Published in final edited form as:

Pharmacoepidemiol Drug Saf. 2016 February ; 25(2): 170–178. doi:10.1002/pds.3919.

Trimethoprim-sulfonamide Use during the First Trimester of Pregnancy and the Risk of Congenital Anomalies

Craig Hansen, PhD^{1,2}, Susan E. Andrade, ScD³, Heather Freiman, MS^{1,4}, Sascha Dublin, MD/PhD⁵, Katie Haffenreffer, BS⁶, William O. Cooper, MD⁷, T.Craig Cheetham, PharmD⁸, Sengwee Toh, ScD⁶, De-Kun Li, MD/PhD⁹, Marsha A. Raebel, PharmD¹⁰, Jennifer L. Kuntz, PhD¹¹, Nancy Perrin, PhD¹¹, A.Gabriela Rosales, MS¹¹, Shelley Carter, MPH/MCRP¹², Pamala A. Pawloski, PharmD¹³, Elizabeth M. Maloney, DRPH¹⁴, David J. Graham, MD¹⁴, Leyla Sahin, MD¹⁵, Pamela E. Scott, PhD¹⁶, John Yap, PhD¹⁷, and Robert Davis, MD^{1,18}

¹Kaiser Permanente Georgia Center for Clinical and Outcomes Research ²South Australian Health and Medical Research Institute, Adelaide, Australia ³Meyers Primary Care Institute, University of Massachusetts Medical School Worcester, Massachusetts ⁴Emory University School of Medicine, Department of Medicine, Georgia ⁵Group Health Research Institute, Seattle, Washington ⁶Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts ⁷Departments of Pediatrics and Health Policy, Vanderbilt University School of Medicine, Nashville, Tennessee ⁸Pharmacy Analytical Services, Kaiser Permanente Southern California, Downey, California ⁹Division of Research, Kaiser Foundation Research Institute, Kaiser Permanente, Oakland, California ¹⁰Kaiser Permanente Colorado Institute for Health Research, Denver, Colorado ¹¹Kaiser Permanente Northwest Center for Health Research, Portland, Oregon ¹²LCF Research, Albuquerque, New Mexico ¹³HealthPartners Institute for Education and Research, Minneapolis, Minnesota ¹⁴Office of Surveillance and Epidemiology, Food and Drug Administration, Silver Spring, Maryland ¹⁵Office of New Drugs, Food and Drug Administration, Silver Spring, Maryland ¹⁶Office of Women's Health, Food and Drug Administration, Silver Spring, Maryland ¹⁷Office of Biostatistics, Food and Drug Administration, Silver Spring, Maryland ¹⁸Center for Biomedical Informatics and Department of Pediatrics, University of Tennessee, Memphis, TN

Abstract

Background—Sulfonamide antibacterials are widely used in pregnancy, but evidence about their safety is mixed. The objective of this study was to assess the association between first-trimester sulfonamide exposure and risk of specific congenital malformations.

Methods—Mother-infant pairs were selected from a cohort of 1.2 million liveborn deliveries (2001–2008) at 11 US health plans comprising the Medication Exposure in Pregnancy Risk

CORRESPONDING AUTHOR: Susan Andrade, Meyers Primary Care Institute, University of Massachusetts Medical School Worcester, Massachusetts, [sandrade@meyersprimary.org], Tel: (508) 791 7392, Fax: (508) 595 2200.

FINANCIAL DISCLOSURE: There are none for all authors.

CONFLICT OF INTEREST: There are none for all authors.

DISCLAIMER: The views expressed are the authors' and not necessarily those of the Food and Drug Administration, or the Department of Health and Human Services.

Evaluation Program (MEPREP). Mothers with first-trimester trimethoprim-sulfonamide (TMP-SUL) exposures were randomly matched 1:1 to 1) a primary comparison group: mothers exposed to penicillins and/or cephalosporins, and 2) a secondary comparison group: mothers with no dispensing of an antibacterial, antiprotozoal, or antimalarial medication during the same time period. The outcomes were cardiovascular abnormalities, cleft palate/lip, clubfoot, and urinary tract abnormalities.

Results—We first identified 7,615 infants in the TMP-SUL exposure group, of which 7595 (99%) were exposed to a combination of TMP-SUL and the remaining 1% to sulfonamides alone. After matching (1:1) to the comparator groups and only including those with complete data on covariates there were 20,064 (n=6,688 per group) in the primary analyses. Overall, cardiovascular defects (1.52%) were the most common and cleft lip/palate (0.10%) the least common that were evaluated. Compared to penicillin/cephalosporin exposure, and no antibacterial exposure, TMP-SUL exposure was not associated with statistically significant elevated risks for cardiovascular, cleft lip/palate, clubfoot, or urinary system defects.

