PERPETUATING FEARS: BIAS AGAINST THE NULL HYPOTHESIS IN FETAL SAFETY OF DRUGS AS EXPRESSED IN SCIENTIFIC CITATIONS

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ABSTRACT

Background
Bias against negative studies (*i.e.*, those showing no issues with fetal safety of drugs) may cause distorted interpretation with apparently safe drugs being labeled as teratogenic, causing women to terminate pregnancy or not to treat serious medical conditions.

Objective
To investigate whether "positive" studies, claiming teratogenic effects of drugs, which were later shown to be safe, have been cited more often than "negative" studies on the same topic.

Methods
We reviewed published studies on the fetal safety of 6 drugs, which were the focus of appreciable controversy over the last 5 decades (oral contraceptives, bendectin®, benzodiazepines, paroxetine, ACE inhibitors and statins). While initial highly publicized papers claimed teratogenic effects, these were subsequently contradicted by large numbers of "negative" studies. We compared medical citation patterns of the "positive" vs. "negative" papers related to these 6 drugs.

Results
"Positive" papers were 70% more likely to be cited than "negative" articles (median 39 vs. 23, p=0.04). In multivariate linear regression, "positivity" of results (p=0.04), the number of years since publication (p=0.01) and journal citation impact (p<0.001) all independently predicted the total number of medical citations.

Conclusions
We documented bias against the null hypothesis in medical citations of fetal drug safety. Acknowledging this source of bias is critical in trying to avert the distortion of the medical knowledge created by it.

Key Words: *Congenital malformations; bias against the null; citation impact; oral contraceptives; bendectin®; benzodiazepines; paroxetine; ACE inhibitors; statins*

Since the thalidomide disaster, medicine is practiced as if every medication 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 and tend not to prescribe or take medications during pregnancy even for life-threatening conditions.[1] Over the last 5 decades a large number of medications have been originally implicated as human teratogens only to be refuted later by larger numbers of negative studies and meta-analyses.[2-5] This has raised serious concerns regarding bias against the null hypothesis, with negative studies (*i.e.*, not showing adverse fetal effects) being less likely to be submitted for publication by their authors[6], less likely to be

accepted to scientific meetings[7], or to be reported by the lay media.[8] However, the role and impact of the medical journals themselves in this type of bias has 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 what health care providers are basing their clinical decisions on.

The objective of the present study was to investigate potential bias in article citations, specifically whether "positive" studies on fetal safety are cited more often than "negative" studies in the context of drugs where the overall current assessment does not show increased fetal risk.

METHODS

We selected 6 drugs which, over the last 5 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" reports.

The selected drugs were:

1) The oral contraceptive pill, which was originally reported to cause major malformations.[9] Subsequently, a large number of studies and two separate meta-analyses refuted this claim.[3] Despite this, the "pill" was designated a "category X" by the FDA, a label that was revised only recently.

2) The antinauseant Bendectin® (doxylamine plus pyridoxine) was used by up to 40% of American women in the late 1970's for morning sickness. Several highly publicized reports and legal cases resulted in removal of the drug from the American market by its manufacturer in 1983[1], despite numerous "negative" studies and 3 meta-analyses showing its apparent safety.[2] The drug has been continually used in Canada and is currently being re-introduced to the US. After its removal from the market American women were left without an FDA-approved drug for morning sickness and the rate of hospitalization of pregnant women for severe vomiting more than tripled.[10]

3) Benzodiazepines are widely used by women of reproductive age. Because half of all pregnancies are unplanned, large numbers of women unknowingly expose their fetuses to this class of medications. A highly publicized study in the 1980's had caused tremendous concerns[11], despite numerous subsequent negative studies.[5]

4) The selective serotonin reuptake inhibitor (SSRI) paroxetine has been the leading SSRI prescribed during the early 2000's. Preliminary, highly quoted reports claimed that this drug was causing cardiac malformation, leading the FDA and Health Canada to issue warnings. As well, some of the research groups still hold the thought that the SSRI causes cardiac malformations. The governmental warnings have not been reversed despite large numbers of studies and a meta-analysis[4] refuting these preliminary claims, causing many women not to treat even life-threatening depression.[12]

