EXHIBIT 4

TTi Health Research & Economics

April Zambelli-Weiner <aweiner@transtechint.com>

Draft of Zofran paper

8 messages

Christina Via <cvia@transtechint.com> Sat, Dec 16, 2017 at 1:32 PM
To: "Kirby, Russell" <rkirby@health.usf.edu>
Cc: "Dr. April Zambelli-Weiner" <aweiner@transtechint.com>

Hi Russ,

Attached is the first draft of our Zofran paper, as well as the next version of the tables. Please note that the orofacial cleft data still needs to be added. I just received that data from Truven, and should be able to get you the updated tables by early next week. If you could give us feedback in the next two weeks (preferably by Friday, 12/29), that would go a long in helping us keep our goal submission date of early January. If you have any questions, feel free to call my office at 800-580-2990 ext 106, or my cell at 203-988-3104.

Thanks and Happy Holidays!
Christina

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Christina Via, Epidemiologist

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Check out our brief video!

2 attachments

NEJM Draft_12.15.17_v4_clean.docx
52K

Ondansetron NEJM tables_12.14.17_v2.xlsx
28K

Christina Via <cvia@transtechint.com> Mon, Dec 18, 2017 at 3:02 PM
To: "Kirby, Russell" <rkirby@health.usf.edu>
Cc: "Dr. April Zambelli-Weiner" <aweiner@transtechint.com>

Hi Russ,

Attached are updated tables with orofacial cleft data added.

Thanks!
Christina
[Quoted text hidden]

Ondansetron NEJM tables_12.18.17_as sent.xlsx
25K

Christina Via <cvia@transtechint.com> Sun, Dec 31, 2017 at 6:52 PM
To: "Dr. April Zambelli-Weiner" <aweiner@transtechint.com>

Hi April,

Just wanted to give you an update on the antiemetic paper. Russ says he should be able to get it back to me by Tuesday. As soon as I get it, I will merge with any additional edits I've made and get it to you as soon as possible. I apologize for the delay!

Thanks and Happy New Year!
Christina

---------- Forwarded message ----------
From: **Kirby, Russell** <rkirby@health.usf.edu>
Date: Sun, Dec 31, 2017 at 6:01 PM
Subject: Re: Draft of Zofran paper
To: Christina Via <cvia@transtechint.com>

Will try to get this back to you Tuesday.

Sent from my iPhone

On Dec 31, 2017, at 5:54 PM, Christina Via <cvia@transtechint.com> wrote:

> Hi Russ,
>
> I hope your holidays are going well! I just wanted to follow up to see if you had a chance to review the Zofran draft manuscript. If you have any questions, please let me know!
>
> Thanks!

NEJM Requirements: 2700 words total, 250 word abstract, 5 figures/tables, 40 references

TITLE: EARLY PREGNANCY EXPOSURE TO ONDANSETRON AND RISK OF STRUCTURAL BIRTH DEFECTS

AUTHORS: Zambelli-Weiner, April; Via, Christina; Yuen, Matt; Weiner, Daniel; Kirby, Russell

ABSTRACT:

Background

Methods

Results

Conclusions

INTRODUCTION

Nausea and vomiting in pregnancy (NVP) is a frequent complaint of women during early pregnancy. According to recent studies, 70-90%[1,2] of women report having experienced NVP, with .5-1.5%[3,4] being diagnosed with the more severe hyperemesis gravidarum (HG). There are numerous approaches to managing NVP and HG, including natural remedies such as ginger,[5–7] over-the-counter drugs including antihistamines,[6,8,9] and prescription pharmaceutical treatments.[6,10] The use of prescription medications for NVP has been increasing in recent years,[11,12] with a total of five drugs listed in the 2004 clinical guidelines from the American College of Gynecology(ACOG): ondansetron, Diclegis (Doxylamine Succinate and Pyridoxine Hydrochloride), metoclopramide, promethazine, and methylprednisolone. Of those five, Diclegis is the only one specifically approved for use in pregnancy.[10] According to a recent paper by Taylor and colleagues, ondansetron represents the most frequently prescribed medication for the treatment of NVP and HG, despite the fact that the 2004 ACOG guidelines algorithm lists it the last line of therapy and the 2015 ACOG guidelines continue to note that, "there are insufficient data on fetal safety with ondansetron use and further studies are warranted".[10,13]

Prior studies on the fetal safety of ondansetron have produced varied results, likely a reflection of the heterogeneity in study populations, methods, and sample size. In general, studies that failed to detect a connection between ondansetron and birth defects examined smaller populations,[2,14,15] while studies showing an association between ondansetron and birth defects relied on large registries.[16–18] Mixed results can also result from differing methods used including: ondansetron exposure definition (recall[14] vs. claims or records),[16,18] or lumping and splitting of outcomes ("major defects"[19,20] vs. multiple birth defect categories).[16–18]

To address these significant limitations and gaps in the literature on the risk of congenital anomalies in the US population, we conducted a population-level study using US administrative claims data to study the association between ondansetron use during early pregnancy and risk of

structural congenital malformations, while considering the impact of important potential modifying factors such as disease severity, timing, and concomitant drug exposure.

