

## Benefits and potential harms of COVID-19 vaccination during pregnancy: evidence summary for patient counseling

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Historically, pregnant women have been excluded from the majority of drug and vaccine trials, a practice that has been widely criticized by the scientific community<sup>1-3</sup>. The result is that pregnant women are routinely denied beneficial, sometimes potentially life-saving, therapeutic and preventive measures, or receive them well after their non-pregnant peers. Data about safety and efficacy in pregnancy subsequently accumulate adventitiously as women receive the drug or vaccine not realising that they were pregnant, or fall pregnant soon after receiving the therapy. In the absence of any significant adverse effects, eventually sufficient confidence is established (either as 'evidence of no harm,' or, more frequently, as 'no evidence of harm') for a formal trial to be considered or alternatively, the use of the intervention in pregnancy simply slips into routine practice.

This pattern has been repeated with COVID-19 vaccines; pregnant women were excluded from the initial trials. Only a small number of women who were unknowingly pregnant or fell pregnant soon after vaccination have been included – this small cohort is currently being followed up as part of the original trials<sup>4,5</sup>. Due to lack of evidence around the safety of these vaccines in pregnancy, international societies have tended to take a cautious approach, recommending that vaccination of pregnant women should be evaluated on a case-by-case basis. The Society of Obstetricians and Gynaecologists of Canada and the International Federation of Gynecology and Obstetrics are notable exceptions as early endorsers of unrestricted vaccination in pregnancy<sup>6,7</sup>. In the United Kingdom (UK), the Royal College of Obstetricians and Gynaecologists (RCOG) suggests that pregnant women at very high risk should be considered eligible for vaccination<sup>8-10</sup>; these criteria are under constant review and were recently updated on 24<sup>th</sup> of February. Proposed risk factors are derived from literature relating specifically to pregnant women with COVID-19 and also extrapolated from non-pregnant women with COVID-19. They consist primarily of chronic diseases or immunosuppressive conditions, as well as women at high risk of exposure to the virus (Table 1). It must also be acknowledged that women can experience severe COVID-19 even in the absence of any of these risk factors<sup>11</sup>. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists have taken a stance similar to the RCOG<sup>12</sup>. The American College of Obstetricians and Gynecologists (ACOG) recommends that 'COVID-19 vaccines should not be withheld from pregnant women who meet criteria for vaccination based on ACIP (Advisory Committee on Immunization Practices) recommended priority groups'. Here we summarize the available evidence to support counseling for women contemplating COVID-19 vaccination during pregnancy.

Most pregnant women with COVID-19 will remain asymptomatic or have a mild illness. Fortunately, severe disease and death are rare outcomes. In the UK, for example, the maternal mortality rate associated with COVID-19 is 2.2 per 100,000 maternities<sup>13-16</sup>. Pregnant women hospitalised with COVID-19, however, are more likely to be admitted to the Intensive Care Unit (ICU) compared to non-pregnant women with the infection, although it is unclear whether this represents more serious illness or a lower threshold for ICU admission<sup>14</sup>. Despite this, according to a large systematic review<sup>14</sup>, pregnant women do not appear to be at greater risk of death. Some studies from both high and low incomes settings, however, report increased maternal mortality<sup>15,17</sup>. Summary findings should be contextualised if used during patient counseling. Compared with pregnant women without COVID-19, those with *symptomatic* COVID are at increased risk of adverse pregnancy outcomes, including maternal ICU admission, iatrogenic preterm birth, preeclampsia like symptoms, Caesarean section and death<sup>13-15</sup>. Reports of stillbirth in the literature are very heterogeneous; rates seem to be increased in low to middle-income countries while there was no significant increase in high-income countries<sup>18,19</sup>. COVID-19 has other indirect effects on maternal and fetal outcomes, such as increased maternal mental distress and intimate partner violence<sup>19,20</sup>.

