HHS Public Access

Author manuscript

Pharmacoepidemiol Drug Saf. Author manuscript; available in PMC 2020 September 01.

Published in final edited form as:

Pharmacoepidemiol Drug Saf. 2019 September ; 28(9): 1211–1221. doi:10.1002/pds.4794.

Identifying Pregnancies in Insurance Claims Data: Methods and Application to Retinoid Teratogenic Surveillance

Sarah C MacDonald[A], **Jacqueline M Cohen**[A], **Alice Panchaud**[A], **Thomas F McElrath**[B], **Krista F Huybrechts**[C], **Sonia Hernández-Díaz**[A]

[A]Department of Epidemiology Harvard TH Chan School of Public Health, Boston, Massachusetts

[B]Division of Maternal-Fetal Medicine, Department of Obstetrics & Gynecology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

[C]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital. Boston, MA.

Abstract

Purpose: To develop an algorithm to identify pregnancies in administrative databases and apply it to assess pregnancy rates and outcomes in women prescribed isotretinoin or tretinoin.

Methods: Using the 2011–2015 Truven Health MarketScan® Database, we identified pregnancies, including losses and terminations. In a cohort design, non-pregnant women filling a prescription for isotretinoin or tretinoin were matched to five women without either prescription. Women were followed for 365-days or until conception, medication discontinuation, or enrollment discontinuation ("prescription episode"). Rates of pregnancy, risks of pregnancy losses, and prevalence of infant malformations at birth were assessed by exposure.

Results: We identified 2,179,192 livebirths, 8,434 stillbirths, 2,521 mixed births, 415,110 spontaneous abortions, 124,556 elective terminations, and 8,974 unspecified abortions. There were 86,834 isotretinoin and 973,587 tretinoin episodes, matched to 5,302,105 unexposed women. Pregnancy rates were 3 (isotretinoin), 19 (tretinoin), and 34 (unexposed) per 1,000 person-years. Risk of pregnancy losses were similar, however terminations were more common in the isotretinoin-exposed (28% [95% CI: 21–36%]), than the tretinoin-exposed (10% [95% CI: 9–11%]) or unexposed pregnancies (6%). Malformations occurred in 4.5% (95% CI:3.5–5.6%) of the tretinoin-exposed pregnancies and 4.2% of the unexposed pregnancies (adjusted odds ratio: 1.16 [95% CI: 0.85–1.58]); isotretinoin-exposed births were too few to assess malformations.

Conclusion: Administrative databases can complement REMS for known teratogens and contribute to safety surveillance for other medications. Here, isotretinoin-exposed pregnancy rates were low, but existent, and many pregnancies were terminated. Tretinoin exposure was not associated with a meaningfully elevated risk of losses or malformations as compared to unexposed pregnancies.

Corresponding Author: Sarah MacDonald, ScD, Department of Epidemiology, Harvard T.H. Chan School of Public Health, 677 Huntington Avenue, Kresge Building, Room 816b, Boston, MA 02115, Tel: 617-615-5763, smacdonald@mail.harvard.edu.

Conflict of Interest: There are no conflicts of interest to declare

Introduction

Increasingly, administrative databases are being used for post-marketing surveillance in pregnancy.[1] An alternative to traditional pregnancy registries, these databases are often large, have prospective prescription recording, and are less costly for research than ad hoc registries.[2] However, administrative databases can be prone to misclassification and missing information.[3] Specifically, in pregnancy studies, identifying early losses and dates of conception can be challenging.[4–7] Indeed, limitations of prior work include missing mother-infant linkages,[5,8–10] exclusion of early loss outcomes,[9,11,12] crude estimation of pregnancy types,[1,8,13] and arbitrary gestational age assignments.[8,10,13,14] The development and validation of algorithms to identify pregnancies in administrative data is needed to improve the development of these cohorts for future research. The current study built upon prior work to propose an algorithm for identifying pregnancies (including stillbirths and early losses) in a large health insurance claims database.

Next, the authors present an application of the cohort for the surveillance of safety in pregnancy for medications with both known and unknown teratogenicity. Specifically, this resource was used to assess pregnancy rates, risks of pregnancy losses, and the prevalence of major congenital malformations at delivery in women exposed to isotretinoin and tretinoin compared to an unexposed reference group. The vitamin-A derivative isotretinoin is considered a teratogenic medication and actively discouraged for use in and immediately prior to pregnancy.[15–17] Since its introduction, a variety of risk evaluation and mitigation strategies (REMS) have been implemented to prevent exposed pregnancies.[15,18] Despite low overall pregnancy rates,[18–20] exposed pregnancies still occur and continued surveillance is needed.[21] On the other hand, a topical version of isotretinoin, tretinoin, is presumed safe for fetal development because of low systemic bioavailability.[22–25] While studies have not identified increased risks of malformations overall,[26–29] given low sample sizes and case reports hinting at potentially rare embryopathy associations,[30] large studies of exposure are needed to define its safety in pregnancy.

Methods

The Truven Health MarketScan® Commercial Claims and Encounters Database (Truven Health Analytics Inc., Ann Arbor, MI, USA) contains health care claims from approximately 350 payers across the United States. The database includes information from inpatient and outpatient services, as well as outpatient prescription claims and enrollment information. Unique enrollee ID numbers are available to link claims from the same individual, and a unique family ID number links family members on the same insurance plan.

Cohort Development

Establish the Source Population & Identify End-of-Pregnancy Date—Within a population of women ages 12–55, with non-missing enrollee IDs, and inpatient or outpatient claims between January 1, 2011 and September 30, 2015, we searched inpatient and outpatient files for *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis, ICD-9-CM procedure, *Current Procedural Terminology* (CPT), *Healthcare Common Procedure Coding System* (HCPCS), and

Diagnosis Related Group (DRG) codes relating to the end-of-pregnancy (e-Appendix A).[1,6–8,11–13,31,32] End-of-pregnancy codes were codes that signaled that the pregnancy had ended (e.g. 'Normal delivery') and were categorized into one of eight outcomes (Livebirth, Stillbirth, Mixed Birth [at least one infant is a livebirth and at least one is a stillbirth], Spontaneous Abortion [SAB], Elective Termination, Unspecified Abortion, Ectopic or Molar Pregnancy, and Unclassified Deliveries). Codes that signaled a delivery but did not indicate live or stillbirth status (e.g. 'caesarean delivery') were classified as 'unclassified delivery' codes.

End-of-pregnancy codes occurring within 30 days of another code were grouped as the same pregnancy. The next code occurring outside of the 30-day window from the first code was considered a second pregnancy and all codes within a 30-day window of *that* code were grouped together. All code groupings were assigned a unique pregnancy ID number. Women could have more than one pregnancy in the study period.

