



# The COVID-19 vaccine evidence gap: Decisions without data for pregnant and breastfeeding women

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On March 11th, 2020, the World Health Organization officially declared the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak a pandemic, setting in motion an unprecedented modern-day global public health response.<sup>1,2</sup> Since that time, COVID-19's impact has been wide-reaching and complex; influenced by a diverse set of biologic, clinical, psychologic, and sociodemographic factors.<sup>3,4</sup> Indeed, not all members of society are at equal risk of SARS-CoV-2 infection or experiencing severe infection-related outcomes.<sup>3,4</sup> For example, older adults and individuals with comorbid conditions (e.g., cardiovascular disease) are at increased risk for severe disease.<sup>5</sup> Further, males are at higher risk of serious COVID-19 outcomes compared to females, underscoring the importance of including sex as a fundamental variable in the design and conduct of

COVID-19 research.<sup>6</sup> Certainly, without sex-disaggregated data, it is impossible to know if, or to what extent, sex-specific approaches to the care and prevention of SARS-CoV-2 infection should be employed.<sup>7</sup>

Just as the findings of male-specific analyses are not necessarily generalizable to females, findings on non-pregnant females should not, by default, be considered generalizable to pregnant and lactating women.<sup>8</sup> Pregnant and breastfeeding women are indeed quite different, both mechanically and physiologically, from non-pregnant individuals.<sup>6,8-11</sup> This necessitates their specific consideration and study as distinct at-risk populations.<sup>12</sup> Pregnant women have increased cardiac output, plasma volume, kidney excretion, and delayed gastric emptying compared to non-pregnant adults, all of which can elicit

a different than average response to medications.<sup>10,11</sup> Further, the immune system is modulated throughout the pregnancy period and the quality of vaccine-induced antibodies influenced heavily by associated hormonal changes.<sup>13</sup> Thus, it is difficult to predict what vaccine-induced immune responses will look like in pregnant women without satisfactory data.<sup>14,15</sup> Unfortunately, while the unique biology of these populations requires specific attention, pregnant and breastfeeding women remain practically non-existent as participants of COVID-19 research.<sup>10, 11, 16-20</sup>

Zika, H1N1 influenza, Ebola, and other coronaviruses have shown the world how infectious diseases can be uniquely devastating to pregnant women and the fetus.<sup>15, 16, 21</sup> The serious risks associated with their infection have highlighted the need to study pregnant women during efforts to tackle infectious disease outbreaks.<sup>15</sup> While questions remain about the impact that SARS-COV-2 infection has on pregnant women and the fetus,<sup>19</sup> a growing amount of evidence suggests that pregnant women with COVID-19 are at higher risk of experiencing disease related complications compared to their non-pregnant counterparts.<sup>9, 22, 23</sup> Additional studies suggest that pregnant women with more severe COVID-19 disease are at increased risk of preterm delivery,<sup>20</sup> which is itself associated with poor fetal outcomes.<sup>24</sup>

Safe and effective vaccines against COVID-19 will be instrumental in controlling the spread of SARS-COV-2 and putting an end to the pandemic.<sup>25, 26</sup> Although four COVID-19 vaccines have been approved for use in Canada as of March 2021,<sup>27</sup> pregnant and breastfeeding women have been systematically excluded from all COVID-19 vaccine trials to date.<sup>20, 22</sup> Indeed, decisions about enrolling pregnant and lactating women in clinical research requires prudent considerations about the risks and benefits of the intervention being studied.<sup>8</sup> These discussions are frequently characterized as “ethically complicated”,<sup>15</sup> as considerations need to be made for both of the mother and fetus<sup>11, 15</sup> Often, the result is a decision to exclude all women of reproductive age out of fear for harming the fetus, which elicits considerable concern about financial and legal liability<sup>14, 28</sup> Judgements of this type align with the widely accepted “precautionary principle” approach to medical ethics, i.e., reduce the risk of harm even before evidence of harm exists<sup>11, 29</sup> As noted by others,<sup>8, 16, 22, 23</sup>

however, when it comes to vaccine trials for COVID-19, this ‘exclude all’ approach does not align with the ethical principles (namely autonomy, beneficence, and justice) purported to be upheld by decision makers. This is especially true for pregnant and lactating women with comorbid conditions that are known to increase their risk of severe disease.<sup>12</sup>

To understand how best to protect pregnant women from COVID-19, we have to understand how their immune system reacts to vaccine candidates throughout the course of pregnancy. This knowledge will help experts decide on the optimal dosing and dose scheduling required in pregnant women to generate an adequate level of protection against SARS-COV-2 infection.<sup>14</sup> Vaccination against influenza, tetanus, diphtheria and pertussis is already recommended for pregnant women<sup>20</sup> and none of the currently approved COVID-19 vaccines contain live virus, ingredients known to be harmful to pregnant women or the fetus, or pose a theoretical risk during pregnancy.<sup>17, 23, 27, 30</sup> Further, previous research has demonstrated that clinical studies on novel vaccines can be safely tested in pregnant females,<sup>31, 32</sup> including during a pandemic,<sup>33</sup> providing vital information about the efficacy, safety, and immunogenicity of vaccines in this unique population. Without clear evidence that COVID-19 vaccines pose substantial and imminent risk of harm to the fetus, mother, or breastfeeding infant, withholding vaccines from these populations not only represents a major missed opportunity to close important knowledge gaps, but denies them the potential to gain significant protective benefit.<sup>15</sup>

Since the Canadian National Advisory Committee on Immunization recommended against routinely offering COVID-19 vaccines to pregnant or lactating women late in 2020,<sup>12</sup> professional specialist societies<sup>22, 23, 30</sup> have released official statements advising that pregnancy and lactation status alone are insufficient reasons to prevent women from accessing an approved COVID-19 vaccine.<sup>12</sup> Their general recommendation is that pregnant and breastfeeding women be allowed to make an autonomous decision about receiving the vaccine in consultation with their health care provider.<sup>23</sup> However, it is unethical to place the burden of responsibility about the appropriateness of taking a COVID-19 vaccine on these women and their healthcare providers without adequate scientific evidence to support in decision-making<sup>8, 22</sup> The best way to gain this much needed evidence is within the setting of a highly structured and monitored clinical trial.<sup>8</sup>

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