METHODS

Database

We conducted a retrospective cohort study using a large US-based administrative health care database, the Truven Health MarketScan Commercial Database. This database captures the full episode of care for each patient during their plan enrollment, including both inpatient and outpatient medical care, prescription drug use and other medical resource utilization. Diagnosis and procedure codes are identified by the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) and Current Procedural Terminology codes. Drug exposures were identified through the specific compilation of lists derived from The National Drug Code Directory.

Institutional Review Board approval was not required, as this study used existing, fully de-identified data and as such is exempt from 45 CFR 46 requirements.

Study Population

The source population included mother-child pairs resulting from all live births between 2000 to 2014 who had one year of follow-up for the infant(s). Mothers were eligible if they were continuously enrolled in the health plan for 16 months prior to delivery and were between the ages of 15 and 49 years old on the date of delivery. Mother-child pairs were excluded if there was an increased baseline risk of congenital malformations due to family history or exposure to known teratogens, defined as: a maternal diagnosis in the 16-month pre-birth period of chromosomal anomalies (ICD-9 758.xx), toxoplasmosis, other, rubella, cytomegalovirus, and herpes (TORCH) infectionsk or if the mother filled a prescription for thalidomide or isotretinoin in the pre-birth period. Those exposed to Diclegis, promethazine, metoclopramide, or methylprednisolone during pregnancy were also excluded.

Exposure Measurement

The number of ondansetron prescriptions or medical administrations occurring during the first trimester was identified using NDC codes and trade names. The period of first trimester exposure was defined as the period from the beginning of the estimated date of conception to the end of the first trimester (91 days following the estimated conception date), specifically 287 to 147 days prior to delivery, based on an estimated conception period of 287-252 days prior to delivery for a singleton birth and 273-238 days prior to delivery for a multiple birth based on a previously published algorithm for a study using the Truven Marketscan data.[21]

In our primary analyses we considered ondansetron exposure as a dichotomous (ever/never) first-trimester (or early pregnancy) exposure. Because antiemetics can be prescribed prophylactively to be used on a "as needed" basis, there is a significant risk of exposure misclassification. It may be difficult to ascertain whether someone who had a

prescription filled actually took the medication. To decrease misclassification bias, we performed a subanalysis examining those with medical administrations of ondansetron only, guaranteeing those in the exposed cohort were truly exposed.

Birth Outcomes

Outcomes were identified using ICD-9-CM diagnosis codes. Cases were identified as having one or more claims with a relevant diagnosis code within 365 days of the date of birth.

Covariates

Potential confounders were identified through a review of the literature and the team's understanding of both the clinical care of pregnant women and the epidemiology of birth defects. Potential confounders that were identified and available in our database included:maternal age at birth, infant year of birth, infant gender, US region of birth, medical history(obesity, diabetes mellitus, epilepsy, hypertension, cancer, prior preterm delivery, family history of birth defects), medications taken in early pregnancy (initiation of acid-reducing therapies, psychotropics, prescription folic acid, macrolide antibioitcs, corticosteroids, anticonvulsants), low birth weight, multiple gestation, high risk pregnancy diagnosis, and diagnosis of NVP or HG. True confounders, by definition, must be associated with both the exposure and the outcome under investigation, but cannot be in the causal pathway or an intermediate (i.e., influenced by exposure). Potential confounders were evaluated by adding the variable to the base exposure-outcome model and evaluating the change in the risk estimate. If the risk estimate changed by $\geq$10% this indicated the presence of confounding and that variable was included in the multivariate models. Further, to control simultaneously for all potential confounders data, a propensity score was developed.

Maternal medical history, comorbidities and other medications were measured from medical and prescription claims occurring during the pre-birth period. Comorbid conditions were flagged as being present if a patient had $\geq$ 1 medical claim with an ICD-9 diagnosis code for the condition of interest in any diagnosis position. Additional medication use was identified if a patient had $\geq$ 1 claim in the early pregnancy period, as previously described.

Statistical Analysis

The statistical analyses were performed with using Stata software, Stata/MP 13.1 (College Station, TX; StataCorp LP). Characteristics of mother child pairs exposed to ondansetron in early pregnancy were compared to mother-child pairs who were unexposed to any antiemetics in early pregnancy using chi-square test or Fisher's exact test for categorical variables and Student's t-test for continuous variables. Logistic regression models were used to test for a statistical association between early pregnancy ondansetron use and risk of specific birth defects in offspring. Prevalence odds ratios and 95% confidence intervals were calculated.

