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Exposure to folic acid antagonists during the first trimester of pregnancy and the risk of major malformations

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Previous studies have suggested a tendency of antifolate drugs to be associated with higher rates of neural tube defects.

WHAT THIS STUDY ADDS

- This study makes use of the data on abortuses, which is missed in many other studies. In this case, the abortion data were critical.
- The study documents that clinicians should avoid, as much as possible, the use of folic acid antagonists during the first trimester of pregnancy, when embryogenesis takes place.

AIM

To investigate the safety of folic acid antagonists during the first trimester of pregnancy in a large cohort.

METHODS

Computerized databases for medications dispensed from 1998 to 2007 to women registered in 'Clalit' HMO, Israel southern district, was linked with maternal and infant hospitalization records, and to therapeutics abortions data. The risk for adverse pregnancy outcomes of folic acid antagonists exposure was assessed by adjusting for known confounders.

RESULTS

Eighty-four thousand, eight hundred and twenty-three infants were born and 998 therapeutic abortions took place; 571 fetuses and infants were exposed to one or more folic acid antagonists in the first trimester of pregnancy. Exposure was associated with an overall increased risk of congenital malformations [odds ratio (OR) 2.43, 95% confidence interval (CI) 1.92, 3.08], due mainly to increased risk for neural tube (adjusted OR 6.5, 95% CI 4.34, 9.15) and cardiovascular defects (OR 1.76, CI 1.05, 2.95).

CONCLUSION

First-trimester exposure to folic acid antagonists is associated with increased risk of congenital malformations.

Introduction

Folic acid supplementation or fortification in early pregnancy reduce the risk for neural tube defects and possibly other congenital malformations [1, 2]. This has led several groups to investigate whether folic acid antagonists increase teratogenic risk in humans. Over the last decade, several case–control studies have shown that intrauterine exposure to folic acid antagonists is associated with specific birth defects, including neural tube, cardiovascular and urinary tract malformations [3–5].

We report the results of a large cohort study that investigated the safety of folic acid antagonists during the first trimester of pregnancy, by linking computerized and non-computerized databases.

Methods

We performed a retrospective cohort study involving members of the Southern District of Clalit Health Services (Clalit) in Israel. The population of the Southern District of Israel is slightly greater than half a million inhabitants [6]. Clalit is the largest Health Maintenance Organization in the country, in which 70% of the district women aged 15–49 years are insured. Soroka Medical Centre (SMC) is the district hospital in which practically all deliveries of the region take place [7].

The clinical, medication and demographic data related to Clalit members are aggregated in Clalit data warehouse and can be queried at the level of an individual member. This database contains information about dispensing date, the Anatomical Therapeutic Classification code of the drug (including the commercial and generic names of the drugs dispensed), and dose schedule of drugs dispensed.

Two computerized SMC databases that draw information directly from original sources were used. All patients' records at SMC originate from a single database, which includes demographic information and hospitalization dates generated at the time of the woman's admission to the hospital and of the infant's birth. The Obstetrics and Gynaecology Department database includes information on maternal health status during pregnancy and delivery, maternal age, gestational age at delivery (in days since the last menstrual period), perinatal mortality, parity, ethnic group, self-reported smoking status during pregnancy, and infant birth weight and Apgar score at 1 and 5 min. The diagnoses are reviewed routinely by a trained medical secretary before entry into the database.

The other electronic SMC database used in the present study was the Demog-ICD9 database, which includes demographic and medical diagnoses during hospitalization, the latter drawn directly from the medical records. Additional infant's diagnoses upon discharge are coded and included into their Demog-ICD9 record. All diagnoses are classified according to the International Classification of Diseases, Ninth revision.

Study population

Women age 15–49 years, registered to Clalit, living in the Southern District of Israel who gave birth at SMC, were included. The study period was January 1998 to March 2007, during which 117 960 deliveries took place. Approximately one-half of the infants in the district are born to Jewish and one-half to Bedouin parents.

The three databases (one from Clalit and two from SMC) described above were encoded and linked by personal identification number to create a registry of medications dispensed during pregnancy and pregnancy outcomes.

