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Use of existing electronic health care databases to evaluate medication safety in pregnancy: Triptan exposure in pregnancy as a case study

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Abstract

Purpose: The recent expansion of electronic health and medical record systems may present an opportunity to generate robust post-approval safety data and obviate the limitations of prospective pregnancy exposure registries. We examined and compared, over the same time frame, the outcomes of triptan exposure in pregnancy using (1) a retrospective claims database and (2) a previously completed pregnancy registry.

Methods: Using the Marketscan database, the risk of major birth defects was ascertained in live-born infants whose birth mothers were exposed to sumatriptan, naratriptan, or sumatriptan/naproxen during pregnancy. The frequencies of outcomes observed were compared with the findings of the 16-year sumatriptan, naratripan, and sumatriptan/naproxen prospective pregnancy registry.

Results: About 5120 pregnancies were identified in the retrospective claims cohort in contrast to 617 included in the prospective registry during the same time frame. The proportion of major birth defects among first-semester sumatriptan exposures was 4.0%, which is exactly the same as the proportion of major birth defects reported for first-semester sumatriptan exposures in the registry. There were very few non-livebirth outcomes in both the claims analyses and registry.

Conclusions: These results confirm broad agreement between the database analysis and the registry regarding the safety of triptans during pregnancy. Of note, the number of triptan-exposed pregnancies identified in this large US database was about 7-fold that included in the prospective registry over the same time frame. The findings of this study support an approach of using existing health care database (s) in the post-approval assessment of medication exposure in pregnancy.

KEYWORDS

health care databases, pharmacoepidemiology, prospective pregnancy registries, safety assessment, triptans

1 | INTRODUCTION

While pregnant women are generally excluded from pivotal trials that generate efficacy and safety data supporting approval of new medications, they may be exposed to these agents once they are approved and marketed.[1] Thus, regulatory authorities have typically required post-approval safety studies in pregnant women if exposures to the medical product in pregnancy are expected to be common. In the United States, the Food and Drug Administration requires industry sponsors to conduct these pregnancy safety studies as part of postmarketing commitments or postmarketing requirements. To date, the primary approach to post-approval safety data collection and evaluation in pregnant women has been the prospective exposure registry.[2]

Prospective exposure registries are observational studies in which pregnant women exposed to a specified medication are enrolled for the purpose of actively collecting information about the exposure and specified associated outcomes.[1] These registries are intended to generate robust safety data that can contribute to understanding of risk-benefit of medications and guide clinical practice as it relates to use of medications in pregnancy. However, challenges to effective implementation of pregnancy exposure registries including difficulties in recruiting exposed patients, lack of adequate power to assess specific birth defects, and lack of adequate internal comparators have resulted in such registries failing to deliver robust information after many years of resource-intensive engagement.[3,4]

Not surprisingly, there is a need for complementary and alternative methods of assessing medication exposure in pregnancy, particularly observational studies using existing electronic administrative health care databases.[4,5] With the expansion and evolution of health and medical records systems over the past 2 decades, it may now be possible for well-designed, pregnancy safety studies using existing databases to provide timely and high-quality data. For some indications, large cohorts of exposed pregnant women and adequate internal comparator(s) can be assembled for robust assessment. Because of the potential methodological challenges inherent in retrospective electronic database studies, it is uncertain whether pregnancy safety information from such studies will provide reliable safety information as compared with that from prospective pregnancy registries.[6]

Triptans are used to treat migraine, a neurological disease characterized by recurrent headache attacks of moderate to severe pain, with associated symptoms such as nausea/vomiting and aggravation of pain with physical activity. Around 75% of migraine patients are women, and the prevalence of migraine is the highest for ages 20 to 50 years, when women are of reproductive age.[7] Pharmacologic treatment of migraine during pregnancy is typically focused on acute medications, and sporadic use of triptans after the first trimester may be considered. Triptan exposure in pregnant migraine patients therefore offers a good example to examine whether assessment of safety using existing databases can provide findings comparable to those from a prospective pregnancy registry. In this analysis, we sought to assess outcomes associated with exposure of 3 triptan products in pregnancy using an existing health care database and compare the key findings with that of a previously completed pregnancy exposure registry.[8]

> **KEY POINTS**
>
> - Prospective exposure registries, the traditional tool for post-approval safety ascertainment, are beset by numerous implementation challenges.
> - There is a need for alternative and or complementary methodological approaches to evaluating the safety of medications during pregnancy.
> - Utilizing existing electronic health records for pregnancy safety surveillance holds the prospect of both reducing the burden and increasing the quality of the information gleaned from these studies.

