DSEN ABSTRACT

Safety and effectiveness of influenza vaccine during pregnancy—a systematic review

Summary

- Seasonal influenza vaccination during pregnancy may be associated with reduced risk of lab-confirmed influenza and hospitalization due to lab-confirmed influenza in both mothers and infants. However, the certainty of the available evidence is low to very low.
- Uncertain evidence suggests maternal vaccination for seasonal influenza does not affect birth outcomes or infant death through six months.
- GRADE assessments demonstrated serious concerns regarding the certainty of evidence for many outcomes. These concerns stemmed mainly from risk of bias, but also incorporated issues with inconsistency, indirectness, and imprecision.

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What is the issue?

Pregnant women are at higher risk of influenza-related complications compared to non-pregnant women. To mitigate these risks, in 2007, the Canadian National Advisory Committee on Immunization (NACI) expanded a recommendation that pregnant women with pre-existing comorbidities be vaccinated for influenza to include all pregnant women, regardless of risk. Since that time, many primary research studies, mainly observational in design, have been conducted on the safety and effectiveness of influenza vaccines during pregnancy.

What was the aim of the study?

The Public Health Agency of Canada has recognized that several primary studies have recently been published on the safety of influenza vaccination during pregnancy. To support further guidance from NACI, a de novo systematic review (SR) was proposed to answer the following review questions:

1. Are influenza vaccines safe for women and their unborn and newborn children, if received at any time during pregnancy?
2. Are influenza vaccines effective for preventing influenza and its complications for women and their newborn children, if received at any time during pregnancy?

How was the study conducted?

A protocol was registered with the PROSPERO registry (CRD42020159030) and posted on the Open Science Framework. We searched Medline, Embase and the Cochrane Register of Controlled Trials to identify randomized controlled trials (RCTs) and non-randomized studies that compared the effects of seasonal or pandemic influenza vaccines to those of placebo, active control, or no vaccine, given at any time during pregnancy, on outcomes of interest in women and their children, through pregnancy to 6 months of age. Study selection involved multiple reviewers, using a liberal accelerated approach. Standard methods for data collection and risk of bias (RoB) appraisal were used. Random effects meta-analyses (MA) were used for most endpoints, while descriptive synthesis was used in cases of high clinical heterogeneity. We used the GRADE framework to appraise the certainty of the evidence for a set of key outcomes.

What did the study find?

- Totals of 8 RCTs, 63 cohort studies and 14 case-control studies were included.
- ***Efficacy***: RCT evidence indicated seasonal influenza vaccination during pregnancy moderately reduced lab-confirmed influenza (LCI) in mothers and infants (VE = 50% and 37%), though with low-certainty evidence due to RoB and imprecision concerns. Maternal vaccine effectiveness for LCI was significant within six months postpartum but not before delivery. In infants, vaccine effectiveness for LCI waned from birth (VE = 61%) to six months (VE = 24%), with significant protection against hospitalization for LCI for both mothers and infants in individual studies. No impact on infant death was observed, and synthesis for influenza-like illness was not possible due to high heterogeneity.
- ***Safety***: No significant safety concerns were found, though the evidence was of low to very low certainty due to the observational designs and concerns about RoB, inconsistency, and imprecision. MAs for spontaneous abortion, preterm birth, small-for-gestational-age birth, and low birthweight showed no significant risk differences. Regarding stillbirth, one study suggested protective effects of vaccination after the influenza season but not before or during it, and only for preterm—not full-term—infants. Another study found no effect of maternal vaccination on stillbirth at any time of year. Due to limited data, diverse outcome definitions, varied follow-up periods, and lack of adjustment for critical confounders, MAs for congenital anomalies and maternal non-obstetric adverse events could not be conducted; no significant effects were identified for these outcomes.

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