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Sources of bias in signals of pharmaceutical safety in pregnancy

Abstract

Every year scores of new pharmaceuticals enter the market, almost never with human fetal safety data. Such data typically accumulate during the first years of clinical use, in the form of case reports, case series, prospective and retrospective cohorts and case control studies. All of these methods suffer from serious sources of bias, often leading to alarming signals of teratogenicity that are later found to be false. This review highlights major sources of bias, including the bias against the null hypothesis in its different forms, ascertainment and recall bias, in fetal exposure to pharmaceutical molecules.

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Because randomized controlled trials are very rarely carried out during pregnancy, and almost never during the first trimester of pregnancy, understanding the cumulative impact of bias is critical for evaluating teratogenic risk and for effectively counseling pregnant women exposed to pharmaceuticals.

Since the thalidomide disaster, medicine is practiced as if every medicinal molecule is a potential human teratogen. While, in reality, very few drugs have been proven to adversely affect the human fetus, women and their health care providers hesitate or even refuse to prescribe or take pharmaceuticals during pregnancy - sometimes even for life-threatening conditions [1].

Due to obvious ethical constraints, randomized control trials are almost never conducted during pregnancy. Even when control trials are conducted, their statistical power to show increased fetal risks is very limited; hence, the assessment of safety of drugs during pregnancy is almost entirely based on observational studies. Such studies, using either prospective or retrospective cohorts or using case control studies, involve collecting data from exposed and unexposed mothers (in cohort studies), or infants who have or have not suffered a given adverse event (in case-control studies). These designs are subject to a large list of potential pitfalls; leaving these pitfalls unrecognized can lead to serious errors in interpretation, as will be documented in the next section. Acknowledging and addressing confounding factors in maternal fetal drug exposure is critical if one considers that every year hundreds of new pharmaceuticals enter the market.

We will describe major sources of confounders and bias typical of observational studies.

Sample Size

Major birth defects are relatively rare, accounting for only 1-3% of all births; hence large numbers of subjects are needed to show excess risk at alpha of 5% and beta of 80%. For example, 800 women are needed in a two arm study to show a doubling of cases of major malformations. The situation is much more complex when trying to quantify one specific major malformation (rather than all malformations combined). For example, neural tube defects occur in 1:1000 births and valproic acid increases that risk to only 20:1000. Thus, hundreds of cases of maternal exposure to valproic acid during the first 28 days post conception may be needed to document a statistically significant increase from baseline risk.

The vast majority of cohort studies published to date are underpowered to show significant differences, a problem acknowledged by many of their authors. A common way to overcome this issue is to combine similar studies into a meta-

analysis, thus gaining a large sample size. As would be expected, lumping studies together into meta-analysis introduces its own set of issues, including heterogeneity among studies, inability to control for confounders, and under-reporting of negative studies (i.e., those showing no excess in adverse effects) [2].

Bias by Indication

Women taking medications during and after conception often suffer from conditions which may affect pregnancy outcome. For example, chronic hypertension during pregnancy is associated with high risk of premature birth, unrelated to which drug is used to treat the hypertension. We have recently shown that hypertensive women have greater than 20% rates of prematurity in their offspring, whether treated with labetalol or methyldopa, in comparison with only 4% among healthy controls [3].

This source of bias can often be corrected by having, in addition to the drug exposed group and healthy control groups, an additional group with the same medical condition but treated with another pharmaceutical treatment. Yet, even this solution may not always resolve the issue, as was acutely shown with the selective serotonin reuptake inhibitors (SSRI).

During the last few years, several studies have suggested that paroxetine may be associated with an increased risk for cardiovascular malformation, and, in particular, ventricular septal defects. To address the potential "bias by indication", several studies compared paroxetine to other SSRIs, still showing increased risk of cardiac malformations with paroxetine [4]. It has been claimed that other SSRIs do not cause malformations. Yet previous studies have shown that there is not another single example where one molecule causes malformations whereas another in the same class of pharmaceuticals does not (e.g., retinoids, ACE inhibitors) [5].

