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Short communication

Field studies versus database studies on the risks and benefits of medication use during pregnancy: Distinct pieces of the same puzzle

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ABSTRACT

Over the past two decades, findings on medication use during pregnancy have been accumulating from observational data. Generally, field studies with prospective recruitment of subjects have better outcome ascertainment, and more control on the longitudinal collection of data, but have lower sample sizes and thus they often lack statistical power to detect increased risks for rare events such as major congenital malformations. In addition, given the rarity of specific drug exposures in a population, even relatively common outcomes, such as low birth weight, may become rare in combination with the specific exposure. On the other hand, administrative databases usually provide larger samples and thus increased statistical power, decrease the probability of selection and recall bias, but often have missing data on potential confounders. Hence, debate amongst researchers, regulators and public health officials has been ongoing with regard to the most appropriate study populations for perinatal epidemiologic research. With this commentary, we aim to highlight the importance of both study populations, which can make complementary and crucial contributions to the iterative determination of causality as well as discuss basic epidemiologic principles that need to be applied in the field of perinatal pharmacoepidemiology for the purpose of causality assessment. This is relevant at present given that the United States Food and Drug Administration (US FDA) has modified their medication label requirements, especially given the international importance of these modifications.

1. Brief report/commentary

Evidence suggests that approximately 75% of women take at least one medication during pregnancy [1]. Given the lack of clinical trial data supporting treatments that are provided in pregnancy, medical care during this period is often less evidence-based than care provided to non-pregnant women or to men. Given the lack of randomized studies of medication safety with pregnant women, observational research is currently the best way to close this important knowledge gap. Both field studies with prospective subject recruitment and administrative (claims) database studies are observational but controversy exists on which should be preferred to collect valid data regarding pregnancy exposures and outcomes.

Until recently, field study designs were the main method utilized to study medications in pregnancy. Pregnant women using medications were recruited in obstetrical or hospital settings, and followed until the end of pregnancy to assess outcomes such as spontaneous or planned abortions, congenital malformations, prematurity, or low birth weight (LBW). The prevalence of adverse pregnancy outcomes was compared to that of pregnant women not using medications or to pregnant women with the same underlying disease who were not using medications. Given the difficulty of recruiting human subjects in general, and of identifying pregnant women taking a specific medication in particular, it became clear that a better framework was needed [2], and thus recruitment from teratology information services (TIS) was initiated. TISs provide telephone counseling to pregnant and lactating women, as well as to women planning to conceive, on the risks and benefits of

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medication treatment. Recruitment via TISs increased subject flow and provided appropriate comparison groups. On the other hand, it has been shown that women calling TISs are of higher socio-economic status (SES) than the general population [3], which can lead to selection bias and limit generalizability. Although recruitment rates were higher, studies often continued to have small sample sizes, which led to lack of statistical power for the majority of medications studied. Indeed, few drugs are associated with adverse reproductive event rates on the order of thalidomide or isotretinoin, which increased the risk of major congenital malformations by a factor of 10 (from baseline risk of 3% to 30%) [4,5]. To detect statistically significant associations for common suspected teratogens, it became clear that studies with much larger sample sizes were needed. Therefore, recently, an increasing number of large administrative (claims) population-based cohorts and pregnancy registries or case-control studies have been built and used for the study of the risks and benefits of medication use during pregnancy [5–9]. Given their increased sample sizes and statistical power, these studies have been able in some cases to show statistically significant associations for adverse pregnancy outcomes for drugs that had not been identified as teratogens or feto-toxic in the past such as valproic acid or selective serotonin reuptake inhibitors for example [10]. This has led to controversies among experts and confusion amongst prescribers and women.

