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ORIGINAL RESEARCH

Changes in Medication Use During Pregnancy for Women with Chronic Conditions: An Analysis of Claims Data

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Abstract

Purpose Evaluation of drug safety during pregnancy is dependent on the number of exposed women during routine clinical practice with data available for analysis. We examined medication fills in pregnant and nonpregnant women within select disease cohorts: general population, migraine, diabetes, and hyperlipidemia to explore the potential use of claims data to assess medication use and safety during pregnancy.

Methods This cohort study, using IBM MarketScan® Research Databases claims data, included women 10–54 years of age with pregnancy resulting in a liveborn infant between January 2010 and September 2015 and matched nonpregnant women. Medication use (antidepressants, antihypertensives, sedatives, glucose-lowering medications, antiepileptics, antipsychotics, lipid-lowering medications) was abstracted from pharmacy claims 180 days before last menstrual period through 180 days postdelivery.

Results Among 753,760 women in the general pregnancy population (including 73,268 migraine, 50,155 hyperlipidemia, and 8361 diabetes; non-exclusive cohorts), antidepressants, antihypertensives, and sedatives were the most commonly used medications during pregnancy. Medications of interest were less commonly used in the pregnancy cohort than in the matched nonpregnant cohort within each time period (e.g., 3.7% vs 13.1% antidepressant use in 1st trimester). Most prescription fills were less common during pregnancy then pre-pregnancy. Post-pregnancy, prescription fills increased to or exceeded pre-pregnancy levels, except antihypertensive and glucose-lowering medications, which increased during pregnancy.

Conclusions Medication use among pregnant women was low and different from that among matched nonpregnant women. The underlying size of large commercial claims databases offer opportunities for efficient evaluation of potential safety concerns, particularly for rare drug exposures, compared to traditional pregnancy registries.

Keywords Pregnancy · Migraine · Diabetes · Hyperlipidemia · Pharmacovigilance

Introduction

Determining the safety of commonly used medications during pregnancy is important, especially in cases where women may become pregnant while they are on medication or may require ongoing treatment to protect their health or prevent complications during pregnancy [1, 2]. However, at the time of regulatory approval, little is known about the safety of many drugs during pregnancy because pregnant women are often excluded from drug development clinical trials [3, 4]. Drug safety during pregnancy is typically evaluated during the post-approval period via pharmacovigilance activities including spontaneous reporting systems and post-marketing studies [5–7].

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When post-marketing studies are required to assess the safety of medications during pregnancy, regulatory authorities have traditionally mandated data collection utilizing pregnancy registries, which prospectively enroll pregnant women and obtain long-term follow-up data on maternal and infant outcomes [8, 9]. However, registries frequently struggle to meet enrollment targets, have limited sample size, and are often underpowered to evaluate outcomes, resulting in inconclusive findings on teratogenicity [10, 11]. Sample size limitations are further compounded by difficulties in patient retention, representativeness of enrolled patients, and difficulty in identifying suitable comparison groups [12].

Due to the challenges associated with pregnancy registries and increasing recognition of the value of real-world data for pharmacovigilance, interest in leveraging large healthcare databases for evaluating drug safety during pregnancy has become more common [3, 13]. Such databases capture information on very large samples of patients, potentially providing more power for analysis and more representative patient populations. Regardless of the data source—a registry or administrative database—study success is dependent on the number of women exposed during pregnancy to the medications of interest during routine clinical practice [10, 11]. Estimating the prevalence of medication use among pregnant women could help inform if prospective registries, database studies, single-arm descriptive studies including both retrospective and prospective data collection, or routine pharmacovigilance including signal detection through spontaneous reporting systems are effective approaches for evaluating drug safety during the post-approval period. Using a large US-based commercial claims database, we examined the frequency of prescription fills within four cohorts of pregnant women including (1) a general population sample, (2) women with migraine, (3) women with diabetes, and (4) women with hyperlipidemia. For comparison, we evaluated medication patterns in matched, nonpregnant women to assess the impact of pregnancy on medication use.

Methods

Data Source

This cohort study used claims data from the IBM MarketScan® Research Databases: Commercial Claims and Encounters Database, which includes de-identified data for more than 250 million geographically diverse, commercially insured individuals living in the United States. These data include administrative health records covering inpatient and outpatient services, and prescription drug use including oral, injectable, and other routes of administration.

The data used for this study did not involve the interaction with or interview of any patients and the data do not include any individually identifiable data. IRB approval was not required. Database records were de-identified and fully compliant with United States patient confidentiality requirements, including the HIPAA of 1996. Data from the MarketScan® database were used under a licensing agreement with IBM Watson Health. In alignment with the IBM Watson Health licensing agreement, the dataset generated and analyzed during the current study is not publicly available.