What these studies did not point out is that, while all SSRIs are prescribed to treat depression, paroxetine has also been used to manage anxiety [6]. There is ample evidence that women suffering from anxiety are more likely than those with depression to visit emergency rooms with their babies and to have diagnostic tests [6]. Hence, there is a higher chance that these babies will be diagnosed with a cardiac malformation. To complicate matters even further, most ventricular septal defects (VSDs) (the most common cardiovascular malformation) are of the muscular type, and tend to close spontaneously in infancy. If assessed later, whether in children exposed to other drugs or those unexposed, the likelihood of detecting VSDs further decreases. This may create an ascertainment bias, wrongly suggesting that the "excess" in VSD is a direct teratological effect of paroxetine.

Time of Enrollment as a Bias

Prospective cohort studies take pride that by enrolling women in early pregnancy, *i.e.*, before the outcome of pregnancy is known, they avoid the serious bias of retrospective data collection. Since most miscarriages occur during the first trimester of pregnancy, the later in gestation that pregnant women are recruited, the less likely they are to have a miscarriage. For example: if a group of women exposed to paroxetine is recruited at five weeks of gestation, whereas women exposed to other drugs are recruited at 10 weeks of gestation, clearly there is a greater chance that miscarriages would be detected and reported in the paroxetine cohort. There are two possible ways to overcome this type of bias:

1. By recruiting women in all arms of the study in the same week of gestation.
2. By post-hoc statistical adjustment for the time of enrollment.

In summary, critical appraisal of studies correlating pharmaceutical exposure in pregnancy with rates of miscarriage must pay close attention to the gestational age at enrollment into the study.

Bias in Retrospective Ascertainment

A large number of studies attempting to associate pharmaceutical exposure with malformation rates are retrospective in nature, that is, the cases were collected *after* pregnancy outcome was known. It is conceivable that women having malformed children would more likely report them to drug companies or to regulatory agencies. This hypothesis was proven in 1999 by Bar Oz and colleagues, who compared a retrospective registry to a prospective one of the same drug (itraconazole) [7].

In the prospectively collected group, there was a 3% malformation rate suggesting no increased teratogenic risk. In contrast, there was a more than four-fold a (14%) malformation rate in the retrospectively ascertained cohort [7]. Acknowledging this serious source of bias is critical, yet there is also a “positive” message here: if, despite this bias, a retrospectively collected cohort *does not* exhibit a higher malformation rate than expected in the general population, it is conceivable that the drug is safe.

Recall Bias

Case-control studies typically enroll children with a specific malformation (*e.g.*, spina bifida) and ask the mothers what pharmaceutical products they had used throughout pregnancy, and particularly during the first trimester of pregnancy.

It has been argued that mothers of malformed children may have a different pattern of recall than mothers of healthy children. Specifically, the malformation may facilitate memory in an attempt to find a pregnancy-related cause. This source of bias can be remedied by collecting data from mothers of children with a different malformation, unrelated to the hypothesis in question. For example, when Pastuszak *et al.* ascertained that Brazilian women giving birth to children with the Mebius sequence had a much higher likelihood of using misoprostol in an attempt to terminate pregnancy, than women giving birth to children with spina bifida [8].

Recall bias in pregnancy is not limited only to remembering the use of pharmaceuticals during pregnancy, but also to recall of disease symptoms. We have shown in 200 women with nausea and vomiting during pregnancy, that when interviewed weeks to months after their symptoms had subsided, they reported significantly worse symptoms than what they had described in real time [9].

A typical prospective cohort study during pregnancy recruits women exposed to pharmaceuticals before the outcome of pregnancy is known, and this is why the term “prospective” is used. At a later follow-up, women are asked about their health *after* the first interview and up till the followup interview. It is important to recognize that this part of the study is retrospective and hence open to recall bias. This becomes very important in trying to correlate, for example, the severity of the disease with outcome.

One of the most cited advantages of prescription databases linked to neonatal registries is that the dose of drug and length of treatment are not dependent on maternal recall. The trade-off is that prescription records do not prove that the pharmaceutical was actually taken by the pregnant mother, only that they were prescribed. The seriousness of this source of error was acutely exhibited when Jick and colleagues correlated maternal prescription of spermicides with congenital malformation [10]. It was argued that prescription of spermicides before conception did not yet mean that the women took them. Indeed, in a follow-up study of the malformed cases in this study, Watkins showed that almost none of the mothers took spermicides only following conception [11].

