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REVIEW ARTICLE

Obstetrics

COVID-19 vaccination in pregnancy: Need for global pharmaco-vigilance

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Abstract

Coronavirus infectious disease has been around for more than 2 years as a pandemic, but now appears to have taken the form of an endemic. COVID-19 vaccination in pregnant women is presently being recommended and followed in most countries. However, robust scientific evidence on safety of the vaccine in the medium or long term, or regarding any adverse effects, is lacking. We searched the PubMed and gray literature for evidence on medium- or long-term effects of COVID-19 vaccination during pregnancy on the mother or her fetus/newborn and found limited data on this subject. Moreover, available evidence comes almost exclusively from the Western world. Any adverse effects of COVID-19 vaccination during or after pregnancy may take time to manifest. Therefore, there is a need to keep the cohort of vaccinated women and their children under scrutiny for any possible adverse effects. This is also needed to build confidence in the long term in the vaccines. A global pharmaco-vigilance or post-marketing surveillance network covering pregnant recipients of COVID-19 vaccines can identify and help to address any medium- or long-term adverse effects of the COVID-19 vaccines on pregnancy and the newborn.

KEYWORDS
adverse events, COVID-19, endemic, global, pandemic, pharmaco-vigilance, post-marketing surveillance, pregnancy, vaccination, vaccine

1 | INTRODUCTION

Wuhan in China was the first place to be affected by the SARS-CoV-2 infection, called COVID-19, in December 2019, quickly spreading to the rest of the world through international travelers. It was declared a pandemic by WHO on March 11, 2020.[1] Its three waves with different variants of the virus hit the world in 2020–2022 and took a huge toll on millions of lives globally.

The first vaccine against COVID-19, an mRNA vaccine by Pfizer/BioNTech, was launched in December 2020. Later, several other types of vaccines were manufactured and launched. Presently there are nine different vaccines against COVID-19 that have obtained WHO's Emergency Use Listing.[2] Two COVID-19 vaccines, Pfizer and Moderna, have received full approval from the United States Food and Drug Administration (US-FDA).[3]

Vaccination against COVID-19 was initially reserved for the most vulnerable population, primarily the elderly, healthcare workers, other front-line workers, and persons with comorbidity. Pregnant and lactating women were specifically excluded from the vaccination drive due to lack of evidence on safety of the vaccine for the pregnant woman, her fetus and her breastfed baby. For ethical reasons, no clinical trials could be conducted to study the effect of

COVID-19 vaccination in pregnancy (VIP). However, some women who were not aware of their pregnancy status and some pregnant healthcare/front-line workers did receive the COVID-19 vaccine, knowingly or inadvertently.

In the meantime, evidence on safety of COVID-19 VIP grew. Moreover, other mRNA vaccines, such as Zika virus vaccines, have been shown to be safe in pregnancy, based on animal studies. Similarly, adenovirus vector-based Zika virus vaccines have also been tested on pregnant mice without any safety concerns. Both the vaccines prevent vertical transmission of the disease.[4]

Developmental and reproductive toxicology (DART) studies on pregnant laboratory animals did not show any adverse results for several COVID-19 vaccines, including Pfizer-BioNtech, Moderna (mRNA vaccines), Johnson & Johnson/Janssen, and Oxford-AstraZeneca vaccines (adenovirus vector vaccines). [5]

There has been growing evidence on additional protection of the unborn and newly born child against COVID-19 when their mothers are vaccinated against the infection. Researchers documented that antibodies generated in response to the vaccine by a pregnant woman were passed on to the fetus and the neonate, providing protection to mother–child duo.[6,7]

Also, the benefits of vaccination far outweighed the risks as the disease, when contracted during pregnancy, often took a serious course. Eventually, prioritization of vaccination of pregnant women against COVID-19 was suggested for countries with the dual burden of high maternal, infant mortality and COVID-19 infection.[8]

Based on all of this, new vaccination guidelines were released, by organizations like WHO, the Centers for Disease Control (CDC) and the Joint Committee on Vaccination and Immunization (JCVI), recommending COVID-19 vaccination of pregnant women.