2 | METHODS

2.1 | Overview

In this analysis, we assembled cohorts of pregnant women with migraine exposed to 1 of 3 triptans during pregnancy using an insurance administrative claims database and assessed pregnancy outcomes and proportion of major birth defects among live-born infants linkable to their birth mothers. The findings of this retrospective analysis using an existing database (hereafter referred to as the "claims analysis") were then compared with results reported for the final analysis of a completed 16-year, international, prospective pregnancy registry designed to evaluate the risk of major birth defects in women with migraine exposed to any one of 3 triptans during pregnancy. The sumatriptan, naratriptan, and sumatriptan/naproxen pregnancy registry (hereafter referred to as the "registry") enrolled 904 pregnant women (between January 1996 and September 2012), and the final results were published in July/August of 2014.[8] Of the exposed pregnant women in the registry, 673 pregnancies and 680 pregnancy exposures were evaluable, with an overall loss to follow-up rate of 25.5%.The detailed methodology for the registry has been previously published.[8] The description of the methodological approach for the claims analysis follows.

2.2 | Data source and study cohorts

The study population for the claims analysis was drawn from administrative claims data contained in the Truven Health Marketscan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits Databases for the period of 1996 to 2012. This database contains deidentified information on geographically diverse, commercially insured patients in the United States. The study population included women with a diagnosis of migraine (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] diagnosis codes 346.xx) or prescription claims for migraine-specific acute medications (triptans or ergotamine-derivatives) between January 1, 1996 and September 19, 2012 (see Appendix S1 for a full description of the migraine case finding algorithm). We identified migraine patients aged 10 to 55 years with pregnancy indicators on

or after the migraine index date who were exposed to sumatriptan, naratriptan, or sumatriptan/naproxen sodium and had evidence of at least 1 of 4 pregnancy outcomes (livebirth, stillbirth, spontaneous abortion, and induced abortion). Pregnancy indicators were a combination of ICD-9-CM diagnosis codes, ICD-9-CM procedure codes, and CPT codes that indicate that a woman is receiving pregnancy-related care and were based on algorithm that was developed by Hornbrook et al.[9] Using an hierarchical approach, this algorithm enables the identification of pregnancy events and outcome dates for pregnancies ending in a livebirth or one of the non-livebirth outcomes.

The pregnancy start date or date of conception is defined as the date of the last menstrual period, which is estimated by subtracting gestation age from the outcome date (ie, delivery date for livebirths and event date for non-livebirth outcomes). For pregnancies resulting in livebirth deliveries, gestational age was estimated using a validated algorithm.[10] This algorithm uses diagnosis codes for preterm and postterm births to estimate completed days of gestation. Gestation age for deliveries without an ICD-9-CM diagnosis code for preterm or postterm birth was assumed to be 273 days. Gestational age for pregnancies resulting in non-livebirth outcomes (stillbirths, spontaneous abortions, and induced abortions) was estimated using a published algorithm based on codes for certain pre-natal screening procedures.[11] This algorithm is hierarchical, and it assigns completed weeks of gestation based on the presence of codes for at least one of common pre-natal procedures including nuchal screen, triple screen, group B strep culture and ultrasound (fetal survey), rubella antibody, and hepatitis B surface antigen. Filled prescriptions of sumatriptan, naratriptan, and sumatriptan/naproxen sodium during the pregnancy episode were identified by National Drug Codes using pharmacy dispensing claims.

Mothers and infants were linked for completed pregnancies resulting in livebirth deliveries using their insurance ID, information on delivery-related claims date, infant birth year, and infants' first enrollment date. Linked infants were required to have 12-month continuous insurance enrolment beginning from the delivery date. Major birth defects in linked infants were grouped into categories according to organ system and ascertained during the first 12 months of life using ICD-9-CM diagnosis codes.[12]

2.3 | Statistical analyses

Characteristics of the pregnant women included in the study cohort for the claims analysis were described using means and proportions for continuous and categorical variables, respectively. The proportion of pregnancies resulting in livebirths, stillbirths, spontaneous abortions, and induced abortions were determined separately for pregnancies exposed to sumatriptan, naratriptan, and sumatriptan/naproxen sodium overall and stratified by earliest trimester of exposure. Among live-born infants linked to birth mothers, the frequency of major birth defects was determined overall and stratified by earliest trimester of exposure to sumatriptan, naratriptan, and sumatriptan/naproxen sodium.

The findings of the claims analysis were then compared with the results of the final analysis of the registry.

3 | RESULTS

In claims analysis using the Marketscan database, 5120 pregnancies among 4797 distinct women were included in the study cohorts (Figure 1). About 4519 pregnancies were exposed to sumatriptan, 230 were exposed to naratriptan, and 371 were exposed to sumatriptan/naproxen sodium. The majority of exposed pregnancies had triptan dispensed in the first trimester. In contrast, the number of exposed pregnancies included in the final analysis of the registry was 617 for sumatriptan, 57 for naratriptan, and 6 for sumatriptan/naproxen sodium, and the majority of exposed pregnancies also had triptan exposure during the first trimester (Table 1). As shown in Table 2, the majority of pregnant women in the claims analysis were aged 30 to 39 (59.3% of the sumatriptan-exposed cohort, 62.2% of the naratriptan-exposed cohort, and 63.9% of the sumatriptan/naproxen sodium). During the 12-month period prior to the pregnancy episode, 25.7% of sumatriptan-exposed women had dispensing of nonsteroidal anti-inflammatory agents while 49.2% had dispensing of opioids. The proportions of nonsteroidal anti-inflammatory agents and opioids dispensed among pregnant women exposed to naratriptan and sumatriptan/naproxen sodium were similar. Prepregnancy maternal medication use and comorbid conditions were not reported in the final results from the registry.

Among 3496 pregnancy outcomes exposed to sumatriptan in the first trimester in the claims analysis, 5.0% were elective abortions, 18.0% were spontaneous abortions, 0.4% were stillbirths, and 77.7% were livebirth deliveries (Table 3). The proportion of major birth defects in this cohort was 4.0%, which is exactly the same as the proportion of major birth defects reported for first-semester sumatriptan exposures in the registry. The proportion of outcomes that were elective abortions, spontaneous abortions, and livebirths for first-trimester naratriptan exposures in the claims analysis were 3.7%, 17.4%, and 78.9%, respectively. There were no recorded stillbirths or major birth defects for first-trimester naratriptan exposures in the claims analysis. Similarly, the proportion of outcomes that were elective abortions, spontaneous abortions, and livebirths for first-trimester naratriptan exposures in the registry were 1.9%, 9.6%, and 88.5%, respectively, and similar to the claims analysis, there were no recorded stillbirths. For the 296 first-trimester sumatriptan/naproxen sodium exposures in the claims analysis, 3.7% of outcomes were elective abortions, 18.9% were spontaneous abortions, 1.4% were stillbirths, and 76.0% were livebirths. The number of first-trimester sumatriptan/naproxen sodium exposures in the prospective registry analysis was too small (N = 5) to afford a meaningful comparison of outcomes.

