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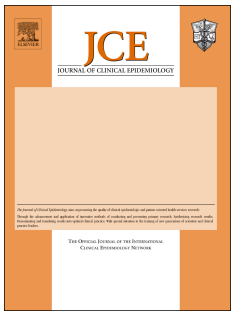

The risk of questioning the safety of drugs considered safe in pregnancy at the era of big data - the everlasting case of doxylamine.

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The risk of questioning the safety of drugs considered safe in pregnancy at the era of big data - the everlasting case of doxylamine.

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Nausea and vomiting of pregnancy (NVP) affects up to 80% of pregnant women. A combination of doxylamine succinate and pyridoxine hydrochloride in a 1:1 ratio is available to treat NVP when symptoms have not been sufficiently relieved by non-pharmacological interventions. This combination has been approved for the treatment of NVP over the past ten years by several national drug agencies; noteworthy as marketing authorizations for treatment specifically in pregnant women are rare.[1] Doxylamine has a turbulent past. Its combination with dicyclomine and pyridoxine was voluntarily withdrawn from the U.S. market by the manufacturer in the eighties due to negative publicity and financial concerns caused by mounting litigation. This reaction by the manufacturer was influenced by the historical context of thalidomide and diethylstilbestrol. The many lawsuits attributing various birth defects removed a treatment option from women with severe NVP, even though evidence to document the safety with respect to teratogenic effect was available at the time.[2] Numerous studies conducted since then confirmed that doxylamine-pyridoxine is not a teratogen.[3-7] Furthermore, evidences provided by ecological studies have suggested its effectiveness as there was a 50% increase in days of hospitalizations for NVP in Canada following the withdrawal of doxylamine-pyridoxine.[8] With its history, doxylamine is nowadays used as a textbook example of how decisions driven by emotive arguments and medicolegal motivations rather than by evidence are not in the best interests of patients.

Recently, the results of a large observational study provided data suggesting that exposure to doxylamine-pyridoxine during the first trimester of pregnancy was associated with a

significantly increased risk of overall and specific major congenital malformations.[9] Findings that contradict previous evidence and clinical practice raise concern among healthcare professionals who have been using this combination as a first-line therapy for years, as well as among women prone to NVP.

These findings illustrate that, in the era of big data, safety assessment of medications in pregnancy is facing completely new challenges. Weak risk associations for specific or pooled malformations, typically minor effect sizes but with confidence intervals excluding the null, are now commonly reported for many intensively studied drugs (e.g. SSRIs, paracetamol). Principally "Big data" approach comes with an inherent risk of detecting wrong signals with great confidence; *"The Big Data Paradox"*.[10] These big data studies provide some of the needed evidence base to treat pregnant women with confidence, but they are also systematically associated with methodological issues due to their observational nature and the underlying data structure. To overcome the lack of safety information provided by pre marketing studies, health care utilization databases, e.g. administrative claims files, electronic medical records, or well-established national registries of health (e.g. from Scandinavian countries) have been increasingly used in the past decade as information sources to conduct large post marketing observational studies in pregnancy.[11,12] While these health data offer an effective solution with respect to cost, number of pregnancies included, validity (e.g., no recall bias) and generalizability (i.e., population-based),[13] they also share some limitations that can threaten their validity and provide distorted risk estimates, misleading the benefit-risk assessment of a drug in pregnancy. Exposure and outcome misclassifications are one of the important limitations as information on "if " and "when" a drug has been taken is almost never available (e.g. unused dispensing, use of old prescription, drug sharing, use after the relevant etiological period), as using billing or diagnostic codes to define outcomes in claims is not straightforward.[14] Confounding by indication and other risk factors are other important limitations as these databases usually lack information on behavioral and lifestyle habits (e.g. smoking, alcohol use, physical exercise) and outpatient health service utilization (e.g. over the counter drugs).[14] The missing information may result in a lack of control for unmeasured confounders.

With these limitations, it seems obvious that slight increases in risk (i.e. RR/OR between 1.01 and 1.1) observed in studies using healthcare utilization databases should be interpreted with great caution. Biffi at al. did an illustrating exercise using probabilistic sensitivity analyses to evaluate the impact of differential misclassification of the exposure-outcome association.[7] They showed, using the risk estimates of safety studies on doxylamine pooled in a meta-analysis, that

exposure or outcome differential misclassification with a frequency up to 12% would allow to negate the conclusions of this study that doxylamine-pyridoxine exposure was associated with a significantly increased risk of overall and specific congenital malformations. Finally, this magnitude of increases in risk (i.e. RR/OR between 1.01 and 1.1) should also be interpreted in the light of clinical significance and the existence of treatment alternatives. Such findings do not justify changes in clinical practice.

ENTIS believes that the evidence brought forward in the above-mentioned study is flawed and inconsistent with the extant literature, and should not change the first line treatment position of doxylamine-pyridoxine in NVP if not relieved by conservative measures. Reluctance to use doxylamine could also likely result in use of alternatives that have less safety data on their use during pregnancy.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: