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Safety and efficiency of COVID-19 vaccination during pregnancy and breastfeeding

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ABSTRACT

Despite the development of effective and safe vaccines, the contributions of pregnant women in clinical trials of vaccines have been excluded. Similarly, vaccine trials did not include breastfeeding women. This article is an overview of studies on immunization during pregnancy and breast-feeding. The manuscript is intended to collect the current data on the effectiveness and safety of COVID-19 vaccines in order to facilitate medical decision.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) spread throughout the world and on March 11th, 2020, The World Health Organization (WHO) declared it a pandemic [1]. Efforts of scientists from around the world have focused on the search for an effective drug or the creation of a vaccine that protects against the development of COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Research on the structure and replication cycle of the virus allowed for the development of effective and safe vaccines [2]. It is known, however, that the participation of pregnant women in clinical trials of therapeutics and vaccines have been eliminated [3]. Hence, when the first COVID-19 vaccines were approved for use, the eligibility of pregnant women for vaccination was not considered. In Poland, decisions were made based on the American College of Obstetricians and Gynecologists (ACOG) recommendations that women should be able to make their own decision about COVID-19 vaccination [4]. The same applies to women who are breastfeeding as the vaccine trial did not include this population [5]. Although, in this case different scientific societies have been more inclined to recommend vaccination of these women [6].

This article is an overview of several studies on immunization during pregnancy and breast-feeding. The manuscript is intended to collect the current data on the effectiveness and safety of COVID-19 vaccines in order to facilitate medical decision.

Humoral and mucosal immunity

There are two ways that infant immune systems can be supported by the mothers' antibodies - the transplacental IgG transfer of antibodies and secretory antibodies included in milk. It is known that IgG antibodies produced after vaccination during pregnancy cross the placenta and provide children passive innate immunity until the third month after birth [7]. A transport of maternal IgG to the fetus results in about 90% of the maternal serum level of IgG antibodies in the full-term newborn in the moment of delivery [8]. These antibodies play a duel role on mucosal membranes and in the circulation. In turn, breast milk antibodies do not enter neonatal circulation. Secretory IgA (SIgA) represents the major immunoglobulin in breast milk, followed by secretory IgM and IgG. Maternal milk antibodies coat infant mucosal surfaces and have a protective role, especially against enteric infections. Differing from many species of animal, IgG from breast milk in humans are not transported across the intestinal epithelium into the neonatal circulation [9].

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VACCINATION OF PREGNANT WOMEN

COVID-19 vaccine research in pregnancy

In Poland, at the beginning of COVID-19 vaccination, the vaccines were offered to healthcare professionals first [10]. Thus, in a study by Zdanowski et al. [11] sixteen women being medical doctors, who were vaccinated with two doses of BNT162b2 mRNA COVID-19 vaccine, were included. The first dose of vaccine was taken between the 29th and 36th week of pregnancy and the second dose between the 32nd and 40th week of pregnancy. Study showed high level of anti-S IgG antibody in cord serum at birth in all included patients (mothers and infants). During publication of results, the study was still in progress and then included 150 female patients who had been vaccinated against SARS-CoV-2 during pregnancy [11].

A study on a larger group of pregnant women was conducted by Gray et al. [12]. Eighty-four pregnant women, 16 nonpregnant and 31 lactating women were qualified into a prospective cohort study. Laboratory parameters were quantified basically, at the second vaccine dose, at two to six weeks after the second dose, and during delivery. Also, concentrations of immunoglobulin were juxtaposed with immunoglobulin level in pregnant women 1–3 months from natural SARS-CoV-2 infection. The study revealed that vaccine-induced antibody concentrations were comparable in all groups of women. What is more, all immunoglobulin levels after vaccination were significantly higher than levels after COVID-19 during pregnancy [12].

Prabhu et al. [13] enrolled 122 pregnant women into study, whom by the time of delivery, 55 were vaccinated one dose, and 67 were vaccinated two doses. At birth level of immunoglobulin was established — 87 women produced an IgG response, 19 — IgM and IgG response, and 16 women had no determinable antibody response (the latter received only one dose of vaccination, up to four weeks before delivery).

Optimizing neonatal immunity

Based on the above information, immunization against COVID-19 resulted in the presence of antibodies anti-SARS-CoV-2 in the blood of mothers and newborns. However, it has not been established what the concentration of antibodies in the newborn has a protective effect, and in which period during pregnancy is the best term to vaccinate pregnant women as newborns gain the best possible post-vaccination protection.

