

Uptake of the COVID-19 vaccine in pregnancy

Miliana Cretu², Nicolae Gica^{1,2}, Radu Botezatu^{1,2}, Gheorghe Peltecu^{1,2},
Anca Maria Panaitescu^{1,2}

¹ "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

² Filantropia Clinical Hospital, Bucharest, Romania

ABSTRACT

Coronavirus disease 2019 (COVID-19) has rapidly become a global pandemic with a devastating morbidity and mortality. Pregnant women seem to be at increased susceptibility to have a severe disease and suffer adverse pregnancy outcomes. The only solution to mitigate this pandemic is prophylaxis by mass vaccination. We report a review based on current literature about the evidence available on efficacy and safety of anti-COVID-19 vaccines in pregnancy to aid women decide whether to vaccinate or not, while being pregnant or lactating. Studies so far did not find concerning maternal or fetal outcomes and show a similar efficiency of mRNA vaccines as in non-pregnant population. Moreover, anti-SARS-CoV-2 antibodies resulted from the vaccination seem to be transferred to the newborn through the placenta or the breastmilk building up the neonatal immunity. However, the exclusion from clinical trials created a great deficiency of evidence regarding the vaccination in this high-risk population resulting in their reluctance.

Keywords: COVID-19, vaccine, pregnancy, safety, efficacy, outcomes, acceptance, studies, guidelines

INTRODUCTION

Since the beginning of the pandemic SARS-CoV-2 millions of women have become pregnant and given birth all over the world during this global health crisis. Anatomical changes along with pro-inflammatory state of gestation and the increased risk of thromboembolic disease explain the higher susceptibility of more severe presentations of coronavirus infections during pregnancy. Pregnant patients with covid infection seem to be 3 times more likely to be admitted to the intensive care unit and to require invasive ventilation and the mortality rate is 1,7 higher comparing to non-pregnant women [1]. Also, adverse pregnancy effects such as preterm birth, premature fetal membrane rupture and low birth weight, as well as cesarean section were higher in COVID positive patients. Therefore, the immunization against coronavirus is necessary in this vulnerable population [2].

Multiple vaccines have been created at an unprecedented speed. Mass vaccination worldwide

has started since December 2020 in an attempt to stop the spread of COVID-19. The most common used, the Pfizer BioNTech BNT162b2 and Moderna mRNA-273, are RNA-messenger containing vaccines encoding for spike membrane proteins, encapsulated in lipid nanoparticles. RNA does not integrate into the genome and therefore it is considered safe (3). The great efficacy reported by randomized clinical trials of mRNA vaccines raised hope of their success. However, these studies excluded participants that declared being pregnant leading to hesitancy of vaccine uptake during pregnancy. To date, only observational studies among pregnant women have been published showing the benefits of available vaccines against COVID-19 infection [3,4].

METHODS

We reviewed the available literature regarding COVID-19 vaccination in pregnant women. For this purpose, we searched PubMed and ClinicalTrials.

Corresponding author:
Nicolae Gica
E-mail: gica.nicolae@umfcd.ro

Article History:
Received: 25 February 2022
Accepted: 7 March 2022

gov databases using keywords such as: “covid-19”, “vaccine” and “pregnancy” along with “safety”, “efficacy”, “outcomes”, “acceptance”, “studies” or “guidelines”. Full-length articles were reviewed with priority for those based on large population studies.

VACCINE RELUCTANCE

Vaccine acceptance is an important factor in obtaining herd immunity and thus eradicating COVID-19 infection. Pregnant women are prone to refuse vaccination given the concerns about safety and the lack of clinical trials during pregnancy. The acceptance of COVID-19 vaccine is low and varies among pregnant women in different countries, from 37% to 77,4%. A global survey among 16 countries found that overall, only 52% of the participants would accept the vaccine while being pregnant. A wide range of factors influence this decision: skepticism about the disease, vaccine safety concerns, fear of harmful side effects on the baby and lack of trust in government and guidelines [5–8].