Study Population

Women 10–54 years of age on the date of their estimated last menstrual period (LMP) with evidence of pregnancy resulting in a live born infant between January 2010 and September 2015 were included. Evidence of pregnancy was determined by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis or procedure codes related to pregnancy (Supplementary Table 1). To be eligible for inclusion, linkage to the record of a child with the same family number as the woman and born on the same day as the woman's delivery date was required. Linkage with infant records was required to provide feasibility to extend follow-up beyond the point of delivery or to assess newborn outcomes. Further, eligibility required continuous healthcare coverage from 180 days prior to LMP through 180 days following delivery. The index date for the pregnancy cohort was defined by LMP calculated using a validated algorithm specific to mothers 10–54 years of age with live birth deliveries [14], which was developed by the Medication Use in Pregnancy Evaluation Program (MEPREP), and comprises 17 health plans to monitor the post-market safety of medical products. This algorithm [14] uses ICD-9 diagnosis codes for pre-term and post-term births to estimate days of gestation. When specified diagnosis codes for pre-term and post-term were unavailable, a 273-day gestational period was imputed, assuming that the pregnancy reached full term (39–40 weeks). In a study of singleton deliveries using this algorithm, 86% of the women reached full-term pregnancy and infants had a mean gestational age of 273.5 days [15]. For each woman, only the first pregnancy episode ending in live birth during the study period was included and linked with an infant record. Women were excluded if during the 180-day period prior to their index date they had evidence of pregnancy based on diagnosis and procedure codes for pre-term and post-term birth, completed weeks of gestation, or pregnancy indicators.

This study included four cohorts of pregnant women: (1) all women; (2) women diagnosed with migraine; (3) women diagnosed with hyperlipidemia; and (4) women diagnosed with diabetes (Supplemental appendix). The three disease-specific cohorts were identified by the presence of ICD-9 codes > 180 days before index date (LMP) to ensure that

conditions were present prior to the pregnancy. The migraine cohort was defined leveraging a combination of inpatient, outpatient, emergency room, and acute migraine drug claims; specific inclusion criteria are detailed in Online Appendix A. A patient was included in the hyperlipidemia cohort if she had ≥ 1 inpatient or outpatient ICD-9 diagnosis code of hyperlipidemia or ≥ 60 days (≥ 2 consecutive fills, regardless of dose) of lipid-lowering medication. A patient was included in the diabetes cohort if she had ≥ 1 inpatient diabetes (Type I or Type II) diagnosis claim or ≥ 2 outpatient or emergency department diabetes diagnosis claims between 7 and 180 days apart.

Due to the large size of the general population pregnancy cohort ($N = 753{,}760$), we randomly sampled 10% of each of the four pregnancy cohorts for inclusion in the study to enable matching of controls. For each woman in the general population, migraine, hyperlipidemia, and diabetes cohorts, we matched 4 nonpregnant women by year of birth, index date (same calendar month and year), and specified criteria for the disease-specific cohorts; that is, 1:4 matching per cohort. As with the pregnancy cohorts, nonpregnant women were required to have continuous enrollment for ≥ 180 days before the matched index date through 180 days following the delivery date of the matched pregnant patient.

Medication Exposure

Medication use was defined by at least one-filled prescription in the pharmacy claims from 180 days pre-pregnancy through 180 days post-pregnancy. Medication use was assessed separately during pre-pregnancy (defined as 180 days before the LMP), each trimester of pregnancy (trimester 1: index date to 90 days, trimester 2: 91–180 days, trimester 3: 181- < delivery date), the entire pregnancy period (defined by the time between LMP and delivery), and post-pregnancy (180 days postdelivery).

We evaluated several medication categories, including antidepressants, antihypertensive medications, sedatives, glucose-lowering medications, antiepileptics, antipsychotics, and lipid-lowering medications. The World Health Organization Anatomical Therapeutic Chemical (ATC) drug classification system was used to categorize medications by drug class [16]. Patients could qualify for multiple medication exposure classes and multiple disease cohorts.

Statistical Analysis

Characteristics of the pregnant and matched nonpregnant women were described using means and proportions for continuous and categorical variables, respectively. Comorbidities were defined using ICD-9 diagnosis codes. Among the general population and each of the disease cohorts, we estimated the frequency of prescription fills prior, during, and post-pregnancy for pregnant women, and during the corresponding time intervals for nonpregnant women. Frequency of prescription fills was also estimated for each trimester of pregnancy. Medication use stratified by age and the trends of medication use over calendar years were evaluated.

Results

We identified 753,760 women with pregnancies ending in live births that met all study inclusion criteria including 73,268 with migraine, 50,155 with hyperlipidemia, and 8361 with diabetes. To enable matching of controls, we selected a random 10% sample of the full cohort, resulting in a cohort of 75,379 pregnant women (Table 1). A total of 228,279 nonpregnant women were matched to this general pregnancy cohort; there were some women for whom four matches could not be identified. We identified 7306 women with pregnancies in the migraine cohort who were matched with 28,297 nonpregnant women with migraine, 4993 in the hyperlipidemia cohort who were matched with 19,964 nonpregnant women with hyperlipidemia, and 845 in the diabetes cohort who were matched with 3274 nonpregnant women with diabetes. The majority of women in each cohort were 25–34 years of age. Within each cohort, pregnant women had fewer comorbid conditions, including depression, hypertension, and hypercholesterolemia, than their nonpregnant counterparts.

