellular pertussis and inactivated polio vaccine (salk vaccine).

Table 3

Summary of vaccines that are given for medical indications in pregnancy

Vaccines	Comments	Real-world experience
RHBV (surface antigen)	CDC and ACOG: Completion of the vaccination scheme that started before conception. High risk of infection with HBV in pregnancy.	No apparent risk of congenital anomalies to the developing fetus.
Pneumococcal (PPSV23 and PCV13)	ACIP: Given before conception. Safety data available in the second and third trimesters.	No increase incidence of congenital anomalies is reported in pregnant women with inadvertent vaccination.
Meningococcal (MenACWY and MenB)	ACIP: Polysaccharide and toxin or recombinant protein vaccine.	Risk of patterns of adverse events after MenACWY vaccination may not be increased.
Rabies (RABV)	CDC: Recommended after an animal bite.	A favorable safety profile during all three trimesters.
Hepatitis A	CDC: Recommended in high risk for exposure to HAV.	VAERS reports did not identify safe issue in pregnancy
IPV	CDC: IPV for pregnant women in high risk.	No risk reports. IVP vaccination combined with Tdap recommended for pregnant women in the United Kingdom.
Japanese encephalitis	CDC: Recommended in high risk for exposure of Japanese encephalitis virus.	
Yellow fever	CDC: A LAIV consulted in high risk for exposure of yellow fever virus.	No identified risk reports.
Typhoid fever	Oral Ty21a: Contraindication for pregnant women Injected Vi: CDC and ACIP: suggested in high risk and delayed to the second and third trimester.	
Smallpox	CDC: Preexposure vaccination is contraindicated in any trimester of pregnancy. Only after direct exposure to smallpox.	Fetal smallpox infection, although the risk is low. Not recommended to terminate pregnancy after vaccination.
Anthrax	CDC: Preexposure vaccination is contraindicated in any trimester of pregnancy. CDC: Only after direct exposure to smallpox.	Birth defects were slightly more common in infants born to mothers vaccinated in the first trimester when compared with infants born to women vaccinated outside the first trimester.

Japanese encephalitis: inactivated mosquito-borne flavivirus; Yellow fever: a live attenuated mosquito-borne flavivirus; Typhoid fever: two types: a live attenuated oral *Salmonella typhi* (Ty21a) and Vi polysaccharide injected vaccine; Smallpox: a live attenuated smallpox (or variola) virus; Anthrax: a live attenuated antigenic protein of Bacillus anthracis.

ACIP = the Advisory Committee on Immunization Practices; ACOG = the American College of Obstetricians and Gynecologists; CDC = the center for disease control; hepatitis A vaccine = inactivated *Hepatitis A virus*; IPV = inactivated poliovirus types 1,2 and 3 (Salk vaccine); MenACWY = *Neisseria meningitidis* meningococcal group A, C, W-135 and Y vaccine (protein-conjugated vaccines); MenB = meningococcal B vaccine (recombinant vaccines); PCV13 = 13-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine; RABV = inactivated *Rhabdoviridae lyssavirus*; RHBV = recombinant hepatitis B vaccine; Tdap = Tetanus- Diphtheria- Acellular pertussis; VAERS = the Vaccine Adverse Event Reporting System.

adjuvants (11 studies), aluminum phosphate in respiratory syncytial virus fusion candidate vaccines (three studies), Tdap vaccines (three studies), different aluminum-based adjuvants in hepatitis vaccines, the replication-deficient simian adenovirus (ChAdOx1) in rift valley fever vaccine, and lipid nanoparticles in mRNA COVID-19 vaccine.[51,52] The authors finally found no evidence of pregnancy-associated safety concerns of COVID-19 vaccines that were selected for review by the COVAX MIWG or of their components or platforms when used in other vaccines. However, the need for further data on several vaccine components and platforms is warranted, given their novelty.[51]

