_(handwritten annotation)_ 10/28/2021 usa
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NO discussion of rates of infection, long-term consequences!

CORONAVIRUS

# Pregnancy influences immune responses to SARS-CoV-2

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Pregnancy and fetal sex influence the quality of antibody responses to SARS-CoV-2 infection and immunization (Atyeo *et al.*, Bordt *et al.*).

For over a year, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has challenged our clinical and scientific expertise, exposing the shortcomings in our understanding of the virus as well as the gaps in health care delivery and access worldwide. During the COVID-19 pandemic, numerous studies have investigated the innate and adaptive immune responses to SARS-CoV-2 infection and vaccination in different clinical cohorts; however, relatively few studies included lactating and pregnant women, a highly vulnerable population for the development of severe COVID-19. Moreover, pregnant women have been sidelined during the clinical trials that eventually led to the approval of the mRNA-1273 and BNT162b2 SARS-CoV-2 vaccines (1, 2). This is not an isolated occurrence, as pregnant women have historically been excluded from the majority of clinical trials, limiting their representation in the development of therapeutics and restricting our understanding of how different stages of pregnancy modulate immune responses to infections and vaccinations (3). This is particularly important given that infections during pregnancy are common contributors to maternal mortality and morbidity (4).

Two recent studies in *Science Translational Medicine* by Atyeo *et al.* (5) and Bordt *et al.* (6) investigate how pregnant women respond to SARS-CoV-2 mRNA vaccines and natural infection, respectively. These studies demonstrate that pregnant and lactating women mount robust antibody responses to vaccination and infection. However, factors such as time of vaccine priming and boosting as well as fetal sex modulate maternal antibody responses and passive immunity conferred on the fetus.

## PREGNANCY AS A UNIQUE IMMUNOLOGICAL STATE

Pregnancy represents a unique biological state in which a balance of immunotolerance toward the developing fetus must be achieved while also protecting the pregnant woman against infectious diseases (7). This balancing act is nontrivial to achieve given that the immune system in pregnancy can be influenced by both maternal and fetal components such as the placenta. The placenta is a fetal-derived organ and thus can be of male or female origin. Due to the numerous systemic changes in innate and adaptive immunity that occur throughout gestation, pregnant women are more susceptible to severe disease resulting from pathogens, including SARS-CoV-2 and influenza virus (7). However, timely maternal immunization against influenza and pertussis can induce a robust immune response that can protect the pregnant woman directly and the fetus through passive antibody transfer. Defining how pregnant and lactating women respond to SARS-CoV-2 infection and vaccination is thus critical to optimize vaccination strategies that protect both mother and infant from COVID-19.

One of the primary contributors to fetal and neonatal immunity is passive transfer of maternal antibodies across the placenta and through breast milk, which equips the infant with an arsenal of functional immunoglobulins (Ig) (8). Maternal IgG antibodies are transferred to the fetal circulation by binding to Fc-domain receptors (FcRs) on the surface of the syncytiotrophoblast, the multinucleated cell layer overlying the placenta. The neonatal Fc receptor (FcRn) is the primary placental IgG transfer receptor, but other placentally expressed Fcγ receptors also modulate transfer efficiency. Thus, antibody-FcR

binding is a key determinant of transplacental transfer, and differential glycation of the antibody Fc-domains can influence the quantity of antibody transferred (8). Following parturition, mothers transfer IgA-isotype antibodies through breast milk, which can protect infants against enteric and respiratory infections. Once in the neonatal circulation, maternal antibodies can coordinate diverse immune functions. These include direct antigen neutralization and non-neutralizing, cell-mediated functions (Fig. 1A), many of which are orchestrated by FcγRs. The diversity of antibody functions demonstrates their unique ability to provide comprehensive immunological protection to fetuses and breastfeeding infants.

Naturally acquired infection and prophylactic immunization are distinct pathways of antigen exposure that generate diverse antibody responses. Therefore, resultant antibodies might differ based on the method of antigen exposure. In pregnant women, these differences can alter the functional nature of antibodies and affect their biological activity and capacity to be delivered to the fetus or infant.

## ANTIBODY QUALITY IN THE CONTEXT OF PREGNANCY AND SARS-COV-2 IMMUNIZATION

Using a system's serology approach, Atyeo *et al.* immunophenotyped anti-SARS-CoV-2 antibodies in the sera of nonpregnant, pregnant, and lactating women following immunization with the mRNA-1273 or BNT162b2 COVID-19 vaccines (Fig. 1B). Compared to immunized nonpregnant women, pregnant and lactating women exhibited overall lower SARS-CoV-2 antibody titers, restricted IgG subclass responses, and a decreased FcR binding capacity following the first dose ("prime") of vaccination. However, following the second dose ("boost"), there were minimal differences between pregnant and