Moreover, guidance has not always been consistent as initially some guidelines did not recommend routine vaccination in pregnancy. For example, in the United Kingdom, at first Joint Committee on Vaccination and Immunization recommendations only included pregnant women with comorbidities and those exposed to coronavirus. Anyway, recommendations shifted as safety data accumulated [9,10].

IMMUNIZATION ADVOCATES

Because pregnant and lactating women were not included in the initial trials, the decision of COVID-19 vaccine uptake in pregnancy is based on a combination of historical experience with other vaccines used in pregnant women, unexpected pregnancies during clinical trials, animal studies and data gathered by various safety surveillance registries.

Over the decades, vaccines such as tetanus, diphtheria and pertussis, and influenza proved their utility and safety and are routinely administered even during pregnancy. Similar to SARS-CoV-2, influenza pandemics used to have an increased rate of morbidity and mortality among pregnant women which included them in the high-risk group targeted for the flu vaccination each season which proved being efficient and safe [11,12]. Moreover, vaccines for tetanus and pertussis are used to offer protection of the newborn by passing immunity from the mother [13].

Even though pregnant women were excluded from clinical trials, 57 participants accidentally became pregnant during Pfizer, Moderna and Astra-

Zeneca trials. There was no significant difference in the rate of miscarriages in the vaccinated groups comparing to the control groups. Also, the rate of accidental pregnancies is comparable between the groups indicating that the vaccines do not affect fertility [14,15]. Moreover Pfizer and Moderna conducted developmental and reproductive toxicity (DART) studies on female rats showing no vaccine-related effect on fertility, pregnancy, or embryo development [16].

SAFETY OF COVID-19 VACCINES IN PREGNANCY

Center of Disease Control created an application available on smartphones where pregnant women can registry voluntary and report effects after vaccination. In April 2021, Shimabukuro et al. provided early preliminary data on the safety of Pfizer and Moderna vaccines in pregnancy based on women who were vaccinated from December 2020 to February 2021, enrolled in this online v-safe pregnancy registry [17]. Mostly, these women got vaccinated because they were included in the highest priority group on account of their profession in health care services. The majority received the first dose in the second (43,3%) or third trimester (25,7%). Among the 712 pregnancies that resulted in a live birth, the adverse outcomes rates such as premature birth (9,4%) and small for gestational age (3,2%) appear to be similar to incidences published before the COVID-19 pandemic. Regarding the congenital anomalies, there were 16 cases reported with no pattern observed and none of them had been vaccinated in the first trimester or during the periconception period [17]. Similar, the United Kingdom, the University of Washington and Harvard School of Public Health have created or are developing registries to evaluate the effects of COVID-19 vaccines among pregnant or lactating women [15].

A study that assessed the outcomes of COVID-19 vaccination in pregnancy found no significant difference. In order to assess the safety of vaccination during pregnancy, this study collected data from 1328 women who gave birth at St. George's University Hospital in London from March 2020 until July 2021, 28,5% of them being vaccinated. The adverse pregnancy outcomes such as fetal abnormalities, small for gestational age, stillbirth, cesarian delivery, postpartum hemorrhage, maternal or neonatal intensive care unit admission, had similar rates in vaccinated women comparing with the other matched cohort of pregnant women who have not been vaccinated [9].

Another early descriptive study of 424 pregnant women from an institution in New York who were vaccinated beginning from the time of FDA Emergency Use Authorization showed no concerning

trends. Following the vaccination, the rate of spontaneous abortions (6,5%) was below the average (10%), there were no stillbirths and, out of 85 women who delivered during the study, only 5 were premature. Looking at fetal outcomes, 0,6% developed intrauterine growth restriction and in 1,5% cases were discovered anomalies. The neonatal intensive care unit admission rate was 15,3% being near the institutional rate (12%) [18].

COVID-19 VACCINES EFFECTIVENESS IN PREGNANCY

The confidence in COVID-19 vaccine effectiveness is an important predictor of vaccine acceptance among pregnant women, therefore studies demonstrating this are necessary.