In a study performed by Gray et al. [12], the titers of antibodies in the serum of the mothers, induced by the vaccine, did not differ depending on the trimester in which the vaccination was performed. When it comes to placental transport of immunoglobulin, specific IgG were detectable in all examined newborns. The cord with the lowest IgG level belonged to a mother who was vaccinated first dose 17 days before delivery. This result may suggest that two doses of the vaccine can be necessary to gain optimal humoral immune transfer to the newborn. Interestingly, in this study, a significant improvement of transferred specific IgG subclasses into the cord with time from boost was found. It suggests time from vaccine might be a key factor determining the rate of transfer of IgG subclasses after maternal vaccination [12]. It is known the amount of maternal IgG transferred across the placenta to the cord depends on the time of vaccination [14].

Zdanowski et al. [11] described the correlation between the week of pregnancy and the concentration of antibodies in the serum of cord blood. There was a significant positive correlation between the number of weeks from the first dose of the vaccine and the level of anti-S antibodies in the cord blood serum. In addition, there was also a significant positive correlation between the gestational week of the first dose and the gestational week of the second dose and the respective cord-to-maternal ratio. It is also interesting that the patient who received the second dose just seven days before delivery, had high levels of anti-S antibodies in the cord blood [11].

According with study of Prabhu et al. [13] as the number of weeks from vaccination elapsed, the number of women who had an antibody response and who conferred passive immunity to their neonates increased. The earliest detection of antibodies in mother blood was noted five days after the first dose of vaccine as well as the earliest detection of antibodies in cord blood was noted 16 days after this first dose. Women vaccinated with only one dose had detectable IgG in 44% of cord blood sample, whereas women vaccinated both doses had detectable IgG in 99%. Maternal IgG levels were increasing starting two weeks after the first vaccine dose and were linearly associated with cord blood IgG levels. What is more, the placental transfer ratio corresponded with the number of weeks since the day of maternal second vaccination [13].

Vaccination at the end of the second or during the third trimester may be most effective, as is the case with Tdap vaccines [15]. However, it remains further confirmation as vaccines like Tdap aim to boost preexisting antibodies, while COVID-19 vaccination is administered *de novo*.

Postvaccination reactions/side effects in mothers and offspring

Based on information tracked by the Centers for Disease Control and Prevention (CDC), no significant differences in side effects in pregnant vs nonpregnant women at the age of 16 to 54 years was found. Verification revealed that after the second dose incidence of fever occurred up to 32% [16]. Hence, it may raise concerns for pregnant women and their offspring as literature supported a 1.5- and nearly 3-fold in-

creased risk of neural tube defects, congenital heart defects, and oral clefts with fever exposure in the first trimester [17].

Shimabukuro et al. [18] based on data available from CDC and Food and Drug Administration (FDA) reported the following local and systemic reactions as the most frequent: injection-site pain, fatigue, headache, and myalgia after each dose of vaccines in pregnant women. However, side effects were observed more frequently after dose number two for both vaccines. Only less than one percent of women during first day after the first dose and eight percent after the second revealed temperature at or above 38°C. According to V-safe Pregnancy Registry among 827 women who had a completed pregnancy, the pregnancy ended in a live birth in 712 (86.1%), in a spontaneous abortion in 104 (12.6%), in stillbirth in 1 (0.1%), and in other results (ectopic pregnancy/induced abortion) in 10 (1.2%). 92.3% of spontaneous abortions occurred before 13 weeks of gestation, and 98.3% of live birth were among women vaccinated first dose in the third trimester. Preterm birth occurred in 9.4%, small size for gestational age (SGA) was noted in 3.2% and major congenital anomalies in 2.2%, among the latter no woman was vaccinated in the 1st trimester or periconceptional period. The calculated proportions of mentioned incidents turned out to be like these available from the literature.

In turn, after analysis data from Vaccine Adverse Event Reporting System (VAERS) authors stated 221 reports involving COVID-19 vaccination among pregnant persons; 70.1% involved nonpregnancy-specific adverse events, and 29.9% involved events such as spontaneous abortion (46 cases), stillbirth, premature rupture of membranes, and vaginal bleeding, with 3 reports for each [18].

Zdanowski et al. [11] state no mothers had severe pregnancy or neonatal complications.

Further monitoring is necessary to assess maternal and neonatal safety associated with maternal COVID-19 vaccination.

