Safety of hepatitis E vaccine in pregnancy: emulating a target trial following a mass reactive vaccination campaign in South Sudan

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Introduction

Hepatitis E causes high mortality among pregnant women, with case fatality risks over 30% and adverse fetal outcomes. There is an evidence gap on the safety of the only licensed vaccine, Hecolin®, in pregnancy. In 2015, WHO recommended vaccine use in response to outbreaks, including pregnant women. In 2022, the first mass reactive vaccination campaign against Hepatitis E was conducted in Bentiu displaced persons camp in South Sudan. We aimed to determine whether vaccination against hepatitis E in pregnancy increased the risk of fetal loss in a cohort of vaccinated and unvaccinated pregnant women.

Methods

An exhaustive pregnancy census was conducted from 16 May 2022 until 30 June 2022 after the second vaccination round, and women were revisited 28 days after delivery date to document the pregnancy outcome. We used an emulated target trial framework to address biases inherent in observational studies. We matched (1:1, with replacement) vaccinated to unvaccinated women on age, gestational age, and vaccination propensity score, and we estimated cumulative incidence functions for fetal loss in vaccinated compared with unvaccinated women using the Nelson-Aalen estimator.

Ethics

This study was approved by the MSF Ethics Review Board and by the South Sudan Ministry of Health Research Ethics Board.

Results

Among 2741 women who had a pregnancy outcome after the start of the vaccination campaign, 67 (2.4%) were vaccinated before conception, 2036 (74.3%) were vaccinated during pregnancy, and 638 (23.3%) were not vaccinated. Among the 2407 women retained in the matched analyses, the cumulative risk of fetal loss in women vaccinated during pregnancy was 6.38% (95% CI 4.93–7.26) compared with 6.26% (3.9–9.19) among unvaccinated women (risk ratio [RR] 1.02 [95% CI 0.64–1.53]). In an analysis restricted to women vaccinated during pregnancy with less than 90 days gestation, the cumulative risk of miscarriage was 11.01% (95% CI 8.45–13.13) among vaccinated women and 11.62% (6.45–17.09) among unvaccinated women (RR 0.95 [95% CI 0.59–1.66]). In sensitivity analyses, we explored the impact of different matching criteria on the estimated RR and found no qualitative differences with the main analyses, with no evidence of increased risk of fetal loss among vaccinated women.

Conclusion

We used an emulated target trial methodology with matching to simulate a vaccine trial in pregnant women after a reactive vaccination campaign. This robust analytical method simulating a vaccine trial attempts to control for bias inherent in observational data. We found no evidence for increased risk of fetal loss among women vaccinated during pregnancy.

Conflicts of interest

All authors declare no competing interests.