Effectiveness of booster (third-dose) COVID-19 vaccination during pregnancy: a target trial emulation study using 4 European databases

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Background

Multiple studies suggest that mRNA vaccines are safe and effective in pregnancy. However, most of the available data is short-term and focussed on primary vaccination.

Objective

To assess the effectiveness of a third mRNA COVID-19 vaccine to prevent COVID-19 infection and COVID-19-related hospitalisation among pregnant women.

Methods

We used primary care data from the UK, linked primary-hospital data from Spain, and linked nationwide registries from Norway and Sweden, all with complete vaccination records.

Exposure was a 3rd mRNA COVID-19 vaccine dose received during pregnancy (≤34 gestational weeks), compared to unboosted pregnant women eligible for vaccination (≥90 days since 2nd dose). Outcomes were COVID-19 infection (positive test/diagnosis) and COVID-19-related hospitalisation (admission with a COVID-19 record from 21 days before to 3 days after).

Cohort enrolment followed a sequential matching 1:1 by calendar week from 10/2021 to 3 months before the end of data (UK: 11/2023, Spain/Norway/Sweden: 08/2023). Exposed persons were matched to eligible comparators based on propensity scores (nearest neighbour, 0.2 calliper) with exact matching on age and gestational time. Follow-up began at index date (vaccination date of exposed pair) and ended at the first of: 1) outcome of interest, 2) pregnancy end, 3) death/end of data, or 4) next COVID-19 vaccination (per-protocol effect). Controls who received the dose of interest could later contribute as exposed if a new match was found.

Bias was assessed using Standardised Mean Differences (SMD) for diagnoses and prescriptions, and Negative Control Outcomes (NCOs). Country-specific Hazard Ratios (HR) were estimated using Cox regression, and meta-analysed using random effects models.

Results

We included 35,278 pregnancies (UK: 3,798, Spain: 4,428, Norway: 19,908, Sweden: 7,144), mostly enrolled between December 2021 and January 2022. Median follow-up ranged from 43 to 117 days, covering the Omicron COVID-19 wave. SMD and NCO results suggested no residual confounding after matching.

HR (95% CI) for COVID-19 infection: UK 0.70 (0.52-0.93), Spain 0.76 (0.65-0.89), Norway 0.42 (0.38-0.45), Sweden 0.80 (0.71-0.91), meta-analysis 0.65 (0.47-0.88). HR for COVID-19-related hospitalisation: Spain 0.81 (0.38-1.72), Norway 0.52 (0.35-0.77), Sweden 0.43 (0.21-0.90), meta-analysis 0.54 (0.40-0.74). No differences were seen by gestational trimester or vaccine brand.

Conclusion

A booster (3rd dose) of mRNA COVID-19 vaccine during pregnancy reduced the risk of COVID-19 infection by a third, and almost halved COVID-19 hospitalisation. These findings reinforce the benefit of COVID-19 vaccine boosters in pregnancy.

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