One report of the Morbidity and Mortality Weekly Report Early Release on the MMWR website (https://www.cdc.gov/mmwr) in the United States can be used to monitor the safety of COVID-19 vaccination to pregnant women because they are eligible for and can receive any of the three COVID-19 vaccines (Janssen/Ad26.COV 2.S [Johnson & Johnson] vaccine, Pfizer/BioNTech Comirnaty or Moderna vaccines) available in the United States via EUL.[53] Additionally, data from Vaccine Safety Datalink, a collaboration between the Centers for Disease Control and Prevention's (CDC's) Immunization Safety Office and nine health care organizations starting from 1990, can be analyzed to assess receipt of one or greater dose of COVID-19 vaccination during pregnancy.[54] Among 135 968 pregnant women between December 14, 2010 and May 8, 2021, 22 197 (16.3%) had received one or greater dose of COVID-19 vaccination during pregnancy.[53] In total, 15 043 pregnant women had a completion of two doses of vaccination (8226 for Pfizer, and 5992 for Moderna) and the remaining had a single shot (3658 for Pfizer, 3496 for Moderna, and 825 for Janssen).[53]

Shimabukuro and colleagues used data from the "v-safe after vaccination health checker" surveillance system, the v-safe pregnancy registry, and the Vaccine Adverse Event Reporting System to characterize the initial safety of mRNA COVID-19 vaccines in pregnant women, and a total of 35 691 v-safe participants (age 16-54 years) were identified as pregnant, with the primary variable of pregnancy.[55] Because 87% of participants were pregnant during vaccination, it can be considered as a real-world data. The most common AE associated with mRNA vaccinations among pregnant women was injection-site pain, which was reported in 90% of cases, and more than half of pregnant women experienced fatigue (or tiredness), headache, myalgia (muscle or body aches) after the second shot of vaccine, and in general, the frequency of AEs is dramatically increased after the second dose of vaccine compared with that after the first dose of vaccine. To compare with AEs of non-pregnant women after mRNA vaccinations, injection-site reactions were slightly more common in pregnant women. However, systemic reactions were less common in pregnant women compared with those in non-pregnant women.[55] In terms of severe reactions, they were also very similar in comparing pregnant and non-pregnant women, except for nausea or vomiting with a more frequent occurrence among pregnant women.[55] For other COVID-19 vaccines, such as AZ vaccine and Janssen vaccines, local infection site reactions, fatigue, headache, fever, and muscle pain were common,

and most common AEs of Janssen vaccines are injection site pain (48.6%), headache (38.99%), fatigue (38.2%), and myalgia (33.2%).[56–58]

Spontaneous abortion rate was 11.6% if GW was defined as <13 GWs.[55] When abortion mildly increases to 12.6%, the GW was defined as <20 GWs. It is interesting to find that more than one quarter (28.6%) of pregnant women received the first shot of mRNA vaccinations, but no congenital anomaly in newborn was reported for these pregnant women.[55] Additionally, although congenital anomaly rate was 2.2%, and all newborns with congenital anomaly were born to pregnant women who received the first shot of mRNA vaccination in their third trimester, these congenital anomalies may be unrelated to mRNA vaccinations because the vaccination time is beyond the period of organogenesis. Moreover, the aforementioned adverse pregnancy outcomes reported by the v-safe vaccine database seemed to be very similar to background data from national statistics measured before the COVID19 pandemic.[55] All suggest that COVID-19 mRNA vaccine has no safety concerns for pregnant women. A summary of the common AEs after COVID-19 vaccination in pregnant women is shown in Table 4.[55,57] Post clinical real-world AE analyses are ongoing, and have revealed some concern for thrombotic disease with use of the Janssen and AZ vaccines. Preclinical developmental and reproductive toxicity studies have been completed for at least three vaccines (Pfizer, Moderna, and Janssen); none found any adverse effects on animal reproduction or fetal development.[58]

