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REVIEW ARTICLE

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Vaccination in pregnancy

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Abstract

The evidence indicates that pregnancy is associated with increased severity of some infectious diseases. Given the high maternal morbidity associated with influenza in pregnancy and the high neonatal morbidity and mortality associated with pertussis, the traditionally two recommended vaccines during pregnancy were those against influenza and Tdap (tetanus toxoid, reduced diphtheria toxoid and acellular pertussis) vaccines. The recent COVID-19 pandemic introduced a third vaccine that after much debate is now recommended for all pregnant women. Other vaccines can be offered based for high-risk pregnant women, and only when the benefits of receiving them outweigh the risks. The soon expected vaccines against group B streptococcus infection and respiratory syncytial virus infection will be a breakthrough in reducing perinatal mortality. In this paper, the recommendations for administration of each vaccine during pregnancy are discussed.

KEYWORDS
best practice, immunization, pregnancy, public health, recommendations, safety, vaccination

Vaccinations can provide cost-effective protection against several diseases throughout life but remains an under-promoted and underused public-health strategy in adults for the advancement of healthy aging.[1] Adult immunization generally has not been meeting established benchmarks and public health standards and goals because of misconceptions about several aspects of vaccination and health care professional barriers. The latter include lack of knowledge about indications for and contraindications to immunization, poorly trained medical staff, and absence of a reminder system for missed vaccinations.[2] Other factors include ineffective supply chains, poor delivery of services, funding gaps, accountability issues and poor data quality. The benefits of vaccination should always outweigh the risks and since vaccines are rigorously tested across multiple phases of trials before they are approved for use, safety issues should not, at least theoretically, be a major deterrent to mass immunization.

In pregnant women, immunization poses an even bigger challenge which resulted in rather poor routine immunization performance although immunization theoretically can avert fulminant maternal disease or offer passive immunity to the fetus.[3] The single most important factor influencing maternal vaccination uptake is her healthcare professional recommendation.[4] However, where data are available, one-third of pregnant women remain unvaccinated despite receiving a recommendation.[2] Vaccine refusal is undoubtedly multifactorial. Therefore, it is imperative to understand the significance of other factors that influence vaccination decision-making among pregnant women. Those include vaccine cost, its accessibility, social influences, prior vaccination history and maternal knowledge and perception of risks and benefits.[5] Several interventions to improve maternal vaccination uptake have been tried with variable success rates including text reminders for expecting mothers, educational material delivered in in-person sessions or through educational videos and even motivational interviewing techniques targeting health care professionals.[6–8] Those interventions should be implemented along with healthcare professional recommendations.[2] Making vaccine readily available in clinics can also enhance vaccine uptake.[9] It is also essential to distinguish between vaccines administered routinely and those offered during outbreaks. During outbreaks, like the 2009 influenza pandemic and recently the 2020 COVID-19 pandemic, the

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effect of the recommendation by the health care professional was still very powerful—increasing the odds of antenatal H1N1 vaccine uptake six times, but it might have been muted by other factors.[2] Such factors might be as or even more influential than the health care professional recommendation and include reassurances about vaccine effectiveness and benefits of the vaccine to the mother and her baby and lack of potential for vaccine-induced harm.[2]

For this paper, a comprehensive literature search of the following databases: MEDLINE [PubMed], Scopus and Google Scholar was undertaken to identify articles focusing on the topic of vaccination in pregnancy that were published between 1980 and 2023. The search included the following keywords: "vaccination", "pregnancy", "vaccine", "immunization", and "recommended vaccines".

1 | RECOMMENDED VACCINATIONS IN PREGNANCY

Official and professional bodies including the Center for Disease Control and Prevention (CDC), the Advisory Committee on Immunization Practices (ACIP), the American College of Obstetricians and Gynecologists (ACOG), International Federation of Gynecology and Obstetrics (FIGO), and Royal College of Obstetricians and Gynaecologists (RCOG) traditionally recommended that all pregnant women receive two vaccinations during pregnancy, namely the inactivated influenza and the Tdap (tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis) vaccines. Although the World Health Organization (WHO) also recommends the inactivated influenza vaccine for all pregnant women, it restricts the Tdap vaccine for pregnant women in settings where the disease burden is known.[10] For at-risk pregnant women, other vaccines could provide maternal protection from severe morbidity related to specific pathogens such as hepatitis, pneumococcus, meningococcus, and should be offered in selected patients. The WHO recommends the following vaccines for disease prevention in specific situations: Cholera, yellow fever, meningitis A (meningococcal), hepatitis A, B, and E, Japanese encephalitis Polio (OPV and IPV), and rabies.[10] This held true until the COVID-19 outbreak was declared a global pandemic on March 11, 2020. Amid the COVID-19 pandemic and shortly after the vaccine against this deadly virus became publically available, controversy arose on whether all pregnant women or only a select population should be offered the vaccine. To date, almost all professional bodies advocate to offer COVID-19 vaccination to all pregnant women[11-13] and even stress that pregnant women should be prioritized over their non-pregnant counterparts to be vaccinated. This raises the number of vaccines that should be universally offered to pregnant women to three (Table 1).