VACCINATION OF BREASTFEEDING WOMEN

Antibodies in breast milk

Gray et al. [12] showed that in the milk of 31 vaccinated women an increase in the titer of IgA, IgG and IgM antibodies was observed, the highest in the case of IgA and IgG. Milk samples were taken after the first and second doses of the vaccine, and between two and six weeks after the mother received the second dose. The greatest increase in the titer of IgA and IgM antibodies was noted after the first dose of the vaccine. In turn, an increase in IgG antibodies was found after the second dose with a parallel increase in their concentration in the mother's serum [12]. A prospective cohort study of breastfeeding women (either exclusive or partial) who chose to be vaccinated was performed in Israel by Perl et al. [19]. Breast milk samples were collected before vaccination and then once weekly after two weeks, two from the first dose till six weeks after this dose. 84 women completed the study, delivering 504 breast milk samples. IgA antibodies were present in 62% of the samples two weeks after the first dose, and one week after the second dose in the majority (86%) of the tested samples. The highest concentration of IgG antibodies was recorded at week five and six (97% of samples). No serious adverse event was reported in mother or infant during the study [19]. Kelly et al. [20] also conducted a study on the presence of specific antibodies in breast milk. Although the study was conducted on a group of only five women, it was confirmed anti spike IgG and IgA levels were significantly elevated relative to the pre-vaccine baseline at all time points [20]. Another longitudinal cohort study included 61 lactating women. In all samples of maternal serum and breastmilk specific IgG were found with a significant positive correlation between the SARS-CoV-2 IgG levels in the serum and breastmilk samples. The same antibody was detected in the oral mucosa of 3 of 5 (60%) breastfed infants, while neither of the dried blood spot samples from 21 infants were positive for these antibodies [21].

In mentioned above study performed by Gray et al. [12] authors examined also the levels of antibodies in breastmilk of lactating mothers finding high induction of IgG, IgA, and IgM after the first and second dose. While levels of IgA and IgM did not rise with boosting, a boost in breastmilk IgG levels was observed (corelating with the boost observed in maternal serum) [12].

Side effects in breastfeeding woman and infants

Regarding side effects of vaccination, Bertrand et al. [22] found that > 85% of 180 participating women reported any symptoms for both the Pfizer-BioNTech and Moderna vaccines following either dose. After the second dose, women who received the Moderna vaccine reported more frequently systemic side effects (chills, muscle or body aches, vomiting, fever) as well as localized symptoms (pain, redness, swelling, or itching at the injection site). Despite the low percentage of reported milk production disturbances, in all cases milk production have reached previous level within 72 hours. Among 180 breast-fed infants whose mother received the SARS-CoV-2 mRNA vaccine, no serious side effects were observed. Single women reported that their children were irritable, had difficulty falling asleep, or conversely, they experienced drowsiness [22].

Summarizing the above reports, it seems that response after COVID-19 vaccination is like previous studies performed in lactating women that have shown high levels of breast milk IgA and IgG production for up to six months after vaccination for influenza and pertussis [23, 24]. According to the fact that SARS-CoV-2 IgG was not detected in the infants

serum, it seems that vaccination during pregnancy may provide better protection to the infants because of transplacental passage of antibodies. As CDC reported that vaccine effectiveness ranges from 91% against the alpha variant to 66% against the delta variant in frontline workers [25], it remains unclear whether vaccines will be effective against the new virus variant. That is because the omicron variant has more than 30 mutations in the spike protein, the part that has been the primary target for current vaccines [26].

CONCLUSION

Pregnant women are particularly vulnerable to infectious diseases because of alterations in their respiratory and cardiovascular system as well as immune changes that occur during pregnancy.

What is more, pregnant women are more likely to require mechanical ventilation than non-pregnant women [27] and SARS-CoV-2 infection during pregnancy generates higher risk for preterm birth [28]. These facts and the potential contamination of newborn suggest pregnant women should be able to vaccinate against COVID-19. It is worth paying attention to the fact that none of currently produced vaccines contain a live, weakened (attenuated) virus. Many expert committees emphasize that these preparations are safe for breastfeeding women as well as state possibility of vaccination should be offered to all pregnant women, after being adequately informed of the benefits and risks [6]. They should have the same right to decide about vaccination as other adults. Vaccines still are the best defense against many infectious diseases, including COVID-19.

Conflict of interest

Author declare no conflict of interest.

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