The date of the first flagged code in each 30-day window was assigned the pregnancy "end date" except when the first date had been identified via only principal codes. Principal codes explain the main reason for the hospitalization and are repeated in every claim for that admission. For example, a woman with an extended hospital stay ending in a delivery may have a principal code for the delivery recorded in claims earlier in her stay than her true delivery date. Thus, when other end-of-pregnancy codes were flagged besides the principal codes, these dates were prioritized.

Linkage to Infants—We identified infants with non-missing enrollee IDs born between 2011–2015 in the inpatient and outpatient claims. As only *year* of birth is available in MarketScan® data, we approximated the infant's birth date using their first claim date. Infants were linked to pregnancies using family ID and year. Linkages where the infant's first claim was more than one day before the mother's pregnancy end date or more than 30 days after were excluded. While multiple infants could be a linked to a single pregnancy, when a single infant was linked to more than one pregnancy, both pregnancies were removed.

Pregnancy Corroboration and Assigning Pregnancy Type—Pregnancies were corroborated and assigned a type using definitions based on prior literature[1,4,8,13,14,31,33,34] and over several iterations of patient claims profile reviews (e-Appendix B). The definitions included at least one form of evidence which identified a particular pregnancy *type* (e.g., livebirth) and at least one which signaled the existence of an ongoing pregnancy rather than a history of a prior pregnancy. Evidence of pregnancy included end-of-pregnancy codes, infant linkage, and pregnancy marker codes (e-Appendix C). Pregnancy marker codes signaled any ongoing pregnancy (e.g. 'ultrasound of pregnant uterus') and were ascertained in the inpatient and outpatient claims within 30 days before and including the pregnancy end date. Pregnancy type was assigned hierarchically (e-Appendix B). This hierarchy was particularly important when distinguishing between pregnancy losses as there was much cross-coding between these types. Particularly, SAB was considered prior to stillbirth because 1% of pregnancies with multiple SAB diagnosis and procedure codes also had stillbirth codes in their claims. Further, elective terminations were considered prior to SABs,

given a tendency for terminations to be mis-coded on the record. Pregnancies not meeting any of the listed definitions or assigned as ectopic or molar, were dropped.

Final Cleaning—We flagged as abnormal, all livebirths, stillbirths, and mixed birth pregnancies that had a pregnancy end date occurring less than 211 days after a prior pregnancy end date in the same woman, and all SABs, terminations, and unspecified abortions that occurred less than 61 days after a prior pregnancy end date.[35] We selected one of the pregnancies within the abnormal sequence based on the following priorities and removed all others: (1) Linked mixed birth (2) Linked livebirth (3) Unlinked mixed birth (4) Unlinked livebirth (5) Stillbirth (6) SAB (7) Elective termination (8) Unspecified Abortions. For example, if a woman had codes for a livebirth pregnancy that linked to an infant in March and then had livebirth codes in May of that same year without infant linkage, the first coded pregnancy (because it is linked) would be selected and the second would be removed (assumed to be post-partum follow up). If both pregnancies fell into the same priority group, we first prioritized the pregnancy with a date not based solely on principal codes (could be inaccurately dated), and then based on the pregnancy with the largest number of unique end-of-pregnancy codes within the 30-day window. This algorithm was looped until no pregnancies were flagged with abnormal timing.

Assign Date of Last Menstrual Period—Claims databases do not contain a field for gestational age at birth, thus this information was estimated using codes (e-Appendix D) based on prior literature.[1,4,8,13,14,31,33,34] Gestational age codes were ascertained in inpatient and outpatient claims for mothers and their infants (where available) in the 30 days after pregnancy.

Rather than weighting all gestational age codes equally,[8] we considered two priority groups: first specific timing codes, and then codes indicating a multi-fetal pregnancy. For pregnancies with conflicting age codes, we assigned the gestational age that had more codes contributing to it, with lower ages selected for ties. In those without age codes, we used the following standard ages (in weeks) based on prior literature:[8,13,33] livebirth: 39, stillbirth: 28, mixed birth: 35, SAB: 8, termination: 10, unspecified abortion: 9. Estimated first day of the last menstrual period (LMP) was assigned by subtracting the gestational age from the pregnancy end date.

Impact of Enrollment Requirements and Cohort Description

We plotted how sample size declined as increasingly longer enrollment restrictions are applied in the mother and infant. Continuous enrollment was defined as evidence of enrollment in an insurance plan for at least 28 days in each month of follow-up. For infants, we required enrollment starting at seven days post-delivery to allow time for administrative delays. As most pregnancy studies require enrollment for all of pregnancy, we presented a selection of maternal characteristics in the original cohort and the group with continuous enrollment from 90 days before LMP until 30 days after the pregnancy end date. We also described maternal characteristics by pregnancy type (codes in e-Appendix E).

Isotretinoin and Tretinoin Application

Assessment of Pregnancy Rates—We ascertained isotretinoin and tretinoin exposure in women aged 12–55 from the general population of insured women in the MarketScan® database who were not currently pregnant, by searching for generic drug names in the prescription dataset. Prescription dispensings occurring within 30 days after the days of supply of a prior prescription were considered part of the same treatment episode and the first identified dispensing was used as the start (index) date. Prescription dispensings occurring *more* than 30 days after the days of supply of a prior prescription counted as a new treatment episode. In sensitivity analyses, we additionally considered definitions of 0 and 60 days after the days of supply of a prior prescription. To each prescription index date, we matched five non-pregnant women from the general population of insured women in the MarketScan® database, without either prescription, enrolled in a health plan (with prescription drug coverage) in the same month and of the same age and region. The index date of the unexposed group was the first day of enrollment in the month matched to the prescription fill (index) date in the exposed. We described baseline characteristics of the groups (codes in e-Appendix E).

Women were followed until one of the following occurred: pregnancy, enrollment discontinuation, one year from the index date, end of the study period, or, for exposed groups, the treatment episode ended.

The end of the study period was selected as November 30, 2014. This is because, as pregnancies in the cohort are identified by their *end*-of-pregnancy codes rather than conception codes, pregnancies that began in 2015 but had not delivered by the end of the *cohort* period (September 30, 2015) were missed. This artificially elevated the proportion of shorter pregnancy types (e.g,. SABs) in the pregnancies identified near the end of the cohort window (Figure in e-Appendix F). Thus, we only followed women with a start of pregnancy occurring before November 30, 2014, allowing ample time for all pregnancies beginning in our study period to reach full-term and be identified in the larger cohort.

Rates of pregnancy per 1,000 person-years (PYs) were calculated to estimate the number of incident pregnancies expected to occur among 1,000 treatment-exposed women followed for 1-year.

Assessment of Risks in Pregnancy—To determine risks of pregnancy losses and prevalence of malformations, we restricted the pregnancy cohort to those with continuous enrollment (including prescription drug coverage) from 90 days before LMP until the end of pregnancy.

