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COVID-19 during pregnancy causes fetal and placental inflammation

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During pregnancy, COVID-19 represents a significant risk both to the mother and the developing fetus. However, little was known about the immune responses elicited in pregnant women, and their developing fetuses, by this novel coronavirus. Therefore, we applied a multifaceted approach to characterize immune responses taking place in expectant mothers with COVID-19, their fetuses, and their placentas.

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Pregnant women with COVID-19, the disease caused by the SARS-CoV-2 virus, are at increased risk of severe disease and mortality as well as pregnancy complications such as preeclampsia and preterm birth. COVID-19 is therefore particularly dangerous during pregnancy, as both the mother and fetus are in jeopardy. Moreover, there is a risk of the mother transmitting the SARS-CoV-2 virus to the developing fetus that can result in long-term consequences later in life. Therefore, understanding the immune response of mothers with COVID-19 is an important first step in finding ways to prevent fetal injury, which could translate in poor outcomes in neonatal life.

Our goal was to perform a comprehensive characterization of immune responses in both the mother and in the fetus, and thus we obtained several samples from pregnant women with or without COVID-19. Prior to delivery, blood was collected from the mother, and shortly after delivery we obtained blood from the fetus (i.e., umbilical cord blood) and samples of the placenta.

Pregnant women with COVID-19 produce protective antibodies, called IgM and IgG, which are specific for the virus. While maternal IgG can be transferred from the mother to the fetus through the placenta, the IgM molecule is too large. We measured these antibodies in maternal and umbilical cord blood and found that both IgM and IgG were increased in pregnant women with COVID-19. Yet, only IgG was increased in the fetal blood, suggesting that these fetuses may not be directly infected by the virus but received transfer of protective maternal antibodies.

We also measured the blood levels of signaling molecules, called cytokines, which can provide information about the immune response. As expected, pregnant women with COVID-19 displayed increased concentrations of multiple cytokines in their blood. Interestingly, we found that only one of these cytokines, named interleukin-8 (IL-8), was elevated in the fetal blood, suggesting that the fetuses of pregnant women with COVID-19 display a milder inflammation than that observed in mothers.

Previous studies have shown that patients with COVID-19 undergo changes in numbers of immune cells in the blood. Therefore, we also explored whether pregnant women with COVID-19 and their fetuses experienced such changes. We found that pregnant women with COVID-19 displayed reduced numbers of immune cells called T cells, which are important for protection against viruses. However, a similar reduction was not seen in fetuses, indicating that this effect is limited to the mother.

The placenta is an important organ that allows exchange of nutrients from the mother to the developing fetus. Moreover, the placenta acts as a barrier to help prevent harmful microbes (e.g., bacteria and viruses) from reaching the fetus. Therefore, we collected the placentas from women with COVID-19 to evaluate gene expression changes in the cells present in this fetal organ. This would allow us to determine whether the placenta was affected by maternal COVID-19, even in the absence of viral infection. We found that placental immune cells (called T cells and macrophages) and tissue cells from women with COVID-19 displayed changes in gene expression. As confirmation of these changes, we compared the placental T cells with another study that investigated blood T cells from hospitalized patients with COVID-19, and observed similarities between these cells. This indicated to us that the cells present in the placenta are affected by maternal COVID-19.

The blood is a rich source of molecules, such as DNA and RNA, that can be used to monitor events such as diseases. Therefore, we performed sequencing of RNA obtained from maternal and fetal blood and compared these samples to determine whether the immune responses observed in mothers could also be found in their fetuses. We observed overlap between the changes in maternal and fetal blood, further indicating that maternal COVID-19 can cause a similar inflammatory response in the fetus.

Given our finding that inflammation is present in the placenta and fetal blood of women with COVID-19, we then evaluated whether the SARS-CoV-2 virus could be detected in the placenta. We looked for viral RNA and proteins in different areas of the placenta, but could not detect the virus. Thus, maternal COVID-19 can lead to inflammation in the placenta and fetus, even when the virus itself is not present.

Our findings highlight the detrimental effects of COVID-19 during pregnancy and provide new evidence that maternal COVID-19 has negative consequences for the developing fetus, even when the virus itself is not transmitted. We hope that these observations can help improve the care of pregnant women with COVID-19 to prevent any negative long-term consequences for the offspring.