International Journal of Infectious Diseases 15 (2011) e336–e341

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Exposure to trimethoprim/sulfamethoxazole but not other FDA category C and D anti-infectives is associated with increased risks of preterm birth and low birth weight

Jianzhou Yang [a,b,c], Ri-hua Xie [c,d,e], Daniel Krewski [b], Yong-jin Wang [f], Mark Walker [c,d,g], Shi Wu Wen [c,d,g,*]

[a] Department of Preventive Medicine, Changzhi Medical College, Changzhi, China
[b] McLaughlin Centre for Population Health Risk Assessment, Institute of Population Health, University of Ottawa, Ottawa, Canada
[c] OMNI Research Group, Department of Obstetrics and Gynecology, University of Ottawa Faculty of Medicine, 501 Smyth Rd, Box 241, Ottawa, Ontario, Canada, K1H 8L6
[d] Ottawa Hospital Research Institute, Clinical Epidemiology Program, Ottawa, Canada
[e] Huaihua Medical College, Department of Nursing, Huaihua, China
[f] Heping Hospital, Changzhi Medical College, Changzhi, China
[g] Department of Epidemiology and Community Medicine, University of Ottawa Faculty of Medicine, Ottawa, Canada

ARTICLE INFO

Article history:
Received 30 July 2010
Received in revised form 18 January 2011
Accepted 22 January 2011

Corresponding Editor: Hubert Wong, Vancouver, Canada

Keywords:
Trimethoprim/sulfamethoxazole
Anti-infectives
Preterm birth
Low birth weight
Folic acid antagonist
Pregnancy

SUMMARY

Objective: To examine the association between trimethoprim/sulfamethoxazole, other US Food and Drug Administration (FDA) C and D anti-infectives, and non anti-infective FDA C, D, and X drugs used during pregnancy with preterm birth and low birth weight.
Methods: We carried out a retrospective cohort study based on a 50% random sample of women who gave birth in the Canadian province of Saskatchewan from 1997 to 2000. The association between trimethoprim/sulfamethoxazole, other FDA C and D anti-infectives (fluconazole, clarithromycin, doxycycline, and tetracycline), and non anti-infective FDA C, D, and X drugs used during pregnancy with preterm birth and low birth weight was evaluated using multiple logistic regression, with adjusted odds ratios (aORs) and 95% confidence intervals (CIs) as association measures.
Results: A total of 17 939 women were included in the final analysis. Trimethoprim/sulfamethoxazole was associated with significantly increased risks for preterm birth (aOR 1.51, 95% CI 1.10, 2.08) and low birth weight (aOR 1.67, 95% CI 1.14, 2.46). Exposure to non anti-infective FDA category C, D and X drugs was also associated with increased risks for preterm birth (aOR 1.17, 95% CI 1.09, 1.31) and low birth weight (aOR 1.14, 95% CI 0.92, 1.42), but to a lesser degree. Other FDA C and D anti-infectives were not (statistically) significantly associated with increased risks for preterm birth (aOR 0.93, 95% CI 0.49, 1.77) or low birth weight (aOR 0.65, 95% CI 0.27, 1.60).
Conclusions: Among FDA C, D and X drugs, trimethoprim/sulfamethoxazole, a folic acid antagonist, has the strongest association with preterm birth and low birth weight.

1. Introduction

Anti-infectives have often been used in pregnancy to treat various infections.[1,2] Some of these anti-infectives are category C or D drugs according to the US Food and Drug Administration (FDA) classification system – a system developed to rate the potential risk to the fetus of drugs. The FDA system classifies a drug into one of five major categories: A, B, C, D and X.[3,4] Most drugs are classified into category C; these should be given only if potential benefits outweigh potential risks to the fetus. Categories D and X indicate evidence of risk in pregnancy.

Trimethoprim/sulfamethoxazole is an effective anti-infective in the treatment of a variety of infections, and is used as first-line therapy for the treatment of acute and uncomplicated urinary tract infections in women.[5,6] Trimethoprim/sulfamethoxazole is an FDA category C drug and the most frequently prescribed folic acid antagonist during pregnancy.[7] Folic acid antagonists include a broad spectrum of drugs with various clinical indications ranging from epilepsy to mood disorders to urinary tract infections. One of the common mechanisms of folic acid antagonists is to deplete folate and to impair folate metabolism.[8] Maternal exposure to folic acid antagonists, including trimethoprim/sulfamethoxazole, has been found to be associated with increased risks of various adverse pregnancy outcomes, such as birth defects, preeclampsia, placental abruption, fetal growth restriction, and fetal death.[7,9,10]

* Corresponding author. Tel.: +1 613 737 8899x73912; fax: +1 613 739 6266.
E-mail address: swwen@ohri.ca (S.W. Wen).

1201-9712/$36.00 – see front matter © 2011 International Society for Infectious Diseases. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.ijid.2011.01.007

Although newer anti-infectives have been on the market, fluconazole and clarithromycin (FDA category C drugs) and doxycycline and tetracycline (FDA category D drugs) are also used to treat infections, including urinary tract infections.[11–15] One major difference of these anti-infectives when compared to trimethoprim/sulfamethoxazole is that they do not have the effect of depleting folate and impairing folate metabolism, although they may have fetal toxic effects through other mechanisms.[16–19] Many studies have examined the associations of various anti-infectives, including fluconazole,[20,21] doxycycline, tetracycline and clarithromycin,[18,22,23] and other anti-infectives[24–28] with adverse pregnancy outcomes, including birth defects, preterm birth, and low birth weight, with inconsistent findings. However, no study has compared the effects of trimethoprim/sulfamethoxazole and other anti-infectives on adverse pregnancy outcomes in the same population. The objective of this study was to examine the associations of pregnancy use of trimethoprim/sulfamethoxazole and other FDA C and D anti-infectives with preterm birth and low birth weight, the two most frequently studied adverse pregnancy outcomes.