Isotretinoin and tretinoin were ascertained in the 90-day interval before LMP. To each exposed pregnancy, we matched 10 unexposed pregnancies of the same age, region, and year. Risks of SAB and elective termination were compared between exposure groups. Major congenital malformations were assessed among pregnancies with a livebirth that had a linked infant continuously enrolled for 90 days after delivery unless they died sooner, a stillbirth, or mixed birth. Malformations were defined using an algorithm described and validated previously[37–39] using CDC guidelines.[40] Odds ratios comparing the prevalence of

malformations at delivery in the exposed groups to the unexposed were calculated using logistic regression and adjusted for pre-existing diabetes, smoking, and acne.

Results

Cohort Development

We identified 30,705,541 eligible women aged 12–55 between January 1, 2011 and September 30, 2015 (Figure 1). Of those, 2,424,278 women (8%) had at least one end-of-pregnancy code during the study period (2,978,707 unique pregnancies).

There were 2,361,090 infants born between 2011–2015 with non-missing enrollee IDs identified in inpatient and outpatient claims. Of 1,625,927 infants (69% of all infants) that successfully linked to a pregnancy (infants under a different insurance than their mothers did not link), 7% were excluded because their first date of appearance occurred >1 day before or >30 days after the mother's delivery date. At this stage, 1,503,208 pregnancies (50% of all pregnancies) were linked to an infant; this linkage is low because we had not yet restricted to pregnancies with corroborated livebirths. A total of 745 infants (1,438 pregnancies [0.1%]) were removed because they linked to more than one pregnancy.

The number of pregnancies in each type is provided in e-Appendix B. Of 2,977,269 pregnancies, 3% (93,707) of pregnancies were excluded because they did not meet any type definition, 3% (83,685) were excluded for being ectopic or molar, and 2% (61,090) pregnancies were removed due to abnormal spacing. After this cleaning, there were 2,179,192 (80%) livebirth pregnancies, 8,434 (0.3%) stillbirths, 2,521 (0.09%) mixed birth pregnancies, 415,110 (15%) SABs, 124,556 (5%) elective terminations, and 8,974 (0.3%) unspecified abortions. A total of 69% of livebirth pregnancies linked to infants.

The proportion of pregnancies assigned a gestational age based on a specific timing or multi-fetal pregnancy code was 31% of livebirths, 16% of stillbirth pregnancies, 69% of mixed birth, 19% of SABs, 1% of terminations, and 0.6% of unspecified abortions. The remainder were assigned the default gestational ages.

Impact of Enrollment Requirements and Cohort Description

Enrollment for both mothers and infants dropped at a rate of ~15% every 90 days from the pregnancy end date (e-Appendix G). Pregnancies with complete enrollment (52%) were similar in measured characteristics to the full cohort (e-Appendix H). Women delivering mixed births were, on average, older (33.1 years) and women with elective terminations were, on average, younger (28.4 years) than women with livebirths (30.3 years; e-Appendix I). The proportion or terminations was 11% in the Northeast, 5% in the West and 2–3% in the other regions. The distributions of other characteristics across types of pregnancy were similar.

Isotretinoin and Tretinoin Application

Assessment of Pregnancy Rates—We identified 86,834 isotretinoin and 973,587 tretinoin treatment episodes in 76,053 and 606,966 non-pregnant women respectively (Figure 3). These episodes were matched to an unexposed group of 5,302,105 non-pregnant

women. Characteristics are presented in Table 1. Pregnancy rate was 3 per 1,000 PYs in the isotretinoin group, 19 per 1,000 PYs in the tretinoin group, and 34 per 1,000 PYs the unexposed group. In sensitivity analyses where women were considered exposed within 0 and 60 days after the last prescription's days of supply, rates of pregnancy were 2 and 4 for isotretinoin and 18 and 19 for tretinoin, respectively.

Assessment of Risks in Pregnancy—From the original cohort, 1,178,280 pregnancies (44%) began on or before November 30, 2014 and were continuously enrolled with prescription coverage from 90 days before LMP until the end of pregnancy (Figure 4). Of these, 131 (0.01%) had a prescription of isotretinoin (or isotretinoin *and* tretinoin [n<11]) in the 90-day interval before LMP and 4,077 had a prescription for only tretinoin (0.4%). Matching 10 unexposed pregnancies to each exposed resulted in an unexposed group of 42,150 pregnancies. Risk of SAB was similar in women exposed to pre-pregnancy isotretinoin (22%), tretinoin (17%), and the unexposed group (19%; Figure 2; Table 2). Elective terminations were more common in the isotretinoin group (28% [95% CI: 21–36%] vs. 10% [95% CI: 9–11%] tretinoin vs. 6% unexposed). In the isotretinoin group, terminations were common when the dispensing occurred closer to LMP (Figure 5).

The prevalence of infant malformation at delivery was comparable in the tretinoin (4.5%) and unexposed (4.2%) groups (crude odds ratio: 1.08 [95% CI: 0.83–1.40]; adjusted odds ratio: 1.16 [95% CI: 0.85–1.58]). While sample size was small, no specific pattern of malformations was apparent. As so few isotretinoin pregnancies reached delivery, we did not have sufficient sample size to assess malformations in this group (cell sizes less than 11 cannot be reported due to the Truven Health privacy agreement).

Discussion

We proposed an algorithm to identify pregnancies in healthcare claims databases and demonstrated a potential application to teratogenic surveillance. We used this cohort to ascertain rates of pregnancy and risks of adverse pregnancy outcomes in women exposed to isotretinoin and tretinoin.

While we are not the first to identify pregnancies in MarketScan® data,[7,8,12] we built upon previous methods to expand the identification and timing of pregnancies in claims data. For example, in our cohort ~35,000 pregnancies had codes from conflicting outcome types and thus specialized algorithms were needed to assign the final pregnancy outcome. Previous studies have varied widely on this assignment.[1,5,8,31] We developed our algorithms based on prior literature, claims reviews of a sample of pregnancies from each definition, further cycles of optimization, and finally, removal of improbable or unclassifiable pregnancies. We believe that the careful development of these algorithms improved the identification of the pregnancy types. The incidence of SAB and stillbirth was similar to US national statistics,[43] indirectly validating the algorithms. However future work will be needed to directly validate these definitions.

Our cohort also built upon prior work estimating gestational age. For example, some studies have estimated gestational age by assigning specific ages to codes and prioritizing the lowest

age in the case of conflict.[8] While incorporating a wide range of dates, this design is vulnerable to an age assigned to a non-specific code overriding a code with more specific timing information (e.g. one specifying weeks of gestation). Based on prior validation studies which indicated that a simple preterm dichotomy may be sufficient,[4] we developed a two-step algorithm which prioritized specific timing codes. We found that approximately 10% of livebirth pregnancies were classified as preterm, in line with overall estimates from the US population.[44] Nonetheless, ongoing validation studies will quantify the accuracy of these estimates for both livebirths and pregnancy losses.