Conclusions—First trimester TMP-SUL exposure was not associated with a higher risk of the congenital anomalies studied, compared to exposure to penicillins and/or cephalosporins, or no exposure to antibacterials.

Keywords

Medications; pregnancy; birth defects; sulfonamides; antibacterial agents

INTRODUCTION

Sulfonamides are widely used to treat common bacterial infections such as urinary tract, respiratory and skin infections.¹ These drugs are first-line agents for treating skin infections when community-acquired methicillin resistant *Staphylococcus aureus* is suspected and also are preferred drugs for preventing some pneumonias in immunosuppressed patients.^{2,3} Approximately 2.5% of pregnant women delivering a live birth from 1996–2000 in the United States received trimethoprim-sulfamethoxazole,⁴ translating to 100,000 infants exposed each year in the US. Despite such widespread use, evidence about the safety of these drugs in pregnancy is limited.⁵

Sulfonamides readily cross the placenta and thus could act as folate antagonists in humans.^{6,7} Folate is critical for organogenesis, especially neural tube development; therefore there is concern that use of sulfonamides early in pregnancy could be teratogenic.¹ However, methods and findings from previous studies examining sulfonamide exposure and congenital anomalies are mixed. For example, the majority of previous studies have been based on exposure to a combination of trimethoprim and a sulfonamide,^{8–14} or a robust majority of exposed women receiving that combination.¹⁵ Of these studies, some have reported statistically significant associations between first-trimester exposure and congenital anomalies including neural tube defects, cleft palate/lip, cardiovascular and urinary tract abnormalities and, club foot,^{8–11,15} while other studies did not find such associations.^{12–14} Whereas, one study examined exposures to trimethoprim alone and sulfonamides alone with a reported increased risk of cleft palate and cleft lip/palate respectively,¹⁶ and one study

examined exposures to sulfonamides with an increased risk of cardiovascular defects and clubfoot.¹⁷

Thus it remains unclear whether exposure to sulfonamides during pregnancy increases the risk of congenital anomalies. Therefore the aim of this study was to assess the association between first-trimester sulfonamide exposure and selected congenital malformations including cardiovascular defects, cleft lip/palate, club foot, neural tube and urinary system defects. We compared the prevalence of selected congenital malformations among sulfonamide antibacterial users to users of other antibacterials with similar indications believed to be non-teratogenic to address confounding by indication that might arise if first-trimester infections themselves increase the risk of congenital defects. Women exposed to penicillins and cephalosporins were chosen as the primary comparison group as these antibiotics are commonly used in pregnancy and are not associated with congenital defects.¹⁸

METHODS

Design/Setting/Participants

We conducted a retrospective cohort study comparing liveborn infants with first-trimester *in utero* sulfonamide antibacterial exposure with 1) liveborn infants exposed to penicillins and/or cephalosporins (primary comparison group), and 2) liveborn infants with no antibacterial exposure (secondary comparison group). It is important to note that our *a priori* hypothesis focused on investigating maternal exposure to sulfonamides, however, as described in the results section, 99% of the overall sulfonamide exposures were to the combination of trimethoprim-sulfonamide, and 1% to other sulfonamide exposures. Given the importance of the *a priori* hypothesis, all mother-infant pairs exposed to either sulfonamide-alone and/or the combination of trimethoprim-sulfonamide, are defined as the main exposure group and from this point forward are referred to as trimethoprim-sulfonamide exposed (abbreviated to TMP-SUL).

Data came from the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), a collaboration between the Food and Drug Administration and researchers at the HMO Research Network, Kaiser Permanente Northern and Southern California, and Vanderbilt University School of Medicine. All 11 participating organizations have linked administrative health plan data for mothers and infants with birth certificate data for deliveries from 2001 through 2008 to support studies of birth outcomes associated with *in utero* medication exposure.¹⁹

The study included women who delivered a singleton live-born infant between 1/1/2001 and 12/31/2008 and the infants born to these women. To be included, mothers were required to have continuous health plan enrollment with pharmacy benefits from 90 days prior to pregnancy through delivery. Infants were required to be enrolled for 30 days or more after delivery or up to the date of death if the infant died before 30 days.

We excluded mother-infant pairs if mothers received medications or vaccines considered possibly teratogenic (see eTables 1 & 2) from 90 days prior to pregnancy through 14 days

after the end of the first trimester, or if infants had a trisomy or congenital rubella or varicella syndrome. The list of exclusion medications and vaccines was developed and confirmed by the collective expertise of the MEPREP research team.

Exposure Assessment and Matching of Comparator Groups

The main exposure of interest was systemic TMP-SUL antibacterial use during the first trimester of pregnancy. Oral and injectable medications dispensed in the outpatient setting were included. TMP-SUL exposure was defined as receiving at least one dispensing during the 90 days prior to pregnancy with days' supply extending into the first trimester, or at any time during the first trimester (i.e., 0 to 90 days after the last menstrual period [LMP]). The median days' supply for the TMP-SUL drugs was 7 days, and 10 days for the comparator group antibacterials. The timing of pregnancy onset was determined from gestational age at delivery, which has previously been validated.²⁰

For the primary and secondary comparison groups, we identified two groups of population-based controls, randomly matched 1:1 to TMP-SUL exposed women by age (5-year bands) and health plan: 1) primary comparison group: mothers exposed to penicillins and/or cephalosporins (presumed non-teratogenic antibacterials – henceforth referred to as 'comparator antibacterials') and not to TMP-SUL during the time period specified above; and 2) a secondary comparison group: mothers with no dispensing of an antibacterial, antiprotozoal, or antimalarial medication during the same time period.

Main Outcomes

Outcomes were congenital anomalies associated with systemic TMP-SUL use in prior studies, specifically: cardiovascular abnormalities, cleft palate/lip, clubfoot, neural tube defects, and urinary tract abnormalities. For neural tube defects there were only 5 confirmed cases in the overall cohort and therefore further analyses on neural tube defects were not performed. Although infants were required to be enrolled for 30 days or more after delivery, we searched for congenital anomaly diagnoses up to the first year of life, infant date of death (as documented in the hospital discharge data), or health plan disenrollment, whichever occurred first. When assessing the enrollment criteria of infants in order to provide the maximum cohort size it was observed that approximately 90% of birth defects were identified within the first 30 days of life. We used specific International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes (Table 1) in infant and mother health plan records and birth certificate data to identify potential congenital anomalies.

We reviewed all available medical records at each site to validate potential anomalies.²¹ A trained abstractor at each site reviewed records using a standardized abstraction instrument created for this study to document the presence of a physician's diagnosis or diagnosis in a surgical, radiology, or echocardiography report. Cases that were unclear were adjudicated by a pediatrician or other clinician with expertise in birth outcomes research, as were the first five cases reviewed at each site and an additional 5% random sample for quality control purposes. All abstractors and adjudicators were blinded to infant exposure status.

Statistical Analyses

Main analyses (pre-specified)—The primary analyses compared infants with *in utero* TMP-SUL exposure to matched infants exposed to comparator antibacterials having similar indications for use. This choice of comparison group was made specifically to mitigate potential confounding by indication. However, to also facilitate comparison of our study to previous studies that did not include such comparisons, our secondary analyses compared infants with *in utero* TMP-SUL exposure to matched infants whose mothers had no dispensing of an antibacterial, antiprotozoal, or antimalarial medication during the first trimester.

For both the primary and secondary analyses multivariable conditional logistic regression models were used to estimate the odds ratios (OR, as estimates of relative risks) for the association between *in utero* TMP-SUL exposure and risk of each congenital anomaly.^{22–24} Models were adjusted for variables considered to be confounders of the relationship between TMP-SUL exposure and congenital anomalies which were selected *a priori* based on published literature, including infant sex, parity (nulliparous vs. parous), maternal race (non-white vs white), and dispensing of other medications containing a sulfonamide moiety (any vs. none; eTable 3), and trimethoprim alone, which was used too infrequently to consider as a separate exposure in this study. For all analyses a complete-case analysis was conducted where subjects were included if they had no missing values for variables in the final models. For example, if a TMP-SUL exposed infant had missing data on the variables in the final model then the matched infants in the comparator antibacterials and non-exposed groups were also excluded from the analyses. Analyses were conducted using SAS Version 9.2 (SAS Institute Inc. Cary, NC, USA).

Additional analyses—In pre-specified analyses, we examined risk with TMP-SUL exposure in specific time windows during the first trimester (0–30, 31–60, and 61–90 days gestation) vs. no antibacterial exposure, where the TMP-SUL exposed infants within each window of exposure were compared to their matched non-exposed infant (results not shown). We could not conduct similar analyses for the comparison of infants exposed to TMP-SUL vs. those exposed to comparator antibacterials using a matched cohort approach because the infants were matched by mother's age within each study site and not by timing of exposure. Therefore, we conducted additional analyses that excluded the matching factors between the infants, thus allowing for the comparison of infants exposed to TMP-SUL vs. those exposed to comparator antibacterials during the same window of exposure. If a mother had multiple dispensings within the first trimester and the timing of the dispensing fell within different 30 day windows of exposure then the mother was included in different analyses examining the windows of exposure (e.g., the windows of exposure are not mutually exclusive).

