

Immunization in pregnancy to protect pregnant people and their newborns against COVID-19

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1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is an RNA virus responsible for the recent coronavirus disease 2019 (COVID-19) pandemic [1]. Pregnant people are at higher risk of severe disease compared with non-pregnant individuals in reproductive years – with higher rates of moderate-to-severe illness, hospitalization, intensive care admission, invasive mechanical ventilation, and death, due to physiological changes in their cardiopulmonary and immunological system functions [2]. Even though not fully explained by the increased severity of the disease [3], infected individuals are also at increased risk of adverse pregnancy complications, such as hypertension, pre-eclampsia, impaired fetal growth, and preterm birth [2]. After infection, anti-SARS-CoV-2 IgG antibodies can be transferred transplacentally [4] and may be present for up to 6 months after birth in the infant [5].

Neonates and infants are susceptible to COVID-19 infection, although they usually represent a minority of pediatric cases and generally develop milder disease than older children or adults [6].

After infection, maternal and infant anti-spike protein antibody concentrations are positively correlated, and increased transplacental antibody transfer occurs with a longer interval between maternal infection and delivery [4].

Immunization in pregnancy can offer advantages for both pregnant and infant populations. Immunization against influenza, for example, decreases maternal morbidity and mortality as well as neonatal morbidity via passive immunity [7]. In the case of COVID-19, vaccination is the most effective long-term strategy to control the pandemic and pregnant people should be a high priority for vaccination.

Several types of COVID-19 vaccines have been authorized in various countries globally,

including mRNA vaccines, adenoviral-vectored vaccines, whole-cell inactivated vaccines, and subunit protein vaccines, with most requiring 2–3 doses required to complete a primary series [8]. Most information to date for use in pregnancy is from the two mRNA vaccines BNT162b2 and mRNA-1273. mRNA vaccines have very high single-dose efficacy and two-dose effectiveness against hospitalization and infection that may persist up to 7 months' post-vaccination, with higher effectiveness with an increased interval between doses from 3–4 weeks to 7–8 weeks

[9]. mRNA vaccines rapidly induce spike protein-specific IgG responses (binding and neutralizing antibody [nAb]) higher than observed after natural infection, as well as antigen-specific T cell responses, which persist for at least 6 months after immunization [10]. While no correlate of protection has yet been established for COVID-19 vaccines, antibody is thought to be an important determinant.

2. COVID-19 vaccine safety in pregnancy

Pregnant people were excluded from initial clinical trials of COVID-19 vaccines, although data from 57 incidental pregnancies in 3 vaccine trials did not suggest an increased rate of miscarriage compared to non-vaccinated groups for the two mRNA vaccines or the viral vectored vaccine ChAdOx1-S [11]. In terms of severe adverse events, a study including over 12,000 pregnant people reported a similar safety profile compared with non-pregnant people [12]. This study also found that COVID-19 vaccination was not associated with higher incidence of congenital malformation, stillbirth, preterm birth, or small for gestational age infants compared with historical rates [12]. A recent review of over 40,000 pregnant people also reported no significant difference between vaccinated and unvaccinated individuals in terms of mode of

delivery, gestational age, Apgar scores, and the incidence of adverse maternal and neonatal outcomes including eclampsia/preeclampsia, gestational hypertension, thromboembolism, birth trauma, uterine rupture, stillbirth, hypoxic-ischemic encephalopathy, low birth weight, and neonatal intensive care admission [13].

3. COVID-19 vaccine immunogenicity in pregnancy

A recent study showed that a single dose of any mRNA vaccine can elicit an antibody response (IgG and IgM) in more than two-thirds of pregnant people (71%) [14]. In another study, the median IgG-binding antibody and nAb levels in pregnant people were several times higher than in infected and non-pregnant individuals [7]. Similar differences were observed for the T cell response in terms of spike protein-specific IFN γ production [7]. These high antibody levels

may support protective antibody levels in newborns and infants for the first few months of life.

4. Timing of vaccination in pregnancy – Impact on safety, immune response, and transplacental antibody transfer

Overall, current data suggest that COVID-19 vaccines are safe and immunogenic during pregnancy, but the optimal timing of vaccination has been a point of recent debate. Most current recommendations support COVID-19 vaccination at any stage of pregnancy [15]. In some countries, vaccination is offered between 14 and 36 weeks' gestation, while others recommend immunization as early as possible [16]. Some have suggested that second-trimester immunization may be the best choice [17]. The suggested timing of COVID-19 vaccination varies from early in pregnancy to maximize protection for the pregnant individual to later in pregnancy to also optimize benefit for the infant. Immunization in early pregnancy may raise the concern about antibody waning by the time of delivery, although emerging data on the durability of antibody

for at least 6 months after vaccination is reassuring in this regard [10]. Delineating the best timing of immunization requires sufficient data about the influence of timing on vaccine safety as well as the relevant immune responses, which is challenging in the absence of a correlate of protection.

Safety data relating to the timing of vaccination in pregnancy are limited. A large study using data from people vaccinated with mRNA vaccines in their third trimester did not find any significant adverse outcome for mother or newborn [12]. A systematic review also did not find any safety signals after vaccination with mRNA vaccines but did not differentiate post-vaccination adverse outcomes by different gestational ages [13].

From an immunological perspective, pregnancy is a dynamic state and is characterized by Th1

suppression and a shift to the predominance of Th2 responses [18]. Moreover, there is a selective process for the type and rate of antibody transfer via the placenta. IgM and IgA are too large to cross the placenta (except in the presence of placental damage). Maternal IgG is detectable at low levels in cord blood as early as 8 weeks of gestation, reaching 10% and 50% of maternal concentration by 17–22 and 30 weeks of gestation, respectively, with maximal transfer rates achieved after 36 weeks' gestation [19].

Individuals who received mRNA vaccines in the third trimester of pregnancy have detectable antigen-specific IgG in their infants' cord blood samples [20,21]. In one of these studies, these antibodies were only detectable if vaccination occurred more than 3 weeks prior to delivery and there was a positive association between the time from first vaccination to delivery and IgG level in newborns [20]. Also, vaccine-induced antibody levels in infants were equal to their mothers' if vaccination occurred in the third trimester [20].

5. Expert opinion & concluding remarks

For maximum protection against COVID-19 infection, high vaccine coverage globally is

required as soon as possible. Pregnant individuals would obtain maximum benefit from

vaccination administered as early as possible in pregnancy and even pre-conception. Given recent data suggesting improved immune responses and improved protection with an interval of at least 7–8 weeks between vaccine doses for mRNA vaccines [9], early immunization would also support completion of the vaccine series as early as possible. In contrast, immunization in the second trimester may be the ideal timing for best protection of the newborn and infant [10]. However, by that time half of the gestation has already passed and the pregnant individual would be unprotected in the first half of pregnancy. In this scenario, maternal infection may compromise fetal wellbeing due to direct effects of the virus and/or antiviral drugs received. Given the increased risk of severe outcomes observed in pregnancy, current data would suggest that priority should be for maximum protection of the pregnant individual – i.e. immunization as

early as possible, if this has not been completed pre-conception. The combination of an extended interval between doses and the robust and persistent antibody responses observed would likely provide some protection to newborns and infants. Well-designed longitudinal studies are required to help inform the optimal COVID-19 immunization schedule for pregnant people and their offspring.

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