In the general pregnancy population, antidepressants, antihypertensive, and sedative medications were the most commonly used medications during pregnancy (Fig. 1). Overall, prescription fills were less common in the pregnancy cohort than in the matched nonpregnant cohort across all time periods (Fig. 1). There was a reduction in most prescription fills during pregnancy compared with that observed pre-pregnancy in the general pregnancy cohort (Fig. 1C and D). In the post-pregnancy time period, prescription fills increased to or exceeded pre-pregnancy levels. The notable exceptions to the reduction in medication use during pregnancy were antihypertensive medications and glucose-lowering medications, which increased during pregnancy. These increases were most marked in the third trimester, with a return to pre-pregnancy levels in the post-pregnancy time period. These changes in medication use were not present in the matched cohort in which there was no evidence that medication use changed over time. A higher proportion of older women were taking each medication compared with younger women, and trends were consistent across calendar years (data not shown).

A similar pattern to the general pregnancy population was present in the disease-specific cohorts across the pregnancy periods (Fig. 2 and Table 2). As expected, the prevalence of medications indicated to treat the underlying conditions

Table 1 Characteristics of pregnant women and matched nonpregnant women from the general population and with migraine, hyperlipidemia, and diabetes

	General		Migraine		Hyperlipidemia		Diabetes	
	Pregnant *N* = 75 379	Nonpregnant *N* = 228 279	Pregnant *N* = 7306	Nonpregnant *N* = 28 297	Pregnant *N* = 4993	Nonpregnant *N* = 19 964	Pregnant *N* = 845	Nonpregnant *N* = 3274
Mean age (SD) at LMP, years	32.1 (4.7)	32.1 (4.7)	32.2 (4.7)	32.3 (4.7)	34.1 (4.6)	34.1 (4.6)	33.5 (5.1)	33.7 (5.1)
< 18	85 (0.1)	251 (0.1)	8 (0.1)	32 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	4 (0.1)
18–24	3173 (4.2)	9337 (4.1)	283 (3.9)	1132 (4.0)	59 (1.2)	236 (1.2)	28 (3.3)	106 (3.2)
25–34	49 993 (66.3)	151 475 (66.4)	4830 (66.1)	18 393 (65.0)	2679 (53.7)	10 708 (53.6)	467 (55.3)	1,768 (54.0)
35–40	18 987 (25.2)	57 514 (25.2)	1880 (25.7)	7520 (26.6)	1840 (36.9)	7360 (36.9)	286 (33.9)	1,144 (34.9)
41–55	3141 (4.2)	9702 (4.3)	305 (4.2)	1220 (4.3)	415 (8.3)	1660 (8.3)	63 (7.5)	252 (7.7)
Comorbidities								
Autoimmune	543 (0.7)	2317 (1.0)	96 (1.3)	648 (2.3)	78 (1.6)	366 (1.8)	12 (1.4)	68 (2.1)
Cardiovascular	1328 (1.8)	6583 (2.9)	299 (4.1)	2251 (8.0)	535 (10.7)	2756 (13.8)	99 (11.7)	517 (15.8)
Cerebrovascular	176 (0.2)	1238 (0.5)	72 (1.0)	663 (2.3)	39 (0.8)	284 (1.4)	15 (1.8)	116 (3.5)
Connective tissue	1538 (2.0)	5919 (2.6)	291 (4.0)	2204 (7.8)	185 (3.7)	994 (5.0)	32 (3.8)	178 (5.4)
Endocrine and metabolic disorders	4004 (5.3)	14 348 (6.3)	557 (7.6)	2754 (9.7)	901 (18.1)	4081 (20.4)	845 (100)	3274 (100)
Gastrointestinal	887 (1.2)	3286 (1.4)	172 (2.4)	1033 (3.7)	155 (3.1)	542 (2.7)	13 (1.5)	67 (2.1)
Hypertension	2101 (2.8)	12 701 (5.6)	416 (5.7)	3048 (10.8)	569 (11.4)	3660 (18.3)	196 (23.2)	1081 (33.0)
Hepatology	154 (0.2)	838 (0.4)	33 (0.5)	264 (0.9)	45 (0.9)	273 (1.4)	23 (2.7)	104 (3.2)
Other (bone disease, cancer, etc.)	705 (0.9)	3428 (1.5)	94 (1.3)	747 (2.6)	103 (2.1)	557 (2.8)	27 (3.2)	132 (4.0)
Psychiatric/CNS	6285 (8.3)	28 415 (12.5)	1319 (18.1)	8188 (28.9)	793 (15.9)	4120 (20.6)	130 (15.4)	746 (22.8)
Respiratory	5108 (6.8)	20 105 (8.8)	1016 (13.9)	5207 (18.4)	777 (15.6)	3236 (16.2)	100 (11.8)	542 (16.6)

Matched sample is based on a 4:1 match to a 10% random sample of cases from the eligible pregnancy sample

Data represent *n* (%) unless otherwise indicated

was commensurate with expected treatments in each disease cohort, with higher use among the disease-specific cohorts than the general population prior to, during, and after pregnancy. Antidepressants, antiepileptics, and sedatives, medications commonly used to treat migraine, were used at the highest rate in the migraine cohort (Fig. 2A). Antihypertensive and hyperlipidemia medications were used by a higher proportion of women in the hyperlipidemia and diabetes cohorts (Fig. 2B), with glucose-lowering medications used by a higher proportion of women in the diabetes cohort (Fig. 2C). Prescription fills decreased during pregnancy compared with pre-pregnancy in all three disease-specific cohorts, except for an increase in the utilization of antihypertensives and glucose-lowering medications, particularly during the third trimester, and a smaller increase in antipsychotic medications.

Discussion

Due to challenges associated with pregnancy registries, including problems with enrollment and retention leading to limited sample sizes, we sought to explore whether large administrative healthcare databases could be used as an alternative source for real-world data for pregnancy safety studies. In this study of women of child-bearing potential, the use of medications of interest during pregnancy was low, even among those with chronic conditions. Medication use was more common among the nonpregnant cohorts, and as expected, a consistent pattern of use was observed across the time periods corresponding to each trimester. The lower use of drugs in the pregnant cohort compared with the nonpregnant cohort may, in part, reflect a "healthy pregnancy" effect, such that those who get pregnant are overall healthier than their nonpregnant counterparts. Additionally, women who are trying to get pregnant may restrict drug intake also contributing to the lower prescription counts in the pregnant cohort. The prevalence of medication use declined substantially during pregnancy (relative to pre-pregnancy levels) with the notable exception of antihypertensive and glucose-lowering medications, which increased. Use of medications was dependent both on the population and the type of medication being assessed. The large sample size available in this analysis of administrative claims indicates that this may be a good source to study drug safety.

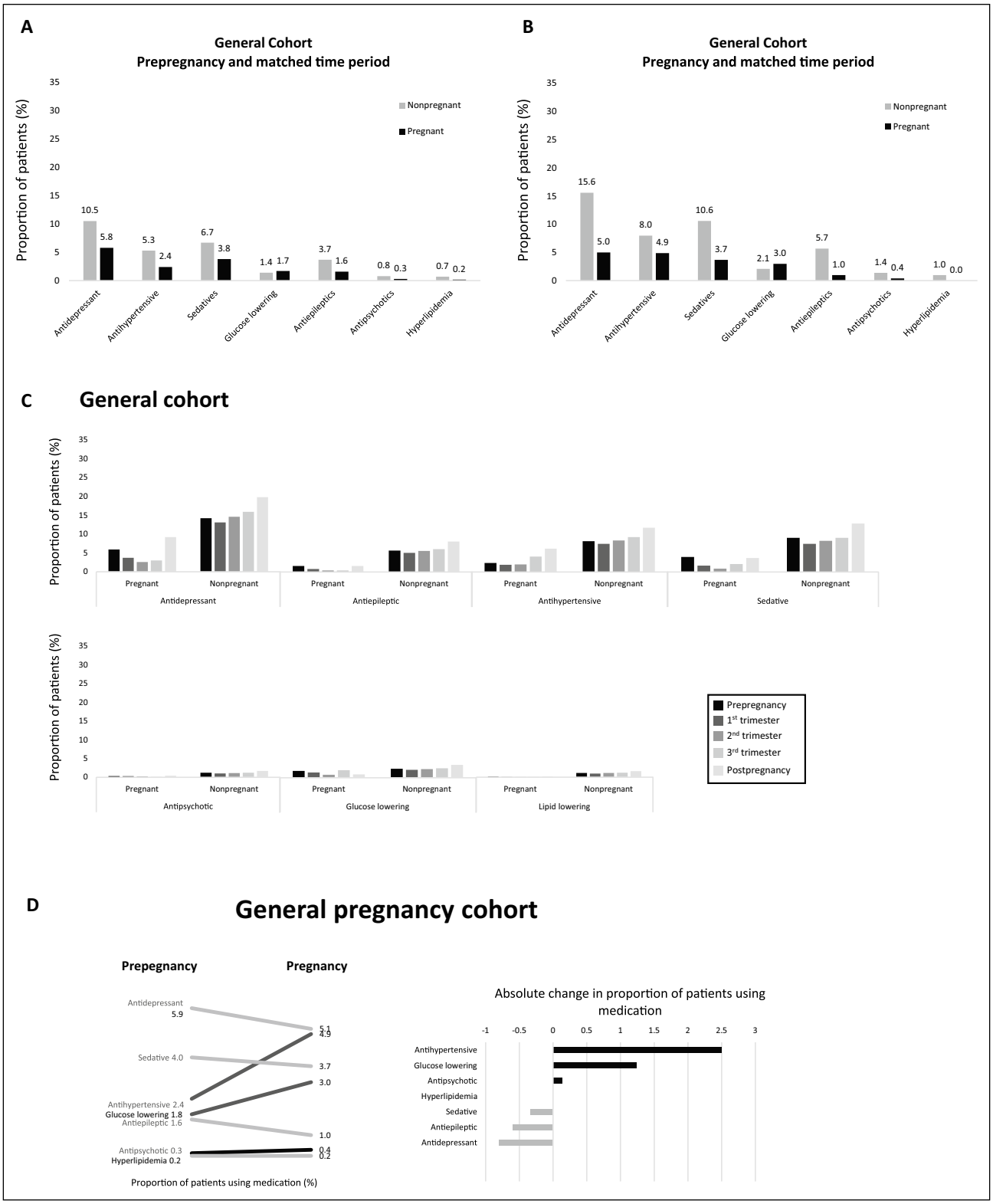

Figure 1 Prescription fills among pregnant women and matched nonpregnant women in the general cohort during pre-pregnancy, pregnancy, post-pregnancy, and matched time periods. Proportion of pregnant and matched nonpregnant women in the general cohort with prescription fills for selected drugs during pre-pregnancy period (**A**), during pregnancy (**B**), and during pre-pregnancy, each trimester of pregnancy and post-pregnancy (**C**). Change in prescription fills between the pre-pregnancy and pregnancy periods in the general cohort (**D**).

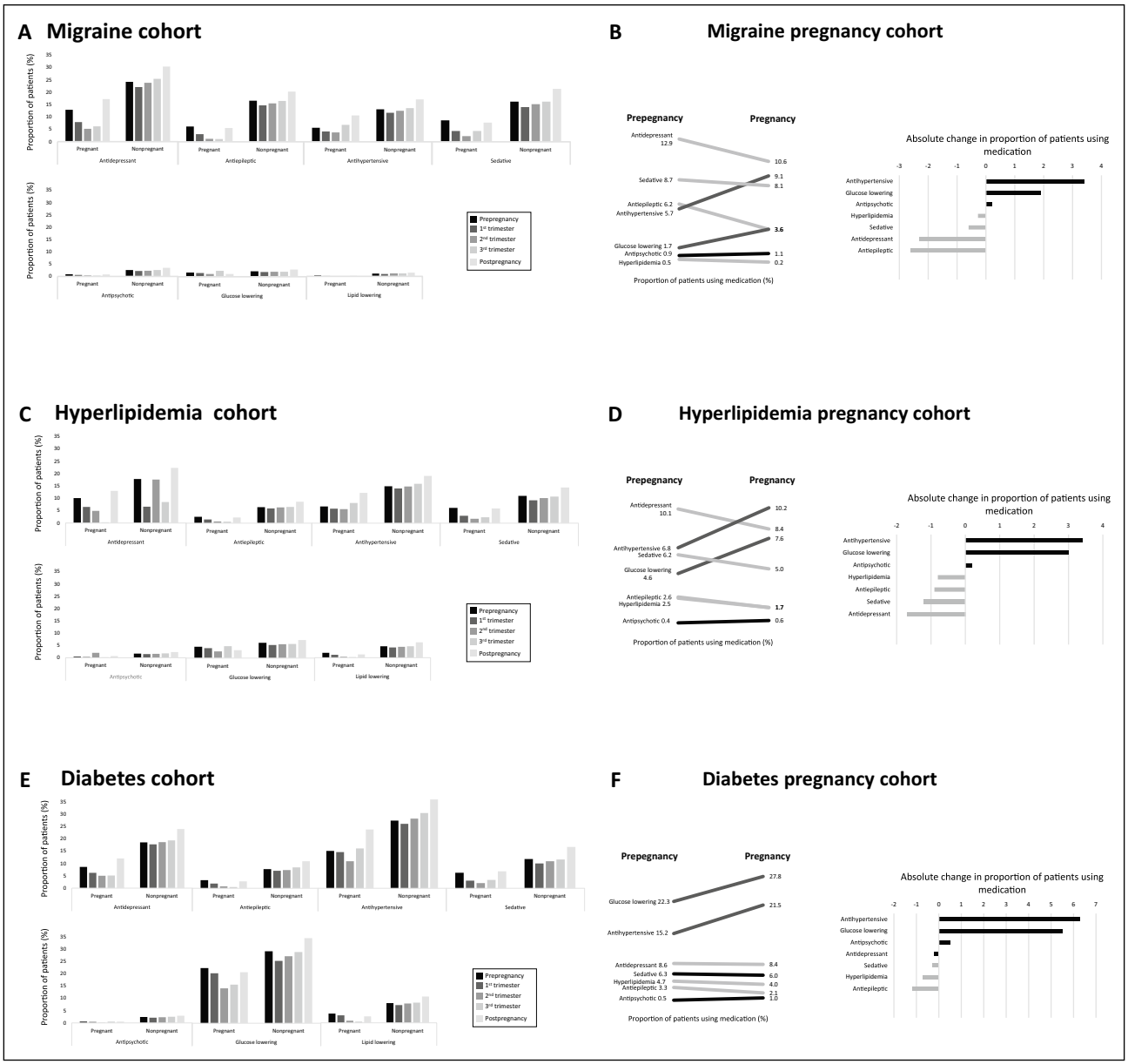

Figure 2 Prescription fills among pregnant women and matched nonpregnant women in the disease cohorts during pre-pregnancy, pregnancy, post-pregnancy, and matched time periods. Proportion of pregnant and matched nonpregnant women with prescription fills for selected drugs during pre-pregnancy, each trimester of pregnancy and post-pregnancy in the migraine cohort (**A**), hyperlipidemia cohort (**C**), and diabetes cohort (**E**). Change in prescription fills between the pre-pregnancy and pregnancy periods in the migraine cohort (**B**), hyperlipidemia cohort (**D**), and diabetes cohort (**F**).

A recent study of the Sentinel System found a three-fold lower exposure to medications for which there is a pregnancy exposure than in nonpregnant women [14]. Additionally, an overall pattern of lower prevalence of prescribed medications before pregnancy to during pregnancy, and a further decrease in use beyond the first trimester has been observed in prior studies [17, 18], suggesting that women who are planning to become pregnant may proactively discontinue their medications for some chronic conditions. These findings have important implications for investigators planning pregnancy studies, as the use of medication among women of child-bearing age may not reflect the use of medication among pregnant women. Our results extend these prior findings and demonstrate that large administrative claims databases can be used to identify treatment patterns during pregnancy and that the prior algorithms are adaptable to different medications and observation periods.

Table 2 Prescription fills during the pre-pregnancy period, each trimester of pregnancy, and in the post-pregnancy period among pregnant women and matched nonpregnant women

	180 days prior	1st trimester	2nd trimester	3rd trimester	180 days post
General cohort					
Antidepressant					
Pregnant	4474 (5.9)	2807 (3.7)	1977 (2.6)	2264 (3.0)	6915 (9.2)
Nonpregnant	32 493 (14.2)	29 981 (13.1)	33 258 (14.6)	36 326 (15.9)	45 080 (19.8)
Antiepileptic					
Pregnant	1216 (1.6)	612 (0.8)	321 (0.4)	323 (0.4)	1168 (1.6)
Nonpregnant	13 095 (5.7)	11 630 (5.1)	12 833 (5.6)	13 954 (6.1)	18 455 (8.1)
Antihypertensive					
Pregnant	1794 (2.4)	1422 (1.9)	1538 (2.0)	3058 (4.1)	4642 (6.2)
Nonpregnant	18 621 (8.2)	17 032 (7.5)	19 059 (8.4)	21 157 (9.3)	26 835 (11.8)
Antipsychotic					
Pregnant	223 (0.3)	205 (0.3)	118 (0.2)	97 (0.1)	266 (0.4)
Nonpregnant	2760 (1.2)	2335 (1.0)	2549 (1.1)	2828 (1.2)	3920 (1.7)
Glucose lowering					
Pregnant	1325 (1.8)	1060 (1.4)	611 (0.8)	1470 (2.0)	676 (0.9)
Nonpregnant	5493 (2.4)	4764 (2.1)	5234 (2.3)	5687 (2.5)	7682 (3.4)
Lipid lowering					
Pregnant	164 (0.2)	102 (0.1)	33 (0.04)	32 (0.04)	141 (0.2)
Nonpregnant	3160 (1.4)	2800 (1.2)	3082 (1.4)	3330 (1.5)	4574 (2.0)
Sedative					
Pregnant	2978 (4.0)	1277 (1.7)	704 (0.9)	1588 (2.1)	2781 (3.7)
Nonpregnant	20 726 (9.1)	17 015 (7.5)	18 949 (8.3)	20 857 (9.1)	29 478 (12.9)
Migraine cohort					
Antidepressant					
Pregnant	939 (12.9)	579 (7.9)	380 (5.2)	450 (6.2)	1255 (17.2)
Nonpregnant	6848 (24.2)	6243 (22.1)	6745 (23.8)	7178 (25.4)	8590 (30.4)
Antiepileptic					
Pregnant	454 (6.2)	224 (3.1)	84 (1.2)	83 (1.1)	408 (5.6)
Nonpregnant	4717 (16.7)	4178 (14.8)	4410 (15.6)	4692 (16.6)	5772 (20.4)
Antihypertensive					
Pregnant	413 (5.7)	304 (4.2)	278 (3.8)	506 (6.9)	778 (10.7)
Nonpregnant	3743 (13.2)	3329 (11.8)	3550 (12.6)	3889 (13.7)	4854 (17.2)
Antipsychotic					
Pregnant	62 (0.9)	47 (0.6)	28 (0.4)	24 (0.3)	59 (0.8)
Nonpregnant	724 (2.6)	613 (2.2)	663 (2.3)	722 (2.6)	1000 (3.5)
Glucose lowering					
Pregnant	127 (1.7)	106 (1.5)	81 (1.1)	178 (2.4)	83 (1.1)
Nonpregnant	614 (2.2)	31 (1.9)	558 (2.0)	556 (2.0)	809 (2.9)
Lipid lowering					
Pregnant	34 (0.5)	14 (0.2)	2 (0.03)	2 (0.03)	18 (0.3)
Nonpregnant	385 (1.4)	330 (1.2)	356 (1.3)	383 (1.4)	525 (1.9)
Sedative					
Pregnant	638 (8.7)	322 (4.4)	169 (2.3)	318 (4.4)	571 (7.8)
Nonpregnant	4602 (16.3)	3980 (14.1)	4317 (15.3)	4608 (16.3)	6096 (21.5)
Hyperlipidemia cohort					
Antidepressant					
Pregnant	506 (10.1)	323 (6.5)	246 (4.9)	263 (5.3)	649 (13.0)
Nonpregnant	3547 (17.8)	3322 (16.6)	3511 (17.6)	3692 (18.5)	4444 (22.3)
Antiepileptic					
Pregnant	132 (2.6)	75 (1.5)	36 (0.7)	29 (0.6)	115 (2.3)
Nonpregnant	1292 (6.5)	1192 (6.0)	1270 (6.4)	1311 (6.6)	1736 (8.7)

Table 2 (continued)

	180 days prior	1st trimester	2nd trimester	3rd trimester	180 days post
Antihypertensive					
Pregnant	339 (6.8)	293 (5.9)	286 (5.7)	408 (8.2)	612 (12.3)
Nonpregnant	3003 (15.0)	2818 (14.1)	2980 (14.9)	3207 (16.1)	3829 (19.2)
Antipsychotic					
Pregnant	19 (0.4)	16 (0.3)	11 (0.2)	12 (0.2)	37 (0.7)
Nonpregnant	345 (1.7)	301 (1.5)	326 (1.6)	349 (1.8)	456 (2.3)
Glucose lowering					
Pregnant	230 (4.6)	200 (4.0)	133 (2.7)	241 (4.8)	162 (3.2)
Nonpregnant	1232 (6.2)	1054 (5.3)	1108 (5.6)	1145 (5.7)	1464 (7.3)
Lipid lowering					
Pregnant	124 (2.5)	75 (1.5)	26 (0.5)	17 (0.3)	87 (1.7)
Nonpregnant	1153 (5.8)	1034 (5.2)	1107 (5.5)	1164 (5.8)	1555 (7.8)
Sedative					
Pregnant	307 (6.2)	148 (3.0)	92 (1.8)	120 (2.4)	301 (6.0)
Nonpregnant	2212 (11.1)	1852 (9.3)	2033 (10.2)	2158 (10.8)	2901 (14.5)
Diabetes cohort					
Antidepressant					
Pregnant	73 (8.6)	52 (6.2)	42 (5.0)	43 (5.1)	101 (12.0)
Nonpregnant	605 (18.5)	578 (17.7)	610 (18.6)	632 (19.3)	781 (23.9)
Antiepileptic					
Pregnant	28 (3.3)	16 (1.9)	7 (0.8)	4 (0.5)	24 (2.8)
Nonpregnant	256 (7.8)	231 (7.1)	241 (7.4)	279 (8.5)	361 (11.0)
Antihypertensive					
Pregnant	128 (15.2)	124 (14.7)	93 (11.0)	137 (16.2)	202 (23.9)
Nonpregnant	899 (27.5)	858 (26.2)	928 (28.3)	1002 (30.6)	1183 (36.1)
Antipsychotic					
Pregnant	4 (0.5)	3 (0.4)	1 (0.1)	4 (0.5)	4 (0.5)
Nonpregnant	78 (2.4)	67 (2.1)	74 (2.3)	82 (2.5)	96 (2.9)
Glucose lowering					
Pregnant	188 (22.3)	171 (20.2)	119 (14.1)	132 (15.6)	174 (20.6)
Nonpregnant	953 (29.1)	824 (25.2)	887 (27.1)	942 (28.8)	1127 (34.4)
Lipid lowering					
Pregnant	40 (4.7)	32 (3.8)	9 (1.1)	5 (0.6)	28 (3.3)
Nonpregnant	327 (10.0)	293 (9.0)	321 (9.8)	335 (10.2)	435 (13.3)
Sedative					
Pregnant	53 (6.3)	26 (3.1)	18 (2.1)	29 (3.4)	58 (6.9)
Nonpregnant	390 (11.9)	331 (10.1)	359 (11.0)	384 (11.7)	551 (16.8)

Data represent *n* (%)

The likelihood of medication use during pregnancy is highly dependent on the treatment of underlying conditions, with higher likelihood of medication discontinuation observed in women having certain conditions (e.g., migraine) versus others (e.g., diabetes). Commonly, migraine prophylaxis is discontinued during pregnancy as the symptoms of migraine are often ameliorated during the 2nd or 3rd trimester; however, up to 8% of pregnant women will continue to experience migraine throughout the course of their pregnancy [19]. In the current analysis, a relatively small proportion of pregnant women with migraine filled prescriptions for drug classes that could be indicated for migraine prevention (e.g., antidepressants, antiepileptics), with the use of these medications decreasing throughout the pregnancy.