Bias in Not Including Elective Abortion Data

Many administrative database studies do not have data on findings among women who elected to have an abortion; rather, they report of “liveborn infants”. Levy and colleagues hypothesized that a significant number of elective abortions are performed due to a major malformation diagnosed *in utero*. Without such data, researchers take the risk of missing a signal.

Using the example of antifolates in pregnancy, known to increase the risk of neural tube defects, Levy *et al.* showed that in their cohort, such an association was apparent only when elective abortion data were considered too, but not when only live births were counted [12].

Bias in Retrospective Ascertainment of Maternal Lifestyle

Alcohol, maternal smoking and other drugs of abuse may increase fetal risks, including: birth defects, prematurity, intrauterine growth retardation, miscarriage, still birth and developmental teratogenicity.

Due to shame, guilt and fears of losing custody of a child, it is conceivable that women seeing adverse effects in their offspring may underreport on drugs and alcohol abuse. This hypothesis was proven by Wong *et al.*, studying a cohort of women who were counseled by a teratology information service during the first trimester of pregnancy. In particular, their reports on cigarette smoking were probed. When re-interviewed after the birth of the child, women who had healthy babies reported a similar patterns of smoking to that which they had reported initially. In contrast, women giving birth to offspring experiencing adverse outcome tended to minimize the numbers of cigarettes consumed when compared to their original reports [13]. This type of bias may seriously impair studies on the effect of alcohol, cigarettes and drugs of abuse by introducing misclassification, i.e., women who smoked are erroneously classified as non-smokers.

Bias Against the Null Hypothesis

Bias against the null hypothesis occurs when “positive” studies (e.g., studies showing a drug to be teratogenic) are more likely to be submitted for scientific meetings and journals, to be presented, published and publicized than “negative” studies (e.g., those suggesting the pharmaceutical is safe).

The seriousness and pervasiveness of this bias has been shown at each step of the act of reporting results. Investigating the fate of studies submitted to the Oxford University ethics committee, Easterbrook and colleagues have shown that “negative” studies were significantly less likely to be submitted or published in peer reviewed journals. Of interest, this was due not only to higher rates of rejection of the papers by the journals [14], but also due to the perception of the investigators that their studies were less likely to be accepted. More related to adverse pregnancy outcome, we have shown that abstracts failing to identify reproductive risks of cocaine were less likely to be accepted by the Society for Pediatric Research than “posi-

tive” studies, despite the better quality of the negative studies [15].

The bias against the null is further augmented by the lay media that tends to publicize significantly more “positive” studies than “negative” ones. This grim reality was documented unequivocally in the case of two studies published back to back by the Journal of the American Medical Association (JAMA). In 1992, JAMA published two studies dealing with the risk of radioactive exposure [15]. A study on the fate of several thousand workers in Oakridge developing the American Atomic bomb in the 1940s has shown increased risk of leukemia. In contrast, a study investigating whether residing near nuclear energy plants failed to show more cases of cancer. Despite similar exposure in the journal, the “positive” study was cited by the lay media significantly more often [16].

It is now evident that the bias against the null hypothesis is pervasive and encompasses every step of the production of new knowledge, starting with the authors believing that they had a lower chance of publishing, continuing with lower probability of selection for presentation at medical meetings, and continuing on to lower rate of publication in science journals.

Because of the confidential nature of the editorial process for selecting peer review papers for publication, it is impossible to verify whether the editorial process also results in bias against the null hypothesis.

Citation Bias by Medical Journals

The last chain of events in the process of distribution of new medical knowledge related to pharmaceutical risk in pregnancy is its citation by medical scientists in subsequent papers. If “positive” studies are cited more often than “negative” studies, then the risk of biased and misleading data is entrenched at the highest level. For the purpose of this review we wished to verify whether this type of bias against the null hypothesis exists.