To be consistent across the comparisons within the additional analyses, for the comparison of the TMP-SUL exposed infants vs. non-exposed infants we report results from analyses using the non-matched cohort approach (e.g., infants exposed to TMP-SUL within each window of exposure were compared to all non-exposed infants (n=6990), and not their matched infant). Unconditional logistic regression models were used for these analyses and

adjusted for the same confounders listed in the main analyses, as well as maternal age at delivery (≤ 30 yrs vs. > 30 yrs).

RESULTS

Study Cohort

Among 548,363 mother-infant pairs who met the eligibility criteria, 10,044 infants were exposed to sulfonamides *in utero* during the first trimester. After excluding 2,429 infants exposed to both sulfonamide and comparator antibacterials, there were 7,615 infants in the sulfonamide group and 61,516 in the comparator antibacterials group (Figure 1). Of the pregnancies exposed to TMP-SUL, 99% were exposed to a combination of trimethoprim-sulfonamide with the remaining 1% to other sulfonamides (See eTable 4 for a list of specific medications within these drug classes that infants in each exposure group were exposed to during the first trimester). Within the list of confounding medications adjusted for in the analyses (eTable 3), only three pregnancies were exposed to trimethoprim alone. One matched set was excluded after medical records revealed that one infant had trisomy 18. After 1:1 matching of TMP-SUL exposed mother-infant pairs to the comparison groups, the final cohort consisted of 22,842 mother-infant pairs (7614 in each group). There were 20,064 ($n=6688$ in each of the groups) with complete data on the variables used in the primary main analyses. Table 2 shows the characteristics of the final cohort by exposure group. Online eTable 5 shows the prevalence of congenital anomalies according to the same characteristics for the entire cohort ($n=22,842$).

Primary Analysis

Table 3 shows the prevalence and adjusted ORs (aOR) for each of the birth defect categories. In comparisons of TMP-SUL exposed infants to those exposed to comparator antibacterials, TMP-SUL exposure was not significantly associated with risk for any congenital anomalies, although an elevated aOR was detected for club foot. The crude estimates for results in Table 3 are presented in eTable 6.

In a sub-analysis we examined individual congenital anomalies within the cardiovascular (ventricular septal defects [$n=137$], atrial septal defects [$n=163$]) and urinary system defect (obstructive defects of the renal pelvis and ureter [$n=64$]) categories. There were no significant associations (Table 3).

Secondary Analysis

In comparisons of TMP-SUL exposed infants to those with no exposure to antibacterials, the aORs were > 1.0 for cardiovascular defects, cleft lip/palate, club foot, and urinary tract defect, although none of these associations were statistically significant (Table 3).

Additional Analyses

Timing of Exposure—64% of infants exposed to TMP-SUL were exposed between 0 through 30 days after LMP, while 36% of infants exposed to comparator antibacterials were exposed during this window (See eFigures 1 and 2). Figure 2 shows the aORs for each birth defect category stratified by specific 30 day exposure windows. There were no statistically

significant increased risks for any of the pairwise comparisons among any of the congenital anomaly categories in specific 30 day windows. Although all results were not statistically significant, when comparing TMP-SUL exposed to non-exposed infants stratified by windows of exposure, most aORs were >1, whereas the aORs for TMP-SUL exposed vs. the comparator antibacterial-exposed infants showed a less consistent pattern.

Sensitivity Analyses—We conducted sensitivity analyses which included only the mother-infant pairs exposed to the combination of trimethoprim-sulfonamide (99% of the TMP-SUL group) and their matched pairs from the two comparator groups, and the results presented in Table 3 did not change.

DISCUSSION

Our study assessed the associations between first-trimester TMP-SUL exposure (99% of which was to a combination of trimethoprim and a sulfonamide) and specific categories of congenital anomalies (cardiovascular anomalies, cleft palate and cleft lip, clubfoot, and urinary tract abnormalities) identified in prior studies as potentially associated with sulfonamide exposure. Because it is possible that the underlying reason for TMP-SUL treatment (infection) could itself increase risk of congenital anomalies, we chose as our main comparator group mothers exposed to antibacterials thought not to be teratogenic (penicillins, cephalosporins), which are prescribed for similar indications. Overall, our findings suggest that the risks of these congenital anomalies among infants exposed to TMP-SUL during the first trimester are not greater than among those exposed to the selected comparator group of non-teratogenic antibacterials during the same time period.