The risk of severe adverse outcomes (e.g., ICU admission, maternal death, or stillbirth) will be modified by individual and societal risk factors, and the availability and performance of healthcare in their setting<sup>19</sup>. Nevertheless, it seems reasonable to counsel pregnant women with obesity, advanced age, or significant chronic conditions (Table 1) that they are at increased risk of severe COVID-19 and, therefore, more likely to benefit from vaccination in terms of protection from life-threatening COVID-19 (Table 2). Observational studies indicate that postnatal transmission of SARS-CoV-2 from mother to baby is rare, and continued breastfeeding appears to be safe<sup>21-23</sup>. The minimal postnatal transmission risk will probably be even lower in vaccinated mothers. The presence of anti-SARS-CoV-2 IgG has been reported in the neonate of a vaccinated mother, but it is not yet possible to say what impact maternal vaccination will have on neonatal protection against infection after birth<sup>24,25</sup>. Other secondary adverse effects of COVID-19 include mother-infant separation in some settings, increased Caesarean section and iatrogenic preterm birth. The incidence of these adverse effects is likely to be reduced by vaccination too and women should be counselled about the probable additional benefits of vaccination over and above protection from severe disease (Table 2).

### *Available vaccines and their safety profiles*

Four different types of COVID-19 vaccine are currently available: mRNA, viral vector, inactivated virus, and recombinant antigen (Table 3). As yet, only three COVID-19 vaccines, two mRNA and one adenoviral vector, are approved for emergency use by both the US Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the Medicines and Healthcare Products Regulatory Agency (MHRA), namely mRNA-1273 (Moderna Therapeutics, Cambridge, MA, USA), BNT162b2 (BioNTech, Fosun Pharma, Pfizer, Mainz, Germany) and Ad.26.COV2 (Janssen Pharmaceutica, Beerse, Belgium). The Oxford-AstraZeneca (AZD1222), another viral vector vaccine approved by the EMA, is commonly used in the UK. The two FDA approved mRNA vaccines were shown to elicit a very strong immune response and protection against severe COVID-19<sup>4,26</sup>. Unpublished mRNA vaccine (mRNA-1273) data from a study of pregnant rats identified no safety concerns regarding malformations or embryotoxicity<sup>27</sup>. Trials of both vaccines excluded pregnant women. Initial reports from regulatory bodies, such as the EMA, show that a small number of women in the trial were pregnant at the time of vaccination; safety data from these pregnancies are still pending but, as yet, no significant adverse effects have been observed<sup>28,29</sup>. More recently, Dr Anthony Fauci, Chief Medical Advisor to US President Biden, stated that more than 20,000 pregnant women have received an mRNA vaccine and to date there have been no concerning 'red flags'<sup>30,31</sup>. These as yet unpublished data illustrate that many pregnant women are willing to be vaccinated when their autonomy is respected and they have the opportunity to weigh their own personal risks and benefits. These preliminary safety data are reassuring and their publication is eagerly awaited.

Although mRNA vaccines have never previously been deployed on such a scale, they are not new. mRNA vaccines are not live virus vaccines and do not use an adjuvant to increase vaccine efficacy. The mRNA does not enter the cell nucleus and cannot alter the human genome in vaccinees. Animal studies have demonstrated the safety, efficacy, and potential benefit of mRNA vaccines in pregnant women, benefits which may extend beyond simply protecting the mother from pathogens. Zika virus is a zoonotic pathogen, like coronavirus, and is capable of intrauterine infection. In 2018, Richner et al. published a report describing the efficacy of an mRNA vaccine against Zika virus in pregnant mice<sup>32</sup>. Following vaccination, pregnant mice were infected with live Zika virus; pups born to vaccinated dams showed no viral load in their brain tissue. Furthermore, the viral load was at or below the detection threshold in placental samples. The authors concluded that the mRNA vaccine was safe in pregnant mice and that it prevented vertical transmission of Zika virus. The principles of this vaccination technology should also apply to COVID-19 vaccines, and

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provides generic reassurance around the use of mRNA vaccines in pregnancy. Furthermore, vaccination is likely to protect not only the pregnant woman but also the fetus and neonate. With regards to COVID-19 vaccines, for example, a recent case report demonstrated transplacental transmission of antibodies against the spike protein following vaccination of the mother<sup>24,25</sup>. Efficient transplacental transfer of SARS-CoV-2 IgG antibodies in the majority of seropositive pregnant women after natural infection has also been shown<sup>33</sup>. The presence of neutralizing antibodies in the fetal/neonatal circulation is potentially an added benefit of vaccination for protection of the baby, in both fetal and neonatal life, against COVID-19.