Several countries revised their vaccination policy, offering the vaccine to pregnant women and giving them the choice to opt in for the vaccine. For regions hard hit by COVID-19 with a pre-existing high maternal mortality rate, it was opined that universal vaccination should be provided to all pregnant women as a matter of default, with the freedom to opt out.[9]

National policies on COVID-19 VIP vary. According to an analysis of vaccination policies of 224 countries/territories, 85% either recommend or permitted VIP to varying degrees. Remaining regions either do not recommend COVID-19 VIP or there is no policy in place. Although national policies have been changing in favor of vaccination against COVID-19 among the last two subsets of nations, policies of as many as 5% of nations do not recommend its use whatsoever.[10]

Despite more and more countries recommending vaccination during pregnancy, acceptance of vaccination continues to be low,[11–13] with less than a third of pregnant women eligible for COVID-19 vaccination agreeing to be vaccinated.[11] In another study, about 52.0% of pregnant women indicated an intention to receive the vaccine as against 73.4% of non-pregnant women.[12]

The main reasons for low rates of acceptance of the COVID-19 vaccine in pregnant women were safety concerns and fear of adverse effects on the fetus.[14–16]

2 | METHODS

We searched the available literature on evidence of medium- and/or long-term adverse effects of COVID-19 vaccines on pregnancy, the fetus, or the newborn. We limited our search to articles in the English language and included manuscripts with both full text and abstracts only. We searched PubMed as well as the gray literature using listed keywords. We also included one study at the pre-print stage.

2.1 | Ethical considerations

Ethical clearance was not required as no patient information with identifiers was collected.

3 | RESULTS

On the basis of existing scientific information, vaccination with COVID-19 seems to cause only mild and transient adverse effects among pregnant women, including pain at the injection site, fatigue, and headache.[17,18] Rates of these adverse reactions to the vaccine are similar in pregnant and non-pregnant women.[19]

Data from an unpublished study on pregnant rats showed no evidence of embryo-toxicity in pregnant rats when exposed to mRNA-1273 COVID-19 vaccine (Moderna).[20] The incidence of birth defects in pregnant women exposed to mRNA vaccines against COVID-19 has been found to be comparable to that expected in the general population.[21]

In the United States, more than 20000 pregnant women have received COVID-19 VIP and their pharmaco-vigilance did not raise any red-flag.[22]

Rates of spontaneous abortions have been found to be no higher in women who have received COVID-19 vaccine.[23]

In a retrospective population-based cohort study, COVID-19 m-RNA VIP was not found to be associated with any increased risk of adverse peripartum outcomes, when compared with those who were vaccinated after pregnancy or did not get vaccinated at all.[24]

4 | DISCUSSION

As vaccines undergo rigorous testing and trials until they meet high safety standards before being approved, serious adverse effects are generally rare.

However, a protective vaccine can have negative, non-specific, and sex-differential effects on overall health. This epidemiological phenomenon of negative, non-specific effects has been linked to innate immune tolerance. Several non-live vaccines are known to enhance the susceptibility of girls to unrelated infections.[25] Epidemiological studies on the effects of certain vaccines, such as measles and malaria, have found that while those vaccines protected

against the target disease, they increased the susceptibility to other diseases. Both these vaccines raised the all-cause mortality in girls. Female recipients of high-titer measles vaccine (HTMV) showed an almost four-fold higher mortality as compared with males, when the vaccine was followed by diphtheria tetanus pertussis (DTP) vaccine; the mortality was higher with each subsequent dose of DTP.[26]

Higher female-to-male mortality ratio has also been observed when HTMV was followed by inactivated polio vaccine (IPV).[27]

The RTS, S/AS01 malaria vaccine was associated with a higher all-cause mortality and fatal malaria in girls but not in boys.[28]

Reprogramming of the innate immune system following administration of certain vaccines is know to occur in the form of either "trained immunity," which involves increased responsiveness, or "innate immune tolerance," which is characterized by decreased cytokine production. A study on a small number of participants showed that the mRNA-based BNT162b2 COVID-19 vaccine from Pfizer/BioNTech induced complex, functional reprogramming of the innate immune response towards bacterial, fungal, and viral ligands. The production of anti-inflammatory cytokines was reduced in response to bacterial lipopolysaccharide and *Candida albicans* after a second dose of the vaccine.[29] Thus, immune response to certain pathogens can be altered in vaccinated individuals.

Other pandemic vaccines have been found to be associated with rare but serious adverse effects. Examples are narcolepsy after the AS03 adjuvanted pandemic strain swine flu influenza vaccine[30] and Guillain–Barré syndrome after the A/New Jersey swine flu influenza vaccine.[31]

Similar to the examples of vaccine–vaccine interactions and altered immunity described, COVID-19 vaccination of pregnant women could interact with childhood vaccines administered at birth and during the initial months of life. This could be gender-specific, as was the case with measles and malaria vaccines. Also, pregnant women receive Tdap vaccine routinely as part of antenatal care, and sometimes flu vaccine. Interaction between these and COVID-19 vaccines needs to be explored and is a potential area for research.