We then used this cohort to show how healthcare databases may be used to monitor REMS programs for teratogens and perform post-marketing surveillance of even relatively rare medications in pregnancy. We showed that isotretinoin-exposed pregnancy rates were lower than an internally matched population, indicating that efforts to reduce exposed pregnancies[15] have been effective, though not infallible. Prior estimates of isotretinoin-exposed pregnancy rates between 1989–2011 ranged from 9 to 37 per 1,000 PYs[18,20] and from 4 to 6 per 1,000 users.[19] Our estimate of 3 per 1,000 PYs in 2011–2015 might be lower because of REMS improvements over time, our study population excluded women covered by Medicaid where pregnancy rates may be higher, or due to an underestimation of terminations. Given incomplete coverage of terminations by insurance companies in the US, some women may have paid out-of-pocket and thus been missed in our data. In the Northeast, where terminations were more common, the isotretinoin-exposed pregnancy rate was higher (4.1 per 1,000 PYs). Despite a likely underestimation of pregnancy rates, we noted that isotretinoin-exposed pregnancies are still occurring in the US. The fact that terminations were increasingly more likely when isotretinoin was dispensed closer to LMP, suggests that many of these pregnancies were unintended, rather than planned pregnancies occurring after a treatment course. Thus, continued work on reducing pregnancies during isotretinoin exposure is needed.

Despite underestimations, we found that, in pregnancies occurring near an isotretinoin dispensing, elective terminations were approximately five times more common than in unexposed pregnancies. While terminations are incompletely captured in any pregnancy study, it is unknown whether such under-recording might be differential for women exposed to isotretinoin versus unexposed women. However, it is unlikely for misclassification to account for a five-fold increased risk. Low pregnancy rates and many terminations resulted in insufficient numbers to evaluate isotretinoin teratogenicity.

To date, much of the evidence for isotretinoin exposure has come from voluntary reports.[17,18,45–47] Surveys or registry-based designs, allow for prospective ascertainment of rare exposures, and prospective follow-up. However, they can be expensive, labor-intensive, prone to selection bias, and often lack control groups,[17,18,45,46] limiting overall efficiency, validity, and generalizability.[48] Healthcare databases can overcome many of these limitations by providing prospective population-based estimates at relatively low cost. At least three studies in North America have employed administrative data to estimate isotretinoin-exposed pregnancy rates[19,20] and adverse birth outcomes,[19,20,49] finding comparable results to the voluntary reports and the results reported here. Together, these

examples highlight the value of large healthcare databases to complement labor-intensive pregnancy registries for REMS evaluation.

Finally, we identified 4,077 tretinoin-exposed pregnancies, more than six times the sample size of all previous studies combined.[30] Confirming prior findings with increased precision, we did not observe an increased risk of SABs,[27–29] an increased risk of terminations,[27,28] nor an increased prevalence of malformations[26–29] in tretinoin-exposed pregnancies.

Strengths of the cohort include the large sample size, family linkage, and the presence of prescription dispensing, inpatient, *and* outpatient claims. However, it is possible that pregnancies may have been missed or misclassified. Due to privacy concerns, the MarketScan® database cannot be linked to medical records or birth certificates for pregnancy type validation. Further, medication exposure was assessed via prescriptions filled and thus it was not possible to determine whether the medication was actually used. Since LMP was estimated, the timing of pregnancy may be misclassified. However, we do not suspect this misclassification to occur differentially by isotretinoin or tretinoin exposure. Finally, malformations were only assessed at birth. Women may be more likely to terminate a pregnancy if a malformation is detected, thus underestimating the total proportion of malformations in the cohort.

Despite limitations, we believe administrative healthcare databases have an important role to play for drug safety surveillance in pregnancy. For some medications they may be more time and cost-effective than ad hoc registries. It is therefore important that when building cohorts within these databases, researchers take the time to develop algorithms carefully. Publication of detailed cohort descriptions are instrumental for ensuring this work continues to be transparent and rigorous.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding:

SCM was supported by the Canadian Institutes for Health Research (CIHR); SHD, JMC, and KH were supported by the National Institute of Mental Health [R01 MH100216].

References

1. Taylor LG, Thelus Jean R, Gordon G, Fram D, Coster T. Development of a mother-child database for drug exposure and adverse event detection in the Military Health System. Pharmacoepidemiology and Drug Safety. 2015;24(5):510–517. [PubMed: 25833769]
2. Andrade SE, Davis RL, Cheetham TC, et al. Medication exposure in pregnancy risk evaluation program. Maternal and Child Health Journal. 2012;16(7):1349–1354. [PubMed: 22002179]
3. Haut ER, Pronovost PJ, Schneider EB. Limitations of Administrative Databases. JAMA. 2012;307(24):2589–2590. [PubMed: 22735421]
4. Margulis AV, Setoguchi S, Mittleman MA, Glynn RJ, Dormuth CR, Hernández-Díaz S. Algorithms to estimate the beginning of pregnancy in administrative databases. Pharmacoepidemiology and Drug Safety. 2013;22(1):16–24. [PubMed: 22550030]

5. Devine S, West S, Andrews E, et al. The identification of pregnancies within the general practice research database. Pharmacoepidemiology and Drug Safety. 2010;19(1):45–50. [PubMed: 19823973]

6. Kuriya B, Hernández-Díaz S, Liu J, Bermas BL, Daniel G, Solomon DH. Patterns of medication use during pregnancy in rheumatoid arthritis. Arthritis Care & Research. 2011;63(5):721–728.

7. Jovanovič L, Liang Y, Weng W, Hamilton M, Chen L, Wintfeld N. Trends in the incidence of diabetes, its clinical sequelae, and associated costs in pregnancy. Diabetes/Metabolism Research and Reviews. 2015;31(7):707–716. [PubMed: 25899622]

8. Ailes EC, Simeone RM, Dawson AL, Petersen EE, Gilboa SM. Using insurance claims data to identify and estimate critical periods in pregnancy: An application to antidepressants. Birth Defects Research Part A: Clinical and Molecular Teratology. 2016;106(11):927–934. [PubMed: 27891779]

9. Andrade SE, Toh S, Houstoun M, et al. Surveillance of Medication Use During Pregnancy in the Mini-Sentinel Program. Maternal and Child Health Journal. 2016;20(4):895–903. [PubMed: 26645616]

10. Andrade SE, Scott PE, Davis RL, et al. Validity of health plan and birth certificate data for pregnancy research. Pharmacoepidemiology and Drug Safety. 2013;22(1):7–15. [PubMed: 22753079]

11. Johnson KE, Beaton SJ, Andrade SE, et al. Methods of linking mothers and infants using health plan data for studies of pregnancy outcomes. 2014;22(7):776–782.

