Pregnancy Pharmacoepidemiology: How Often Are Key Methodological Data Elements Reported in Publications?

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DISCLOSURES

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BACKGROUND

- Key information needed to fully understand studies on drug utilization and safety in pregnancy is sometimes omitted from publications—e.g., how the date of beginning of pregnancy was ascertained or whether multifetal pregnancies are included in the study population—which can impact the prevalence of some outcomes.
- This missing information can also limit researchers' ability to compare results across studies.

OBJECTIVES

- To identify key methodological data elements necessary for understanding observational pharmacoepidemiological research in pregnancy
- To quantify the proportion of studies that report these key data elements in a sample of published studies

METHODS

- Key methodological data elements were identified from the pregnancy pharmacoepidemiology draft guidelines from the Food and Drug Administration[1] and the European Medicines Agency,[2] relevant literature, and subject matter knowledge.
- These elements included pregnancy start and end (source of information); mother-infant, birth certificate, and other linkages (process, success rate); the composition of the study population (whether multifetal pregnancies, non-live births, and fetuses with various anomalies were included in the study population), and analytical aspects (unit of analysis, intrafamily correlation).
- We searched PubMed for observational studies published in 2015-2018 on drug utilization or safety during pregnancy. After screening of titles and abstracts, full-text review was conducted for a sample of 50 eligible study reports. For quality control, an independent reviewer confirmed the extracted data against the publication. We estimated the prevalence of the reporting of key data elements across studies.

RESULTS

- The PubMed search retrieved 1,981 entries; data were extracted from a convenience sample of 50 eligible papers (Figure 1). Of these, 6% were published in epidemiology or pharmacoepidemiology journals, 16% were drug utilization studies, and 84% were safety studies. The mean study size was 109,060 subjects.
- None of the studies reported having been conducted to meet regulatory requirements, even though some studies were analyses of spontaneous reports in pharmacovigilance databases or pregnancy exposure registries maintained or funded by pharmaceutical companies.
- 33% of studies reported the method for determining pregnancy start (Table 1); 59%, whether the study population included multifetal pregnancies; 44%, whether more than one pregnancy per woman was included; 61%, fetuses with major congenital malformations; 17%, fetuses with chromosomal abnormalities; and 85%, non-live births (Table 2). Of the 5 studies that sought mother-infant linkage, 40% described the process, reported the linkage success rate, and specified which outcomes had been ascertained from maternal or infant files (Table 3).
- The unit of analysis was reported for 100% of studies with pregnancy outcomes and for 89% of studies with fetal or infant outcomes (Table 4). Among the studies with more than one pregnancy/offspring per woman, 27% reported methods to address sibling correlation (Table 4).
- Often, the key information was not presented in the methods but was mentioned for the first time in the results or discussion sections.

Table 1. Source of Information on Dates and Beginning of Pregnancy

#	Item	Why Considered Relevant	Studies With Information, n/N (%)	Example of Information Provided
1.	**Source of information for beginning of pregnancy (e.g., electronic algorithm, ultrasound)**	• To give a clear frame for exposure ascertainment in studies where the gestational timing of exposure is important.	16/48 (33.3%)	"Gestational age was determined by ultrasound during first trimester or, if not available, by the last menstrual period."[3]
2.	**Source of information for pregnancy outcome date (e.g., recorded codes for spontaneous abortion, date estimated using an algorithm)**	• If no reliable records for date of birth or other pregnancy outcomes are available, this date may need to be estimated, creating a challenge for mother-infant linkage and exposure ascertainment.	40/46 (87%)	"…The date of birth of the offspring and the gestational age at birth that was recorded in the MEDECHO database."[4]

Note: 50 articles were reviewed. For some studies, some items evaluated in this study were not applicable; those items were removed from the denominator of percentages reported in that row. For example, for a cross-sectional study on the utilization of medications in hospitalized women who are currently pregnant, the item source of information on date of birth was not applicable. This study was removed from the denominator for the column "Studies With Information." Red background was used for cells with percentages of 0%-25%, yellow for 26%-75%, and green for 76%-100%

Table 2. Composition of the Study Population

#	Item	Why Considered Relevant	Studies With Information, n/N (%)	Example of Information Provided
3.	**Multifetal pregnancies included in study population?**	• To assess the potential for intrafamily correlation. • To provide context on whether the study population is at greater risk for outcomes that are known to be associated with multifetal pregnancies.	29/49 (59.2%)	"All pregnancies of single and twin births were considered."[5]
4.	**More than one pregnancy per woman included in study population?**	• To understand the composition of the study population. • To identify the potential for intrafamily correlation.	20/45 (44.4%)	"…131 women (144 pregnancies) were exposed…"[6]
5.	**Fetuses with chromosomal abnormalities included in study population?**	• To assess the potential for recall bias in self-reported exposure. • To understand the outcome definition in research on congenital malformations (most infants with chromosomal abnormalities have congenital malformations, some of which might be related to the chromosomal abnormality).	8/46 (17.4%)	"Birth defects include genetic syndromes and chromosomal abnormalities, but both these types of abnormalities were excluded from the calculation of the birth defect rates."[7]
6.	**Fetuses with major malformations included in study population?**	• To assess the potential for recall bias in self-reported exposure. • To put in context results from analyses of outcomes that might be affected in the presence of major malformations, such as infant's size at birth.	28/46 (60.9%)	"We analyzed…among non-malformed singleton controls in the National Birth Defects Prevention Study."[8]
7.	**Fetuses with minor malformations included in study population?**	• To understand whether fetuses with minor malformations are considered noncases in research on major congenital malformations.	18/46 (39.1%)	"Table 3. All observed major and minor birth defects…"[9]
8.	**Are non-live births included in denominator?**	• To assess any potential for bias due to not including in the population all fetuses at risk.	34/40 (85%)	"In this population based study we included women…who gave birth to a live singleton infant…"[10]

