Commentaries

Safe Expectations: Current State and Future Directions for Medication Safety in Pregnancy Research

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ABSTRACT

Medication use in pregnancy is common, but information about the safety of most medications in pregnant women or their infants is limited. In the absence of data from randomized clinical trials to guide decisions made by regulators, clinicians, and patients, we often have to rely on well-designed observational studies to generate valid evidence about the benefits and risks of medications in pregnancy. Spontaneous reporting, primary case–control and cohort studies, pregnancy exposure registries, and electronic health data have been used extensively for studying medication safety in pregnancy. This article discusses these data sources, their strengths and limitations, and possible strategies and approaches to mitigating limitations when planning studies or interpreting findings from the literature. Strategies discussed include combining data sources across institutional or national borders, developing and using more sophisticated study designs, and taking advantage of existing analytic methods for more complex data structures, such as time-varying exposure or unmeasured confounding. Finally, we make recommendations for study designs that aid in better risk-related communication. (*Clin Ther*. 2019;41:2467–2476)

Key words: medications in pregnancy, pharmacoepidemiology.

INTRODUCTION

While it is now well-recognized that exposure to medications during pregnancy may pose a risk to the mother or fetus, until the mid-20th century many within the medical field believed that the uterus and placenta acted as barriers to harmful substances, protecting the developing fetus.[1] Our views have changed markedly, partly due to a number of drug "crises" that have occurred within the past 6 decades, the most notable being the case of thalidomide. Thalidomide was a widely used hypnotic/sedative during the late 1950s. In the early 1960s, 2 clinicians independently recognized that use during pregnancy was associated with severe limb malformations and a number of other anomalies.[2] The recognition of the adverse effects of thalidomide on the developing fetus occurred several years after the initial marketing of the product, with >10,000 infants affected worldwide. The case of thalidomide not only increased the awareness of health care providers and the general public about the potential harm of medications in pregnancy, it also influenced drug regulations in the United States and internationally, leading to enhancements to drug-safety systems and requirements for the preclinical testing of medications.

The thalidomide disaster focused substantial attention on immediate pregnancy outcomes following drug exposure, such as malformations. Perhaps the first case that demonstrated the long-term effects of *in utero* exposure to medications involved diethylstilbestrol, which was prescribed for the prevention of spontaneous abortion and preterm births in millions of pregnant women in the United States and Europe during the 1950s and 1960s.[3] In

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1970, a report by Herbst et al described a cluster of cases of adenocarcinoma of the vagina in patients aged 15–22 years in one Massachusetts hospital, with a subsequent report in 1971 that described a strong association with prenatal exposure to diethylstilbestrol.[4] The findings were particularly striking given that adenocarcinoma of the vagina was extremely rare in that age group.

Throughout the decades since the thalidomide disaster, a number of other reported associations between *in utero* exposure to medications and adverse pregnancy and birth outcomes have led to increased caution and warnings (eg, labeling changes). However, a number of purported associations have not been supported by the totality of the pharmacoepidemiologic evidence. One example is the case of Bendectin (pyridoxine/doxylamine/dicyclomine), a medication widely prescribed for the alleviation of nausea and vomiting in pregnant women. In the early 1970s, reports of infants born with various malformations after *in utero* exposure to Bendectin were publicized in the media, causing public concern.[5] While several epidemiologic studies suggested an association between *in utero* exposure to Bendectin and various malformations, many more studies reported no association.[5–7] Even with this evidence of safety, the manufacturer discontinued manufacturing the drug in 1983 due to numerous lawsuits and adverse publicity.[5] Another manufacturer introduced a medication with the same ingredients as Bendectin (doxylamine-pyridoxine) in 2013, and it is the only medication currently approved in the US for nausea and vomiting in pregnancy.

While these and other instances highlight the importance of the possible risks of medication use during pregnancy, evidence to support the safety of most medications for use during pregnancy is inadequate. Although preclinical animal studies for teratogenicity and developmental toxicity are required for new drugs, animal models are often not predictive of human risks.[8,9] Premarketing randomized trials to evaluate the safety and efficacy of medications generally exclude pregnant women. In addition, well-designed postmarketing studies of most currently marketed medications have not been performed.[9] Thus, limited data exist to guide decision-making by pregnant women and their health care providers, underscoring the need for rigorous postmarketing observational studies to fill the evidence gap. This article describes currently available data sources for conducting such studies and suggests future directions for improving and refining our approach to assessing the safety of medications in pregnancy.