Table 4

Adverse events of messenger RNA vaccinations in pregnant women

Adverse events	First shot P–M (Total)	Second shot P–M (Total)	Janssen
Injection-site pain (%)	84–92.8 (88.1)	88.7–95.6 (91.9)	48.6
Fatigue (%)	26.6–33 (29.6)	63.7–80.6 (71.5)	38.2
Headache (%)	16.5–19.1 (18.1)	47.3–65 (55.4)	38.9
Myalgia (%)	8.8–14.7 (11.6)	43.9–66.1 (54.1)	33.2
Chills (%)	2.8–5.6 (4.1)	26.3–48.9 (36.7)	
Fever (%)	2.8–5.7 (4.2)	24.8–46 (34.6)	
≥38°C (%)	0.3–0.8 (0.5)	4.7–11.8 (8)	
Nausea (%)	5.4–8.0 (6.7)	20.4–33.9 (26.6)	
Joint pain (%)	2.3–4.3 (3.2)	19.1–33.2 (25.6)	
Injection-site swelling (%)	3.5–9.3 (6.2)	6.2–18.7 (11.9)	
Pregnancy outcome	Number/total number (%)		
Abortion (<20 GW)	104/827 (12.6)		
Abortion (<13 GW)	96/827 (11.6)		
Stillbirth (≥20 GW)	1/725 (0.1)		
Preterm birth (<37 GW)	60/636 (9.4)		
SGA	23/724 (3.2)		
Congenital anomalies	16/724 (2.2)		
Neonatal death	0/724		

The data are presented as percentage (%) from P (Pfizer-BioNTech vaccinations) to M (Moderna vaccinations) and a combination of both (total).

The data are presented as number/total number (percentage: %).

First shot is based on 9052 pregnant women with Pfizer-BioNTech vaccinations and 7930 pregnant women with Moderna vaccinations.

Second shot is based on 6638 pregnant women with Pfizer-BioTech vaccination and 5635 pregnant women with Moderna vaccinations.

Total is based on 16 982 pregnant women with the first shot of messenger RNA vaccinations and 12 273 pregnant women with the second shot of messenger RNA vaccinations.

Congenital anomaly is defined according to the Metropolitan Atlanta Congenital Defects Program 6-Digit Code Defect List (https://www.cdc.gov/ncbddd/birthdefects/macdp.html).

Neonatal death is defined as newborn died within the first 28 days after delivery.

The data were modified from references [55] and [57].

GA = gestational weeks; GW = gestational week; M = Moderna; P = Pfizer-BioNTech; SGA = small size for gestational age.

According to the results of Shimabukuro et al,[55] as a member of the healthcare team, the following information about the safety of application of mRNA COVID-19 vaccination to the pregnant women can be given, because of no obvious adverse events among women who received mRNA COVID-19 mRNA vaccines during the pregnancy period.

4.2. Immunogenicity after COVID-19 vaccination in pregnancy

Immunogenicity after vaccination is a determinant factor to evaluate the efficacy of the vaccination. Arunachalam et al[15] tested the immunogenicity of Pfizer vaccine in healthy adult volunteers, and they found that the second dose of Pfizer vaccination resulted in the robust production of neutralizing Abs against the wild-type SARS-CoV-2 as well as significant increases in antigen-specific polyfunctional CD4 and CD8 T cells. Additionally, the second shot stimulated a notably enhanced innate immune response when compared with the first shot of vaccination, including (1) a greater frequency of $CD14^{+}CD16^{+}$inflammatory monocytes; (2) a higher concentration of plasma IFNγ; (3) a transcriptional signature of innate antiviral immunity; and (4) 100-fold increase in the frequency of a myeloid cell cluster enriched in IFN-response transcription factors and reduced in AP-1 transcription factors, after secondary immunization.[15] All suggested that at least two shots of Pfizer vaccinations are needed to achieve the goals of protection to be against SARS-CoV-2 infection.

What is the effect of mRNA vaccinations in pregnancy? One study showed that pregnant women had significantly lower SARS CoV-2 IgG levels in the maternal serum, regardless of which trimesters or GWs they were vaccinated with Pfizer vaccination compared with non-pregnant women (27.03 ± 10.72 vs 34.35 ± 10.25).[59] In contrast, another study showed no difference of maternal to neonatal anti-COVID-19 Abs ratio between Pfizer vaccination and Natural SARS CoV-2 infection.[60] Collier et al[31] found there are no differences of binding, neutralizing, and functional non-neutralizing Ab responses as well as CD4 and CD8 T-cell responses among pregnant, lactating, and nonpregnant women following vaccination by either Moderna or Pfizer vaccines. Gray's study found that Ab titers induced by both vaccines were not statistically significantly different among pregnant, lactating, and nonpregnant women.[61] However, Gray's study found that the titers of Ab were higher in the vaccination group than in the natural SARS CoV-2 infection group.[61] Although binding and neutralizing Ab titers against the SARS-CoV-2 B.1.1.7 and B.1.351 variants of concern were reduced, T-cell responses were preserved against viral variants.[31] All studies demonstrated that vaccinations to pregnant women will deliver the IgG Ab to fetus via placental transfer and to newborns via breastmilk feeding.