Antidepressants are an example of this phenomenon. Antidepressants, specifically SSRIs, represent one example of a widely prescribed class of medications used in pregnant or potentially pregnant women for which data became available relatively soon after the first drug in this class was marketed 25 years ago. Although a few small studies published in the 1990s suggested an overall increased risk for adverse pregnancy outcomes with exposure to these medications [11,12], sample sizes were often insufficient to rule out increased risks for even the more commonly occurring specific birth defects, such as heart defects, neural tube defects and oral clefts. More recently, some claims database and case-control studies with larger sample sizes have suggested an approximate doubling of the risk for heart defects and other congenital malformations with first trimester exposure to SSRIs [5,6,9,13–17]. Although they showed elevated risk, they were not all statistically significant. In these instances, absence of statistical significance should not be mistaken for absence of effect. Indeed, the sample size required to obtain and odds ratio (ORs) of 2, knowing that the prevalence of heart defects in the general population is approximately 1% [18] and of antidepressant exposure during pregnancy is around 6–7% [19] (with a significance level of 5% and a statistical power of 80%), is 17,500 subjects (out of which 1200 are exposed to antidepressants); using the same pre-defined criteria, 78,830 subjects (out of which 6017 are exposed to antidepressants) are required to study neural tube defects (population prevalence of 0.2% [18]). Hence, large claims databases have large sample sizes but can remain underpowered for very rare events when looking at specific medication exposure. Finally, large claims databases often lack information on potentially important confounders such as whether the women actually took the medication, folic acid use, smoking and alcohol use, and maternal stress, which could result in residual confounding.

Field studies and database studies both have advantages and limitations in our assessment of causation, and complement each other. Indeed, field studies with recruitment in TISs or in hospital or community settings have the advantage of potentially collecting information on known risk factors for adverse pregnancy outcomes such as maternal body mass index, folic acid intake, lifestyles such as smoking and alcohol use as well as information on severity of underlying disease and comorbidities, which are all important variables that are often missing in claims databases. They also have the advantage of being able to have standardized dysmorphology evaluations of the child or other validated measures of major congenital malformations, which are essential to identify patterns of malformations. However, they often lack statistical power which increases the likelihood of non-statistically significant associations, they often have incomplete information on dosage and timing of medication exposure during pregnancy, suffer from exposure misclassification (recall bias) when exposure assessment is reported by the mother at the end of pregnancy, and they are not population-based and thus not readily generalizable. Data collection related to behaviors perceived as sensitive or illegal (elective termination of pregnancy, alcohol, tobacco or drug use in pregnancy) might also be underreported during interviews or medical encounters.

Administrative database studies have large sample sizes, hence increased statistical power, are able to study medication class and type effects as well as dose-response effect, can assess timing of medication filling during pregnancy, and are often population-based which decreases selection bias. Although compliance and non-adherence can be difficult to assess [20], some have reported high validity of data on prescription fillings to quantify medication use during pregnancy [21]. The validity of data on adverse pregnancy outcomes has also been reported [22–24]. However, claims databases often have missing information on potential confounders, and only provide information on prescribed medication use as well as over-the-counter medication use when prescribed by the treating physician. Although data on clinical measures such as serum levels are missing, studies have shown that pregnant women usually maintain or decrease their pre-pregnancy dosage during gestation [19]. It also remains that the ability to detect a statistically significant association depends on the number of exposed cases, and thus can be limited in administrative database studies of rare events such as major congenital malformations, which is also true in prospective studies.

A limitation both study types suffer from is left truncation [25] with the calculation of miscarriage prevalence. When assessing the prevalence of miscarriage, usually only clinically detected prevalences are displayed. These prevalences might be biased. Indeed, the subjects that can be observed in a study exclude those women who already had the event, i.e., the spontaneous abortion due to delayed study entry. Data from TIS are affected by this kind of bias as women might call in for information only later in pregnancy. Although pregnant women usually see their health care providers at the end of their first trimester of pregnancy on average, all data collection, especially on medication use, are assessed prospectively as part of usual managed care in claims databases. Therefore, studies using claims databases are minimally affected but only consider clinically detected spontaneous abortions. Ideally, databases should include women at an earlier stage in pregnancy because they are recorded as soon as they have any diagnosis related to pregnancy, which also includes diagnoses related to early spontaneous abortion. Nevertheless, unless databases follow all women from pre-conception, left truncation still plays a role [26].

Field and administrative database studies are complementary. Both are sources of data on which inclusion and exclusion criteria are applied to generate study populations. In order to better understand the evidence, general epidemiologic principles have to be applied to the field of perinatal pharmacoepidemiology. Indeed, given the observational nature of studies we rely on to quantify the risk of medication exposure during the gestational period, a number of methodological issues need to be addressed in order to weight each study results.

1.1. Study design

Randomized controlled trials (RCTs) are experimental designs. Epidemiology study designs include cohort studies, case-control studies, and case series reports; pregnancy registries, and