Hepatitis E vaccine and fetal loss: the potential pathophysiological basis

Authors' reply

We appreciate the insightful comments by Kuan Liu and Qiuwei Pan regarding our study on the potential fetal risks associated with the administration of the hepatitis E virus (HEV)239 vaccine within 90 days before pregnancy or during pregnancy.[1] The observed elevated risk of miscarriage linked to HEV239 vaccination is a concern that merits further investigation. The hypothesis proposed by Liu and Pan about the role of immune responses, particularly the activation of inflammatory pathways by virus-like particles of the HEV239 vaccine,[2] offers a perceptive direction for understanding the underlying mechanisms of our findings, especially since the elevated risk of miscarriage was specifically related to vaccine exposure in the 90 days before pregnancy and during pregnancy.

We agree that exploring the immune system's role, especially during the critical early gestation period, is essential. The idea that virus-like particles might trigger an adverse inflammatory response, possibly through NLRP3 inflammasome activation as suggested by Liu and Pan, is an intriguing hypothesis that warrants further exploration. Although our study did not focus on immunological aspects, we emphasised the need for a detailed examination of the placental–fetal interface and the immune environment, as this could yield valuable insights.[1] The suggestion to analyse aborted fetuses and placentas for evidence of immune-mediated damage is particularly compelling and could help to clarify the potential mechanisms of vaccine-related pregnancy loss.

That said, as has been written elsewhere in discussions of epidemiological studies in general,[3] the establishment of an exact biological mechanism should not be a prerequisite for acceptance of the credibility of adverse events, especially when they are observed in the context of well conducted, randomised, suitably blinded, controlled trials with adequate statistical power. Moreover, after the alarming report of an increased risk of preterm births associated with maternal receipt of the prefusion F protein respiratory syncytial virus vaccine at 24–34 weeks' gestation, our study is the second recent example of a randomised trial that identified important maternal–fetal complications of maternal immunisation with an inactivated vaccine.[4] Although maternal immunisation constitutes a very important approach to preventing illnesses in mothers and infants, the safety of inactivated vaccines given during pregnancy cannot be assumed and deserves rigorous investigation.

We declare no competing interests.

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1 Aziz AB, Dudman S, Julin CH, et al. Receipt of hepatitis E vaccine and fetal loss in rural Bangladesh: further analysis of a double-blind, cluster-randomised, controlled trial. *Lancet Glob Health* 2024; **12:** e1300–11.
2 Mazalovska M, Kouokam JC. Progress in the production of virus-like particles for vaccination against hepatitis E virus. *Viruses* 2020; **12:** 826.
3 Savitz DA. Epidemiology and biological plausibility in assessing causality. *Environ Epidemiol* 2021; **5:** e177.
4 Dieussaert I, Hyung Kim J, Luik S, et al. RSV prefusion F protein-based maternal vaccine—preterm birth and other outcomes. *N Engl J Med* 2024; **390:** 1009–21.