Study design

In this retrospective cohort study the exposed group included women to whom folic acid antagonists were dispensed during the first trimester of pregnancy (≤13 weeks' gestation). The first day of the last menstrual period was defined as the first day of gestation. Folic acid antagonists were subdivided to dihydrofolate reductase inhibitors, including trimethoprim, sulfasalazine and methotrexate, which block the conversion of folate to its more active metabolites, and 'other' folic acid antagonists, which produce low serum and tissue concentrations of folate due to various pharmacokinetic mechanisms, and include mainly antiepileptics (carbamazepine, phenytoin, lamotrigine, primidone, valproic acid and phenobarbital), and cholestyramine [8]. Exposure was defined as dispensing of at least one of these medications during the first trimester of pregnancy.

Data on therapeutic abortions were manually collected from the SMC Committee for Termination of Pregnancies registry, encoded and linked to SMC and Clalit databases using the encoded women identifying number.

Prenatal ultrasound is performed routinely to practically all pregnant women in the Negev. Thus, major birth defects are diagnosed prenatally, both in Jewish and in Bedouin women in our setting.

Congenital malformations data were obtained from the SMC databases. We used the definitions of major congenital malformations developed by the Centers for Disease Control and Prevention Metropolitan Atlanta Congenital Defects Program [9, 10]. This program has been conducting surveillance for birth defects since 1967, and its definitions have been validated in several previous studies [11]. Chromosomal diseases were excluded.

The following pregnancy outcomes were investigated in both live neonates and stillborns: major malformations (including therapeutic pregnancy terminations), perinatal mortality, preterm delivery (delivery at a gestational age of <37 weeks), low birth weight (<2500 g), very low birth

Table 1

Characteristics of women exposed and unexposed to folic acid antagonists in the first trimester of pregnancy

Variable	Exposure to folic acid antagonists Yes, *n* = 571	No, *n* = 85 250	*P*-value
Maternal age (mean ± SD)	28.3 ± 6.5	28.0 ± 6.0	0.266
Ethnic group*			
Jews	185 (32.4%)	31,028 (36.4%)	0.053
Bedouins	386 (67.6%)	54,208 (63.6%)	
Maternal smoking	12 (2.1%)	2173 (2.5%)	0.587
Maternal diabetes	45 (7.9%)	5658 (6.6%)	0.269
Peripartum fever†	9 (1.7%)	792 (0.9%)	0.111
Mean parity (mean ± SD)	3.6 ± 2.8	3.7 ± 2.7	0.477

*Data regarding ethnicity were missing in 14 therapeutic pregnancy terminations. †Not included pregnancy terminations.

weight (<1500 g) and Apgar score at 1 and 5 min (categorized as Apgar ≤7, or 8 or greater). Peripartum fever was defined as pyrexia ≥38°C.

The following potential confounders were included in the statistical analysis: maternal age, parity, maternal reported smoking in pregnancy, maternal diabetes mellitus, peripartum fever and ethnicity (i.e. Jewish or Bedouin Moslems).

Folic acid is a nonprescription medication in Israel and is bought not only in Clalit but also in private pharmacies. The dispensing rate of folic acid in the Clalit database was assessed.

The study was approved by the institutional Helsinki Ethics Committee for Human Investigations. No written informed consent was required.

Statistical analysis

The statistical analyses were performed using the SPSS package (SPSS, 14th version; SPSS Inc., Chicago, IL, USA). The exposed group was compared with the unexposed by means of χ^2 test or Fisher's exact test for differences in categorical variables and the *t*-test for differences in continuous variables. Multivariate logistic regression models were constructed to identify independent risk factors associated with adverse pregnancy outcomes.

Results

A total of 117 960 deliveries took place at SMC in the study period, 84 823 (or 72%) of which to women registered at Clalit; 527 (0.62%) of the latter were exposed to at least one folic acid antagonist during the first trimester: 349 were exposed to dihydrofolate reductase inhibitors (346 to trimethoprim/sulfamethoxazole, two to methotrexate and one to sulfasalazine) and 179 to one or more 'other' folic acid antagonists (112 to carbamazepine, 35 to valproic acid, 21 to phenobarbital, 14 to phenytoin, eight to lamotrigine, and one to primidone and cholestyramine).