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Table 3. Mother-Infant, Father-Infant, and Birth Certificate Linkages

#	Item	Why Considered Relevant	Studies With Information, n/N (%)	Example of Information Provided
9.	**If mother-infant linkage implemented: process described?**	• To understand the risk for mismatches and lack of matches when linking maternal and infant files in the data source.	2/5 (40%)	"We linked mothers with their infants in both data sources deterministically using family identifiers and delivery dates corresponding to birth dates."[11]
10.	**If mother-infant linkage implemented: success rate reported?**	• To quantify any loss of study participants. • To assess the potential for bias from loss of study participants that is differential on key characteristics (e.g., exposure).	2/5 (40%)	"Of all the delivering women, 677,075 (62.8%) successfully matched to a newborn."[12]
11.	**If mother-infant linkage implemented: information taken from maternal vs. infant files?**	• To assess any risk for under-ascertainment of outcomes that can be recorded in either maternal or infants files, such as intrauterine growth restriction/small for gestational age.	3/6 (50%)	"Medical documentations are requested by us from obstetricians in cases with an unusual pregnancy course (e.g., stillbirth, elective termination of pregnancy) or from paediatricians if anomalies are reported in the infants."[13]
12.	**If father-infant linkage implemented: process described?**	• To understand the risk for mismatches and lack of matches.	1/1 (100%)	"The personal identification number enabled identification of paternity and linkage to pregnancy data in the MBRN…"[14]
13.	**If father-infant linkage implemented: success rate reported?**	• To quantify any loss of study participants. • To assess the potential for bias from loss of study participants that is differential on key characteristics (e.g., exposure).	0/1 (0%)	None available

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Table 4. Analytical Aspects

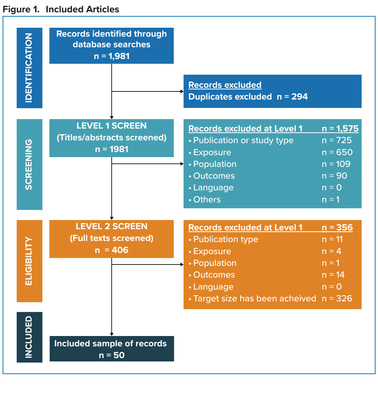
#	Item	Why Considered Relevant	Studies With Information, n/N (%)	Example of Information Provided
14.	**Unit of analysis for pregnancy outcomes**	• To assess whether the denominator for proportions and rates is correct, as each woman included in the study might have contributed more than one pregnancy, and each pregnancy might have had more than one count of some outcomes. • To assess the potential for correlation of pregnancy outcomes.	34/34 (100%)	"…The proportion of infections in mothers treated with anti-TNFα drugs during gestation was higher in the exposed cohort…"[15]
15.	**Unit of analysis for fetal or infant outcomes**	• To assess whether the denominator for proportions and rates is correct, as each pregnancy included in the study can result in more than one offspring, and offspring might have had more than one count of some outcomes. • To assess the potential for correlation of fetal or infant outcomes.	31/35 (88.6%)	"Birth defects were not mutually exclusive, so total count of infants with any birth defect may add up to fewer than total birth defects in sample." (table footnote)[16]
16.	**Gestational age at start of follow-up**	• To assess the potential for bias due to left truncation and left truncation that is differential by exposure status; this is especially important in studies that prospectively recruit women who are already pregnant.	20/43 (46.5%)	"The median gestational age at recruitment was 39 days (range, 4-91 days)…"[17]
17.	**Intrafamily correlation considered?**	• Sibling clusters in the study population determine a correlation that, if considered substantial, should be accounted for in the analysis in order to obtain correct estimates.	12/45 (26.7%)	"…The treatment effects were assessed with the use of generalised estimating equations to account for the potential correlation between pregnancies within a patient…"[18]

Note: 50 articles were reviewed. For some studies, some items evaluated in this study were not applicable; those items were removed from the denominator of percentages reported in that row. For example, for a cross-sectional study on the utilization of medications in hospitalized women who are currently pregnant, the item source of information on date of birth was not applicable. This study was removed from the denominator for the column "Studies With Information." Red background was used for cells with percentages of 0%-25%, yellow for 26%-75%, and green for 76%-100%

DISCUSSION

- In this review of 50 publications on drug utilization or drug safety in pregnancy, reporting of key methodological data elements varied broadly across data elements.
- For transparency and to promote a full understanding of decisions behind the study design, we recommend that information on whether studies have been conducted to meet regulatory requirements be included in scientific publications.
- To facilitate reading and comprehension of papers, we recommend that all key methodological data elements related to study design be presented in the methods section.
- We propose that a short checklist for pregnancy pharmacoepidemiology studies, possibly shaped like a section of the ENCePP checklist for study protocols (http://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml), might help improve the reporting of key methodological elements.

Figure 1. Included Articles



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CONCLUSIONS

- In this sample of pregnancy pharmacoepidemiology studies, completeness of methods reporting can be improved. A pregnancy-specific checklist would help to increase transparency in the dissemination of study results.