12. Martin AS, Monsour M, Kissin DM, Jamieson DJ, Callaghan WM, Boulet SL. Trends in Severe Maternal Morbidity After Assisted Reproductive Technology in the United States, 2008–2012. Obstet Gynecol. 2016;127(1):59–66. [PubMed: 26646124]

13. Korelitz JJ, McNally DL, Masters MN, Li SX, Xu Y, Rivkees SA. Prevalence of thyrotoxicosis, antithyroid medication use, and complications among pregnant women in the United States. Thyroid. 2013;23(6):758–765. [PubMed: 23194469]

14. Andrade SE, Moore Simas TA, Boudreau D, et al. Validation of algorithms to ascertain clinical conditions and medical procedures used during pregnancy. Pharmacoepidemiology and Drug Safety. 2011;20(11):1168–1176. [PubMed: 22020902]

15. US Food and Drug Administration. iPLEDGE program. http://www.ipledgeprogram.com. Published 2016 Accessed February 9, 2019.

16. Stern RS, Rosa F, Baum C. Isotretinoin and pregnancy. Journal of the American Academy of Dermatology. 1984;10(5):851–854. [PubMed: 6233342]

17. Dai WS, Hsu MA, Itri LM. Safety of Pregnancy After Discontinuation of Isotretinoin. Archives of Dermatology. 1989;125(3):362–365. [PubMed: 2923442]

18. Mitchell AA, Van Bennekom CM, Louik C. A Pregnancy-Prevention Program in Women of Childbearing Age Receiving Isotretinoin. New England Journal of Medicine. 1995;333(2):101–106. [PubMed: 7777014]

19. Henry D, Dormuth C, Winquist B, et al. Occurrence of pregnancy and pregnancy outcomes during isotretinoin therapy. Canadian Medical Association Journal. 2016;188(10):723–730. [PubMed: 27114489]

20. Bérard A, Azoulay L, Koren G, Blais L, Perreault S, Oraichi D. Isotretinoin, pregnancies, abortions and birth defects: A population-based perspective. British Journal of Clinical Pharmacology. 2007;63(2):196–205. [PubMed: 17214828]

21. Shin J, Cheetham TC, Wong L, et al. The impact of the iPLEDGE program on isotretinoin fetal exposure in an integrated health care system. Journal of the American Academy of Dermatology. 2011;65(6):1117–1125. [PubMed: 21565419]

22. Chen C, Jensen BK, Mistry G, et al. Negligible systemic absorption of topical isotretinoin cream: Implications for teratogenicity. Journal of Clinical Pharmacology. 1997;37(4):279–284. [PubMed: 9115052]

23. Buchan P, Eckhoff C, Nau H, Shroot B, Schaefer H. Repeated topical administration of all-trans-retinoic acid and plasma levels of retinoic acids in humans. Journal of the American Academy of Dermatology. 1994;30(3):428–434. [PubMed: 8113456]

24. Latriano L, Tzimas G, Wong F, Wills RJ. The percutaneous absorption of topically applied tretinoin and its effect on endogenous concentrations of tretinoin and its metabolites after single

doses or long-term use. Journal of the American Academy of Dermatology. 1997;36(3 Pt 2):S37–46. [PubMed: 9091507]

25. Jensen BK, McGann LA, Kachevsky V, Franz TJ. The negligible systemic availability of retinoids with multiple and excessive topical application of isotretinoin 0.05% gel (Isotrex) in patients with acne vulgaris. Journal of the American Academy of Dermatology. 1991;24(3):425–428. [PubMed: 1829464]
26. Jick SS, Terris BZ, Jick H. First trimester topical tretinoin and congenital disorders. The Lancet. 1993;341(8854):1181–1182.
27. Shapiro L, Pastuszak A, Curto G, Koren G. Safety of first-trimester exposure to topical tretinoin: prospective cohort study. The Lancet. 1997;350:1143–1144.
28. Loureiro KD, Kao KK, Jones KL, et al. Minor malformations characteristic of the retinoic acid embryopathy and other birth outcomes in children of women exposed to topical tretinoin during early pregnancy. American Journal of Medical Genetics. 2005;136A(2):117–121.
29. Panchaud A, Csajka C, Merlob P, et al. Pregnancy outcome following exposure to topical retinoids: A multicenter prospective study. Journal of Clinical Pharmacology. 2012;52(12):1844–1851. [PubMed: 22174426]
30. Kaplan YC, Ozsarfati J, Etwel F, Nickel C, Nulman I, Koren G. Pregnancy outcomes following first-trimester exposure to topical retinoids: A systematic review and meta-analysis. British Journal of Dermatology. 2015;173(5):1132–1141. [PubMed: 26215715]
31. Hornbrook MC, Whitlock EP, Berg CJ, et al. Development of an algorithm to identify pregnancy episodes in an integrated health care delivery system. Health Services Research. 2007;42(2):908–927. [PubMed: 17362224]
32. Grisso JA, Carson JL, Feldman HI, Cosmatos I, Shaw M, Strom B. Epidemiological pitfalls using Medicaid data in reproductive health research. The Journal of Maternal-Fetal Medicine. 1997;6(4):230–236. [PubMed: 9260122]
33. Butler AM, Layton JB, Li D, et al. Predictors of low uptake of prenatal tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis immunization in privately insured women in the United States. Obstetrics and Gynecology. 2017;129(4):629–637. [PubMed: 28277354]
34. Andrade SE, Gurwitz JH, Davis RL, et al. Prescription drug use in pregnancy. American Journal of Obstetrics and Gynecology. 2004;191(2):398–407. [PubMed: 15343213]
35. Devine S, West SL, Andrews E, et al. Validation of neural tube defects in the full featured—general practice research database. Pharmacoepidemiology and Drug Safety. 2008;17(5):434–444. [PubMed: 18344214]
36. Martin JA, Hamilton BE, Ventura SJ, et al. Births: Final Data for 2009. National Vital Statistics Reports; Vol 60 No 1. Hyattsville, MD; 2011.
37. Huybrechts KF, Hernández-Díaz S, Patorno E, et al. Antipsychotic Use in Pregnancy and the Risk for Congenital Malformations. JAMA Psychiatry. 2016;66(4):444–449.
38. Cooper WO, Hernandez-diaz S, Rn PG, et al. Positive predictive value of computerized records for major congenital malformations y. 2008;(December 2007):455–460.
39. Palmsten K, Huybrechts KF, Kowal MK, Mogun H, Hernández-Díaz S. Validity of maternal and infant outcomes within nationwide Medicaid data. Pharmacoepidemiology and Drug Safety. 2014;23(6):646–655. [PubMed: 24740606]
40. Rasmussen SA, Olney RS, Holmes LB, Lin AE, Keppler-Noreuil KM, Moore CA. Guidelines for case classification for the national birth defects prevention study. Birth Defects Research Part A: Clinical and Molecular Teratology. 2003;67(3):193–201. [PubMed: 12797461]
41. Naleway AL, Gold R, Kurosky S, et al. Identifying pregnancy episodes, outcomes, and mother-infant pairs in the Vaccine Safety Datalink. Vaccine. 2013;31(27):2898–2903. [PubMed: 23639917]
42. Lammer EJ, Chen DT, Hoar RM, et al. Retinoic Acid Embryopathy. New England Journal of Medicine. 1985;313(14):837–841. [PubMed: 3162101]
43. Curtin SC, Abma JC, Ventura SJ, Henshaw SK. Pregnancy Rates for U.S. Women Continue to Drop. NCHS Data Brief, No 136. Hyattsville, MD: National Center for Health Statistics; 2013.
44. Martin JA, Hamilton BE, Osterman MJK, Curtin SC, Mathews TJ. National Vital Statistics Reports Births: Final Data for 2015. National Vital Statistics Reports. 2017;66(1):1–70.