It is interesting to find that Bearer and colleagues showed IgG transfer ratio at birth was significantly lower for third-trimester as compared with second-trimester infection.[60] Adhikari and Spong further emphasized this critical point that SARS-CoV-2–specific Abs appear to be inefficiently transferred across the placenta following third-trimester maternal infection compared with Ab transfer following natural infection with influenza or pertussis.[62] Additionally, changes in SARS-CoV-2–specific Ab glycosylation patterns and placental selectivity for these Abs may compensate for suboptimal protection and could be an important lesson for vaccine development.[62–68] Furthermore, the gestational age of de novo maternal Ab production influences the level of SARS-CoV-2–specific Ab in the cord blood, implying that there may be an ideal time for maternal vaccination prior to delivery to optimize protection of the fetus.[62] Taken together, it can be supposed that mRNA COVID-19 vaccination applied to pregnant women in the

second trimester or earlier may be a better choice than given in the third trimester.

In conclusion, the guidance from professional societies, agencies, and governments has been limited, without an explicit recommendation for COVID-19 vaccination in pregnancy.[63] The lack of adequate data to support the safety, immunogenicity, and efficacy in pregnant and lactating women has made the decision of COVID-19 vaccination during pregnancy much challenging for nearly all.[53,58,69–76] To face this challenge, inclusive, reactive, self-reflecting, and inspiring science communication based on honesty, transparency, and a genuine intention to apply science for the common good should become central to the mission of science, especially for those pregnant women who are a vulnerable population to infection pandemics but often excluded in new therapeutic studies or clinical trials, with the fact that COVID-19 causes significant morbidity and mortality, with respiratory illness requiring hospitalization in 5%–6% of all SARS-CoV-2-infected pregnant women.[57,69–76] A health-provider (an obstetrical doctor), as part of the discussion, should acknowledge with empathy the limited available evidence, and the tension over the potential benefits of COVID-19 vaccination weighted against the potential risks (whether it is real or theoretical) and be prepared to dispel myths.[9,62,76]

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REFERENCES

1. Khan DSA, Pirzada AN, Ali A, Salam RA, Das JK, Lassi ZS. The differences in clinical presentation, management, and prognosis of laboratory-confirmed COVID-19 between pregnant and non-pregnant women: a systematic review and meta-analysis. *Int J Environ Res Public Health* 2021;**18**:5613.
2. Yang DM, Lin FC, Tsai PH, Chien Y, Wang ML, Yang YP, et al. Pandemic analysis of infection and death correlated with genomic open reading frame 10 mutation in severe acute respiratory syndrome coronavirus 2 victims. *J Chin Med Assoc* 2021;**84**:478–84.
3. Tsai PH, Lai WY, Lin YY, Luo YH, Lin YT, Chen HK, et al. Clinical manifestation and disease progression in COVID-19 infection. *J Chin Med Assoc* 2021;**84**:3–8.
4. Pountoukidou A, Potamiti-Komi M, Sarri V, Papapanou M, Routsi E, Tsiatsiani AM, et al. Management and prevention of COVID-19 in pregnancy and pandemic obstetric care: a review of current practices. *Healthcare (Basel)* 2021;**9**:467.
5. Lai YJ, Chang CM, Lin CK, Yang YP, Chien CS, Wang PH, et al. Severe acute respiratory syndrome coronavirus-2 and the deduction effect of angiotensin-converting enzyme 2 in pregnancy. *J Chin Med Assoc* 2020;**83**:812–6.
6. Huang HH, Wang PH, Yang YP, Chou SJ, Chu PW, Wu GJ, et al. A review of severe acute respiratory syndrome coronavirus 2 infection in the reproductive system. *J Chin Med Assoc* 2020;**83**:895–7.
7. Abedzadeh-Kalahroudi M, Sehat M, Vahedpour Z, Talebian P, Haghighi A. Clinical and obstetric characteristics of pregnant women with Covid-19: a case series study on 26 patients. *Taiwan J Obstet Gynecol* 2021;**60**:458–62.
8. Salma U. Relationship of COVID-19 with pregnancy. *Taiwan J Obstet Gynecol* 2021;**60**:405–11.
9. Wang PH, Lee WL, Yang ST, Tsui KH, Chang CC, Lee FK. The impact of COVID-19 in pregnancy: part I. Clinical presentations and untoward outcomes of pregnant women with COVID-19. *J Chin Med Assoc* 2021;**84**:813–20.
10. Zambrano LD, Ellington S, Strid P, Galang RR, Oduyebo T, Tong VT, et al.; CDC COVID-19 Response Pregnancy and Infant Linked Outcomes Team. Update: characteristics of symptomatic 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**:1641–7.
11. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, et al; for PregCOV-19 Living Systematic Review Consortium. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *BMJ* 2020;**370**:m3320.
12. Ko JY, DeSisto CL, Simeone RM, Ellington S, Galang RR, Oduyebo T, et al. Adverse pregnancy outcomes, maternal complications, and severe illness among US Delivery Hospitalizations with and without a coronavirus disease 2019 (COVID-19) diagnosis. *Clin Infect Dis* 2021;**73**(Suppl 1):S24–S31.
13. Wang LM, Lai SP, Liang SJ, Yang ST, Liu CH, Wang PH. Maternal and fetal outcomes of the pregnant woman with COVID-19: the first case report in Taiwan. *Taiwan J Obstet Gynecol* 2021;**60**:942–4.
14. Yang ST, Yeh CC, Lee WL, Lee FK, Chang CC, Wang PH. A symptomatic near-term pregnant woman recovered from SARS-CoV-2 infection. *Taiwan J Obstet Gynecol* 2021;**60**:945–8.