Over the last five decades, a large number of medications were initially implicated as human teratogens only to have these conclusions refuted later by larger numbers of negative studies and meta-analyses. This has raised serious concerns regarding bias against the null hypothesis: where negative studies (*i.e.*, not showing adverse fetal effects) being less likely to be submitted for publication by their authors [17] less likely to be accepted to scientific meetings, or be reported by the lay media. The role and impact of medical journals themselves on this type of bias have not been studied.

Several recent cases, where major medical journals published initial reports suggesting a drug to be teratogenic, only to be subsequently refuted by numerous other studies, have prompted us to examine determinants of scientific citation.

The focus of our interest was the number of citations that “positive” (*i.e.*, showing adverse fetal events) *vs.* “negative” scientific articles have accumulated. We surmised that cumulative citation numbers reflect the effectiveness of knowledge transfer and determines on what health care providers are basing their clinical decisions on.

For the purpose of this review, we selected six drugs which, over the last five decades, have been the focus of appreciable controversy over their teratogenic potential in humans. In all selected drugs, initial reports in major medical journals implicated the drug as a human teratogen, but these claims have been later refuted by large numbers of negative trials.

1. The oral contraceptive pill, reported in the 1960s as causing sexual malformations [18]. Subsequently, a large number of studies and two separate meta-analyses refuted this claim [19]. Despite this, the “pill” was designated a “category X” by the FDA, a label that was corrected only recently.
2. The antinauseant Bendectin® (doxylamine plus pyridoxine) was used by up to 40% of American women in the late 1970s for morning sickness. Several highly publicized reports and legal cases resulted in removal of the drug by its manufacturer from the American market in 1983 [1], despite numerous “negative” studies and three meta-analyses showing its apparent safety [2]. The drug has been continually used in Canada and is being introduced again in the US. After its removal, leaving American women without an FDA-approved drug for morning sickness, the rate of hospitalization of pregnant women for severe vomiting more than tripled [20].
3. Benzodiazepines are widely used by women of reproductive age. Because half of all pregnancies are unplanned, large numbers of women unknowingly exposed their fetuses to this class of medications. A highly publicized study in the 1980s caused tremendous concern [21], despite numerous negative studies [22]. On a molecular level, it has been argued that the GABA receptor antagonist properties of benzodiazepines may explain their teratological effects [23].
4. The selective serotonin reuptake inhibitor, paroxetine, has been the leading SSRI during the early 2000s. Preliminary, highly advertised reports claimed that the drug causes cardiac malformation, leading the FDA and Health Canada to issue warnings. These warnings were not reversed, despite large numbers of studies and a meta-analysis [4] refuting these preliminary claims, and causing large numbers of women not to treat even life-threatening depression [24].
5. The cholesterol synthetase inhibitors statins have been implicated as human teratogens based on uncontrolled case series in a highly publicized paper [25]. Several later papers and a systematic review refuted this claim [26]. The statins inhibit the synthesis of cholesterol, which is critical for fetal brain development. Indeed, animal studies have shown high rates of adverse central nervous system effects [27].
6. A highly publicized paper claimed that the antihypertensive ACE inhibitors cause congenital malformations [28]. This class of drugs is typically discontinued as soon as pregnancy is recognized, because it has been proven to cause fetal renal damage and hypocalvaria in late pregnancy, yet the researchers claimed that the ACE inhibitors caused first trimester malformation. Consequently, large numbers of women with pre-pregnancy hypertension were advised that the use of ACE, before they recognized that they had conceived, may have caused fetal malformations. Importantly, all other studies on this topic to date have failed to show increased teratogenic risk [29-31].

We reviewed all papers included in the systematic reviews and meta-analyses of the six selected drugs (oral contraceptives, bendectin, benzodiazepines, paroxetine statins and ACE inhibitors). Papers were classified as “positive” if the primary endpoint (rates of malformations) was significant at $p < 0.05$ in comparison with the control (unexposed) group. Papers were classified as “negative” if the rates of malformation in the exposed group were not significantly higher than in the comparison group. The following characteristics were identified for each study:

- a. Year of publication.
- b. The impact factor of the journal in the year of publication as reported in ISI Web of Knowledge Journal Citation Reports.
- c. The total number of scientific citations of the study. The number of citations to each study was retrieved through a cited reference search in Web of Science

In analyzing the data, we first compared the numbers of citation of “positive” *vs.* “negative” studies using the Mann Whitney U test. Subsequently, we conducted multivariate linear regression analysis with the total number of citations per paper as the dependent variable, and the journal citation impact, year of publication and being “negative” or “positive” as independent variables. This analysis aimed at identifying determinants that predict the total number of citations of a paper.

