Expecto Patronum! Leveraging the Positive Force of COVID-19 Vaccines for Pregnant and Lactating Individuals

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ABSTRACT

For over a year, the world has been gripped by the coronavirus disease 2019 (COVID-19) pandemic, which has had far-reaching effects on society. The integrity of national health care systems has also been challenged, owing to shifts in guidance and misinformation. Although initial reports suggested that pregnant people were not at increased risk of severe COVID-19, current data arising from the "third wave" paint a much more concerning picture. In addition, pregnant and lactating people were excluded from vaccine trials, which has hindered the ability of health care professionals to provide evidence-based counselling regarding the safety and efficacy of the available vaccines in these populations. This commentary reviews the current data on the safety of COVID-19 vaccines in pregnancy. The evidence is clear that the risks of hospitalization and severe maternal and potentially fetal morbidity from COVID-19 in pregnancy far outweigh the very minimal risks of COVID-19 vaccination in pregnancy.

RÉSUMÉ

Depuis plus d'un an déjà, le monde est frappé par la pandémie de maladie à coronavirus 2019 (COVID-19), dont la portée s'étend à toute la société. L'intégrité des systèmes de santé nationaux a aussi été remise en question à cause des changements de directives et de la mésinformation. Bien que les rapports initiaux aient laissé entendre que les personnes enceintes n'étaient pas plus susceptibles de développer une atteinte sévère de la COVID-19, les données actuelles colligées dans la ≪ troisième vague ≫ brossent un portrait beaucoup plus préoccupant. De plus, les personnes enceintes ou allaitantes ont été exclues des essais sur les vaccins, ce qui nuit à la capacité des professionnels de la santé de donner des conseils fondés sur des données probantes relativement à l'innocuité et à l'efficacité des vaccins disponibles chez ces populations. Le présent commentaire examine les données actuelles sur l'innocuité des vaccins anti-COVID-19 administrés pendant la grossesse. Les données montrent clairement que les risques d'hospitalisation et de morbidité maternelle, et potentiellement fœtale, grave associés à la COVID-19 pendant la grossesse sont nettement plus importants que les risques minimes associés à la vaccination contre la COVID-19 pendant la grossesse.

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For over a year, world attention has been gripped by the impact of the coronavirus disease 2019 (COVID-19) pandemic, with far-reaching effects on society at large and on the integrity of national health care systems. The speed and severity of this disease, induced by the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) virus, has disrupted every dimension of our lives. The scientific community has responded swiftly by shifting its focus to address the nuances of every aspect of the pandemic, producing new insights and effective care pathways at an unprecedented pace. Although this prolific output

has been invaluable, its speed and scale has meant an ever-changing series of advisory statements and clinical practice recommendations.

The frequent shifts in guidance in response to our evolving understanding of the effects of COVID-19 have created dissonance and distrust within some segments of the population, notably in vulnerable and racialized communities. Such conditions have been ripe for the propagation of misleading narratives, unsupported by credible data. This development has in turn had unintended consequences (e.g., vaccine hesitancy), nowhere more so than within the pregnant population.

Daily life involves choices, each with a series of intended and unintended consequences. These decisions commonly extend to various facets of our health. At this juncture, it is imperative to consider the fears that accumulate on both sides of the vaccination equation, and in particular to use current best evidence to reframe risk perceptions around susceptibility to SARS-CoV-2, especially the consequences of infection versus possible vaccine-related side effects and the potential unknowns that remain.

Although initial reports suggested that pregnant women were not at increased risk of severe COVID-19 infection, current data arising from the "third wave" paint a much more concerning picture. In retrospect, this new concern is not surprising, given the known increased pregnancy-related morbidity attributed to other respiratory viruses, including influenza, severe acute respiratory syndrome, and Middle East Respiratory Syndrome.[1]

The most recent report from the Canadian Surveillance of COVID-19 in Pregnancy, based on data obtained from the first and second waves of the pandemic, had already demonstrated a five-fold increased risk of hospitalization and intensive care unit (ICU) admission for pregnant women with COVID-19 compared with the equivalent non-pregnant female population, a risk that also included higher rates of preterm birth (12%) and small for gestational age (9%) and a four-fold (1.2%) excess risk of stillbirth.[2]