Approximately 1% of pregnancies in the US are affected by pregestational diabetes [20]. Poorly controlled diabetes during pregnancy has been associated with both maternal and neonatal morbidity, with increased risk of poor outcomes in the mother, fetal distress, fetal death, and major congenital malformations [21]. Because of the risk to both the mother and fetus if diabetes is not controlled,

glucose-lowering medications may be expected to continue throughout pregnancy. Indeed, in the current study, the highest medication usage occurred among patients with diabetes, namely for glucose-lowering medications.

The National Lipid Association (NLA) recommends discontinuation of cholesterol lowering medications four weeks prior to attempting to conceive, and the National Institute of Clinical Excellence (NICE) guidelines recommend stopping cholesterol lowering medications three months before attempting to conceive. Both the NLA and NICE guidelines state that women should not take cholesterol medications during pregnancy or while nursing [22, 23]. A recent study in the FDA Sentinel distributed data network suggests approximately 0.22% of all pregnant women are prescribed a statin during pregnancy, with use decreasing by trimester of pregnancy [14]. In the current study, 1.5% of pregnant women with pre-existing hyperlipidemia filled a prescription for a lipid-lowering medication during their first trimester (possibly prior to recognizing the pregnancy), with prescription fills decreasing to 0.5% and 0.3% during the second and third trimesters, respectively.

The limited use of many drugs among pregnant women presents a challenge to studying their safety in pregnancy. Although use of most medications evaluated in the current analysis was low in the months leading up to and during pregnancy, because of the large size of the underlying database, prescriptions for each class of medication were filled by over 1000 women in the general population during pregnancy. Thus, administrative healthcare databases may offer a more efficient approach to evaluating potential safety concerns, particularly for rare drug exposures, where low frequency of medication use presents difficulties in identifying and enrolling patients in pregnancy registries. Further, in the pre-approval time period, use of such healthcare databases to examine the use of analogs (e.g., similar medications within the condition of interest) during pregnancy can help inform and develop more reliable estimates for exposure levels during pregnancy of novel drugs required for planning of pregnancy studies. Although additional assumptions regarding medication use will be required and can further complicate the projected use, estimating prevalence of medication use during pregnancy from large databases can help inform whether a pregnancy registry or database study would be feasible in the post-approval time frame. In addition to feasibility as it relates to sample size, investigators must also consider critical elements of study design and analysis to reduce bias and obtain not only precise but also valid results.

A number of limitations of our analysis must be considered. First, drug use was defined by prescription fills, which do not necessarily reflect if the medication was taken. It is possible that a woman filled a prescription but did not take the medication after becoming aware of her pregnancy. Researchers can consider requiring two prescription fills to define drug exposure rather than one, as women with two fills are more likely to be taking the medication of interest [13]. Therefore, the current study could represent an overestimate of drug use. However, medication exposure was assessed based on prescription fills rather than days of supply, so there is a potential for exposure misclassification within the time intervals if days of supply from a prior interval extend into a new interval (e.g., a prescription fill pre-pregnancy reflected days supply that extended into the first trimester). Furthermore, we restricted the analysis to women with livebirths for whom infants were linkable to the maternal records, and therefore, our findings may not be reflective of the broader pregnancy population, which includes the ~ 35% of pregnancies that end in non-live birth, miscarriage, or abortion and excludes any women who died during pregnancy [24]. The data used were collected from patients with private commercial insurance, which may present a potential bias toward patients with better economic resources and better access to healthcare. Demographic variables such as socioeconomic status, race/ethnicity, and state of residence were not evaluated, which have the potential to explain different patterns in medication use across each of the cohorts [2]. The results may not be generalizable to the Medicaid population, the inclusion of which may increase the sample size of patients from different socioeconomic statuses. The use ICD-10 codes, more recently released than the ICD-9 codes used in this analysis, could provide increased granularity and pregnancy identification in future studies or pharmacovigilance activities [25]. Part of the criteria for the migraine and hyperlipidemia cohorts were medication use claim > 180 days prior to LMP. There is not a direct overlap in medication use during pregnancy; however, patients previously exposed may be expected to have a higher likelihood of exposure to these medications during pregnancy.

In this large, population-based drug utilization study in pregnancy, medication use was lower during pregnancy compared with nonpregnant periods of equal length from a matched cohort, as well as when compared with the pre-pregnancy period. These nuances indicate that medication use among women of child-bearing age is not a direct corollary to medication use during pregnancy, which has implications for sample size when planning post-approval pharmacovigilance studies. Nonetheless, the underlying size of many large commercial claims database may provide sufficient sample size to evaluate potential safety concerns, particularly for rare medication exposures, if outcomes of interest, including miscarriages and stillbirths, are available.

Author Contributions

Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: All authors. Drafting the work or revising it critically for important intellectual

content: All authors. Final approval of the version to be published: All authors. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: RH.

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Declarations

Conflict of interest

Rohini K Hernandez, Lisa Bollinger, Brian D Bradbury, Eric Ng, and Victoria Chia are or were employees and stockholders of Amgen Inc. at the time of the study. Susan Jick reports consulting fees from Amgen Inc. Sonja S Nakasian reports no conflicts of interest in this work. Paul Muntner receives research support and consulting fees from Amgen, Inc.

Supplementary Information

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