TABLE 1 Recommended vaccines in pregnancy and the gestational age recommended for administration.

Type of vaccine	Recommended GA for administration
Influenza vaccine	Any GA during the Influenza season
Tdap vaccine	Between 27 and 36 weeks of gestation
COVID-19 vaccine	Any GA

Abbreviations: GA, gestational age; Tdap, tetanus, diphtheria and acellular pertussis.

1.1 | Influenza vaccine

Seasonal influenza is a highly contagious viral infection of the respiratory tract that can cause severe respiratory morbidity with the potential of life-threatening complications. Owing to its yearly antigenic shift, the virus continues to cause outbreaks worldwide. Influenza continues to cause up to 5 million cases of severe illness that result in 500 000 deaths worldwide.[14,15] Since the COVID-19 pandemic began, a significant decline in the number of influenza cases has been reported probably due to closed international borders, social distancing measures and wearing face masks.[16] However, after borders reopened in most countries, influenza flourished again. In temperate climates, the influenza season is usually between the start of fall and the end of spring. However, in tropical regions, influenza may occur throughout the year, causing outbreaks more irregularly representing a year-round disease burden.[17]

Most people recover from influenza symptoms without requiring medical attention. However, pregnant women are at increased risk of severe illness[18] due to the physiological alterations that occur during pregnancy including alteration of the cellular immunity, increased heart rate and stroke volume, and increased oxygen consumption.[19,20]

The recommendations for influenza vaccination during pregnancy have evolved over time, as has the evidence on the impact of influenza disease and prevention among pregnant women. Soon after the "Asian flu" pandemic and as early as 1957, it was recommended that pregnant women be included among the high-risk groups who should receive the annual influenza vaccine.[21] Despite this, the uptake of the vaccine remained very low. The 2009 H1N1 pandemic resulted in 109 maternal deaths in the United States alone, a number that was 20 times greater than the mean number of annual possible influenza deaths.[22] The sharp decline in influenza deaths that was noted as of December 2009 suggests that vaccine availability coupled with educational campaigns by the CDC, ACOG and other public health agencies may have had a substantial impact on influenza vaccine uptake among pregnant women in the USA. Subsequently, evidence started to emerge on the effectiveness of the influenza vaccine in significantly reducing the risk of hospital admission and the risk of flu-associated acute respiratory infection by 40% and 50%, respectively among pregnant women.[23,24] The 2009–2010 influenza pandemic that severely affected pregnant women serves as a call to reinforce the efforts of professional organizations to provide yearly immunization to this vulnerable group. It would be very difficult to predict when the next pandemic strain will emerge. Even to date and with all such evidence and a good longstanding safety profile,[20] the overall uptake of the vaccine remains low, and most low- and

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middle-income countries continue to not offer routine maternal influenza immunization.[21] Most medical bodies recommend that all pregnant women receive the influenza vaccine once in the index pregnancy. Any of the licensed, recommended, age-appropriate inactivated influenza vaccines can be safely given during any trimester before or during the influenza season.[20,25]

1.2 | Tetanus, diphtheria, and pertussis (Tdap) vaccine

Unlike tetanus and diphtheria where the childhood vaccination campaigns were successful in almost eliminating those potentially life-threatening bacterial infections[26] from most parts of the world, pertussis continues to pose a serious risk on infants.[4] Pertussis can present with the classic whooping cough that can progress to multi-organ failure and culminate in death.[19,27]

In 2018, the WHO reported 151074 pertussis cases globally. However, a publication modeling pertussis cases and deaths with data from 2014 reported that 16–20 million cases of pertussis occur yearly worldwide, with approximately 160000 deaths in children younger than 5 years.[28] The overwhelming majority of mortality attributable to pertussis infection occurs in infants who are younger than 3 months. However, infants do not start their own vaccine series against pertussis until approximately 2 months of age and would need around four extra months to attain protection against the infection.[29] Hence, they are vulnerable during this 3-month window to this infection which they usually contract from their asymptomatic infected parents.[4,28] Today, maternal vaccination has proven to be the best way to confer protection for the fetus through passive immunity.[19] It is recommended that pregnant patients receive Tdap vaccine between the 27th and 36th week of gestation in each pregnancy, even if they have received it before since levels of maternal antibodies decline with time.[27] However, the Tdap vaccine can be safely given at any time during pregnancy if needed for wound management (mostly for tetanus) and in the event of pertussis outbreaks, or other mitigating circumstances. Evidence suggests that antenatal Tdap administered during second and third trimester is not associated with any adverse effects on the fetus or the neonate.[30] If Tdap is not administered during pregnancy, it still can be given immediately postpartum.[31]

