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Maternal Exposure to Methotrexate and Birth Defects: a Population-Based Study

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Abstract

Methotrexate is an anti-folate medication that is associated with increased risk of multiple birth defects. Using data from the National Birth Defects Prevention Study, a case-control study of major birth defects in the United States, we examined mothers exposed to methotrexate. The study population included mothers of live-born infants without major birth defects (controls) and mothers of fetuses or infants with a major birth defect (cases), with expected dates of delivery between October 1997 and December 2009. Mothers of cases and controls were asked detailed questions concerning pregnancy history, demographic information, and exposures in a telephone interview. Approximately 0.06% (n=16/27,623) of case and 0.04% (n=4/10,113) of control mothers reported exposure to methotrexate between three months prior to conception through the end of pregnancy. Of the 16 case infants, 11 (68.8%) had a congenital heart defect (CHD). The observed CHDs included atrial septal defects, tetralogy of Fallot, valvar pulmonary stenosis, ventricular septal defects (VSDs), and total anomalous pulmonary venous return. One case infant had microtia in addition to a VSD and another had VACTER association. Exposed cases without a CHD had one of the following birth defects: cleft palate, hypospadias, congenital diaphragmatic hernia, or craniosynostosis. Based on a limited number of methotrexate-exposed mothers, our findings support recent case reports suggesting an association between early pregnancy exposure to methotrexate and CHDs. Because of the rarity of maternal periconceptional exposure to methotrexate, long-term, population-based case-control studies are needed to confirm these findings and better evaluate the association between methotrexate and birth defects.

Keywords

methotrexate; birth defects; congenital heart defects

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INTRODUCTION

Methotrexate is a successful and widely used medication for cancer chemotherapy and a variety of other conditions [Lloyd et al., 1999]. Methotrexate is a folic acid antagonist that inhibits dihydrofolate reductase, thus blocking the synthesis of thymidine and inhibiting DNA synthesis. In addition to the treatment of malignancy, methotrexate has been used to treat rheumatic, dermatological, autoimmune, and inflammatory disorders, and in the termination of pregnancy [Lloyd et al., 1999]. Methotrexate has also become widely used in the successful non-surgical management of ectopic pregnancy [Richardson, 2012].

While methotrexate is a successful therapeutic agent, it also has potential deleterious effects, and methotrexate use is contraindicated during pregnancy. However, fetal exposure can occur, for example, as a result of the failed termination of a misdiagnosed ectopic pregnancy. The use of methotrexate by women of child-bearing age may be problematic as there have been many case reports of congenital malformations attributed to the use of folic acid antagonists during pregnancy [Milunsky et al., 1968]. Some authors have described a complex association of congenital malformations as “methotrexate embryopathy” [Chapa et al., 2003, Addar, 2004, Seidahmed et al., 2006]. Several previous literature reviews examined case reports of methotrexate use during pregnancy [Milunsky et al., 1968, Feldkamp and Carey, 1993, Hyoun et al., 2012]. The 1993 and 2012 reviews suggested specific malformations are associated with methotrexate exposure between six and eight weeks of gestation. However, recent case reports suggest additional malformations, including congenital heart defects (CHD), may be associated with exposure outside of the proposed sensitive period [Piggott et al., 2011]. In particular, recent case reviews reporting methotrexate exposure prior to six weeks gestation suggest the possibility of a distinct early-exposure syndrome. Historically, descriptions of methotrexate embryopathy have not emphasized CHDs; however, tetralogy of Fallot and other neural crest cell-related abnormalities may be features of this early syndrome [Piggott et al., 2011, Poggi and Ghidini, 2011, Hyoun et al., 2012]. These reports suggest that the embryopathy attributable to methotrexate should be expanded beyond what was originally described [Nguyen et al., 2002]. The objective of this study was to use a case-series approach to examine clinical information on case and control infants with maternal methotrexate exposure and to describe use of the medication during pregnancy.

MATERIALS AND METHODS

We examined data from the National Birth Defects Prevention Study (NBDPS), a multi-center case control study of major, structural birth defects conducted in ten U.S. states. Institutional Review Boards at each site have approved the study. Study methods for recruitment of participants and data collection for the NBDPS have been described in detail elsewhere [Yoon et al., 2001, Rasmussen et al., 2003]. NBDPS cases include infants with major birth defects identified through population-based surveillance systems at each site. Infants with birth defects with a known etiology, including those with recognized chromosomal syndromes or single-gene disorders, are excluded. NBDPS controls, live-born infants with no major birth defects, were selected at random from the same ascertainment area as case infants using birth certificates or birth hospital records. Our study population

included mothers of cases, including live born infants, fetal deaths, and pregnancy terminations, and mothers of controls with estimated dates of delivery (EDD) between October 1, 1997 and December 31, 2009.