Results

A total of 53 papers were included in the analysis, pertaining to the six selected drugs. Four of the papers were excluded from the multiple regression analysis because citation impacts of the journals publishing them are not available. The median number of citations was 70% higher for a “positive” study in comparison with a “negative” study [39 (range 28-206) *vs.* 23 (range 0-113)] ($p=0.04$). Multiple linear regression analysis revealed that the “positivity” of the results ($p=0.04$), the journal citation impact ($p<0.001$) and the number of years since publication ($p=0.01$), all predicted the total number of citations of a paper. The best fit is given by the formula:

$$\text{Number of citation} = -16.3 + 1.45 (\text{journal impact}) + 0.86 (\text{years since publications}) + 23.4 (\text{“positive”}).$$

$$(r^2=0.42, P<0.001).$$

The power of the performed analysis with alpha of 0.05 was 99.9%. It has been recognized that citations, the “act of connecting text statement through reference to the broader literature”, cannot always be considered as an impartial method, and that citations can lead to distortion of the overall conclusion regarding scientific truth [32].

Perception of teratogenic risk and resultant fears of birth defects lead some women to terminate otherwise wanted pregnancies, even when the drug has been shown by strong evidence not to pose fetal risks [33]. In addition, such fears often lead physicians and pregnant women not to treat serious medical conditions in pregnancy [34]. The pervasive litigious atmosphere surrounding birth defects in pregnant women exposed to drugs has led health care providers to avoid use of medications “to be on the safe side”. Yet, quite often not treating the maternal condition does not improve maternal safety but rather the opposite. This has been sadly documented with the tripling of hospitalization for severe vomiting after removal of bendedin[®] [20], and with the increase in depression relapse in pregnant women discontinuing their SSRIs [34].

To try and identify determinants leading to the citation of papers dealing with drug-induced birth defects, we have deliberately selected six drugs that had received wide public notoriety, based on initial “positive” studies, but refuted later by large numbers of “negative” studies.

It was our preliminary impression that despite strong evidence of fetal safety emanating from emerging “negative” trials, the ability to reshape and re-state a medical consensus is difficult. This is clearly shown in FDA’s persistent use of “category X” for oral contraceptives 15 years after two negative meta-analyses were published (1), and in FDA and Health Canada’s persistent warning of risk of paroxetine based on initial unpub-

lished, uncontrolled studies, despite being opposed by a large number of negative studies [4].

As expected, our analysis shows that studies published in high impact journals result in larger numbers of citations, and a similar expected effect was observed for the length of time that has elapsed since publication. Yet, our study also documents a significant bias in favor of “positive” studies, leading them to be cited 70% more often than “negative” studies and, thus, help creating a false scientific interpretation against the overall existing evidence.

Importantly, when a “positive” initial study is published in a high impact journal, as was the case with oral contraceptives [18], benzodiazepines [21], ACE inhibitors [28] and statin [25], it is almost impossible to reverse this impact by numerous negative trials. In at least one case, we are aware of “negative” papers, submitted to the same major journal after it had published a “positive” paper, having being rejected.

“Citation bias” is defined as “systematic ignoring of papers that contain content conflicting with a claim” [32]. Acknowledging this source of bias is critical in trying to avert the distortion of medical knowledge created by it. This is especially critical in the case of fetal drug safety, where wrong perceptions of fetal risk lead women to terminate otherwise-wanted pregnancies or avoid treatment of life-threatening medical conditions [1,31].

Conclusion

Due to an inability to collect fetal safety data of sufficiently high quality, assessment of pharmaceutical molecules is one of the most challenging areas of pharmacoepidemiology.

It will be important to continue and refine the methodology involved in this quest for critical data, and to avoid misinformation, which may lead to either unwarranted anxiety or an unjustified sense of safety.

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