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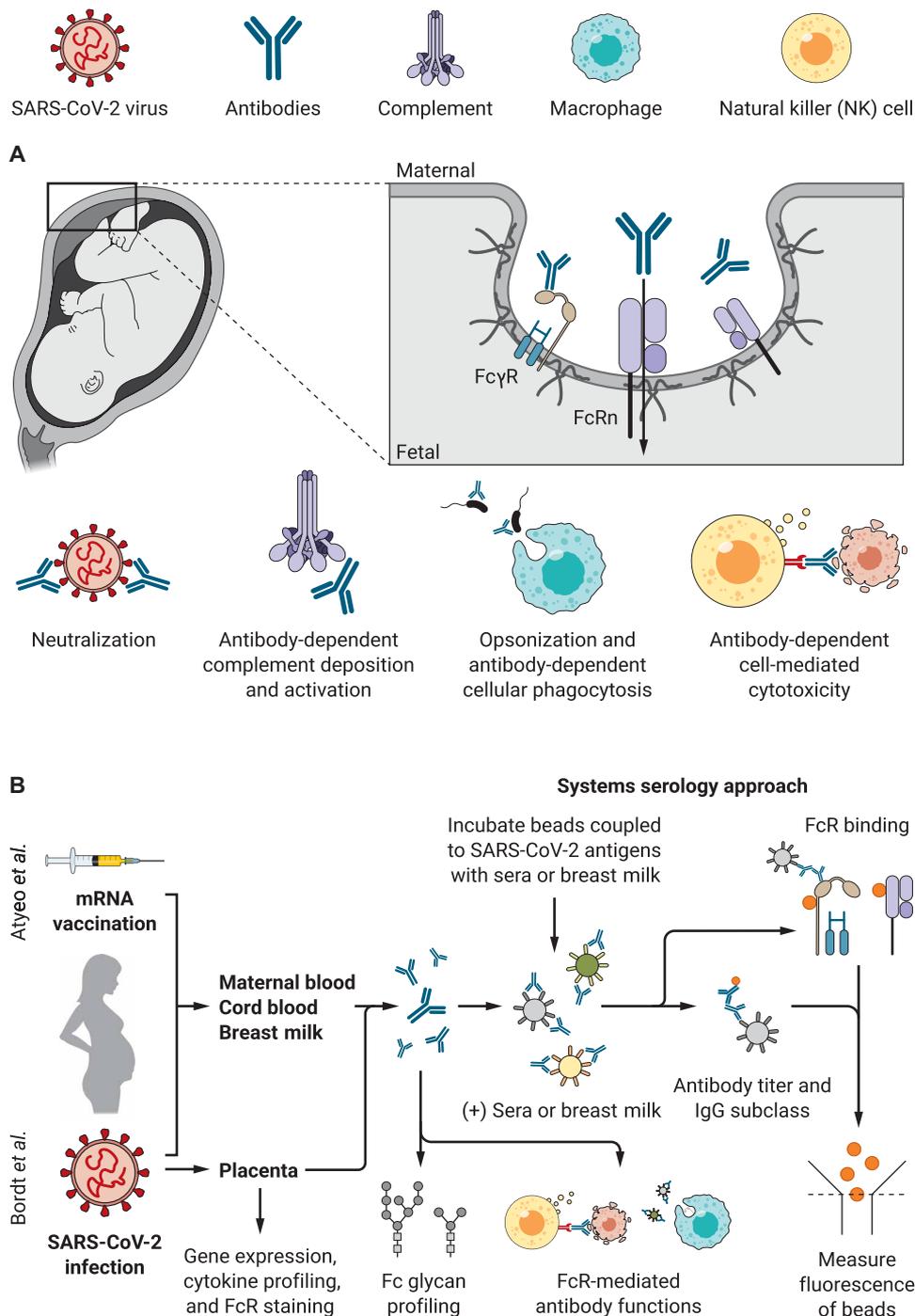*Corresponding author. Email: carolyn.coyne@duke.edu

**Fig. 1. Characterization of the maternal immune response to SARS-CoV-2 infection and vaccination.** (**A**) Maternal antibodies are transferred across the placenta to the fetus by binding neonatal Fc receptors (FcRn) and Fcγ receptors. The functional role of these antibodies includes direct neutralization of antigens, antibody-dependent complement deposition and activation, antigen opsonization, antibody-dependent cellular phagocytosis, and antibody-dependent cell-mediated cytotoxicity. (**B**) Atyeo *et al.* (*5*) and Bordt *et al.* (*6*) applied a systems serology approach to characterize the humoral immune response to SARS-CoV-2 vaccination or natural infection in pregnancy. The authors used maternal and cord blood sera or breast milk to measure anti-SARS-CoV-2 antibody titers, glycosylation patterns, FcR binding, and FcR-mediated antibody functions. They also used placental biospecimens to characterize gene expression and cytokine release in the placenta of women infected with SARS-CoV-2.

lactating versus nonpregnant women, indicating that boosting could overcome the attenuated immune responses to the first dose during pregnancy, supporting the importance of vaccine boosting. Moreover, lactating women had a unique increase in natural killer (NK) cell–activating antibodies following the second dose of the vaccine. The authors observed some differences in responses to each mRNA vaccine formulation. Notably, mRNA-1237 induced immune responses that were enriched for neutrophil and NK cell–recruiting antibodies, whereas BNT162b2 was slightly enriched for less-specific IgG1- and FcγRIIIa-binding antibodies, findings that were more prominent in pregnant and lactating women than in nonpregnant women. Further exploring these differences could inform future vaccine strategies to elicit antibody responses in pregnancy that would best protect the mother-infant dyad. Whether the coordination of immune responses between the two mRNA vaccine platforms results in different clinical outcomes remains to be determined, but using strategies similar to those demonstrated by this work would be helpful for rational maternal vaccine design.