The WHO does not recommend the Tdap vaccine for pregnant women who have completed a six-dose series of a tetanus toxoid-containing vaccine during infancy.[32]

Side effects of the Tdap vaccine are limited to erythema, pain and swelling at the site of injection with most symptoms resolving within 72 h.[33]

1.3 | COVID-19 vaccine

Soon after the first cases were reported, COVID-19 triggered by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection was declared a pandemic by WHO on March 11, 2020. The rapid accumulation of data on COVID-19 and pregnancy proved without any doubt that pregnant women are at a significantly higher risk for severe COVID-19-associated morbidities requiring hospitalization, intensive care unit admission, mechanical ventilation and death compared to non-pregnant women, even after controlling for many confounding variables.[34] Evidence also supports that SARS-CoV-2 infection during pregnancy is associated with several adverse pregnancy outcomes comprising preeclampsia, preterm birth, and stillbirth, especially among pregnant women with severe COVID-19 disease.[35] Offering the COVID-19 vaccine to pregnant women was as controversial as many aspects of this novel infection. This was particularly so, given that pregnant women were excluded from the initial COVID-19 vaccine phase 3 trials, which prevented the acquisition of pregnancy-specific safety data and limited the ability of professional organizations to make evidence-based recommendations on COVID-19 vaccination in pregnancy at the initial phases of vaccine implementation. Back then, pregnant women were not prioritized over non-pregnant women in most parts of the world and the language used to address vaccination shortly after the vaccine became publically available can be best described as cautious. The CDC recommended that vaccination could be offered to pregnant women but added that it was "a personal choice". The WHO initially advised that vaccination in pregnant women be offered when the benefits outweigh the potential risks, such as in pregnant women at high risk of exposure to COVID-19 (e.g., healthcare workers) and those with underlying medical conditions that place them in a high-risk group for severe COVID-19.[36] A similar approach was followed in countries like the United Kingdom. The WHO had to reword its guidance later and eventually endorsed vaccination in November 2021.[37] FIGO, ACOG, and the Society for Maternal-Fetal Medicine were from the beginning more supportive of offering the vaccine to all pregnant women and in its statement published on March 2, 2021, FIGO considered "that there are no risks—actual or theoretical—that would outweigh the potential benefits of vaccination for pregnant women. We support offering COVID-19 vaccination to pregnant and breastfeeding women".[38] The publication of more safety data[39] and increasing evidence of considerable harms of COVID-19 to pregnant people led to a major shift in recommendations of many professional organizations, and they now explicitly "recommend" vaccination of pregnant women and some even advocate to prioritize them over age-matched women.[40] Substantial policy changes were undertaken during the pandemic in several countries worldwide to adopt more liberal policies for vaccination of pregnant women. Despite all that, vaccine hesitancy among both providers and pregnant women remains high.[40,41] Several initiatives were undertaken worldwide to enhance COVID-19 vaccination globally in the general population. The WHO initiative that was undertaken in 2021 to achieve a target for 70% global vaccination coverage by mid-2022 did not meet its goals in several regions.[42] As of June 2022, only 58 of the 194 WHO Member States had achieved the 70% target,

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TABLE 2 Vaccines reserved to high-risk pregnant women.

Type of vaccine	Obstetric complications	Number of doses	Indication	Adverse effects
Hepatitis A	Preterm labor, placental abruption	Two doses: at 0 and 6 months[46]	Users of injection drugs, those with comorbidities like clotting factors disorders and chronic liver disease and travelers to endemic areas[47]	Possible small for gestational age[48]
Hepatitis B	Vertical transmission	Three doses: at 0, 1, and 6 months[49]	Women with more than one sexual partner in the past 6 months, those with a history of HbsAg-positive sexual partner, and intravenous drug users[4]	Does not seem to be teratogenic No adverse pregnancy outcomes[50]
Meningococcal		Single injection[51]	Women with asplenia, complement deficiencies and those living with close contacts such as in dormitories[52]	
Pneumococcal		Two doses[53]	Pregnant women with risk factors such as chronic lung disease including asthma, chronic liver disease, immunodeficiencies, sickle cell disease, asplenia, pre-gestational diabetes mellitus, cigarette smoking, and alcoholism[4]	