15. Arunachalam PS, Scott MKD, Hagan T, Li C, Feng Y, Wimmers F, et al. Systems vaccinology of the BNT162b2 mRNA vaccine in humans. *Nature* 2021;**596**:410–6.
16. Amanat F, Thapa M, Lei T, Ahmed SMS, Adelsberg DC, Carreño JM, et al.; Personalized Virology Initiative. SARS-CoV-2 mRNA vaccination induces functionally diverse antibodies to NTD, RBD, and S2. *Cell* 2021;**184**:3936–48.e10.
17. Dolgin E. How COVID unlocked the power of RNA vaccines. *Nature* 2021;**589**:189–91.
18. Brüssow H. COVID-19: vaccination problems. *Environ Microbiol* 2021;**23**:2878–90.
19. Castells MC, Phillips EJ. Maintaining Safety with SARS-CoV-2 Vaccines. *N Engl J Med* 2021;**384**:643–9.
20. Cheng H, Peng Z, Luo W, Si S, Mo M, Zhou H, et al. Efficacy and safety of COVID-19 vaccines in phase III trials: a meta-analysis. *Vaccines (Basel)* 2021;**9**:582.
21. Röbl-Mathieu M, Kunstein A, Liese J, Mertens T, Wojcinski M. Vaccination in Pregnancy. *Dtsch Arztebl Int* 2021;**118**:262–8.
22. Arora M, Lakshmi R. Maternal vaccines-safety in pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2021:S1521-6934(21)00017-1. Doi: 10.1016/j.bpobgyn.2021.02.002. Epub ahead of print.
23. Beigi RH. Emerging Infectious Diseases in Pregnancy. *Obstet Gynecol* 2017;**129**:896–906.
24. Silva CRACD, Oliveira LV, Lopes LP, Santos WAGD, Agra IKR. Immunological aspects of coronavirus disease during pregnancy: an integrative review. *Rev Assoc Med Bras (1992)* 2020;**66**:696–700.
25. Rendell V, Bath NM, Brennan TV. Medawar's paradox and immune mechanisms of fetomaternal tolerance. *OBM Transplant* 2020;**4**:26.
26. Szekeres-Bartho J. The role of progesterone in feto-maternal immunological cross talk. *Med Princ Pract* 2018;**27**:301–7.
27. Lai YJ, Chang HS, Yang YP, Lin TW, Lai WY, Lin YY, et al. The role of micronutrient and immunomodulation effect in the vaccine era of COVID-19. *J Chin Med Assoc* 2021;**84**:821–6.
28. Chavan M, Qureshi H, Karnati S, Kollikonda S. COVID-19 vaccination in pregnancy: the benefits outweigh the risks. *J Obstet Gynaecol Can* 2021;**43**:814–6.
29. Voysey M, Costa Clemens SA, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al.; Oxford COVID Vaccine Trial Group. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. *Lancet* 2021;**397**:881–91.
30. Barrett JR, Belij-Rammerstorfer S, Dold C, Ewer KJ, Folegatti PM, Gilbride C, et al.; Oxford COVID Vaccine Trial Group. Phase ½ trial of SARS-CoV-2 vaccine ChAdOx1 nCoV-19 with a booster dose induces multifunctional antibody responses. *Nat Med* 2021;**27**:279–88.
31. Collier AY, McMahan K, Yu J, Tostanoski LH, Aguayo R, Ansel J, et al. Immunogenicity of COVID-19 mRNA vaccines in pregnant and lactating women. *JAMA* 2021;**325**:2370–80.
32. Heath PT, Galiza EP, Baxter DN, Boffito M, Browne D, Burns F, et al; 2019nCoV-302 Study Group. Safety and efficacy of NVX-CoV2373 Covid-19 vaccine. *N Engl J Med* 2021. Doi: 10.1056/NEJMoa2107659. Epub ahead of print.
33. Auriti C, De Rose DU, Santisi A, Martini L, Piersigilli F, Bersani I, et al. Pregnancy and viral infections: mechanisms of fetal damage, diagnosis and prevention of neonatal adverse outcomes from cytomegalovirus