Prescriptions for dihydrofolate reductase inhibitors were given for 7.4 ± 5.7 days (mean ± SD). In the 'other' folic acid antagonists group, 80.1% of the women had at least one refill of their prescription (one mother was switched to vigabatrim and one mother received cholestyramine).

A total of 1327 women underwent pregnancy termination in the study period, 998 among woman registered in Clalit, 44 of whom had been exposed to folic acid antagonists during the first trimester.

Characteristics of mothers exposed and unexposed to folic acid antagonists are indicated in Table 1. One or more congenital malformations were identified in 4465 (5.3%) fetuses and infants (4.3% in Jewish *vs.* 5.8% in Bedouin). The risk for congenital malformations in fetuses and infants exposed to folic acid antagonists in the first trimester of pregnancy is shown in Table 2. The crude odds ratios (ORs) were similar to the multivariate adjusted ORs; therefore we included only the latter for each group of defects. The proportion of congenital malformations identified in infants exposed to folic acid antagonists in the first trimester was 14.5% compared with 6.2% in the unexposed group [adjusted OR 2.43, 95% confidence interval (CI) 1.92, 3.08]. In ethnic group subgroup analysis, the risk associated with exposure to folic acid antagonists was higher in Jews than in Bedouins (adjusted OR 4.11, 95% CI 1.92, 3.08, $P < 0.001$ *vs.* 1.65, 95% CI 1.17, 2.31, $P = 0.004$, respectively). However, the ORs were significant for both subgroups.'

In further analysis, both dihydrofolate reductase inhibitors and 'other' folic acid antagonists were significantly associated with an increased risk for major birth defects. Folic acid antagonists were associated with a significant increased risk for neural tube (adjusted OR 6.30, 95% CI 4.34, 9.15) and cardiovascular defects (adjusted OR 1.76, 95% CI 1.05, 2.95); dihydrofolate reductase inhibitors were significantly associated with an increased risk for urinary tract defects (adjusted OR 3.05, 95% CI 1.13, 8.23). The adjusted OR for 'other' folic acid antagonists for all major congenital malformations was 2.10 (95% CI 1.36, 3.25). There was only one infant born with oral cleft who had

been exposed to folic acid antagonists during the first trimester compared with none in the unexposed group.

The folic acid dispensing rate during the first trimester of pregnancy was 22.3% (n = 19 132) in the Clalit drug database. Data on folic acid dispensing in private pharmacies were not available. Comparison of the characteristics of women in the cohort by folic acid dispensing showed a higher rate of folic acid dispensing among women exposed (34.7%, n = 198) compared with those unexposed (22.2%, n = 18 934) to folic acid antagonists ($P < 0.001$).

Exposure to folic acid antagonists was not associated with an increased risk for premature delivery or perinatal mortality (Table 3), for Apgar scores ≤7 at 1 and 5 min, or for delivery of low birth weight (<2500 g) or very low birth weight (<1500 g) infants (Table 3).

Discussion

In this large cohort study we found that folic acid antagonists are significantly associated with an increased risk for several groups of congenital malformations, including neural tube, cardiovascular and urinary tract defects. When the two subgroups of folic acid antagonists were assessed separately, it was found that both dihydrofolate reductase inhibitors and 'other' folic acid antagonists were associated with an increased risk of congenital malformations. These results corroborate the findings of earlier case–control studies on folic acid antagonists [3–5].

The present investigation has several major strengths. Linking administrative databases obviates potential recall bias inherent in case–control studies. Importantly, our system is one of very few that also assesses and links malformations among cases of therapeutic abortions. In this study there were 998 pregnancy terminations and 44 of these fetuses had been exposed to folic acid antagonists during the first trimester. Published case–control studies and most cohort studies did not have access to complete data on therapeutic abortions, which may have a major impact on the results.