DATA SOURCES USED IN MODERN POSTMARKETING RESEARCH OF MEDICATION SAFETY IN PREGNANCY

Spontaneous Reporting and Individual Case Safety Reports

Postmarketing data on the safety of medications in pregnancy can be obtained from the spontaneous reporting systems designed to collect safety-related data about medical products in the broader patient population (Table I). For example, the US Food and Drug Administration's (FDA) Adverse Event Reporting System[15] and the Vaccine Adverse Event Reporting System[16] allow manufacturers, health care professionals, patients, and other consumers to report medication-related adverse events, including those that involve pregnant women. The World Health Organization maintains Vigibase, a global database of 19 million individual case safety reports contributed by > 100 countries.[10] In one study, researchers analyzed reports submitted to Vigibase to explore the associations between antipsychotic use during pregnancy and congenital malformations.[17] The study found a higher number of reports of gastrointestinal congenital abnormalities associated with prenatal exposure to antipsychotics. Teratology Information Services, including the European Network of Teratology Information Services, which covers Europe, Israel, and Latin America,[11] as well as the Organization of Teratology Services, which includes North America,[18] provide a counseling resource for pregnant women. Data from these services have been used, for example, to compare effects in metformin-exposed pregnancies to those from an unexposed group, which found that the slightly elevated risk for malformations was likely due to the underlying condition (pregestational diabetes) and not the drug itself.[19]

DATA GATHERED FOR THE PURPOSE OF SURVEILLANCE OR RESEARCH

Case–control Studies of Birth Defects

There have been considerable efforts in collecting data specifically for the surveillance or research of medication safety in pregnancy. Initiated in 1976

Table I. Summary of currently used data sources for research of medication safety in pregnancy, with strengths, limitations, and possible improvements.

Data Source	Example	Strengths	Limitations	Ways to Improve
Spontaneous case reports	Vigibase[10]	Early signal detection	Stimulated reporting bias; lack of data harmonization across systems; does not include noncases	Standardize case report forms across reporting systems
Teratology Information Services	European Network of Teratology Information Services[11]	Early signal detection	Stimulated reporting bias; small sample size	Pool data across Teratology Information Services centers
Case-control studies using primary data	National Birth Defects Prevention Study[12]	Excellent detail on specific birth defects; often highly detailed exposure and confounder data, including genetic and other biological data	Retrospective exposure reporting may induce information bias; limited data on other pregnancy outcomes not used in the creation of the case-control studies	Nest case-control studies in larger population databases; verify exposure data from other sources
Birth cohort studies using primary data	Norwegian Mother and Child Cohort Study[13]	Highly detailed data, including confounders, over-the-counter drugs, genetic and other biological data	Selection bias; small sample size	Link multiple cohorts; nest cohorts in larger population databases
Studies that repurpose existing data	Medicaid Analytic Extract[14]	Sample size; representative sample of the population	Minimal measurement of some important confounders; short follow-up period for some data sources	Augment with linkage to other data sources, such as birth certificates or other population databases

and ended in 2015, the Pregnancy Health Interview Study (previously known as the Birth Defects Study) was a large multicenter case–control study designed to investigate potential associations of medications and other exposures with birth defects.[20] The cases and controls were identified in several US states. Cases included infants with birth defects, and controls comprised infants without birth defects. Trained nurse–interviewers collected data from >51,000 mothers via telephone. In one study, researchers analyzed data from the Pregnancy Health Interview Study and found that folic acid antagonists (eg, trimethoprim, carbamazepine) were associated with higher risks for neural tube defects, cardiovascular defects, oral cleft, and urinary tract defects.[21]

The National Birth Defects Prevention Study is an ongoing case–control study that employs a study design similar to that of the Pregnancy Health Interview Study.[12] In that study, >35,000 women who gave birth to infants with birth defects (cases) and infants without birth defects (controls) in 10 US states have been interviewed. In addition to study of the effects of medication use in pregnancy, the study

also evaluates genetic and environmental factors associated with birth defects. In one study, researchers found that the use of selective serotonin reuptake inhibitors was not associated with an elevated risk for congenital heart defects or most other categories of birth defects.[22]