Mothers of case and control infants participated in a computer-assisted telephone interview, which included detailed questions concerning pregnancy history, demographic information, and exposures that occurred from three months prior to conception through the end of the pregnancy. Mothers were interviewed in English or Spanish between six weeks and 24 months after their EDD. Mothers had two opportunities to report methotrexate exposure during the interview. First, mothers were asked if they had any "other chronic diseases or illnesses," at which time interviewers could probe for report of conditions including rheumatoid arthritis, psoriasis, and lupus. Then mothers were asked to provide information on any medication(s) used to treat the reported condition. Secondly, mothers were questioned about use of a list of specific medications, which included "methotrexate," but in these instances were not asked for indication.

Cases and controls in which the mother reported any exposure to methotrexate from three months prior to pregnancy through the end of the pregnancy were included in this study. A clinical geneticist and a pediatrician trained in cardiology reviewed the abstracted clinical records for each case infant. Clinical records for control infants were not available for review because infants with major birth defects are ineligible to be NBDPS controls [Cogswell et al., 2009]. Available information was also examined on the indication for use, the timing, frequency, and duration of methotrexate exposure during pregnancy as well as information on other possible risk factors for defects, including maternal age at delivery, race/ethnicity, pre-gestational or gestational diabetes, body mass index, and use of a folic acid-containing multivitamin.

Although the NBDPS is a case-control study with over 27,000 case and 10,000 control mothers, the minimum detectable odds ratio for the association between any methotrexate exposure and all birth defects combined was 3.8 [Dupont and Plummer, 1990]. However, because the etiology of individual birth defects varies, it is preferable to examine associations for each phenotype. Minimum detectable odds ratios ranged from 7.7 for secundum atrial septal defect, one of the most common birth defect phenotypes in the NBDPS, to 13.8 for congenital diaphragmatic hernia, one of the more rare defects we observed. Additionally, it would be preferable to examine associations by trimester and to control for potential confounders, which would further increase the minimum detectable odds ratios. Therefore, due to the rarity of this exposure and the specific birth defect phenotypes observed we elected to present a descriptive review of the characteristics of methotrexate-exposed mothers and the birth defects of their offspring, where applicable.

RESULTS

Approximately 0.06% (n=16/27,623) of case mothers and 0.04% (n=4/10,113) of control mothers reported exposure to methotrexate between three months prior to conception through the end of pregnancy. Ten of the case mothers reported methotrexate use during the first trimester, five mothers reported only preconceptional use, and one mother reported

methotrexate use after the first trimester (Table I). Two of the four control mothers reported only preconceptional use of methotrexate and two reported methotrexate use during the preconceptional period through the second week of pregnancy. The indication for methotrexate use was not reported in most cases, but indications that were reported included systemic lupus erythematosus, polyarticular juvenile rheumatoid arthritis, and a neoplasm of the endocrine glands.

Several maternal and infant characteristics of exposed cases and controls were assessed. The mean maternal age was 31 years for cases (range 22–39 years) and 33 years for controls (range 29–36 years). The majority of mothers were non-Hispanic white (cases, n=8; controls, n=4), had at least some college education (cases, n=14; controls, n=4), and were overweight or obese (body mass index >25 kg/m^2; cases, n=10; controls, n=3). The desire to become pregnant at the time of conception was similar between case and control mothers (6 of 16 case mothers, 2 of 4 control mothers). All cases were live-born except for one fetus that was electively terminated at 22 gestational weeks. Among live-born infants, the mean gestational age was 36.3 weeks (standard deviation (SD) 3.1) and 37.3 weeks (SD 2.1) for cases and controls, respectively; the mean birth weight was 2,688g (SD 822.7) and 2,753g (SD 648.8) for cases and controls, respectively.

The exposed cases had a variety of birth defects (Table I). Among the 16 case infants whose mother reported use of methotrexate at any time, 11 (68.8%) had a CHD. In comparison, approximately 39.9% of all NBDPS cases have a CHD. The observed CHDs included atrial septal defects, tetralogy of Fallot, valvar pulmonary stenosis, ventricular septal defects, and total anomalous pulmonary venous return. Exposure timing for cases with CHD varied. All cases that were exposed during the preconceptional period and the case exposed in the second trimester had at least one CHD, while five of 10 cases exposed during the first trimester had CHD. Other defects included cleft palate, hypospadias, congenital diaphragmatic hernia, craniosynostosis, and microtia.