45. Dai WS, LaBraico JM, Stern RS. Epidemiology of isotretinoin exposure during pregnancy. Journal of the American Academy of Dermatology. 1992;26(4):599–606. [PubMed: 1597546]

46. Robertson J, Polifka JE, Avner M, et al. A survey of pregnant women using isotretinoin. Birth Defects Research Part A - Clinical and Molecular Teratology. 2005;73(11):881–887. [PubMed: 16228976]

47. Schaefer C, Meister R, Weber-Schoendorfer C. Isotretinoin exposure and pregnancy outcome: An observational study of the Berlin Institute for Clinical Teratology and Drug Risk Assessment in Pregnancy. Archives of Gynecology and Obstetrics. 2010;281(2):221–227. [PubMed: 19444462]

48. Gelperin K, Hammad H, Leishear K, et al. A systematic review of pregnancy exposure registries: examination of protocol-specified pregnancy outcomes, target sample size, and comparator selection. Pharmacoepidemiology and Drug Safety. 2017;26(2):208–214. [PubMed: 28028914]

49. Shin J, Cheetham TC, Wong L, et al. The impact of the iPLEDGE program on isotretinoin fetal exposure in an integrated health care system. Journal of the American Academy of Dermatology. 2011;65(6):1117–1125. [PubMed: 21565419]

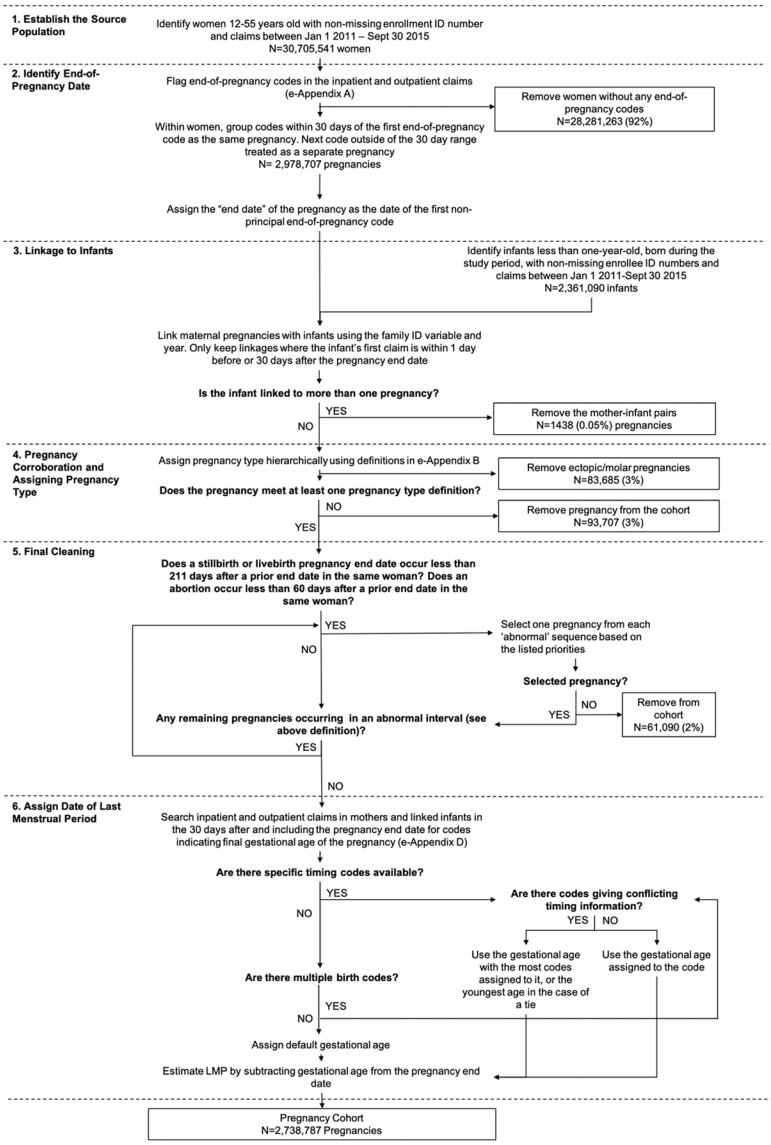

Figure 1.
Steps of the Pregnancy Cohort Creation

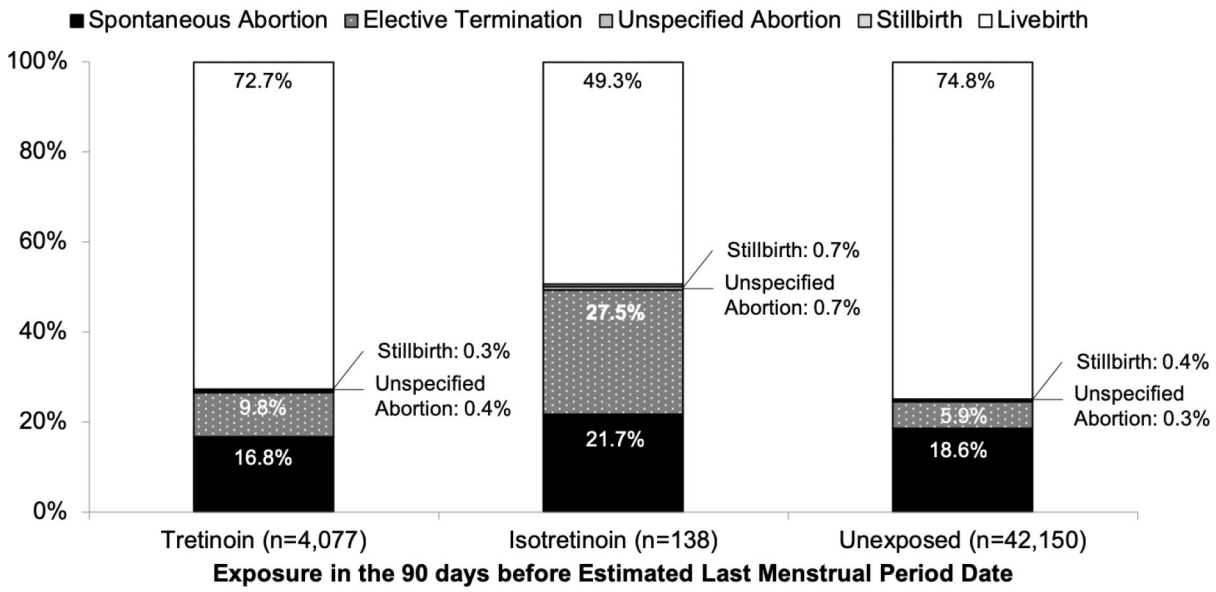

Figure 2.