5) The cholesterol synthetase inhibitors statins have been implicated as human teratogens based on uncontrolled case series in a highly publicized paper.[13] Several later papers and a systematic review refuted this claim.[14]

6) The antihypertensive ACE inhibitors have been claimed to cause congenital malformations in a highly publicized paper.[15] This class of drugs is typically discontinued when pregnancy is recognized due to its proven fetal renal damage and hypocalvaria in late pregnancy. Yet, the paper claiming they cause first trimester malformation meant that large numbers of women with pre-pregnancy hypertension have been advised that their ACE exposure before recognizing they had conceived may cause fetal malformations. Importantly, subsequent studies on this topic to date have failed to show increased teratogenic risk.[16-18]

We reviewed all papers included in the systematic reviews and meta-analyses of the 6 selected drugs (oral contraceptives, bendectin, benzodiazepines, paroxetine statins and ACE inhibitors).[2-5] They were selected from Medline, EMBASE and Chochrane databases. We reviewed all publications included in these systematic reviews and meta-analyses.[2-5] Our review process was not blinded. Papers were classified as "positive" if the primary endpoint (rates of malformations) was significant at $p<0.05$ as compared to the comparison (unexposed) group. Papers were classified as "negative" if the rates of malformations in the exposed group were not significantly higher than in the comparison group.

The following characteristics were identified in 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 of 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 6 selected drugs. Four of them were excluded from the multiple regression analysis because citation impacts of the journals publishing them were not available and were not reported. The median number of citations was 70% higher for a "positive" study as compared to a "negative" study [39 (range 28-206) vs. 23 (range 0-113), respectively] ($p=0.04$) (Mann Whitney U test). 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 independently predicted the total number of citations of a paper.

The best fit is given by the formula:
Number of citation = -16.3+1.45 (journal impact) + 0.86 (years since publications) + 23.4 ("positive"). ($r^2=0.42$, $P<0.001$).

The power of the performed analysis with alpha of 0.05 was 99.9%.

DISCUSSION

It has been recognized that citations, the "act of connecting text statement through reference to the broader literature" cannot be always considered as an impartial method, and can lead to distortion of the overall conclusions regarding scientific truth.[19]

Perception of teratogenic risk and resultant fears of birth defects lead women to terminate otherwise-wanted pregnancies even when the drug has been shown by strong evidence not to pose fetal risks.[1] In addition, such fears often lead physicians and pregnant women not to treat serious medical conditions in pregnancy.[20]

The pervasive litigious atmosphere surrounding birth defects in pregnant women exposed to drugs has led health care providers to often avoid use of medications "to be on the safe side".[1] Yet, quite often, not treating the maternal condition does not render maternal and fetal safety, but rather the opposite. This has been sadly documented with the tripling of hospitalization rates for severe vomiting after removal of bendectin®[10], and the increase in depression relapse among pregnant women discontinuing their SSRIs.[20] To try and identify determinants leading to the citation of papers dealing with drug-induced birth defects, we deliberately selected 6 drugs that had received wide public notoriety, based on initial "positive" studies, contradicted 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 has been difficult. This has clearly been shown in the FDA's persistent use of category X for oral

contraceptives 15 years after two negative meta-analyses were published[1], and in the FDA and Health Canada's persistent warning of risk of paroxetine based on initial unpublished, uncontrolled studies, and some positive trials despite being opposed by a large number of negative studies.[4]

As expected, our analysis confirms that studies published in high impact journals lead to 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, helping to create 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[9], benzodiazepines[11], ACE inhibitors[15] and statins[13], it is exceedingly difficult 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, being rejected. "Citation bias", as in the cases presented by us, is defined as "systematic ignoring of papers that contain content conflicting with a claim".[19]

Acknowledging this source of bias is critical in trying to avert the distortion of the medical knowledge created by it. This is especially critical in the case of fetal drug safety, where distorted perceptions of fetal risk may lead women to terminate otherwise-wanted pregnancies or avoid treatment of life-threatening medical conditions.[1, 20]

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