The number of second or third trimester-exposed pregnancies is shown in Table 4. About 940 sumatriptan-exposed, 35 naratriptan-exposed and 68 sumatriptan/naproxen-exposed pregnancy outcomes were included in the retrospective claims analysis while the corresponding numbers for the pregnancy exposure registry analysis were 96 for sumatriptan, 5 for naratriptan, and 1 for sumatriptan/naproxen. There were very few non-livebirth outcomes in both the claims analysis and registry. For pregnancies exposed to sumatriptan during the second or third trimester, the proportion of major birth defects among linked infants was 3.9% in the claims analysis and 3.1% in the registry.
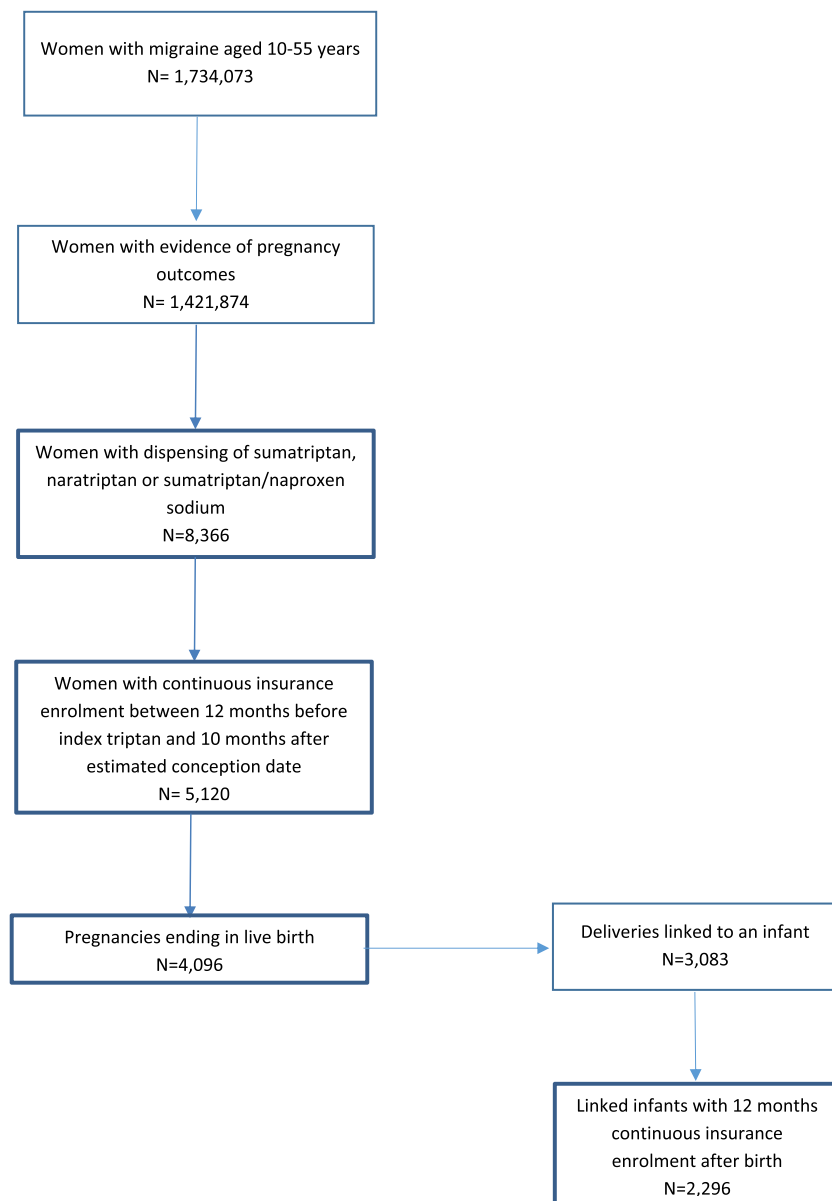
FIGURE 1 Retrospective claims analysis cohort identification flowchart [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Number of pregnancies by earliest trimester of exposure to sumatriptan, naratriptan, and sumatriptan/naproxen

	Sumatriptan		Naratriptan		Sumatriptan/Naproxen Sodium	
	Claims Analysis[a]	Registry[b]	Claims Analysis[a]	Registry[b]	Claims Analysis[a]	Registry[b]
Any time during pregnancy,	4519	617	230	57	371	6
Earliest trimester of exposure, n (%)						
First	3496 (77.4)	519 (84.1)	190 (82.6)	52 (91.2)	296 (79.8)	5 (83.3)
Second or third	940 (20.8)	94 (15.2)	35 (15.2)	5 (8.8)	68 (18.3)	1 (16.7)
Unknown	83 (1.8)	4 (0.6)	5 (2.2)	0 (0.0)	7 (1.9)	0 (0.0)

[a]Reported data are from the retrospective analysis of insurance claims data from the Truven Health Markestcan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits Databases for the period of 1996 to 2012.

[b]Reported data are from the final analysis of the 16-year (1996 to 2012) sumatriptan, naratriptan, and treximet pregnancy registry.