It is important to note that as in most previous studies, almost all of the TMP-SUL exposures in our study were to a combination of trimethoprim-sulfonamide and there was little or no use of either sulfonamide or trimethoprim alone, respectively; thus we (like many prior studies) could not separate potential effects of these two medication classes.^{8–15,17} From a clinical standpoint, it may not be important to distinguish these medications' effects given that they are almost exclusively used in combination.

Similar to previous studies that chose comparators without considering confounding by indication,^{11–15,25} our second comparison group was mothers with no first-trimester antibacterial exposure, and although the aORs associated with TMP-SUL exposure were not statistically significant, for most outcomes the aORs suggest a stronger association than the aORs yielded in the primary analyses that used an 'active' comparator group (e.g., exposure to penicillins/cephalosporins). Given that our primary results suggest no increased risk of congenital anomalies associated with first-trimester TMP-SUL exposure compared to comparator antibacterial exposure, it is possible that these associations from the secondary analyses (TMP-SUL vs. non-exposed) reflect a higher risk associated with the underlying infection (confounding by indication) as studies have reported an association between maternal infections during pregnancy and selected birth defects,^{26–28} and adverse birth outcomes.^{29,30}

There have been five case-control studies^{8–10,15,17} and two retrospective cohort studies^{11,16} reporting significant positive associations between sulfonamide exposure during pregnancy and congenital anomalies (see eTable 7); all but two studies were based on exposure to a combination of trimethoprim and a sulfonamide;^{8–11,15} one study also examined sulfonamides alone,¹² one study was based solely on exposure to sulfonamides,¹⁷ and one study examined exposure to trimethoprim alone and a sulfonamide alone.¹⁶ These studies vary in design, method of exposure assessment and the congenital anomalies investigated which make direct comparisons difficult. In general, several case-control studies^{8–10,15,17} reported greater than two-fold risks for cardiovascular defects (various), cleft palate/lip, clubfoot, NTDs, and urinary tract defects (see eTable 7). These studies ascertained medication exposure through maternal interviews after delivery, which could reflect recall bias that may have contributed to positive results, particularly in the three studies that did not include a control group of mothers of infants with other congenital anomalies.^{8,15,17} Although the retrospective cohort studies^{11,16} were not susceptible to recall and selection biases, however confounding by indication^{13,14} and concomitant medications¹³ may have contributed to their positive results.

Our study has several strengths. We excluded mothers and infants exposed to a wide range of medications believed to be potentially teratogenic (eTables 1 & 2), unlike many other studies that did not address this potential confounder.^{9–15} Maternal exposure to medications was measured using pharmacy dispensing data which eliminates recall bias, minimizes misclassification of medication exposures, and allows for examination of specific time windows of exposure. Our study cohort was geographically diverse.¹⁹ All congenital anomalies were confirmed via medical record review, minimizing misclassification of birth defects. Lastly, a control group of mothers exposed to penicillins or cephalosporins was used to address potential confounding by indication.

Our study had limitations. We could not confirm whether patients actually ingested the dispensed medication. The MEPREP data are limited to outpatient medications, thus medications administered in an inpatient setting were not captured. Due to the rarity of particular congenital anomalies, we had limited statistical power for certain categories of defects (e.g. clubfoot, NTD), and we could not study individual types of defects (e.g., uncommon specific heart defects) separately. Hence, the main analyses focused on broader “categories” of anomalies grouped by organ system, and subgroup analyses focused on larger subgroups within these categories. By grouping distinct anomalies together we may have missed a true association. Our study was restricted to live births, and we did not ascertain cause of death if death occurred following delivery, thus we may have under-ascertained congenital anomalies that resulted in therapeutic abortion or were severe enough to result in spontaneous abortion, stillbirth, or death after live birth. This may have biased our results toward the null if sulfonamide exposure is associated with severe congenital anomalies resulting in death before birth, or after livebirth if not otherwise diagnosed before death.

CONCLUSION

Overall, our study found no difference in the risk of certain congenital anomalies in liveborn infants exposed to TMP-SUL during the first trimester versus those exposed to penicillins or cephalosporins (antibiotics prescribed for similar indications). Our study highlights the need for further studies using ‘active’ comparator groups as a method of minimizing confounding by indication.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to thank De-Kun Li, George Tiller, William Cooper, and Todd Callahan for their expertise and contribution in adjudicating the medical records for congenital anomalies, and Ariel Porcalla, for his assistance with protocol development; and the project managers, data programmers and abstractors at each study site.

