

Time to enhance COVID-19 vaccination in women of reproductive age

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Previous evidence, including major works from the Intercovid multinational consortium, showed that COVID-19 in pregnancy is associated with adverse maternal and neonatal outcomes such as hypertensive disorders, preterm birth (particularly with iatrogenic aetiology), gestational diabetes, foetal distress and reduced foetal growth.^{1–4} In contrast, pregnant women with complete or boosted vaccination status showed reduced risks of severe morbidity and complications compared to unvaccinated, underscoring the importance of vaccination coverage.⁵ Two studies from the same consortium, published in The Lancet Regional Health – Europe, reinforce the importance of COVID-19 vaccination in reducing risks of adverse outcomes, including stillbirth and preterm birth.^{6,7}

In a population-wide study by Raffetti and colleagues,⁶ data from 865,654 pregnancies, of which 60,134 (6.9%) affected by with COVID-19, between 8th December 2020 and 31st December 2021 in England and Wales were analysed. The study showed that pre-conception vaccination, particularly with mRNA vaccines, significantly reduced risks of preterm birth, small for-gestational age infants (SGA), and stillbirth. This population was classified into vaccinated and unvaccinated, focusing on pre-conception vaccination, and several confounders were considered, such as prevalent viral strain. The findings confirmed the well-known association of COVID-19 with adverse pregnancy outcomes, with greater risks in the third trimester and within 14 days from diagnosis. Furthermore, the study confirmed that COVID-19 vaccination, particularly with mRNA, was associated with a reduced risk of preterm birth (hazard ratio [HR]: 0.9; 95% CI: 0.86–0.95), very preterm birth (HR: 0.84; 95% CI: 0.76–0.94), SGA (HR: 0.93, 95% CI 0.88–0.99) and stillbirth (HR: 0.67, 95% CI 0.49–0.92), whereas the risk of venous thromboembolism was slightly higher with the viral-vector vaccine,

although the incidence remained low. Similarly, Suseeladevi and collaborators,⁷ analysed data from 186,990 singleton pregnancies between 25th May 2021 and 28th October 2022 in England. They showed that pre-conception vaccination, particularly with mRNA vaccines, was associated with a significantly reduced risk of adverse outcomes, including early preterm birth (HR: 0.74, 95% CI 0.63–0.88), SGA after 36 weeks of gestation (HR: 0.94; 95% CI: 0.88–1.00) and stillbirth in the case of the mRNA vaccine (HR: 0.72, 95% CI 0.52–1.00). Slightly greater risk of venous thromboembolism after viral-vector but not after mRNA vaccine was also shown (HR1.54: 95% CI: 1.10–2.16).

In summary, the results from both studies suggest that pre-conception vaccination, particularly with mRNA vaccines, is associated with significant reductions in adverse pregnancy outcomes. However, the actual real-world benefits, considering the baseline incidence of these conditions, are more modest. Vaccination reduced the risk of preterm birth by about 10% (translating to 10 fewer cases per 1000 pregnancies), very preterm birth by 16% (corresponding to a decrease from 15 to 13 cases per 1000 pregnancies), SGA by 7% (implying about 6 fewer cases per 1000 pregnancies) and stillbirth by 33% (resulting in about 2 fewer cases per 1000 pregnancies). Although viral-vector vaccines increase venous thromboembolism risk by 54%, the absolute increase is small, rising from 0.2% to 0.3% (1 extra case per 1000). Nonetheless, given the low absolute increase in venous thromboembolism risk and the more substantial reductions in other adverse outcomes, COVID-19 vaccination remains beneficial, especially with mRNA vaccines.

Analyses of both studies warrant additional comments concerning thrombotic risks. Firstly, COVID-19, even in milder forms, increases the risk of venous thromboembolism, particularly in unvaccinated women. Secondly, COVID-19 favours placental thrombosis potentially leading to dysfunction and damage of the trophoblast. This event is the final common pathway involved to different extent in various adverse outcomes including preterm birth,^{8,9} preeclampsia and foetal growth restriction, more common in COVID-19 infected pregnant women. Therefore, future studies may assess the extent to which heparin treatment, often used in pregnancies complicated by symptomatic COVID-19, may prevent some abnormal outcomes. Importantly, the



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findings on venous thromboembolism should not lead to vaccine hesitancy, as the risk increase associated with viral-vector vaccine is probably much lower than that caused by the disease.

The evidence from these studies reinforces the importance of COVID-19 vaccination for women of reproductive age, particularly those planning to conceive within the next year. While mRNA vaccines are the most effective and safest option, any vaccination is preferable to remaining unvaccinated. This is particularly relevant in the current post-pandemic epidemiological phase, where reduced perceptions of risk generate less concern than in the past, potentially resulting in decreased vaccine uptake. However, viral circulation persists as it transitions to an endemic state, and this may lead to an increase in abnormal pregnancy outcomes. A major clinical translation of this evidence should be to increase patient monitoring in the first two weeks following diagnosis of COVID-19, particularly to mitigate the risk of stillbirth in the third trimester. This risk is frequently associated with placental dysfunction and may be predicted by progressively more sophisticated prognostic models, integrating maternal variables, ultrasound, Doppler studies and biochemical indicators, with the aid of artificial intelligence.¹⁰

Contributors

Paolo Ivo Cavoretto: methods and conceptual design, draft writing, revision, supervision; Antonio Farina: draft writing, revision, supervision.

Declaration of interests

The authors have no competing interests related to this article.

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