Three adenoviral vaccines Oxford-AstraZeneca AZD1222, Janssen Ad.26.COV2 and Gam-COVID-Vac, (also known as Sputnik V) have recently reported Phase 3 trial data showing high levels of efficacy against COVID-19, especially against severe disease and hospitalization<sup>5,34,35</sup>. As with the mRNA vaccines there are limited data on the safety of adenovirus vector vaccines in pregnancy, though adenovirus vector-based Zika vaccines have been tested in pregnant mice without safety concerns<sup>36</sup>. These vaccines do not contain live virus and neither the COVID protein nor the adenovirus vector replicates in humans, and are eliminated from the tissues following injection.

Two inactivated virus vaccines from China (BBIBP-CorV, Beijing Institute of Biological Products, China; CoronaVac, Sinovac Life Sciences, Beijing, China) and one from India (Bharat Biotech) are commercially available. Varying efficacy rates for preventing symptomatic infection have been reported<sup>37-41</sup>. However, they had similarly high protection against severe COVID-19 and death. Inactivated virus vaccines are considered safe in pregnancy, though the aluminium oxide adjuvant used in these vaccines do not have a designated FDA safety category due to the lack of data<sup>42,43</sup>. However, alum adjuvants are used in many vaccines, including Hepatitis B, DTaP and human papillomavirus (HPV). Inadvertent vaccination with HPV vaccines during pregnancy has not been associated with any safety concerns<sup>44</sup>. A similar safety profile was observed with respiratory syncytial virus vaccine, which also uses alum adjuvant<sup>45</sup>.

There is one recombinant antigen vaccine (Novavax) that showed high efficacy against symptomatic SARS-CoV-2 infection<sup>46</sup>. The antigens produced by recombinant technology are coupled with a saponin-based proprietary adjuvant in order to elicit an immune response. Recombinant vaccines are considered safe in pregnancy due to their non-replicating nature. However, the saponin-based proprietary adjuvant used in this vaccine lacks safety data in pregnant women.

### *Ongoing trials and pending safety data*

Pregnancy trials of BNT162b2 (BioNTech, Fosun Pharma, Pfizer) and Ad.26.COV2 (Janssen Pharmaceutica) are due to start soon. However, enrolment to prospective trials is threatened by the current global demand for vaccines, which will only increase with time. Worldwide, pregnant women are already choosing to be vaccinated against COVID-19, and safety data accumulating in official registries are likely to play a key role for expectant mothers considering vaccination. It is essential that countries establish national registries of pregnant women receiving the different types of COVID-19 vaccine as a matter of urgency; where possible, international registries should be developed <sup>47,47</sup>. Monitoring pregnancy, foetal and neonatal outcomes in vaccinated women and comparing them with those in unvaccinated pregnant women must be a priority.

Moreover, the ethics of enrolling pregnant women into placebo controlled trials is increasingly questionable, at a time when more and more pregnant women, particularly those with risk factors for severe COVID-19, are already receiving the vaccine. These vaccines are likely to deliver similar benefit to pregnant women as to non-pregnant individuals, and are likely to be safe. Withholding such a vaccine from prospective mothers who understand and accept the uncertainty of available preventive measures, while offering them enrolment into a placebo-controlled trial, might prove ethically challenging. Nevertheless, there are a number of advantages in recruiting pregnant women into trials in which they receive a licensed COVID-19 vaccine. This includes addressing questions around optimal timing of vaccinations, number of doses, dose intervals and need for boosters in future pregnancies. In the meantime, animal studies should be rapidly undertaken to provide safety information about the current unknowns of COVID-19 vaccines, such as transplacental passage of mRNA containing lipids or the safety of adjuvants and adenoviral vectors. There is an urgent need to focus and allocate more resources to research COVID-19 vaccination in pregnancy while awaiting safety data from official registries.