4 | DISCUSSION

We aimed to estimate frequencies of major birth defects and pregnancy outcomes among pregnant women with migraine exposed to sumatriptan, naratriptan, or sumatriptan/naproxen sodium using a retrospective electronic health care database and to informally compare the findings with those reported for a completed 16-year prospective pregnancy registry. For the analysis using the retrospective claims database, 5120 exposed pregnancies were analyzed in comparison with 670 exposed pregnancies in the registry. Overall, there was

TABLE 2 Retrospective claims analysis: Maternal characteristics of pregnancies exposed to sumatriptan, naratriptan or sumatriptan/naproxen sodium

	Sumatriptan	Naratriptan	Sumatriptan/Naproxen Sodium
Number of exposed pregnancies, N	4519	230	371
Year of exposure, n (%)			
1996-2000	126 (2.8)	10 (4.3)	0 (0.0)
2001-2005	816 (18.1)	71 (30.9)	0 (0.0)
2006-2010	2452 (54.3)	113 (49.1)	264 (71.2)
2011-2012	1125 (24.9)	36 (15.7)	107 (28.8)
Earliest trimester of exposure, n (%)			
First	3496 (77.4)	190 (82.6)	296 (79.8)
Second	615 (13.6)	22 (9.6)	51 (13.7)
Third	325 (7.2)	13 (5.7)	17 (4.6)
Unknown	83 (1.8)	5 (2.2)	7 (1.9)
Age at pregnancy, n (%)			
≤19	75 (1.7)	3 (1.3)	5 (1.4)
20-29	1177 (26.1)	45 (19.6)	84 (22.6)
30-39	2681 (59.3)	143 (62.2)	237 (63.9)
40+	586 (13.0)	39 (17.0)	45 (12.1)
Comorbid conditions[a], n (%)			
Diabetes	139 (3.1)	4 (1.7)	6 (1.6)
Hypertension	300 (6.6)	13 (5.7)	33 (8.9)
Prepregnancy medications[a], n (%)			
Oral antidiabetics	165 (3.7)	7 (3.0)	18 (4.9)
Insulin	29 (0.6)	4 (1.7)	2 (0.5)
Antihypertensives	138 (3.1)	5 (2.2)	16 (4.3)
Acute migraine medications			
Triptans	573 (12.7)	48 (20.9)	71 (19.1)
Ergotamine derivatives	20 (0.4)	3 (1.3)	2 (0.5)
NSAID	1163 (25.7)	56 (24.4)	108 (29.1)
Opioid	2221 (49.2)	107 (46.5)	170 (45.8)
Prophylactic migraine medications			
Topiramate	193 (4.3)	14 (6.1)	29 (7.8)
Other anticonvulsants	94 (2.1)	9 (3.9)	15 (4.0)
Cardiovascular meds	241 (5.3)	16 (7.0)	27 (7.3)
Antidepressants	54 (1.2)	3 (1.3)	5 (1.4)
Other	18 (0.4)	4 (1.7)	3 (0.8)
Region, n (%)			
Northeast	577 (12.8)	25 (10.9)	63 (17.0)
Midwest	1140 (25.2)	52 (22.6)	72 (19.4)
South	1793 (39.7)	102 (44.4)	174 (46.9)
West	984 (21.8)	49 (21.3)	61 (16.4)
Missing	25 (0.6)	2 (0.9)	1 (0.3)

Abbreviation: NSAID, nonsteroidal anti-inflammatory drugs.
[a]Identified during the 12 months prior to the pregnancy episode.

broad agreement between the findings of the claims analysis and the registry. The frequency of major birth defects among pregnancies with first-trimester exposure to sumatriptan was 4.0% in both the claims analysis and the registry.