FUNDING SOURCE: Funding for this project was contract number HHSF223201000009I. Funding for Dr Dublin was from grant number K23AG028954.

ABBREVIATIONS

MEPREP	Medication Exposure in Pregnancy Risk Evaluation Program
NTDs	neural tube defects

References

1. Lee M, Bozzo P, Einarson A, Koren G. Urinary tract infections in pregnancy. *Can Fam Physician*. 2008; 54(6):853–854. [PubMed: 18556490]
2. Kaplan JE, Benson C, Holmes KH, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep*. 2009; (RR-4):1–207. quiz CE201-204.
3. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. *Clin Infect Dis*. 2011; 52(3):285–292. [PubMed: 21217178]
4. Andrade SE, Gurwitz JH, Davis RL, et al. Prescription drug use in pregnancy. *Am J Obstet Gynecol*. 2004; 191(2):398–407. [PubMed: 15343213]
5. Thorpe PG, Gilboa SM, Hernandez-Diaz S, et al. Medications in the first trimester of pregnancy: most common exposures and critical gaps in understanding fetal risk. *Pharmacoepidemiol Drug Saf*. 2013; 22(9):1013–1018. [PubMed: 23893932]
6. Ylikorkala O, Sjostedt E, Jarvinen PA, Tikkanen R, Raines T. Trimethoprim-sulfonamide combination administered orally and intravaginally in the first trimester of pregnancy: its absorption into serum and transfer to amniotic fluid. *Acta Obstet Gynecol Scand*. 1973; 52(3):229–234. [PubMed: 4743777]
7. Reid DW, Caille G, Kaufmann NR. Maternal and transplacental kinetics of trimethoprim and sulfamethoxazole, separately and in combination. *Can Med Assoc J*. 1975; 112(13 Spec No):67–72. [PubMed: 1137830]
8. Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. The teratogenic risk of trimethoprim-sulfonamides: a population based case-control study. *Reprod Toxicol*. 2001; 15(6):637–646. [PubMed: 11738517]

9. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Folic acid antagonists during pregnancy and the risk of birth defects. *N Engl J Med*. 2000; 343(22):1608–1614. [PubMed: 11096168]
10. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Neural tube defects in relation to use of folic acid antagonists during pregnancy. *Am J Epidemiol*. 2001; 153(10):961–968. [PubMed: 11384952]
11. Matok I, Gorodischer R, Koren G, et al. Exposure to folic acid antagonists during the first trimester of pregnancy and the risk of major malformations. *British Journal of Clinical Pharmacology*. 2009; 68(6):956–962. [PubMed: 20002091]
12. Czeizel A. A case-control analysis of the teratogenic effects of co-trimoxazole. *Reprod Toxicol*. 1990; 4(4):305–313. [PubMed: 2136050]
13. Hill L, Murphy M, McDowall M, Paul AH. Maternal drug histories and congenital malformations: limb reduction defects and oral clefts. *J Epidemiol Community Health*. 1988; 42(1):1–7. [PubMed: 3418278]
14. Meijer WM, de Walle HE, Kerstjens-Frederikse WS, de Jong-van den Berg LT. Folic acid sensitive birth defects in association with intrauterine exposure to folic acid antagonists. *Reprod Toxicol*. 2005; 20(2):203–207. [PubMed: 15907654]
15. Crider KS, Cleves MA, Reefhuis J, et al. Antibacterial medication use during pregnancy and risk of birth defects: National Birth Defects Prevention Study. *Arch Pediatr Adolesc Med*. 2009; 163(11):978–985. [PubMed: 19884587]
16. Molgaard-Nielsen D, Hviid A. Maternal use of antibiotics and the risk of orofacial clefts: a nationwide cohort study. *Pharmacoepidemiol Drug Saf*. 2012; 21(3):246–253. [PubMed: 22125260]
17. Czeizel AE, Puho E, Sorensen HT, Olsen J. Possible association between different congenital abnormalities and use of different sulfonamides during pregnancy. *Congenit Anom (Kyoto)*. 2004; 44(2):79–86. [PubMed: 15198720]
18. Briggs, GG.; Freeman, RK.; SJ, Y. *Drugs in Pregnancy and Lactation: A reference guide to fetal and neonatal risk*. Philadelphia, PA: Lippincott Williams & Watkins; 2008.
19. Andrade SE, Davis RL, Cheetham TC, et al. Medication Exposure in Pregnancy Risk Evaluation Program. *Maternal Child Health Journal*. 2011 Oct 15. [Epub ahead of print] PubMed PMID: 22002179.
20. Andrade SE, Scott PE, Davis RL, et al. Validity of health plan and birth certificate data for pregnancy research. *Pharmacoepidemiol Drug Saf*. 2013; 22(1):7–15. [PubMed: 22753079]
21. Sever, L. *National Birth Defects Prevention Network (NBDPN). Guidelines for Conducting Birth Defects Surveillance*. Atlanta, GA: National Birth Defects Prevention Network, Inc.; 2004.
22. Connolly MA, Liang KY. Conditional logistic regression models for correlated binary data. *Biometrika*. 1988; 75(3):501–506.
23. Stokes, M.; Davis, CS.; Koch, GG. *Categorical data analysis using the SAS system*. Second. Cary, NC: SAS Institute Inc.; 2000.
24. Allison, P. *Logistic Regression using SAS system: Theory and Application*. Cary, NC: SAS Institute; 1999.
25. Werler MM, Bower C, Payne J, Serna P. Findings on potential teratogens from a case-control study in Western Australia. *Aust N Z J Obstet Gynaecol*. 2003; 43(6):443–447. [PubMed: 14712948]
26. Carter TC, Olney RS, Mitchell AA, et al. Maternal self-reported genital tract infections during pregnancy and the risk of selected birth defects. *Birth Defects Res A Clin Mol Teratol*. 2011; 91(2):108–116. [PubMed: 21319278]
27. Cleves MA, Malik S, Yang S, Carter TC, Hobbs CA. Maternal urinary tract infections and selected cardiovascular malformations. *Birth Defects Res A Clin Mol Teratol*. 2008; 82(6):464–473. [PubMed: 18452156]
28. Feldkamp ML, Reefhuis J, Kucik J, et al. Case-control study of self reported genitourinary infections and risk of gastroschisis: findings from the national birth defects prevention study, 1997–2003. *BMJ*. 2008; 336(7658):1420–1423. [PubMed: 18558640]