With regard to passive antibody transfer, Atyeo *et al.* (*5*) observed a higher abundance of SARS-CoV-2 antibodies in maternal compared to cord sera, suggesting low transplacental antibody transfer rates to the fetal circulation. However, since all women in the study were immunized in the third trimester, this reduction in transfer is likely attributable to the timing of vaccination in later pregnancy, as noted by the authors. The authors propose that this reduction in transfer may result from a lower abundance of FcγRIIIa binding antibodies in pregnant women, leading to decreased transfer efficiency across the placenta. Importantly, lactating women's breast milk was highly enriched for antibodies capable of greater functional and FcR-binding qualities after vaccine boosting. These results imply that vaccination earlier in pregnancy and boosting later in pregnancy will help to maximize transplacental and breast milk antibody transfer and show that immunization across different stages of gestation results in unique antibody profiles.

Atyeo *et al.* demonstrate how nonpregnant, pregnant, and lactating women

diverge in their respective responses to mRNA-based immunizations against SARS-CoV-2, yet show that vaccine boosting remains an effective strategy to equalize the quality of antibody responses across groups. It is clear from this systems serology analysis that characterizing humoral responses following vaccination can greatly enhance our understanding of maternal immunity during pregnancy and inform vaccine administration strategies.

### FETAL SEX AND MATERNAL IMMUNITY TO SARS-COV-2 INFECTION

In a complementary study, Bordt *et al.* (6) investigated the antibody and antiviral interferon responses in SARS-CoV-2 uninfected and infected pregnant women and whether fetal sex modulated these responses. Given that the placenta is a fetal-derived tissue, understanding how fetal sex might impact immune responses and transplacental antibody transfer could shed light on sex-associated differences in COVID-19 outcomes in infants and children.

Bordt *et al.* quantified anti-SARS-CoV-2 antibody titers, specificities, and functions in the maternal and cord blood sera of pregnancies with male and female fetuses (Fig. 1B). The group found that mothers carrying male fetuses had lower maternal titers of IgG antibodies against all specific SARS-CoV-2 antigens tested. This finding of dampened immune responses to SARS-CoV-2 in mothers with male fetuses suggests that fetal sex modifies maternal antibody responses to infection during pregnancy. Additionally, the transfer ratio of SARS-CoV-2 antibodies into cord blood was lower in male versus female pregnancies. Importantly, the authors found that transplacental transfer of IgG against other pathogens, such as those causing pertussis and influenza, was not reduced in male versus female pregnancies.

The authors further explored whether fetal sex-specific differences in placental FcR expression modulated the observed decrease in SARS-CoV-2 IgG transfer. Placental staining and gene expression analyses revealed sexually dimorphic expression of placental FcRs with an up-regulation of FcRn, FcγRII, and FcγRIII, and an increase in co-localization of FcRn and FcγRIII in male-derived placentas. Given that this increase in placental

FcR expression and co-localization should theoretically enhance transplacental IgG transfer, the authors examined alternative hypotheses as to why transport of maternal SARS-CoV-2 IgG into cord blood was reduced in male pregnancies. Glycan profiling revealed that SARS-CoV-2-infected mothers with male pregnancies produced higher titers of antibodies modified by fucosylation and galactosylation. As fucosylated antibodies are less efficiently transferred by FcγRIII receptors, these findings help to elucidate why SARS-CoV-2 IgG transfer was decreased in male pregnancies (9).

Overall, the findings of this study suggest dynamic and divergent immune responses to SARS-CoV-2 in pregnant women based on fetal sex. Mothers with male fetuses had lower SARS-CoV-2 antibody titers with differential FcR binding and glycosylation following infection and lower rates of anti-SARS-CoV-2 IgG transfer across the placenta. These observations have important implications for SARS-CoV-2 vaccination in male- versus female-expectant mothers and, following parturition, the care of at-risk male children. It is essential that we continue to study these dichotomous fetal sex responses to infection in pregnancy across gestation.

### IMPLICATIONS FOR TRANSLATION

Infections during pregnancy contribute to high rates of maternal and fetal morbidity and mortality. However, the study of maternal-fetal immune responses to such infections remains underwhelming. The studies by Atyeo *et al.* and Bordt *et al.* on the immune responses to SARS-CoV-2 vaccination and infection demonstrate the critical nature of investigating maternal-fetal immune responses during pregnancy, a highly unique biological state. The findings of these studies have direct clinical implications for the COVID-19 pandemic and future maternal-fetal vaccination strategies, as they reveal that pregnant and lactating women have distinct immune responses to immunization and natural infection. Furthermore, these studies echo the call to action to incorporate women at different stages of gestation into clinical trials, thereby increasing their representation in the development of vaccines.

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