to SARS-CoV-2 and Zika virus. *Biochim Biophys Acta Mol Basis Dis* 2021;**1867**:166198.
34. Castillo E, Patey A, MacDonald N. Vaccination in pregnancy: challenges and evidence-based solutions. *Best Pract Res Clin Obstet Gynaecol* 2021:S1521-6934(21)00047-X. Doi: 10.1016/j.bpobgyn.2021.03.008. Epub ahead of print.
35. Visalli G, Facciolà A, Mazzitelli F, Laganà P, DI Pietro A. Health education intervention to improve vaccination knowledge and attitudes in a cohort of obstetrics students. *J Prev Med Hyg* 2021;**62**:E110–6.
36. Kim C, Pae J, Kim WJ, Jang Y, Wie JH, Park IY, et al. Current status of pertussis vaccination during pregnancy and influencing factors in Korea. *Taiwan J Obstet Gynecol* 2021;**60**:273–80.
37. Li WF, Huang SY, Peng HH, Chang YL, Chang SD, Cheng PJ; Taiwan Prenatal Pertussis Immunization Program (PPIP) Collaboration Group. Factors affecting pregnant women's decisions regarding prenatal pertussis vaccination: a decision-making study in the nationwide Prenatal Pertussis Immunization Program in Taiwan. *Taiwan J Obstet Gynecol* 2020;**59**:200–6.
38. Atyeo C, Alter G. The multifaceted roles of breast milk antibodies. *Cell* 2021;**184**:1486–99.
39. COVID-19 vaccines: Safety surveillance manual. Module on safety surveillance of COVID-19 vaccines in pregnant and breastfeeding women. Available at https://www.who.int/publications/i/item/WHO-MHP-RPQ-PVG-2021.1. Accessed July 12, 2021.
40. Kochhar S, Bauwens J, Bonhoeffer J; GAIA Project Participants. Electronic address: http://www.gaia-consortium.net/. Safety assessment of immunization in pregnancy. *Vaccine* 2017;**35**(48 Pt A):6469–71.
41. Munoz FM, Jamieson DJ. Maternal immunization. *Obstet Gynecol* 2019;**133**:739–53.
42. Keller-Stanislawski B, Englund JA, Kang G, Mangtani P, Neuzil K, Nohynek H, et al. Safety of immunization during pregnancy: a review of the evidence of selected inactivated and live attenuated vaccines. *Vaccine* 2014;**32**:7057–64.
43. Lin CL, Shih SF, Tsai PH, Liang AC. Is birth cohort 1985/9-1990/8 a susceptibility window for congenital rubella syndrome in Taiwan? *Taiwan J Obstet Gynecol* 2016;**55**:368–73.
44. World Health Organization. Coronavirus disease (COVID-19) pandemic. COVID-19 Vaccines. Available at https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines. Accessed July 12, 2021.
45. Minkoff H, Ecker J. Balancing risks: making decisions for maternal treatment without data on fetal safety. *Am J Obstet Gynecol* 2021;**224**:479–83.
46. Ndaya-Oloo P, Pitisuttithum P, Tornieporth NG, Desgrandchamps D, Munoz FM, Kochhar S, et al. Vaccine update: recent progress with novel vaccines, and new approaches to safety monitoring and vaccine shortage. *J Clin Pharmacol* 2018;**58**(Suppl 10):123–39.
47. Psarris A, Sindos M, Daskalakis G, Chondrogianni ME, Panayiotou S, Antsaklis P, et al. Immunizations during pregnancy: how, when and why. *Eur J Obstet Gynecol Reprod Biol* 2019;**240**:29–35.
48. Gidengil C, Goetz MB, Newberry S, Maglione M, Hall O, Larkin J, et al. Safety of vaccines used for routine immunization in the United States: an updated systematic review and meta-analysis. *Vaccine* 2021;**39**:3696–716.
49. Azziz-Baumgartner E, Grohskopf L, Patel M. Realizing the potential of maternal influenza vaccination. *JAMA* 2021;**325**:2257–9.
50. Mehrabadi A, Dodds L, MacDonald NE, Top KA, Benchimol EI, Kwong JC, et al. Association of maternal influenza vaccination during pregnancy with early Childhood Health Outcomes. *JAMA* 2021;**325**:2285–93.
51. Ciapponi A, Bardach A, Mazzoni A, Alconada T, Anderson S, Argento FJ, et al. Safety of COVID-19 vaccines, their components or their platforms for pregnant women: a rapid review. *medRxiv* [Preprint]. 2021 Jun 6:2021.06.03.21258283. Doi: 10.1101/2021.06.03.21258283.
52. Kosalaraksa P, Jeanfreau R, Frenette L, Drame M, Madariaga M, Innis BL, et al. AS03B-adjuvanted H5N1 influenza vaccine in children 6 months through 17 years of age: a phase 2/3 randomized, placebo-controlled, observer-blinded trial. *J Infect Dis* 2015;**211**:801–10.
53. Razzaghi H, Meghani M, Pingali C, Crane B, Naleway A, Weintraub E, 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**:895–9.