SMC is a district hospital in which practically all deliveries of the region take place; all infants are examined after birth at the Neonatology Department, under the supervision of board-certified neonatologists. This may explain the higher detection rate of congenital malformations in the current report compared with previous reports. Higher rates of congenital malformations have been documented among Bedouins compared with Jews, which may be attributable to increased rates of consanguinity [12, 13]. The risk of birth defects related to consanguinity in Middle East populations appears to be due primarily to recessive gene defects, both single gene and polygenic [14, 15]; thus, exclusion of chromosomal diseases in our study could not eliminate most birth defects attributed to consanguinity.

A retrospective case controlled study by Hernandez-Diaz *et al.* suggested that folic acid antagonists increase

Table 2
Risk for congenital malformations in fetuses and infants exposed to folic acid antagonists in the first trimester of pregnancy

Variable	Exposure to folic acid antagonists			Exposure to dihydrofolate reductase inhibitors*			Exposure to other folic acid antagonists†		
	Yes (%), n = 571	No (%), n = 85 250	Adjusted OR‡ (95% CI)	Yes (%), n = 385	No (%), n = 85 436	Adjusted OR‡ (95% CI)	Yes (%), n = 187	No (%), n = 85 634	Adjusted OR‡ (95% CI)
Major congenital malformations	83 (14.5)	5258 (6.2)	2.43 (1.92, 3.08)	59 (15.3)	5282 (6.2)	2.57 (1.94, 3.42)	24 (12.8)	5317 (6.2)	2.10 (1.36, 3.25)
Neural tube defects	31 (5.4)	703 (0.8)	6.30 (4.34, 9.15)	29 (7.5)	705 (0.8)	8.52 (5.76, 12.60)	2 (1.1)	732 (0.9)	1.28 (0.32, 5.19)
Cardiovascular defects	15 (2.6)	1237 (1.5)	1.76 (1.05, 2.95)	13 (3.4)	1239 (1.5)	2.25 (1.29, 3.92)	2 (1.1)	1251 (1.5)	0.73 (0.18, 2.93)
Urinary tract defects§	4 (0.8)	299 (0.4)	2.08 (0.77, 5.60)	4 (1.1)	299 (0.4)	3.05 (1.13, 8.23)	0 (0)	303 (0.4)	

*Medications that were dispensed in this group: trimethoprim, sulfasalazine and methotrexate. †Medications that were dispensed in this group: carbamazepine, valproic acid, phenobarbital, phenytoin, lamotrigine, primidone, cholestyramine. ‡The models were controlled for maternal age, ethnicity, maternal diabetes, maternal smoking, and parity. §Pregnancy terminations were not included in the analysis since data about this defect were not available in the noncomputerized pregnancy terminations files.
Note: One infant was exposed both to one dihydrofolate reductase inhibitor and to one other folic acid antagonist.

Table 3

The risk for other adverse pregnancy outcomes of infants exposed to folic acid antagonists in the first trimester of pregnancy

Variable	Exposure to folic acid antagonists Yes (%)	No (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)
Preterm delivery (<37 weeks)	22 (4.2)	8237 (7.4)	0.55 (0.36, 0.84)	0.63 (0.41, 1.01)
Perinatal mortality	6 (1.1)	1907 (2.3)	0.50 (0.22, 1.11)	1.07 (0.40, 2.86)
Low birth weight (<2500 g)	62 (11.8)	8816 (10.5)	1.14 (0.88, 1.49)	1.14 (0.88, 1.49)
Very low birth weight (<1500 g)	3 (0.6)	1513 (1.8)	0.31 (0.10, 0.98)	0.31 (0.10, 1.01)
Apgar ≤7 at 1 min	35 (6.8)	4827 (6.0)	1.14 (0.81, 1.61)	1.12 (0.79, 1.58)
Apgar ≤7 at 5 min	7 (1.4)	846 (1.0)	1.30 (0.61, 2.74)	1.27 (0.60, 2.69)

*The models were controlled for maternal age, ethnicity, maternal diabetes, maternal smoking, peripartum fever and parity.