The consistency observed between the key findings of the retrospective claims analysis and the registry regarding pregnancy outcomes in the setting of sumatriptan exposure supports the feasibility of retrospective observational study approaches in evaluating post-approval safety of triptan exposure in pregnancy. In addition, the findings of this study show that for some medications and disease indications, an observational cohort study using existing data may offer a viable alternative to prospective pregnancy registries in meeting the objectives of a postmarketing pregnancy safety surveillance. Not surprisingly, regulators have recently shown an openness to consider alternatives to the classic prospective pregnancy exposure registry in evaluating risks associated with exposure of medications during pregnancy.[13,14] Overall, the frequency of abortions among triptan-exposed pregnant women were higher in the claims analysis than in the registry, and this is possibly because of a biased self-selection of subjects into the registry and under-reporting of these adverse pregnancy outcomes in the registry.[15]

One strength of using administrative databases in evaluating pregnancy outcomes includes the possibility of accruing large numbers of exposures and pregnancy outcomes, particularly when multiple databases are combined. A recent review of 34 pregnancy registries reported a median enrolment of 36 exposed pregnancies.[16] In this study, the number of pregnancy exposures identified in one US database was over 7-fold that evaluable in the registry (which recruited patients from 18 countries) over the same time period. Having a large cohort of identified pregnancy exposures may facilitate the assessment of individual and often rare congenital abnormalities. Other strengths of administrative database studies include consistent ascertainment of medication exposure, pregnancy outcomes and potential confounders, and reduced study costs.

There are several potential methodological challenges associated with the use of administrative claims databases in investigating outcomes of drug exposure during pregnancy that may benefit from further exploration. In particular, key challenges relate to the identification of pregnancy episodes, determination of gestational age, the linkage of mothers and infants, ascertainment of exposures and outcomes, and the careful interpretation of results in light of study and data limitations. The algorithm used for identification of pregnancy episodes and outcomes in this claims analysis has been shown to be very robust for livebirths, with almost complete agreement between claims and chart review, and less robust for non-livebirth outcomes.[9] While valid determination of gestational age is essential for assigning trimester of medication exposure, for abortions and stillbirths, ascertainment of gestational age is very challenging. In the original validation study of the algorithm used to assign gestational age for non-livebirth outcomes in the present claims analysis, about 20% of pregnancies resulting in non-livebirth outcomes had none of the procedures that were used in the algorithm.[11] However, any misclassification arising from imperfect ascertainment of gestational age is likely nondifferential across the 3 exposure cohorts and poses minimal bias to our study findings. The generation of mother-infant pairs is dependent on the infant being covered under the same insurer as the mother, and mother-infant linkage algorithm used in this study linked 75.3% of live-born infants to their mothers. We have no reason to suspect differential linkage across pregnancy outcomes—as such we expect that incomplete linkage between mothers and infants is not likely to bias our study results.

TABLE 3 Pregnancy outcomes and major birth defects among pregnancies with first trimester of triptan exposure

	Sumatriptan		Naratriptan		Sumatriptan/Naproxen Sodium	
	Claims analysis[a]	Registry[b]	Claims analysis[a]	Registry[b]	Claims analysis[a]	Registry[b]
Number of pregnancies, N	3,496	519	190	52	296	5
Elective abortion, n (%)	136 (5.0)	15 (2.9)	7 (3.7)	1 (1.9)	11 (3.7)	0
Spontaneous abortion, n (%)	629 (18.0)	34 (6.6)	33 (17.4)	5 (9.6)	56 (18.9)	1 (20.0)
Stillbirth, n (%)	14 (0.4)	5 (1.0)	0	0	4 (1.4)	0
Livebirth events, n (%)	2717 (77.7)	465 (89.6)	150 (78.9)	46 (88.5)	225 (76.0)	4 (80.0)
Major birth defects	65/1608 (4.0)[c]	20/478 (4.0%)[d]	0/93 (0.0)[c]	1/46 (2.2%)[d]	5/137 (3.6)[c]	0/5 (0.0)[d]

[a]Reported data are from the retrospective analysis of insurance claims data from the Truven Health Marketscan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits Databases for the period of 1996 to 2012.

[b]Reported data are from the final analysis of the 16-year (1996 to 2012) sumatriptan, naratriptan, and treximet pregnancy registry.

[c]Denominators differ from the number of live-born infants because included infants were those (1) linkable to birth mothers and (2) had 12-month continuous insurance enrolment. Risk of major birth defects was calculated as number of infants with birth defects divided by the number of linkable livebirths with 12-month continuous insurance enrolment.