29. Mazor-Dray E, Levy A, Schlaeffer F, Sheiner E. Maternal urinary tract infection: is it independently associated with adverse pregnancy outcome? *J Matern Fetal Neonatal Med.* 2009; 22(2):124–128. [PubMed: 19085630]
30. Banhidy F, Acs N, Puho EH, Czeizel AE. Pregnancy complications and birth outcomes of pregnant women with urinary tract infections and related drug treatments. *Scand J Infect Dis.* 2007; 39(5): 390–397. [PubMed: 17464860]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

KEY POINTS

- First trimester trimethoprim-sulfonamide exposure is not associated with a higher risk of the congenital anomalies studied.
- Maternal exposure to medications was measured using pharmacy dispensing data which eliminates recall bias.
- It is important for studies to use 'active' comparator groups exposed to antibacterials other than trimethoprim-sulfonamides as a method of minimizing confounding by indication.

Figure 1.
Schematic of the selection process for the final cohort.

TMP-SUL VS COMPARATOR ANTIBACTERIALS

TMP-SUL VS NON-EXPOSED

Figure 2.

Adjusted odds ratios (aORs) for sulfonamide-associated congenital anomalies for specific 30 day exposure windows (non-matched cohort analyses). SULF= TMP-SUL; ANTI=Comparator antibacterials; NEXP=Non-exposed. Note: TMP-SUL group was comprised of 99% trimethoprim-sulfonamide and 1% sulfonamide exposures.

Table 1

Congenital anomaly categories of interest and associated International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes

Outcomes of interest	ICD-9-CM codes
Cardiovascular abnormalities	745–745.×, 746, 746.0×–746.9×, 747.0–747.4×, 747.6×, 747.8×
Cleft palate and/or lip	749.00, 749.0, 749.1, 749.2
Club foot	754.5, 754.6, 754.7
Neural tube defects	740.0 – 740.2, 741.0–741.3, 742.0, 741.9, 756.17
Urinary system anomalies	753.0 – 753.9, 752.61, 752.62
Exclusion anomalies	
Trisomy 13, trisomy 18, trisomy 21	758.0, 758.1, 758.2
Congenital varicella syndrome	N/A ^a
Congenital rubella syndrome	771.0

^a. Congenital varicella syndrome does not have an ICD-9-CM. It was identified by medical record review

Table 2

Characteristics of the final matched cohort, by first trimester antibacterial exposure