Pregnancy Outcomes by Exposure Status (n=46,365). White bars represent livebirth, black bars represent spontaneous abortion, grey bars with white dots represent elective terminations, grey bars without dots represent unspecified abortion and stillbirth.

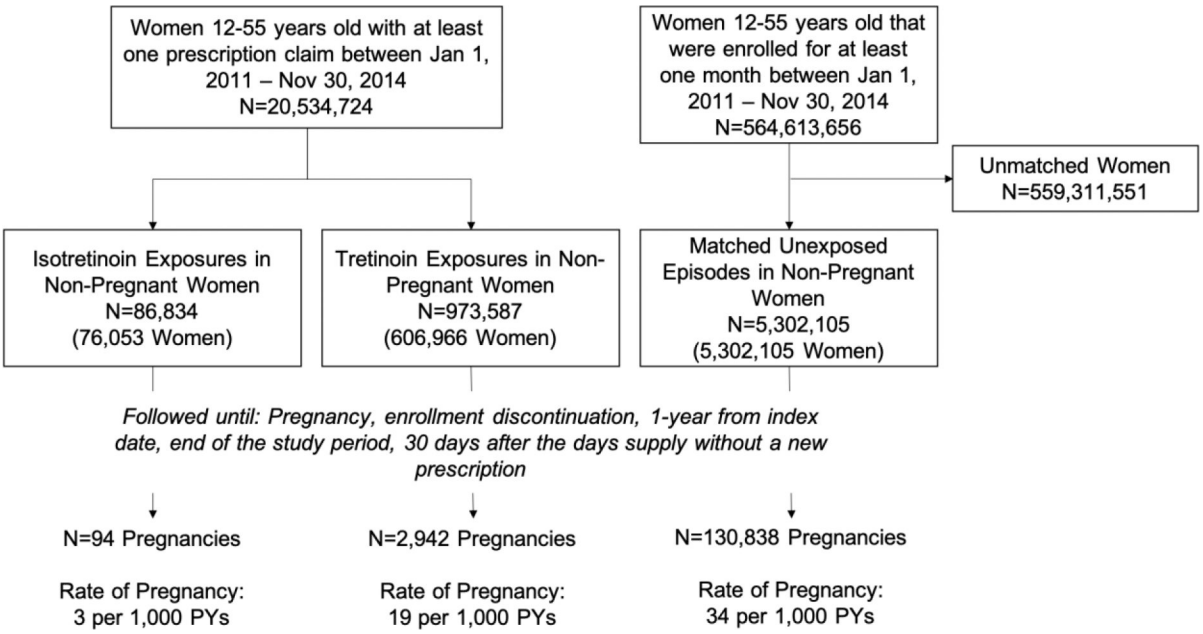

Figure 3.
Attrition Flow Chart for the Assessment of Pregnancy Rates

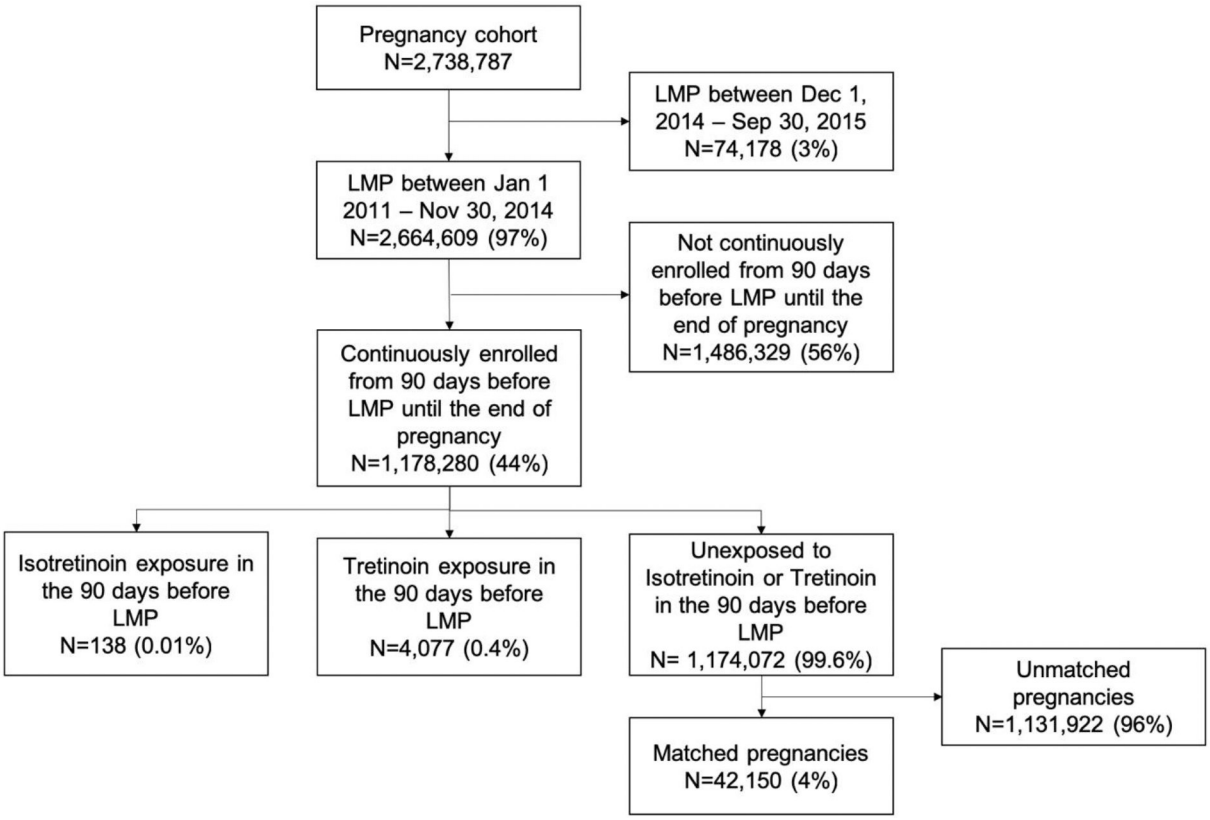

Figure 4.