54. Vaccine safety. CDC Centers for Disease Control and Prevention. CDC 24/7: Saving Livers, Protecting PeopleTM. Available at https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/index.html. Accessed July 17, 2021.
55. Shimabukuro TT, Kim SY, Myers TR, Moro PL, Oduyebo T, Panagiotakopoulos L, et al; CDC v-safe COVID-19 Pregnancy Registry Team. Preliminary findings of mRNA COVID-19 vaccine safety in pregnant persons. *N Engl J Med* 2021;**384**:2273–82.
56. Ramasamy MN, Minassian AM, Ewer KJ, Flaxman AL, Folegatti PM, Owens DR, et al; Oxford COVID Vaccine Trial Group. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. *Lancet* 2021;**396**:1979–93.
57. American College of Obstetricians and Gynecologists. COVID-19 Vaccination Considerations for Obstetric–Gynecologic Care. 2020. Last updated July 2, 2021. Available at https://www.acog.org/clinical/clinical-guidance/practiceadvisory/articles/2020/12/vaccinating-pregnantand-lactating-patients-against-covid-19. Accessed July 12, 2021.
58. Wang EW, Parchem JG, Atmar RL, Clark EH. SARS-CoV-2 vaccination during pregnancy: a complex decision. *Open Forum Infect Dis* 2021;**8**:ofab180.
59. Bookstein Peretz S, Regev N, Novick L, Nachshol M, Goffer E, Ben-David A, et al. Short-term outcome of pregnant women vaccinated by BNT162b2 mRNA COVID-19 vaccine. *Ultrasound Obstet Gynecol* 2021;58:450–6.
60. Beharier O, Plitman Mayo R, Raz T, Nahum Sacks K, Schreiber L, Suissa-Cohen Y, et al. Efficient maternal to neonatal transfer of antibodies against SARS-CoV-2 and BNT162b2 mRNA COVID-19 vaccine. *J Clin Invest* 2021;**131**:150319.
61. Gray KJ, Bordt EA, Atyeo C, Deriso E, Akinwunmi B, Young N, et al. Coronavirus disease 2019 vaccine response in pregnant and lactating women: a cohort study. *Am J Obstet Gynecol* 2021;225:303e1–e17.
62. Adhikari EH, Spong CY. COVID-19 vaccination in pregnant and lactating women. *JAMA* 2021;**325**:1039–40.
63. Lee WL, Wang PH. Immunology and ovarian cancers. *J Chin Med Assoc* 2020;**83**:425–32.
64. Lee WL, Wang PH. Aberrant sialylation of immune cells in rheumatoid arthritis. *J Chin Med Assoc* 2019;**82**:341–2.
65. Lee FK, Lee WL, Wang PH. Sialylated autoantibodies involved in disease activity of rheumatoid arthritis. *J Chin Med Assoc* 2021;**84**:123–4.
66. Lee WL, Wang PH. Aberrant sialylation in ovarian cancers. *J Chin Med Assoc* 2020;**83**:337–44.
67. Lee WC, Lee WL, Shyong WY, Yang LW, Ko MC, Yeh CC, et al. Altered ganglioside GD3 in HeLa cells might influence the cytotoxic abilities of NK cells. *Taiwan J Obstet Gynecol* 2012;**51**:199–205.
68. Lee WC, Lee WL, Shyong WY, Yang LW, Ko MC, Sheu BC, et al. Increased concentration of sialidases by HeLa cells might influence the cytotoxic ability of NK cells. *Taiwan J Obstet Gynecol* 2012;**51**:192–8.
69. The Royal College of Obstetricians and Gynaecologists. Information for healthcare professionals. Coronavirus (COVID-19) infection in pregnancy. Version 13. Available at https://www.rcog.org.uk/globalassets/documents/guidelines/2021-02-19-coronavirus-covid-19-infection-in-pregnancy-v13.pdf. Accessed July 12, 2021
70. Riley LE. mRNA COVID-19 vaccines in pregnant women. *N Engl J Med* 2021;**384**:2342–3.
71. Halscott T, Vaught J. Society for Maternal-Fetal Medicine Management Considerations for Pregnant Patients with COVID-19 Developed with guidance from Torre Halscott, MD, MS and Jason Vaught, MD. Available at https://s3.amazonaws.com/cdn.smfm.org/media/2334/SMFM_COVID_Management_of_COVID_pos_preg_patients_4-29-20_final.pdf. Accessed July 12, 2021.
72. Cohen J. 'Landmark' African vaccine trial faces impasse. *Science* 2021;**372**:1135–6.
73. Gebre MS, Brito LA, Tostanoski LH, Edwards DK, Carfi A, Barouch DH. Novel approaches for vaccine development. *Cell* 2021;**184**:1589–603.
74. Rubin R. Pregnant people's Paradox-Excluded from vaccine trials despite having a higher risk of COVID-19 complications. *JAMA* 2021;**325**:1027–8.
75. Cottin J, Benevent J, Khettar S, Lacroix I. COVID-19 vaccines and pregnancy: what do we know? *Therapie* 2021;**76**:373–4.
76. Contera S. Communication is central to the mission of science. *Nat Rev Mater* 2021:1–2. Doi: 10.1038/s41578-021-00316-w.