MI-CRE 2025 Annual Research Symposium and Policy Forum

Association between first trimester medication exposure in pregnancy and congenital anomalies: A scoping review of cohorts, exposure, trimester, and congenital anomaly definitions

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Disclosure of Interests Statement: The authors have no conflicts of interest to declare.

Is the presenter an HDR student? Yes

Has this research been submitted or presented elsewhere? If so where and when? The manuscript has recently been submitted to Pharmacoepidemiology and Drug Safety.

Abstract

Background and Aims: The risk of congenital anomalies following first trimester medication exposure is an important indicator of medication safety during pregnancy. Retrospective cohort studies using routinely collected data are commonly used to assess this risk, yet methodological inconsistencies, such as how cohorts, exposures, timings, and outcomes are defined, can compromise reproducibility and validity. This scoping review examined the methodologies used in retrospective cohort studies assessing the association between first trimester prenatal medication exposure and congenital anomalies.

Design and Methods: Medline, PsycInfo, Embase, CINAHL, and Global Health were searched for retrospective cohort studies published in English between 2014 and 2024 examining the association between first trimester medication exposure and congenital anomalies. Screening and data extraction were performed by two reviewers, using Covidence.

Results: A total of 156 studies were included. Most were conducted in Europe (56%) using registry or population-registry data (87%). Common exclusions included stillbirths (58%), multiple pregnancies (41%) and exposure to teratogenic medications (39%). Exposure was typically defined as a minimum of

one prescription during pregnancy (79%), however, the definition of the start of pregnancy varied across studies: 29% used the date of the last menstrual period, while 42% used the estimated day of conception, with the remaining studies not providing a definition. The end of the first trimester was most commonly defined as week 13 (30%), week 12 (16%), or week 14 (15%), with a substantial proportion (31%) leaving it undefined. There was variation in the types of anomalies considered, with chromosomal (48%), minor (14.5%), and genetic anomalies (13.5%) frequently excluded. Comparison groups included untreated individuals without the condition (65%), untreated individuals with the condition (22%), or alternative treatments (23%).

Conclusions: Substantial methodological variation exists in studies examining first trimester medication exposure and congenital anomalies. This variation may arise both from inherent differences in data sources and from discretionary methodological decisions made by investigators. Standardised definitions are needed to improve consistency, reliability, and interpretability of research in this field.