Pregnancy Exposure Registries

Regulatory agencies such as the FDA may require manufacturers to establish a pregnancy exposure registry to collect data from women who are exposed to certain prescription medications during pregnancy. The risks for maternal or infant outcomes identified from women (and their infants) within the registry are compared with the risks obtained from other sources. In one study that analyzed data from a prospective pregnancy exposure registry, researchers compared the risks for birth defects and pregnancy outcomes among women exposed to natalizumab, a medication used to treat multiple sclerosis, with the risks estimated from the general population. They found that while the rate of congenital malformations was higher in the exposed pregnancies, there was no pattern of specific defects suggesting an effect of drug exposure.[23]

Birth Cohort Studies

Large birth cohorts may also provide opportunities for studying medication safety in pregnancy. Examples include the Norwegian Mother and Child Cohort Study[13] and the Danish National Birth Cohort[24]; each contains data from ~100,000 pregnancies in which participants reported on many exposures, including medication use. Both studies have been successfully linked to population databases, and recently, the cohorts have been combined to permit the study of very rare outcomes, such as cerebral palsy.[25] Importantly, birth cohort studies that ascertain exposure through self-report or interview can capture data on over-the-counter medications, such as acetaminophen, which has been linked to attention deficit/hyperactivity disorder and related symptoms.[26] In addition, detailed confounder data may be much richer in these studies, which was important in a recent assessment of selective serotonin reuptake inhibitor exposure and neurodevelopmental outcomes in children that adjusted for time-varying maternal depression severity.[27]

Existing Data Repurposed for Research

Electronic health data collected as part of routine health care delivery, such as insurance claims data and electronic health record data, have been widely used to generate evidence about the safety and effectiveness of medical treatments. Although these databases are not created for research purposes, they contain longitudinal data on a large number of individuals, including pregnant women and their infants, which enable population-based studies of medication safety in pregnancy.[28] In one study, researchers analyzed data from Medicaid beneficiaries in the United States to assess the association between prenatal exposure of antidepressants and the risk for cardiac defects.[29] The large sample size allowed researchers to examine individual antidepressants and specific cardiac defects. In another study, researchers uses population-based databases (typically also referred to as registries) in Norway to study the association between exposure to either influenza vaccination in the second or third trimester or exposure to influenza infection, and fetal death.[30] They found that vaccination was associated with no increased risk for fetal death, while influenza infection itself increased the risk for fetal death substantially.[30]

Limitations of Existing Data Sources for Research of Medication Safety in Pregnancy

Despite their strengths, each source of data for research on medication safety in pregnancy comes with its own set of limitations. Spontaneous reports are susceptible to under-reporting or stimulated reporting bias. Because these reports by definition come from exposed cases, studies using this kind of data often do not allow for the estimation of absolute risks and may not fully capture long-term adverse outcomes.[31,32] Case–control studies of birth defects often rely on maternal recall, after delivery, of medication use during pregnancy, which may lead to differential exposure misclassification if women who gave birth to infants with birth defects recall their medication use in different ways than do women who gave birth to infants without birth defects.[33] Many pregnancy exposure registries do not achieve the desired sample size and most do not collect data on comparison groups (eg, women who use another drug for the same indication).[34] Birth cohort studies are often too small-scale for confirmatory safety

studies, especially for rare outcomes or rare exposures.[35] Sources of existing data repurposed for research are generally large enough to evaluate rare outcomes or rare exposures, but data on important variables may be insufficiently detailed to offer adequate confounding adjustment.[28] Furthermore, as these secondary data sources rely on insurance claims, billing codes, and prescription fills, misclassification of the exposure, outcome, and confounders can be problematic. Additionally, for administrative cohorts in which eligibility is based on employment status, duration of enrollment is often short, limiting the examination of long-term outcomes.