[d]The risk of major birth defects was calculated as the number of pregnancy outcomes with major birth defects divided by the sum of the number of livebirths without defects and the number of pregnancy outcomes with major birth defects.

TABLE 4 Pregnancy outcomes and birth defects among pregnancies with second or third trimester of triptan exposure

	Sumatriptan		Naratriptan		Sumatriptan/Naproxen Sodium	
	Claims analysis[a]	Registry[b]	Claims analysis[a]	Registry[b]	Claims analysis[a]	Registry[b]
Number of pregnancies, N	940	96	35	5	68	1
Elective abortion, n (%)	5 (0.53)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.9)	0 (0.0)
Spontaneous abortion, n (%)	27 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	5 (7.4)	0 (0.0)
Stillbirth, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Livebirth events, n (%)	908 (96.6)	96 (100.0)	35 (100.0)	5 (100.0)	61 (89.7)	1 (100.0)
Major birth defects	17/436 (3.9)[c]	3/96 (3.1)[d]	2/14 (14.3)[c]	0/5 (0.0)[d]	2/28 (7.1)[c]	0/1 (0.0)[d]

[a]Reported data are from the retrospective analysis of insurance claims data from the Truven Health Marketscan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits Databases for the period of 1996 to 2012.

[b]Reported data are from the final analysis of the 16-year (1996 to 2012) sumatriptan, naratriptan, and treximet pregnancy registry.

[c]Denominators differ from the number of live-born infants because included infants were those (1) linkable to birth mothers and (2) had 12-month continuous insurance enrolment. Risk of major birth defects was calculated as number of infants with birth defects divided by the number of linkable livebirths with 12-month continuous insurance enrolment.

[d]The risk of major birth defects was calculated as the number of pregnancy outcomes with major birth defects divided by the sum of the number of livebirths without defects and the number of pregnancy outcomes with major birth defects.

As with any observational study conducted within the context of an insurance claims database, drug exposure and timing of exposure is never entirely certain. While there is evidence in the claims of patients receiving a prescription dispensing at an outpatient pharmacy, we are unable to verify that patients used the medication. Conversely, pregnant patients may take medication during pregnancy that was obtained from a prescription written and dispensed prior to the conception date. In addition, the prescription database lacks information on medication dispensed during hospital admissions or obtained from the doctor's office as samples. Thus, there is a possibility of misidentifying the exact date of triptan exposure, but this should have minimal impact on the accuracy of assignment of trimester of exposure. It should be noted that prospective registries have similar limitations in assessing drug exposure during pregnancy.

Consistent with many pregnancy exposure registries, pregnant women in the sumatriptan, naratriptan, and sumatriptan/naproxen sodium registry could be enrolled at any time during the course of the pregnancy, whereas follow-up for outcomes in the claims analysis began at the earliest date of triptan exposure as determined by filled prescriptions. Thus, adverse outcomes that are more likely to occur earlier during the course of the pregnancy are likely to be underestimated in the registry relative to the claims analysis. In both the claims and registry analyses, we cannot assume a causal relationship between adverse pregnancy outcomes and triptan exposure, as there may be other important contributory factors including exposure to other medications (that may result in adverse outcomes) and even known or potential teratogens.

In this study, live-born infants linked to their birth mothers were required to have 12-month continuous insurance enrolment beginning from the delivery date. This criterion would exclude infants that die during the first year of life (perhaps due to serious congenital malformations or other causes). The proportion of infants with major birth defects would thus be underestimated in the database study relative to the registry. Also, under/overestimation of major birth defects would occur if infants with major congenital malformations differentially disenrolled from insurance coverage during the first year of life relative to infants

without these birth defects. In the registry study, birth defects were ascertained in livebirths, stillbirths, and induced abortions, while in the database study, we are only able to ascertain birth defects in live-born infants. However, the numbers of major birth defects found in stillbirths and induced abortion in the registry were very small.

In conclusion, the findings of this study show that a sizable cohort of pregnant women exposed to medications of interest can be assembled using existing electronic health care databases. Our findings of high agreement between the results of a retrospective analysis using an existing database and a prospective pregnancy registry for the frequency of major birth defects in triptan-exposed pregnancies reinforce the utility of using existing databases for post-approval safety assessment of pregnancy exposures.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.