Among cases with CHD, six of 11 mothers began use of folic acid-containing multivitamins after the first month of pregnancy; three of the five mothers of infants who reported first-trimester exposure of methotrexate did not begin use of folic acid-containing multivitamins until at least the second month of pregnancy. Among case infants without CHD, four of five mothers reported use of folic acid-containing multivitamins beginning in the preconceptional period. All of the mothers of controls reported use of folic acid-containing multivitamins from the preconceptional period through the end of pregnancy.

DISCUSSION

Our finding of CHDs and other birth defects among infants of methotrexate-exposed mothers adds to the literature, suggesting a multi-organ embryopathy may be associated with early exposure to methotrexate [Piggott et al., 2011, Poggi and Ghidini, 2011, Hyoun et al., 2012]. Although five of the case mothers reported only preconceptional use of methotrexate, preconceptional use may result in fetal exposure during the first trimester of pregnancy due to variability in red blood cell elimination of methotrexate metabolites. Wide inter-patient variability in the accumulation and elimination of oral methotrexate from red blood cells has

been observed in rheumatoid arthritis patients, with the half-life of elimination ranging from approximately one week to more than 13 weeks [Dalrymple et al., 2008]. Similarly, a recently developed population pharmacokinetic model of low-dose methotrexate and corresponding red blood cell metabolites, specifically polyglutamated metabolites $MTXGlu_{2-5,}$ highlights the complex and variable nature of methotrexate metabolism [Korell et al., 2013]. Polyglutamated forms of methotrexate have been shown to persist long term within cells of the liver and have also been associated with a reduction in folate stores [Kremer et al., 1986]. Product labeling approved by the U.S. Food and Drug Administration acknowledges the interpatient variability of methotrexate elimination and recommends women of child-bearing potential to delay conception at least one ovulatory cycle after discontinuing treatment [U.S. Food and Drug Administration, 2011]. Previous case reports have inconsistently described use of folic acid during methotrexate-exposed pregnancies, but it has been suggested that use of a folic acid-containing multivitamin may reduce some of the adverse effects resulting from use of folic acid antagonists [Hernández-Díaz et al., 2000].

Our report was limited by several factors. First, the small number of exposed cases necessitated a case-series approach and limited our ability to infer an association between methotrexate and birth defects. One limitation of case reports is that the likelihood that the birth defects were observed by chance cannot be assessed. However, case reports may be useful in describing possible embryopathy attributed to a suspected teratogen when similar patterns in defects are observed independently across time and study population. Therefore, the main objective of this report was to describe methotrexate-exposed cases in the NBDPS and compare the defects observed with those that have been described previously.

Second, the reported methotrexate exposure is potentially subject to inaccurate maternal recall as the exposures were based on maternal self-report following the delivery of the affected offspring. It is possible that women who were exposed to methotrexate during a failed pregnancy termination did not know the name of the medication. Because we did not specifically ask interviewed mothers about all conditions for which methotrexate is indicated, and not all interviewed mothers received the interviewer probe regarding specific chronic medical conditions, it is possible that we might have some exposure misclassification. We were also not able to separate the effects of the medication from those of the underlying conditions. Methotrexate is used in the termination of pregnancy, therefore it is likely that we have under-ascertained some cases of major birth defects that resulted in spontaneous abortion or fetal death, particularly those deaths that occurred prior to 20 weeks gestation. This report excluded infants that had defects that did not meet the NBDPS case definition or infants suspected of having a recognizable syndrome, therefore we may have under-ascertained cases of minor or non-eligible major birth defects that occurred in the source population of NBDPS.

Strengths of this study include use of a population-based sample from ten different states across the United States, which provided a demographically diverse sample. We were able to examine a wide range of maternal exposures and sociodemographic characteristics. Finally, case abstractions were examined by two clinicians.

In conclusion, based on a limited number of cases, our findings support recent case reports suggesting an association between early pregnancy methotrexate exposure and CHD [Piggott et al., 2011, Poggi and Ghidini, 2011, Hyoun et al., 2012]. Although our data do not provide conclusive evidence that the proposed window of sensitivity to methotrexate embryopathy could be expanded, our findings may be helpful to healthcare providers who counsel women prenatally exposed to methotrexate. Because of the rarity of maternal periconceptional exposure to methotrexate, long-term, population-based case-control studies are needed to confirm these findings and better evaluate the association between methotrexate and birth defects.