In order to capture any serious adverse effects, particularly those that may be rare or delayed, it is important to replicate the practice in the USA and institute global pharmaco-vigilance over a reasonable period of time, preferably by pooling multinational data.[32]

This is especially relevant in the context of COVID -19 VIP, as these vaccines could not be subjected to pre-testing and trials with the usual rigor, in view of the emergency nature of the pandemic and the vulnerability of pregnant women. If continued passive as well as active surveillance is done by all countries and the information is compiled, the global scientific community would be more confident in declaring COVID-19 vaccine as safe in pregnancy.

For this to happen, creating a regulatory portal for reporting of any adverse outcome following vaccination among pregnant women needs to be done. This would be similar to the Adverse Drug Reporting (ADR) system by WHO in relation to drugs for the treatment of COVID-19.[33]

The yellow card scheme, which is a passive pharmaco-vigilance system in the UK, has added a COVID-19 interface to capture any adverse effects of VIP. Also, data on women vaccinated during pregnancy in the UK are proposed to be linked with babies registered in The National Congenital Anomaly and Rare Disease Registration Service (NCARDRS), to retrospectively analyze any association between VIP and fetal congenital anomalies.[34]

Another example is the V-safe COVID-19 Vaccine Pregnancy Registry, maintained by CDC, of women who have received the vaccine during pregnancy or shortly before conception.[35]

Similar pharmaco-vigilance systems need to be initiated in all countries for a more definitive understanding of long-term safety of the vaccines. WHO should maintain a database of results of such pharmaco-vigilance and declare a policy to share with the public any adverse event as well as the results of its investigation.

A list of adverse events of special interest (AESI) following COVID-19 vaccine exposure among pregnant women has been suggested,[36] as follows:

- Maternal death
- Maternal hospitalization
- Maternal thrombotic events
- Hypertensive disorders of pregnancy
- Miscarriage/spontaneous abortion
- Stillbirth
- Preterm birth
- Neonatal death
- Microcephaly
- Major congenital anomalies
- Infant death.

The COVID-19 virus has undergone several mutations ever since it first hit humans in December 2019. The disease came in the form of three waves and swept the world to variable extents. Presently the number of cases has settled, maintaining a more or lest steady level, without further spikes. Possible explanations for this stable state are vaccination, emergence of herd immunity, and lowered virulence of the pathogen. It can be stated that COVID-19 infection is tending to become endemic in the world.[37] With transition from pandemicity to endemicity, there is a need to revisit and revise vaccination policy, especially for pregnant women, taking into consideration the reduced virulence and incidence of COVID-19 infection, safety, and any evidence of long-term adverse effects on the health of the mother or her baby. To facilitate an evidence-based shift in policy, there is a need for global pharmaco-vigilance and longitudinal follow-up of all COVID-19-vaccinated women for any maternal or fetal adverse outcomes.[38]

Transition from epidemic to endemic and vice versa depends on the number of susceptible people in a geographical area. As pregnant and lactating women constitute a large chunk of the population, more so in low-income countries with narrowly-spaced, repeated childbirths, we strongly recommend the following:

- Countries not vaccinating pregnant and lactating women against COVID-19 should start doing so.

- Countries vaccinating but not conducting pharmaco-vigilance on COVID-19-vaccinated women should institute pharmaco-vigilance initiatives.
- Countries carrying out pharmaco-vigilance (such as USA, UK) should continue to do so and share their findings with the scientific community around the world to build robust evidence on safety and capture any medium- and long-term adverse effects of the vaccine administered to these two vulnerable groups of population.

5 | CONCLUSIONS

- There is a call for global policy in favor of vaccination of pregnant women against COVID-19. Regions that restrict or forbid vaccination during pregnancy should promptly reverse this policy.
- There is a need for global pharmaco-vigilance to capture any immediate or late adverse effects of vaccination on pregnancy and the exposed fetus.
- Any possible interaction between a COVID-19 vaccine administered to a pregnant woman and vaccines administered to the newborn subsequently should be an area of research.
- As the pandemic moves towards becoming an endemic, any complacency should be avoided, and the vaccination drive should be continued with the same rigor, including that of pregnant women.

AUTHOR CONTRIBUTIONS

Yamini Sarwal conceived the research idea, and Yamini Sarwal and Rakesh Sarwal together framed the research question. Yamini Sarwal did the literature search and wrote the paper. Rakesh Sarwal edited the paper.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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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