At the time of writing, Canada finds itself in the epicentre of the third wave of this pandemic, in which variants of concern are not only more prevalent but now dominate the burden of disease. In contrast to the previous waves, pregnant women are now clearly disproportionately affected, with a higher incidence of respiratory compromise, hospitalization, and ICU admission.[3] Estimates suggest that 1 in 10 pregnant persons with COVID-19 infection will be hospitalized, and 1 in 100 will be admitted to the ICU.[3]

This increased propensity for severe illness mirrors the second wave experience from the United Kingdom, where the number of pregnant women with severe or critical COVID-19 was noted to escalate, with many requiring ICU admission. A very disturbing trend, is that of referrals for extracorporeal membrane oxygenation treatment doubling in some units.[4] Unfortunately, this is now commensurate with our institutional experience in the current third wave.

The dire global impact of this pandemic spurred robust international scientific efforts, which, with unprecedented speed, have culminated in the development of a number of COVID-19 vaccines. In Canada, two messenger RNA (mRNA) vaccines (Pfizer/BioNTech and Moderna) and a nonreplicating viral vector-based vaccine (AstraZeneca-Oxford) have received emergency Health Canada authorization.

The mRNA vaccines do not contain live virus and therefore cannot induce infection in the host. These vaccines are composed of modified nucleotides encoding the SARS-CoV-2 spike protein, with intracellular delivery achieved by a lipid nanoparticle structure. The mRNA does not gain entry to the nucleus and is incapable of interacting with or altering human DNA. Once inside the cell cytoplasm, the mRNA supplies directions to generate the transmembrane spike protein antigen within the deltoid muscle, which in turn induces both humoral and cellular immune responses. The mRNA, spike protein, and lipid nanoparticle are thereafter degraded and excreted within days to weeks.[5] The nonreplicating viral vector vaccine, in contrast, uses a modified form of chimpanzee adenovirus (incapable of replication) to transport genes that code for the SARS-CoV-2 spike protein into the cells, where these genes are transcribed into mRNA within the nucleus and translated into proteins within the cytosol.[5]

The Pfizer/BioNTech, Moderna, and AstraZeneca-Oxford Trials have enrolled 45 000, 30 000, and 20 000 participants, respectively, and have reported 95%, 94.5%, and 70.4% efficacy.[6] Importantly, all three vaccines are now known to be extremely effective with respect to prevention of severe disease, as represented by mortality, hospitalization, and ICU admission rates.[7] Regrettably, none of these trials included pregnant or lactating people.[6] This exclusion is disappointing but not surprising; yet again, a paternalistic approach, driven by a misguided desire to protect a "vulnerable" pregnant population, has overridden the opportunity for such individuals to provide informed consent for trial participation, with disregard for the violation of the right of pregnant and lactating persons to

autonomy and self-determination.[8] Thus, despite the pleas of pregnant and lactating people to participate in trials, they were once again excluded from vaccine trials. This has had a major impact on the ability of health care practitioners to provide evidence-based counseling regarding the safety and efficacy of the available vaccines.

Reassuringly, to date no animal or human studies have raised any specific concerns about COVID-19 vaccines during pregnancy or lactation. The Centers for Disease Control and Prevention's v-safe COVID-19 vaccine pregnancy registry, conducting ongoing surveillance of pregnant people, has registered 35 691 individuals who reported being pregnant at the time of vaccination. Of 3598 participants enrolled in the v-safe pregnancy registry, 827 have completed their pregnancies, and no concerning safety signals have been identified thus far.[9] Furthermore, evidence of passive antibody transfer to infants through placenta and breastmilk has been found.[3]

The side effects of vaccination in pregnant individuals are similar to those experienced by non-pregnant persons; the most common include local tenderness at the injection site, transient fatigue, myalgias, and low-grade fever,[9] all of which can be treated safely with acetaminophen.