Attrition Flow Chart for the Assessment of Risks (Spontaneous Abortion, Elective Termination, Infant Malformation) in Pregnancy

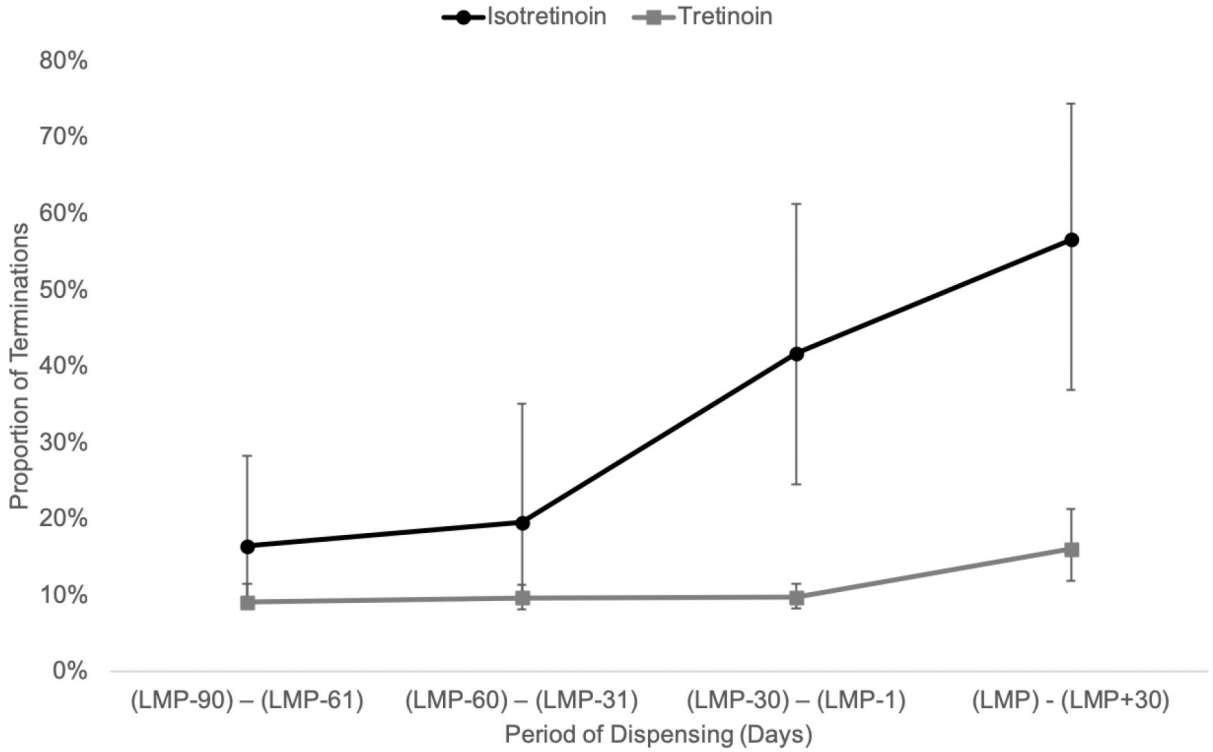

Figure 5.
Proportion of Terminations by Period of Dispensing (n=4,215). LMP: last menstrual period. Error bars represent 95% confidence intervals.

Table 1.

Demographic and Clinical Characteristics by Prescription Episodes (Truven Health MarketScan® Commercial Claims & Encounters Database, USA, 2011–2014, N=6,362,526)

Characteristics[a]	Unexposed Episodes[c] (n=5,302,105)	Isotretinoin Prescription Episode[b] (n=86,834)	Tretinoin Prescription Episode[b] (n=973,587)
Age (mean, SD)	27.4 (12.1)	23.9 (9.8)	27.7 (12.2)
Year			
2011	1,503,815 (28.4%)	24,847 (28.6%)	275,916 (28.3%)
2012	1,467,755 (27.7%)	22,336 (25.7%)	271,215 (27.9%)
2013	1,208,005 (22.8%)	19,907 (22.9%)	221,694 (22.8%)
2014	1,122,530 (21.2%)	19,744 (22.7%)	204,762 (21.0%)
Region			
Northeast	1,094,090 (20.6%)	12,837 (14.8%)	205,981 (21.2%)
North Central	1,122,610 (21.2%)	17,158 (19.8%)	207,364 (21.3%)
South	1,844,325 (34.8%)	36,507 (42.0%)	332,358 (34.1%)
West	1,142,365 (21.5%)	18,616 (21.4%)	209,857 (21.6%)
Unknown	98,715 (1.9%)	1,716 (2.0%)	18,027 (1.9%)
OC Use	756,784 (14.3%)	32,706 (37.7%)	206,197 (21.2%)
Hypertension	128,076 (2.4%)	997 (1.1%)	18,814 (1.9%)
Asthma	88,167 (1.7%)	1,357 (1.6%)	20,318 (2.1%)
Thyroid Disorder	133,679 (2.5%)	1,894 (2.2%)	33,129 (3.4%)
Depression	180,344 (3.4%)	3,916 (4.5%)	50,996 (5.2%)
Bipolar Disorder	27,502 (0.5%)	548 (0.6%)	7,771 (0.8%)
Anxiety Disorder	168,008 (3.2%)	3,527 (4.1%)	51,296 (5.3%)
Chronic Renal Disease	6,503 (0.1%)	53 (0.06%)	1,116 (0.1%)
Alcohol or Substance Abuse	20,445 (0.4%)	271 (0.3%)	4,089 (0.4%)
Acne	80,637 (1.5%)	82,730 (95.3%)	513,306 (52.7%)
Pregnancy Test in the 30 Days Prior to Index Date	59,895 (1.1%)	27,526 (31.7%)	14,558 (1.5%)

OC = Oral Contraceptives; SD = Standard Deviation

[a] Characteristics were ascertained on the index date of the prescription episode or in the +/− 45 days of the index date, depending on the characteristic (see e-Appendix E).

[b] A prescription episode was defined as a prescription, or group of consecutive prescriptions (within 30 days from the prior prescription's days of supply) for the listed medication. Women could have more than one prescription episode during the study period.

[c] Unexposed episodes were (currently) non-pregnant women matched to isotretinoin- and tretinoin-prescription episodes 5:1 on age, region, and month of index date

Table 2.

Risks of Pregnancy Outcomes by Exposure Group (Truven Health MarketScan® Commercial Claims & Encounters Database, USA, 2011–2014, N=46,365)

Pregnancy Outcome	Unexposed Pregnancies (n=42,150)	Tretinoin-Exposed Pregnancies (n=4,077)	Isotretinoin-Exposed Pregnancies (n=138)
Livebirth	31,547 (74.8%)	2,963 (72.7%)	68 (49.3%)
Spontaneous Abortion	7,823 (18.6%)	685 (16.8%)	30 (21.7%)
Elective Termination	2,487 (5.9%)	400 (9.8%)	38 (27.5%)
Unspecified Abortion	136 (0.3%)	16 (0.4%)	<11
Stillbirth	157 (0.4%)	13 (0.3%)	<11
Infant Malformations[a]	631 (4.2%)	65 (4.5%)	<11

[a]Among eligible pregnancies. Pregnancies eligible for infant malformation assessment were stillbirth pregnancies, livebirths with linked infants continuously enrolled for the 90 days after delivery, or livebirths with linked neonatal deaths; n=1,430 tretinoin-exposed pregnancies, n=18 isotretinoin-exposed pregnancies, n=14,879 unexposed pregnancies