FUTURE DIRECTIONS FOR STUDIES OF MEDICATION USE IN PREGNANCY

Inclusion of Pregnant Women in Randomized Clinical Trials

Although pregnant women have historically been excluded from randomized clinical trials due to ethics-related concerns, current thinking on this topic has evolved. In a recent draft guideline, the US FDA acknowledged that "development of accessible treatment options for the pregnant population is a significant public health issue."[36] Some situations in which the FDA suggests that including pregnant women in a randomized clinical trial could be ethically defensible include the case of postmarketing trials, in which findings on efficacy cannot be extrapolated to pregnant women or safety cannot be assessed by other methods, provided that adequate nonclinical studies have been completed, and safety is established in nonpregnant women or preliminary safety-related data on pregnant women exist.[36] For preclinical studies, the trial must hold a prospect of direct benefit to the mother or fetus that would not be available outside of the research setting.[36] These recommendations are highly specific to the context of each drug and disease, but the larger point is that there are many situations in which pregnant women can and should benefit from participation in randomized clinical trials. A recent report from the Task Force on Research Specific to Pregnant or Lactating Women provides specific recommendations on moving this initiative forward.[37]

Further Development of Infrastructure and Collaborations for Active Surveillance

Despite movement in the direction of including pregnant women in randomized clinical trials, the bulk of studies of medication safety in pregnancy are still likely to occur in the observational setting. Newer studies of the safety of rarer drugs have taken a lesson from international genetics consortia. A recent initiative, the InPreSS consortium, has pooled nationwide data from the Nordic countries (Norway, Sweden, Denmark, Finland, and Iceland) with Medicaid data in the United States to study the association between stimulant medications and cardiac malformations in infants.[38] While increased risks were noted in databases from individual countries, the small sample size meant that confidence intervals were very wide, making interpretation difficult. The combined analysis allowed for separate models of methylphenidate versus amphetamines, and found that methylphenidate but not amphetamines was associated with an increased risk for cardiac malformations.[38] Smaller-scale initiatives have pooled data from only the Nordic countries,[39] or from public and private payer systems in the United States, as in the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), a multicenter study that includes data from 1.2 million infants in 11 health plans within 9 states.[14] To further improve the validity of its studies, MEPREP linked the health plan data with infants' birth-certificate files, which provide information not otherwise available in the health plan data (eg, gestational age, parity). Using the MEPREP data, researchers investigated the association between trimethoprim/sulfonamide use during the first trimester of pregnancy and the risk for congenital birth defects, which was supported by chart review.[40] There have also been efforts in developing more rapid surveillance capabilities using electronic health data. For example, the FDA-funded Sentinel System, which uses a distributed data network of 17 health plans to monitor the postmarketing safety of approved medical products, is developing standardized analytic tools to facilitate the investigation of emerging safety issues related to medication use during pregnancy.[41]

Examination of Long-term Outcomes

Many studies of medication safety in pregnancy have focused on immediate pregnancy and birth outcomes, such as preterm birth, stillbirth, and congenital malformations. However, there is an increasing recognition that prenatal medication exposure can have profound effects on outcomes beyond pregnancy and infancy. Several medications, including

antidepressants[42,43] and analgesic opioids,[44] have been independently associated with an increased risk for a diagnosis of autism in offspring. Perhaps most worrisome, acetaminophen, widely regarded as safe for use during pregnancy, has been associated with asthma[45] and neurodevelopmental problems in children, particularly attention deficit/hyperactivity disorder or related behaviors.[26] For medications linked to neurodevelopmental problems or delays in early childhood, it is vital to determine whether this association persists into adolescence or adulthood.

Use of Cutting-edge and Proven Methods for Bias Control

Most studies of medication safety do some variation on the following: look for evidence of an exposure (eg, self-report or filling a prescription), and if that exposure falls in the relevant window (eg, first trimester when studying malformations), categorize the mother or fetus as exposed. For short-term, 1-time exposures, such as to antibiotics for a brief infection or opioids for an acute injury, these methods produce satisfactory results. However, many medications are used in far more complicated ways during pregnancy,[46] either with sustained exposure or intermittent use that changes over time, as we might expect to see with anticonvulsant drugs or benzodiazepines, respectively. Failing to account for timing of exposure or cumulative dose can lead to bias from exposure misclassification. Some studies have assessed time-varying exposures by estimating trimester-specific effects of triptans on neurodevelopment[47] and acetaminophen on cerebral palsy,[48] using marginal structural models. Additional methods such as group-based trajectory models[49] and k-means longitudinal cluster analysis[50] have been used to identify groups of women with specific exposure patterns. Future research should consider whether these more complex methods are relevant for the questions they are trying to answer.