reflecting serious global injustice. In low-income countries, only 37% of healthcare workers had received a complete course of primary vaccination. Most recently, the CDC recommended urgent action to increase vaccination uptake among pregnant women, for whom the benefits of vaccination outweigh any theoretical risks. All pregnant women need to be adequately counseled about the benefits of COVID-19 vaccination during pregnancy, including the provision of an up-to-date summary of safety data. Currently, four types of COVID-19 vaccines (mRNA, viral vector, inactivated, and protein subunit) are available worldwide. Vaccines using mRNA technology are by far the most used type in pregnant women and have the largest accumulated safety data so far.[43] However, if not available, pregnant women can receive any of the available vaccines since none of them use live viruses, and therefore they are not capable of causing disease.[44]

The primary vaccination schedule is considered complete after receiving two doses taken 3–8 weeks apart.[45] If the second dose is delayed more than 2 months, there is no need to repeat the first dose. Booster shots, that are given to reverse the decline in the humoral response, are recommended at least 5 months after the primary vaccination series. However, there are no pregnancy-specific data on the subject. Given the severe morbidity associated with COVID-19 in pregnancy, offering a booster shot seems to be a reasonable option. Pregnant women without a competent immune system (e.g., organ transplant recipients, acquired immunodeficiency, etc.) require three doses for completion of their primary vaccination schedule to be followed up by booster shots 3 months later. Although initially it was advisable to space the COVID-19 vaccines by 2-week intervals from other vaccines like Tdap or Flu vaccines, nowadays, it is acceptable to give all in the same visit where applicable. As for the timing of vaccination, the current evidence suggests that these vaccines are safe at any point in pregnancy, including the first trimester. Women who elect to delay vaccination until after 12 weeks of gestation should be supported in their decision.

There will always be unanswered questions (at least for the moment) as to the preferential use of a particular COVID-19 vaccine, the best timing to take the vaccine, the need for a fourth booster dose and the long-term safety of COVID-19 vaccination during pregnancy.

2 | OPTIONAL VACCINES

Pregnant people who are at high risk of certain infections due to travel, occupational risk or existing comorbidities should consider additional vaccines (Table 2).

3 | FUTURE DIRECTIONS

Two vaccinations are under development: group B streptococcus (GBS) and respiratory syncytial virus vaccines.

GBS is a leading cause of neonatal morbidity and mortality worldwide, resulting in 3.5 million preterm births, 90 000 infants born with disabilities and 147 000 neonatal deaths annually.[54,55] Although efforts towards the development of a GBS vaccine had started almost 40 years ago, a licensed GBS vaccine might become a reality within a few years.[56] Such a vaccine is expected to prevent 231 000 cases of perinatal infection, 41 000 stillbirths, and 66 000 neonatal deaths annually.[54]

The respiratory syncytial virus (RSV) is a major cause of respiratory illness and mortality in infants and young children and is responsible for ≈27 300 neonatal deaths annually.[52, 57] Even before GBS, attempts at RSV vaccine development date back to the early 1960s and were not successful.[55, 58] Recently, with better understanding of

the structure and function of the RSV surface fusion (F) glycoprotein, a candidate vaccine has been tested in a phase I clinical study with very promising results.

4 | CONCLUSION

Pregnant women and their unborn babies are among the vulnerable populations that can be negatively affected by communicable diseases. For this reason, some vaccines like the influenza, the Tdap and more recently the COVID-19 vaccines are strongly recommended in pregnancy, with good safety profiles.

Other vaccines can be offered based on risk factors, only when the benefits of receiving them outweigh the theoretical risks. Worldwide, national immunization programs have led to significant decrease in vaccine-preventable diseases. However, the numbers seem to be below the target level when it comes to immunization of pregnant women, mostly due to concerns about the safety of vaccines and their potential long-term effects. Health care professionals—obstetricians in specific—have a crucial role in promoting maternal vaccination. Soon, vaccines against two deadly infections—GBS infection and respiratory syncytial virus—are expected to have a major impact on reducing perinatal mortality rate. Vaccine justice should also be a global concern necessitating global efforts.

AUTHOR CONTRIBUTIONS

Anwar H. Nassar was responsible for writing and doing the final editing of the manuscript. Elie Hobeika was responsible for doing the literature review, writing the section about future vaccines and reviewing the final version of the manuscript. Dina Chamsy was responsible for writing the section about the Influenza vaccine and reviewing the final version of the manuscript. Faysal El-Kak was responsible for writing a part of the section of the COVID-19 vaccine and he helped in reviewing the final version of the manuscript. Ihab M. Usta was responsible for revising the whole manuscript.

CONFLICT OF INTEREST STATEMENT

All authors do not have any conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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