Further analyses evaluated disease severity and ascertainment bias. We controlled for confounding by indication (disease severity) by comparing the exposed cohort to only those with both no antiemetic exposure during pregnancy and a diagnosis of NVP/HG. We controlled for ascertainment bias by stratifying the analysis by year, with yearly cut-off points relating to increased awareness/publicity of possible risks associated with taking ondansetron in early pregnancy. This includes the first study published showing ondansetron crosses the placenta in 2006[22] and the FDA warning regarding risks of adverse events when using ondansetron in late 2011.[23]

RESULTS

Study Population

After exclusions, a total of 991,060 mother-infant pairs were identified. Early exposure to ondansetron occurred in 88,695 mother-infant pairs (8.95%), and early exposure to medical administration of ondansetron occurred in 6,442 mother-infant pairs (0.71%). The median number of prescriptions overall was 1 per mother-baby pair (interquartile range, 1-2 prescriptions).

Table 1 shows the characteristics of women included in the analysis by disease status. There were 927,215 infants with no birth defects, 73,593 infants with structural birth defects, 38,538 infants with cardiovascular birth defects, and xxx infants with orofacial cleft defects. Because of the large sample sizes, most variables differed significantly between birth defect cohorts. However, when potential confounders were evaluated by adding the variable to the base exposure-outcome model, none of them reached the 10% change threshold. We therefore only adjusted for infant year of birth, infant gender, and mother's age at infant birth in the main analyses.

Primary Analysis

Table 2 shows the analyses of birth defects associated with exposure to ondansetron in early pregnancy, with and without adjustment for mother's age at birth, infant gender, and infant year of birth. Pregnant women who were exposed to ondansetron were at increased risk of cardiac defects (unadjusted OR: 1.11 (1.04-1.16); adjusted OR: 1.04 (1.00-1.08) and orofacial cleft defects (unadjusted OR: x.xx (x.xx-x.xx); adjusted OR: x.xx (x.xx-x.xx)). This association was strengthened when analysis is restricted to eliminate exposure misclassification bias (OR: 1.52 (1.35-1.70) for cardiac defects and x.xx (x.xx-x.xx) for orofacial cleft defects).

Sensitivity Analyses

Table 3 shows results from the two sensitivity analyses. After only includine those with the disease (NVP/HG) in those control group, an association between ondansetron use in early pregnancy and subsequent specific structural birth still existed: (cardiac defects: unadjusted OR: 1.51 (1.24-1.85); adjusted OR: 1.56 (1.21-2.03). Therefore it is unlikely that counfounding by indication is biasing our results. Similarly, stratifying the results by year does not eliminate the

associated between ondansetron use and birth defects, making ascertainment bias unlikely (cardiac defects: 2000-2006 – OR: 1.54 (0.79-3.01); 2007-2011 – OR: 1.30 (1.10-1.54); 2012-2014: 1.60 (1.35-1.89)).

DISCUSSION

Our retrospective observational study is the first to demonstrate a statistically significant association between early pregnancy (i.e., first trimester) exposure to ondansetron and a range of specific structural defects birth defects in offspring in a large, nationally representative US population. Previous studies have demonstrated an increased risk of cardiovascular defects[16,24] and septal defects,[16,24] with particularly elevated risks for specific septal defects.[16] Data has been more limited in the US with studies showing increased risk of cleft palate[25] and clubfoot.[25]

Our results in a US population are markedly similar to the results published by previous studies examining the relationship between early pregnancy ondansetron exposure and risk of birth defects in offspring. Specifically, Daniellson and colleagues report elevated risks for cardiovascular defects and septal defects ($OR_{cardiovacsular}$=1.62, 95% CI: 1.04-2.14; OR_{septal}=2.05, 95% CI: 1.19-3.28)[24] comparable to those reported in our study (OR=1.52, 95% CI: 1.35-1.701.35-1.70); OR=1.53, 95% CI: 1.36-1.71), respectively). In the study by Pasternak and colleagues unadjusted relative risks for septal defects are calculated to be 1.22 (95% CI 0.62-2.39) in Pasternak et al[19] and are 1.53, 95% CI: 1.36-1.71in our study. Pasternak and colleagues show risk to be highest for atrioventricular septal defects (OR=4.8, 95% CI: 0.25-63.91) and similarly highest in our study (OR=2.68, 95% CI: 1.61-4.47). Similar trends are observed in an abstract by Andersen and colleagues.[16]