Worthy of discussion are the recent reports of cerebral venous sinus thrombosis with the AstraZeneca-Oxford vaccine in non-pregnant individuals. Close examination of these very rare events has resulted in the recognition of what was originally termed "vaccine-induced prothrombotic immune thrombocytopenia" and has now been renamed "vaccine-induced thrombosis with thrombocytopenia" (VITT).[10] Thus far, VITT has not been reported after administration of either of the available mRNA vaccines. VITT shares similarities with heparin-induced thrombocytopenia (HIT), a disease characterized by an immune-mediated adverse reaction to heparin. In HIT, antibodies to platelet factor emerge and bind to platelets, resulting in their activation, which then leads to thrombosis and "paradoxical" thrombocytopenia.[11] As in HIT, but without heparin exposure, high levels of antibodies to platelet factor have been discovered in individuals with VITT.[10] VITT-related thromboses may occur at atypical sites, including the cerebral venous sinus and the portal, splanchnic, or hepatic venous circulations, in addition to the more typical presentations of pulmonary embolism, deep vein thrombosis, and arterial thrombosis.[10] Potential risk factors such as younger age and female sex have been noted, though these may, in fact, reflect the fact that the vast majority of the vaccines were administered to health care workers, who often fulfill both these factors. The associated thrombocytopenia, significantly elevated D-dimers, and hypofibrinogenemia indicate activation of the coagulation system. However, the syndrome is thought to be the result of an atypical autoimmune antibody-mediated reaction. At present, the occurrence of VITT is estimated at around 1 in 100 000.[10] Symptoms typically manifest 4–28 days after vaccination.[12] Awareness of symptoms is critical to allow for early assessment and treatment, which consists of intravenous immunoglobulin and non-heparin anticoagulants (in pregnancy these include danaparoid sodium and fondaparinux).[12]

Currently, there is no indication that the risk of VITT is increased in the presence of prior thrombosis or thrombophilia, and guidance from various thrombosis organizations, including the International Society on Thrombosis and Haemostasis,[12] suggests that these are not contraindications to vaccination with the AstraZeneca-Oxford vaccine. Thus, given the autoimmune rather than hypercoagulable state origins of VITT, pregnancy is not considered a contraindication to administration of the AstraZeneca-Oxford vaccine if other vaccines are not available. In comparison, a systematic review demonstrated a strikingly high risk of thromboembolic events mediated by COVID-19 (21%), which in one study rose to 31% among those admitted to the ICU.[13] In a recent statement, the Society of Obstetricians and Gynaecologists of Canada concurred in favour of vaccination in pregnancy.[3] Consideration of the balance of these risks may be aided by comparisons of the relative risk of other potential events (Table).

In summary, the evidence is clear that the risk of hospitalization and severe maternal and potentially fetal morbidity secondary to COVID-19 in pregnancy far outweighs the

Table. Relative risks of potential life events

Comparative events	Risk per million
Hospitalization if pregnant with COVID-19[3]	100 000
ICU admission if pregnant with COVID-19[3]	10 000
VTE if hospitalized with COVID-19[13]	21 000
VTE in pregnancy[14,a]	1200
VITT with AstraZeneca-Oxford[10,a]	10
Significant harm from vaccine-related adverse events[b]	4–11
Death from traffic-related accident [b]	23–38
Accidental death[b]	110–180
Being struck by lightning[b]	1

[a] VTE risk in pregnancy is secondary to hypercoagulability, whereas VITT risk is secondary to an autoimmune reaction.

[b] Adapted from Cuffe.[15]

COVID-19: coronavirus disease 2019; ICU: intensive care unit; VITT: vaccine-induced thrombosis with thrombocytopenia; VTE: venous thromboembolism.

very minimal risks of COVID-19 vaccination in pregnancy. The Society of Obstetricians and Gynaecologists of Canada agrees that current data support the safety of all COVID-19 vaccines available in Canada and encourages their utilization in any trimester of pregnancy and during lactation.[3] Thus, it is incumbent upon all obstetric providers to strongly encourage every pregnant person to get the COVID-19 vaccine and, when they do so, to encourage them to participate in the Canadian COVID-19 Vaccine Registry for Pregnant and Lactating Individuals (COVERED), a web-based, longitudinal survey aiming to record outcomes and opinions regarding COVID-19 vaccine experiences. This will be available at https://ridprogram.med.ubc.ca/vaccine-surveillance/.

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