2. Materials and methods

2.1. Study population

This study was based on the linked maternal–infant database of the Canadian province of Saskatchewan. Details of the dataset have been described elsewhere.[29]

All live births and stillbirths in Saskatchewan to Saskatchewan residents that occurred between January 1, 1997 and December 31, 2000 were identified. The database includes prescription information for most residents (>90%) of the province of Saskatchewan. According to Saskatchewan provincial regulations, Saskatchewan Health cannot release the health care information of an entire segment of the population (e.g., all pregnant women during a defined period of time), even if all personal identifiers are removed. To respect the provincial regulations and to maximize the study power, a random sample (by mother's provincial health care number) of approximately 50% of the eligible women during the period of interest was selected. Infants born to mothers of registered Indians had to be excluded from the study because drug information is not available for them; women with less than one year of health coverage were also excluded from this study. Subjects with multiple birth pregnancies (twins and triplets or higher order multiples) were excluded because of concerns for the correlated outcomes and also potentially major confounding from multiple pregnancy (multiple birth pregnancy has significantly higher rates of preterm birth and low birth weight), which may be difficult to adjust for by regression analysis alone.

2.2. Ascertainment of pregnancy drug exposure

Ascertainment of FDA category C, D, and X drug use during pregnancy was determined using information in the outpatient prescription drug database. Each mother was assigned an index date equal to the date of delivery. Pregnant women with at least one prescription for medications dispensed during pregnancy were considered as exposed. The pregnancy period of drug exposure was calculated based on the combination of gestational age, date of delivery, and drug dispensing dates. Information on maternal and neonatal characteristics, such as age, parity (based on numbers of live births and stillbirths), and social assistance plan status were obtained from the provincial population registry and birth registration files. Chronic disease status was based on a chronic disease score calculated using outpatient prescription drug data in the year prior to the index date, following previously established methods.[30] These variables were considered as confounding variables affecting the association between FDA category C, D, and X drugs during pregnancy and adverse pregnancy outcomes.

2.3. Statistical analysis

Preterm birth and low birth weight were the study outcomes. Preterm birth was defined as a gestational age of <37 completed weeks, and low birth weight was defined as a birth weight of <2500 g. Pregnant women with at least one FDA category C, D, or X drug dispensed during pregnancy were considered as exposed. The study subjects were divided into four groups according to their pregnancy exposure to FDA category C, D, and X drugs: trimethoprim/sulfamethoxazole (exposed I), other FDA C and D anti-infectives (fluconazole, clarithromycin, doxycycline, and tetracycline; exposed II), non anti-infective FDA C, D, and X drugs (exposed III), and no exposure to any FDA C, D, or X drugs (non-exposed). Because of the privacy issues precluding identification of multiple pregnancies, the analyses did not account for women having had more than one pregnancy during the study period.

The baseline characteristics of the four study groups were compared. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) associated with the different exposure groups (no exposure as the reference) were estimated. The aOR was obtained through the use of a multiple logistic regression model with adjustment for year of birth, maternal age, parity, chronic disease score, and Saskatchewan Assistance Plan coverage (an indictor of poverty). Finally, the proportions of women who used trimethoprim/sulfamethoxazole and other FDA category C and D anti-infectives during pregnancy were examined. All analyses were performed using SAS v. 9.1.3 (SAS Institute Inc., Cary, NC, USA).

3. Results

A total of 17 949 eligible pregnant women were identified from the database. Ten women were excluded because they were exposed to both trimethoprim/sulfamethoxazole and at least one other FDA C or D anti-infective, leaving 17 939 women for the final analysis.

Maternal characteristics in the four study groups are shown in Table 1. Women exposed to FDA C, D, or X drugs (including those exposed to trimethoprim/sulfamethoxazole or other FDA C and D anti-infectives) tended to be younger, to have a chronic disease, and to be on the Saskatchewan Assistance Plan.

Tables 2 and 3 present aORs and 95% CIs for preterm birth and low birth weight, respectively, associated with the different drug exposures. After adjustment for year of birth, maternal age, parity, chronic disease score, and Saskatchewan Assistance Plan coverage, exposure to trimethoprim/sulfamethoxazole was associated with significantly increased risks for preterm birth and low birth weight. The differences in event rates between the exposed vs. unexposed groups were substantial (34/447 vs. 715/14 537 in the case of preterm birth, and 30/447 vs. 509/14 537 in the case of low birth weight) and very little of these differences appears to be explained by the confounders entered into the model (crude OR 1.59 vs. aOR 1.51 for preterm birth and crude OR 1.98 vs. aOR 1.67 for low birth weight). Exposure to non anti-infective FDA category C, D or X drugs was also associated with increased risks for preterm birth and low birth weight. On the other hand, exposure to other FDA C or D anti-infectives was associated with decreased (statistically non-significant) risks for preterm birth and low birth weight compared with no pregnancy exposure.

Table 4 presents the proportions of pregnancy uses of trimethoprim/sulfamethoxazole and other FDA C and D anti-infectives. Trimethoprim/sulfamethoxazole was the most frequently used (2.59%), fluconazole (0.62%) and doxycycline