### Conclusions

Pregnant women should be provided with a balanced and clear assessment of their risk of COVID-19 in pregnancy, taking into account their individual circumstances, local practices and available evidence from similar healthcare settings. In addition, they should be counselled with a balanced summary of the potential direct and indirect benefits of COVID-

19 vaccines, while acknowledging the limited safety data. Whilst these vaccines have not yet been trialled in pregnancy, they are being offered to pregnant women with risk factors for severe COVID-19 during the national rollout of vaccine programmes in the UK. These vaccines are also currently offered to pregnant women with a high risk of exposure to SARS-CoV-2, including health and care workers. In the UK, the MHRA is receiving regular feedback from the vaccination programme and any concerns are met with appropriate action. So far, no safety concerns in vaccinated pregnant women have been reported in either the UK or the US. We believe that COVID-19 vaccination should not be withheld from pregnant women who have received adequate counselling and understand the uncertainties, minimal potential harms, and likely benefits of these vaccines. We also encourage further research to address current and future issues around COVID vaccines in pregnancy.

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**Table 1.** Risk groups for pregnant women, for whom vaccination should be considered according to the Royal College of Obstetricians and Gynaecologists (RCOG).

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**Risk factors for serious COVID-19**

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- Underlying medical conditions such as immune conditions, diabetes, high blood pressure, heart disease or asthma
  - Overweight
  - Age over 35
  - Third trimester pregnancy (over 28 weeks)
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**Risk factors for catching COVID-19**

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- Health or social care worker in the same household
  - Increased rate of COVID-19 infections in the woman's community
  - Frequent contact with people outside the home
  - Not being able to comply with social distancing
  - Crowded household
  - Black, Asian or minority ethnicity background
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**Table 2.** Direct and indirect detrimental effects of COVID-19 on pregnant women and the potential effect of vaccination

<b>Adverse effects</b>	<b>Incidence</b>	<b>Mediator</b>	<b>Potential effect of vaccination</b>
Maternal ICU admission	Rare	COVID-19, direct	Prevention
Mechanical ventilation or ECMO	Rare	COVID-19, direct	Prevention
Maternal death	Rare	COVID-19, direct	Prevention
Iatrogenic preterm birth	Common	COVID-19, indirect	Reduction
Caesarean section	Common	COVID-19, indirect	Reduction
Stillbirth	Rare	Severe COVID-19, reduced healthcare access	Reduction
Increased mental distress scores	Common	Reduced healthcare access, pandemic or mitigation measures	Unknown
Mother-infant separation following delivery	Uncommon	Perceived risk of transmission	Reduction
Interruption of breast-feeding following delivery	Uncommon	Perceived risk of transmission or COVID-19 treatment incompatible with nursing	Reduction
Vertical transmission	Rare	COVID-19, direct	Reduction/Prevention

ICU: intensive care unit; ECMO: extracorporeal membrane oxygenation

**Table 3.** Available vaccines with available phase III trial results. All listed vaccines have very high protection rates against serious and life-threatening COVID-19 infection.

<b>Vaccine</b>	<b>Technology</b>	<b>Property</b>	<b>Direct safety data</b>	<b>Indirect safety data from vaccines using similar technology</b>	<b>Unknowns and theoretical safety concerns</b>
mRNA-1273	mRNA	Non-replicating	Tested on pregnant mice: no signs of embryonal, fetal or postnatal developmental problems	mRNA based ZIKA virus vaccine used in pregnant mice	Transplacental passage of mRNA containing lipids
BNT162b2	mRNA	Non-replicating	NA	Adenovirus based ZIKA virus vaccine used in pregnant mice	
AZD1222	Viral vector	Non-replicating	NA		
Ad.26.COV2 Gam-COVID-Vac	Viral vector Viral vector	Non-replicating Non-replicating	NA NA		
BBIBP-CorV	Inactivated virus with aluminium hydroxide adjuvant	Non-replicating	NA	Inactivated vaccines are considered safe during pregnancy. Alum adjuvant has been used in vaccines that are considered safe during pregnancy (HPV, RSV)	Alum adjuvant
CoronaVac	Inactivated virus with aluminium hydroxide adjuvant	Non-replicating	NA		Alum adjuvant
Novavax	Recombinant antigen with saponin based adjuvant	Non-replicating	NA	Recombinant vaccines are considered safe during pregnancy.	Saponin based proprietary adjuvant