Because studies of medication safety in pregnancy rely primarily on observational data, confounding bias is a paramount concern. Multiple methods exist to address measured confounding, and in pharmacoepidemiology, the propensity score method is commonly used. Propensity scoring is a summary score method that involves first fitting a model for the treatment or exposure, deriving a predicted probability of exposure conditional on measured confounders from that model, and then using this probability, known as the propensity score, to reduce confounding in the outcome model via matching, weighting, stratification, or modeling.[51] Newer refinements of the basic propensity score idea include high-dimensional propensity scores[52] and the use of machine learning for confounder selection.[53]

The issue of unmeasured confounding is more complex. One solution is to increase efforts to measure important confounders, as in studies that link multiple data sources together. For example, as discussed earlier, MEPREP linked the health plan data with infant birth certificate files to obtain important variables not available in the health plan data (eg, gestational age, parity).[14] In another example, the Stockholm youth cohort is an intergenerational record-linkage study comprising all individuals under age 18 years living in Stockholm County, Sweden, between 2001 and 2011; the study was created using linked data from multiple administrative, social, and health care databases. Researchers used these data to study the association between prenatal antidepressant exposure and the risk for autism spectrum disorder in offspring.[54]

Unmeasured confounding can also be addressed with analytic or study-design tools. To the extent that they capture some of the variance due to unmeasured confounders using high-dimensional proxy data, high-dimensional propensity scores may control unmeasured confounding.[52] Other methods include sibling-comparison designs, in which siblings born to the same mother but with different prenatal exposure histories are compared with respect to their outcomes.[55] Sibling-comparison designs control for any confounding that is stable over the pregnancies; thus, stable sources of confounding such as genetics and maternal personality, which are difficult to measure in large data sources, are controlled by design. However, sibling-comparison designs are particularly vulnerable to specific biases from selection and carryover effects,[56,57] and should be used with careful attention paid to the confounding structure.

Many studies of medication safety are carried out only in full-term pregnancies or among only live births, as most commonly used data sources have limited capture of data from early pregnancy losses. If the medication under study causes pregnancy loss, this can result in substantial bias, known more generally as selection bias. Huybrechts et al[29] carried out

substantial sensitivity analyses in their study of antidepressant exposure to determine the potential for bias from conditioning on live birth, and found that the effect of exposure on pregnancy loss would need to be extremely strong to result in serious bias. However, in a methodologic investigation, Liew et al[58] noted multiple conditions in which so-called "live birth bias" can be much more problematic. Researchers should carefully assess their research question to determine whether selection bias from conditioning on live birth is a serious threat to validity. Quantitative bias analysis[59,60] is relatively straightforward with widely available tools, and should be a standard component of any research project.

Designing Studies that Aid in Risk-related Communication

An unfortunate side effect of the focus on medication safety is that the reason for taking the medication can be forgotten. Confounding by indication occurs when we attribute a poor outcome to a drug, when in fact it is the reason for taking the drug that causes the poor outcome. The recent focus in designing hypothetical trials may provide an informative way forward:[61] where possible, studies should begin by selecting a group of pregnant women who could plausibly have received treatment. In particular, the treatment decision design has been proposed as a pharmacoepidemiology study design focused on clinical decision making.[62] For long-term medications such as antihypertensives, antidepressants, or anticonvulsants, the relevant clinical decision is often not whether drug treatment should be initiated (the new-user design) but whether therapy should be modified or discontinued during pregnancy. The most important clinical question that pharmacoepidemiology studies in pregnancy must try to answer is, among women with this diagnosis, what is the effect of this treatment versus alternatives?

CONCLUSIONS

For research on medication safety in pregnancy, there are more data resources available than ever before. With international collaborations, sharing of data, and linkage of complementary databases—combined with the development of advanced statistical tools to analyze these data—we may increasingly be able to quickly and accurately answer important questions about the effects of specific drugs, at specific times, on specific outcomes.

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