	TMP-SUL *	COMPARATOR ANTIBACTERIALS	NON-EXPOSED
	n=7614	n=7614	n=7614
Infant Sex	n (%)	n (%)	n (%)
Female	3722 (48.9)	3714 (48.8)	3660 (48.1)
Male	3892 (51.1)	3900 (51.2)	3954 (51.9)
Race			
White	3647 (47.9)	4008 (52.6)	3589 (47.1)
Non-white	3812 (50.1)	3453 (45.4)	3867 (50.8)
Missing	155 (2.0)	153 (2.0)	158 (2.1)
Maternal Age at Delivery^a			
Mean ±SD	26.4 ±6.3	26.4 ±6.3	26.4 ±6.2
Previous Births			
None	2679 (35.2)	2499 (32.8)	2666 (35.0)
1 or more	4414 (58.0)	4588 (60.3)	4423 (58.1)
Missing	521 (6.8)	527 (6.9)	525 (6.9)
Concomitant Medications^b			
No	6539 (85.9)	6814 (89.5)	7162 (94.1)
Yes	1075 (14.1)	800 (10.5)	452 (5.9)
Chronic Conditions^c			
No	6696 (87.9)	6670 (87.6)	6871 (90.2)
Yes	918 (12.1)	944 (12.4)	743 (9.8)
Maternal Education			
College or Above	3104 (40.8)	3162 (41.5)	3216 (42.2)
High School or Less	4224 (55.5)	4213 (55.3)	4142 (54.4)
Missing	286 (3.8)	239 (3.1)	256 (3.4)
Smoking During Pregnancy			
No	3427 (45.0)	3269 (42.9)	3514 (46.2)
Yes	1044 (13.7)	1220 (16.0)	967 (12.7)
Missing	3143 (41.3)	3125 (41.0)	3133 (41.1)

* TMP-SUL group was comprised of 99% trimethoprim-sulfonamide and 1% sulfonamide exposures.

^a. Matching variable (matched on 5yr age bins).

^b. Maternal use of a non-antibacterial medication that contains sulfonamide moiety (see eTable 3) during the first trimester.

^c. Cardiac disease or pre-gestational diabetes.

NOTE: This table shows results for the entire final cohort prior to the sample being reduced for the complete-case regression analyses.

Table 3

Prevalence of, and adjusted^a odds ratios (aORs) for, congenital anomalies in infants with first trimester TMP-SUL or other antibacterial exposure (matched cohort analyses^b).

	PREVALENCE OF CONGENITAL ANOMALIES BY EXPOSURE GROUP, n (%)			TMP-SUL versus COMPARATOR ANTIBACTERIALS ^c	TMP-SUL versus NON-EXPOSED
	TMP-SUL*	COMPARATOR ANTIBACTERIALS ^c	NON-EXPOSED		
TOTAL COHORT	6688	6688	6688	aOR (95% CI)	aOR (95% CI)
Cardiovascular (all)	109 (1.63)	115 (1.72)	93 (1.39)	0.94 (0.71, 1.23)	1.20 (0.89, 1.61)
- Atrial Septal Defect	46 (0.69)	56 (0.84)	45 (0.67)	0.83 (0.56, 1.25)	0.98 (0.63, 1.51)
- Ventricular Septal Defect	35 (0.52)	51 (0.76)	38 (0.57)	0.70 (0.44, 1.13)	1.01 (0.60, 1.69)
Cleft lip/palate	8 (0.12)	5 (0.07)	7 (0.10)	0.83 (0.18, 3.88)	1.80 (0.38, 8.51)
Club foot	18 (0.27)	11 (0.16)	13 (0.19)	1.58 (0.71, 3.50)	1.58 (0.67, 3.70)
Urinary system (all)	56 (0.84)	51 (0.76)	40 (0.59)	1.08 (0.70, 1.65)	1.59 (0.97, 2.59)
- OBRPU	18 (0.27)	24 (0.36)	9 (0.13)	0.78 (0.39, 1.54)	2.05 (0.82, 5.14)

* TMP-SUL group was comprised of 99% trimethoprim-sulfonamide and 1% sulfonamide exposures.

^a . Adjusted for: infant sex, previous births, race, concomitant medications.

^b . Where study subjects have no missing values for covariates in the final model (complete-case analyses).

^c . Penicillins and cephalosporins.

Selected sub-groups (based on the specific defects with largest numbers in the main categories): ASD=Atrial septal defect; VSD=Ventricular septal defect; OBRPU=Obstructive defects of the renal pelvis and ureter