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Table I

Case-series reports of methotrexate exposure from the National Birth Defects Prevention Study, 1997–2009

Birth defect(s)[a]	Time of exposure[b,c]	Reported indication for methotrexate use	Gestational age (weeks)	Maternal age at delivery (years)	Maternal race/ethnicity	Maternal diabetes and pre-pregnancy BMI category[d]	Use of folic acid-containing multivitamin[c]
Perimembranous ventricular septal defect, atrial septal defect	Preconception	None	37	26	Non-Hispanic Black	No diabetes, overweight	Month 2 – end of pregnancy
Secundum atrial septal defect	Preconception	Neoplasm of endocrine glands	38	35	Non-Hispanic White	No diabetes, overweight	Month 4 – end of pregnancy
Tetralogy of Fallot	Preconception	None	35	37	Non-Hispanic White	No diabetes, normal weight	Preconception – Month 7
Total anomalous pulmonary venous return, atrial septal defect	Preconception	None	36	36	Asian/Pacific Islander	Gestational diabetes, obese	Preconception – end of pregnancy
Valvar pulmonary stenosis, secundum atrial septal defect	Preconception	None	40	29	White, Native American	No diabetes, obese	Month 2 – end of pregnancy
Secundum atrial septal defect	Preconception - Week 1	None	38	22	Non-Hispanic White	No diabetes, normal weight	Preconception – end of pregnancy
Cleft palate	Preconception - Week 2	None	38	24	Non-Hispanic Black	No diabetes, overweight	Month 2 – end of pregnancy
Tetralogy of Fallot	Preconception - Week 2	Rheumatoid arthritis	38	35	Hispanic	No diabetes, normal weight	Month 3 – end of pregnancy
Secundum atrial septal defect	Preconception - Week 3	None	38	33	Non-Hispanic White	Gestational diabetes, overweight	Month 2 – end of pregnancy
Multiple congenital diaphragmatic hernias (Bochdalek, Morgagni, hiatal)	Preconception - Week 4	None	22	26	Non-Hispanic White	No diabetes, obese	Preconception – end of pregnancy
Third degree hypospadias	Preconception - Week 6	Systemic lupus erythematosus	41	39	Non-Hispanic Black	No diabetes, overweight	Preconception – end of pregnancy
VACTER (thoracic hemivertebrae, tracheo-esophageal fistula, esophageal atresia, ectopic kidney, and cardiac [**double-inlet left ventricle with mitral atresia, transposed great arteries,**	Preconception - Week 9	None	34	24	Non-Hispanic White	No diabetes, normal weight	Month 2 – end of pregnancy

Birth defect(s)[a]	Time of exposure[b,c]	Reported indication for methotrexate use	Gestational age (weeks)	Maternal age at delivery (years)	Maternal race/ethnicity	Maternal diabetes and pre-pregnancy BMI category[d]	Use of folic acid-containing multivitamin
and hypoplastic ascending aorta])							
Bilateral foot ectrodactyly, metopic craniosynostosis	Week 5	None	37	30	White, Hispanic	No diabetes, normal weight	Preconception – end of pregnancy
Third degree hypospadias	Week 5	None	29	29	Non-Hispanic White	No diabetes, obese	Preconception – end of pregnancy
Right microtia, **muscular ventricular septal defect**	1 dose between weeks 6–10	None	33	31	Hispanic	Gestational diabetes, obese	Month 1 – end of pregnancy
Valvar pulmonary stenosis	Week 22	None	33	36	Hispanic	No diabetes, normal weight	Preconception – end of pregnancy
Control	Preconception	None	35	34	Non-Hispanic White	No diabetes, normal weight	Preconception – end of pregnancy
Control	Preconception	Polyarticular juvenile rheumatoid arthritis	39	33	Non-Hispanic White	Gestational diabetes, obese	Preconception – end of pregnancy
Control	Preconception - Week 1	None	36	36	Non-Hispanic White	No diabetes, overweight	Preconception – end of pregnancy
Control	Preconception - Week 2	None	39	29	Non-Hispanic White	No diabetes, overweight	Preconception – end of pregnancy

[a] Birth defect diagnoses organized by cases appearing first followed by controls; within sub-group, cases and controls arranged chronologically by timing of exposure; congenital heart defects in bold

[b] Exposure defined as any reported maternal use of methotrexate

[c] Preconception defined as the period from three months prior to conception through the estimated date of conception. Week refers to gestational week. Month refers to gestational month.

[d] Body mass index (BMI) categories: 18.5–24.9 mg/kg^2 - normal, 25.0–29.9 - overweight, >29.9 - obese