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## COVID-19 RISK IN PREGNANCY: ANOTHER REASON TO LIMIT COMMUNITY TRANSMISSION

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Pregnancy is associated with many dramatic changes to a woman's physiology, not least of which is a degree of immune suppression, or "immune tolerance". Without changes to her immune system, a pregnant woman's body would reject a gestating fetus. While this immune suppression allows carriage of a pregnancy to term, it also carries risks to pregnant women which do not apply to men, or to women in the non-pregnant state. This is manifest in elevated risk of severe illness, and even death, from a variety of infectious diseases, including listeriosis, chicken pox, some kinds of hepatitis and malaria.

Influenza has long been thought to be more severe in pregnant women, and pregnant women were far more likely than others of the same age to be hospitalized with severe illness during the 2009 influenza A H1N1 pandemic. A recent meta-analysis by researchers at McMaster University found that pregnant women have a 7-fold higher risk of hospitalization for influenza than non-pregnant women, after adjusting for antiviral drug use, underlying medical conditions and age. This analysis did not find an elevated risk of ICU admission or death in pregnant women with influenza, suggesting that at least some of the elevated hospitalization risk might reflect hospitalization out of an abundance of caution, or for fetal monitoring, by care providers.

What about COVID-19? Over the summer, the US Centers for Disease Control (CDC) published an analysis that found that pregnant women were not only at increased risk of hospitalization, but of severe illness, due to COVID-19. The unfortunate lack of control of COVID-19 transmission in the United States allowed these investigators to study a large number of pregnant women with COVID-19 (over 8,000) who were compared to non-pregnant women with COVID-19. Pregnant women were 5 times as likely to be hospitalized as non-pregnant women, and also 50% more likely to become ill enough to require intensive care. At that time, the CDC researchers did not find an association between pregnancy and increased risk of COVID-19 death, but when they re-ran their analysis in October (now with over 23,000 pregnant women with COVID-19), they now found that pregnant women were 200% more likely to require intensive care hospitalization, and 70% more likely to die, than non-pregnant women with COVID-19.

Are these data applicable to the current COVID-19 outbreak in Canada? It's hard to know. While Canada's COVID-19 response has not been perfect, it has been far stronger than that seen in the United States, and our country is also much smaller. That means that we have less "statistical power" to find such effects in Canada. To answer this question in Ontario, we created a cohort of pregnant and non-pregnant women from Ontario's COVID-19 case dataset. Thanks to a smaller population and less widespread transmission of COVID-19, only 527 pregnant women had been infected with SARS-CoV-2 in Ontario by mid-November of 2020. Because clinical practice has changed over the course of the COVID-19 pandemic, we matched pregnant and non-pregnant women by age, but also by the week of onset of their infection. We found that the pattern of risk of infection in pregnant women exactly paralleled risk of infection in the population as a whole (Figure). As in the US, and as with influenza, pregnant women were much more likely to be hospitalized than non-pregnant women with COVID-19. However, the elevation in hospitalization risk in Ontario was significantly lower than in the US, which could reflect

differences in prenatal care or clinical practice. Pregnant women in Ontario were 90% more likely than non-pregnant women to be admitted to intensive care with COVID-19, but this difference could have been due to chance alone and was not statistically significant. However, we were also unable to exclude the possibility that elevated risk of ICU admission in pregnant women due to COVID-19 in Ontario is the same as that reported in a far larger sample of women studied in the US. At the time of writing no pregnant women had died of COVID-19 in Ontario. This suggests that COVID-19 related risks from the immune suppression associated with pregnancy are lower than the risks associated with immunosuppression from immunosuppressive medications, which we have found to be an important risk factor for fatal outcome among individuals with COVID-19 infection in Ontario.

Whether or not COVID-19 increases the risk of stillbirth or preterm birth is unclear. A recent study from England found no increase in risk of stillbirth during the period when the country was under lockdown. However, among pregnant women with severe COVID-19, the risk of preterm delivery seems to be increased, perhaps as much as fourfold according to a recent Italian analysis. At the same time, overall rates of preterm birth during lockdowns seem to be lower, perhaps because of decreased air pollutants due to reduced traffic. Fine particulate air pollutants were known to increase the risk of preterm delivery prior to the pandemic.

What are the policy implications of this information? First, risk patterns for COVID-19 infection in pregnant women parallel those seen in the wider population; the best way to protect pregnant women from COVID-19 is to reduce transmission in the community. We are able to state with confidence that pregnancy increases the risk of hospitalization in reproductive-age women with COVID-19. Ontario numbers remain too small to determine whether pregnancy increases the risk of ICU admission or death in pregnant women with COVID-19. As we wait for vaccines to become available, it is clear: out of an abundance of caution we should try to keep Canadian numbers so low to protect pregnant women. Collaborative research, led by obstetrical researchers in British Columbia, is currently underway to evaluate pregnancy-related risk by combining data from several Canadian provinces.