In contrast, other studies failed to detect a connection between ondansetron and specific birth defects. However, this may be due to biases and study design limitations. Some studies may have lumped all examined birth defects into a binary categorical variable rather than investigating specific birth defects individually, due to smaller sample sizes and power issues.[19,20] Given a larger sample size and adequate power, the most accurate estimate of any individual birth defect would investigating each birth defect rather than an aggregate lumping of birth defects. For example, multiple studies where significant correlation was detected for ondansetron and some individual birth defects also found no correlation in lumped major birth defects in the same study.[16,18,24] Additionally, other studies relied on subject recruited cohorts or a single hospital system which introduce selecton bias and generalizability issues.[14,15]

The goal in epidemiology is always to minimize the risk of bias (that is, maximize internal validity) in a study, and there are various biases to be concerned with. Our study sought to address some of the concerns around bias present in previous studies such as recall bias in case control studies and exposure misclassification and limitations suchas low exposure prevalence and small sample sizes that reduce study power and may have precluded important subgroup analyses. Utilizing an administrative claims database removes the risk of recall bias that may be present in case-control studies. However, there is always a concern when prescription claims are used as a marker of exposure that the prescription may not be representative of true exposure (meaning the patient may fill the prescription and not take any of

the drug) or not representative of relevant exposure, such as during the critical exposure time period – in this case, first trimester or early pregnancy exposure. We were able to address this concern in our study by setting a more stringent exposure definition where the probability of exposure is certain: ondansetron administered in a medical or hospital setting. By presenting results for both combined medical and prescription claims and medical claims alone, the impact of misclassification of exposure becomes clear, revealing a significant biasing of the risk estimate towards the null – and illustrating the point made by Danielsson and colleagues.[24]

Regarding the timing of exposure, because diagnosis codes for gestational age are not widely utilized, administrative database studies must rely on an estimation of pregnancy duration and first trimester exposure, as is the case with our study. It is common to estimate the date of conception as 270 or 287 days prior to delivery.[21,26] This approach carries with it the limitation that not all pregnancies are equal in length and, therefore, the estimation of the exposure period may be off. For example, for a premature delivery (36 weeks, 252 days), the first trimester would be 252-161 days prior to the date of delivery. Based on our estimation, the relevant exposure period would include 35 days in the pre-conception period and would include 14 days of the second trimester. While this can present a more significant risk of bias for prescriptions that are taken for non-pregnancy indications and may be initiated prior to conception, it's less of a concern for antiemetics that are initiated in response to nausea and vomiting in pregnancy.

In addition, to overcome potential detection bias, whereby offspring may have an underlying birth defect that had not yet been diagnosed, infants in our study were followed for one year post delivery to allow latent diagnosis of birth defects.

However, our study is not without limitations. The inability to control for all potential confounders is a limitation of epidemiological research and of administrative claims databases, in particular. Data were unavailable on maternal sociodemographic variables such as race, education and parity as well as lifestyle risk factors such as smoking, alcohol consumption and over the counter drug use in the pre-conception and early pregnancy periods. Also, because dose response analysis was prohibitive, as antiemetics can be taken on an "as needed" bases, and because days-supply associated with prescriptions is not always uniformly recorded in administrative claims data.[26] However, the prevalence of ondansetron exposure is similar rates d derived from a comparable US-based commercially insured population.[12]

In conclusion, our study is the largest observational study to date on ondansetron safety in pregnancy. By studying a large number of exposed pregnancies, isolating the independent effect of ondansetron on risk, minimizing the risk of exposure misclassification and controlling for potential confounders, we have demonstrated significantly elevated risks for cardiac defects. Birth defects carry a significant burden on individuals, public health, and the health care system. Birth defects are associated with increased risk of,[27]) and many are associated with life-long. It is incumbent upon us as public health professionals and medical practitioners to use the best available data at any given point in time to inform policy and practice in ways that improve

health outcomes and quality of life for the patients and populations we serve. Drug exposures represent a modifiable risk factor, particular for those in which there are alternative therapies available. The confluence of the evidence supports a causal relationship between early pregnancy ondansetron exposure and risk of major structural birth defects in offspring. Previous researchers in the field have called for action in this case: "Irrespective of the mode of action, if an association between use of ondansetron and an increased risk for cardiovascular defects is true, the strongly increasing off label use of the drug at nausea and vomiting in pregnancy must be regarded as unsuitable and should be avoided.[24]

FIGURES/TABLES [see excel spreadsheet]

Figure 1: Study Design / Flow Chart

Table 1: Characteristics of Women Included in the Analysis

Table 2: Association of Ondansetron Exposure with Structural Birth Defects

Table 3: Sensitivity Analyses

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