While pregnancy was initially an exclusion criterion from COVID-19 vaccination, Israel started in December 2020 an unprecedented campaign to immunize even the pregnant women and conducted a study reporting the maternal and neonatal humoral immune response. Data showed that Pfizer BioNTech mRNA vaccine determine a rapid rise in IgG titers in maternal blood samples which are being transferred through the placenta to the fetus. These antibodies, reaching the neonatal bloodstream within 2 weeks after the first dose, provide protection against SARS-CoV-2 to the newborn. Also, maternal and cord blood anti-COVID antibodies were elevated in women who had a PCR confirmed SARS-CoV-2 infection in the second trimester of the pregnancy. Comparing to these two groups, the antibody transfer ratio is lower for infections in the last trimester (>30 gestational week) [19,20]. The largest birth center in Israel also studied the immediate pregnancy adverse outcomes and newborn complications showing no difference in women who received one or two doses of Pfizer COVID-19 vaccine during pregnancy comparing to those who were not vaccinated [21].

Moreover, studies show that IgG and IgA antibodies are being transferred to the maternal breast-milk possibly adding up to the immunity of breast-fed newborns, but the potential benefits for them are still to be determined. A recent prospective study found antibodies in all breast milk (31 cases) and umbilical cord blood (10 cases) samples collected after delivery from vaccinated women. Comparing to participants who had SARS-CoV-2 infection during pregnancy, the vaccinated women had significantly higher antibody titers [22,23].

A large observational cohort study compared vaccinated pregnant women to matched unvaccinated controls and showed that the Pfizer vaccine's effectiveness for documented infections is 96% after the second dose. Therefore, BNT162b2 COVID-19 mRNA vaccine is equally effective in pregnancy as in general population [24].

VACCINE TIMING

Choosing the moment of COVID-19 vaccine first dose uptake is also difficult for pregnant women. Most of them are waiting until the second or even the third trimester because of the concerns regarding the safety of vaccination during first trimester although there is no evidence of an increased risk of miscarriage [6,25]. On the other hand, women with underlying conditions should consider vaccinating as soon as possible in order to avoid serious complications of coronavirus infection during pregnancy.

Even after giving birth women might be reluctant to vaccinate being afraid that they should interrupt breastfeeding the newborn. In contrary, guidelines recommend maintaining breastfeeding after inoculation as protective passive immunoglobulins might also help in preventing infectious morbidity for the neonate. Moreover, mRNA from anti-COVID vaccines is not detected in human breast milk so there is no reason to suspect that the vaccine would put the newborn at risk [26].

ADVERSE EFFECTS

Pregnant women do not have more serious adverse reactions than general population. The most frequent complaint was pain at injection site. Other mild side effects such as headaches, myalgia and chills were encountered even in less cases. A common systemic adverse effect of the anti-COVID vaccines is fever which was thought to be teratogenic during the first trimester of the pregnancy, but this was disproven [17,27].

DISCUSSIONS

At present, the evidence-based recommendations regarding COVID-19 and vaccination for pregnant women are limited. The ethics of drugs and vaccines testing during pregnancy have been a long subject of debating for decades. Exclusion of reproductive aged women from clinical trials was implemented in 1974 to protect them from undesired adverse effects on the pregnancy. Nevertheless, gestational changes put women and their fetuses at risk for more serious morbidities from infectious diseases, including the coronavirus. Also, the lack of data on most drugs in pregnancy restricts their access to effective treatment in case of severe infection. Taking this into consideration, pregnant women should be given the opportunity to enroll in vaccine studies if the benefits are assumed to outweigh the risks and be considered candidates for anti-COVID vaccination as a preventative measure. Therefore, it is an important need to demonstrate the safety, immunogenicity, reactogenicity and efficacy of available vaccine products during pregnancy in clinical trials [28,29].

Starting from February 18, 2021, Pfizer and BioNTech started a 2/3 phase trial in 4000 pregnant women getting vaccinated assessing the safety and protection offered by two doses of BNT 162b2 in these women and their babies [30].

CONCLUSION

With the ongoing pandemic, anti-COVID vaccination is a critical prevention strategy. Because of deficient evidence about available vaccines use during

Conflict of interest: none declared

Financial support: none declared

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