the risk of cardiovascular and urinary tract defects and oral clefts [3]. In that study 68 fetuses were exposed to folic acid antagonists during the first trimester in the control group, 63 in the cardiovascular defect group, 36 in the oral clefts group and 16 in the urinary tract group. Another case controlled study by the same investigators, with 94 pregnancies exposed to folic acid antagonists during the first trimester (27 in the case group and 67 in the control group), found that folic acid antagonists may increase the risk for neural tube defect [4]. Meijer *et al.* found that only the antiepileptics group was associated with an increased risk of folic acid-sensitive defects [5]. However, their study included only 27 infants or fetuses exposed to folic acid antagonists during the first trimester (16 in the control and 11 in the case group). When they looked at all exposures to folic acid antagonists (dihydrofolate reductase inhibitors and antiepileptics combined) they detected no significant association between folic acid antagonists and birth defects. Our study corroborates the finding of Czeizel *et al.* that trimethoprim–sulfamethoxazole is associated with an increased risk for neural tube and urinary tract defects [16]. Similarly, our study confirms the Hernandez-Diaz *et al.* findings of neural tube and cardiovascular defects [3, 4].

In this large population-based cohort we found no significant association between exposure to folic acid antagonists in the first trimester and preterm delivery, perinatal mortality, low birth weight or low Apgar scores.

The databases used in this study contained information regarding folic acid antagonists dispensed to pregnant women, but we have no direct knowledge of the degree of adherence with folic acid antagonists therapy. However, available evidence suggests that the extent of adherence to medications in our population is good. In a recent study [17], we found that rates of medication adherence were >90% in two subgroups of our cohort (women with deep vein thrombosis treated with enoxaparin and women with familial Mediterranean fever treated with colchicine). It is reasonable that these high adherence rates can be generalizable to women treated with folic acid antagonists. A recent study using the same Clalit database found that overall adherence to iron preparations dispensed for Israeli infants was high, as confirmed by laboratory tests [18]. Similar to our data, previous studies have shown that computerized pharmacy records may be an accurate source of medication data and have high rates of concordance with self reports of medications used by patients in general and by pregnant women in particular [19, 20]. The high refill rate of prescriptions for 'other' folic acid antagonists in this cohort supports the concept that the degree of adherence was good. Some mothers may have elected not to refill their prescriptions upon finding of being pregnant, out of fear of risk to the fetus.

Another potential limitation of the present study is the lack of data on spontaneous abortions. However, if neural tube defects caused by folic acid antagonists were more lethal, our subjects would represent only the surviving cohort that would lead to underestimation of the true risk of birth defects.

Although we included known confounders in the analysis, there might be more confounders that were not considered. Trimethoprim in combination with sulphonamides was primarily used for the treatment of urinary tract infections. Another population-based case–control study has also found that trimethoprim–sulphonamides may increase the risk for congenital malformations [16]. Investigations have shown that addition of folic acid may prevent neural tube defects and urinary tract defects [21, 22]. Other antimicrobial drugs used for urinary tract infection such as nitrofurantoin were not associated with either urinary tract or other defects [23, 24].

While it is expected for women already exposed to chronic medications to be at greater risk, those women and their caregivers are likely to be more conscious of the risk of those medications, allowing them to lower the risk for adverse effects by taking folic acid supplement [21, 22]. Women with epilepsy usually consult their caregiver before pregnancy, thus allowing a change in the antiepileptic treatment, such as from polytherapy to monotherapy, if possible according to guidelines [25]. Women who were exposed to a short course of trimethoprim/sulfamethoxazole either were not aware of their pregnancy at the time of treatment (>50% of pregnancies are not planed), or they and their caregivers were not aware of the fetal risk such a treatment can cause.

Our study enrolled women from the year 1998, well after it was established that addition of folic acid reduces the risk of neural tube and other birth defects. As folic acid is a nonprescription medication bought not only at Clalit but also at private pharmacies, information on folic acid dispensed in this study was not complete. With this reservation, we observed that the rate of folic acid dispensed to women exposed was larger compared with those unexposed to folic acid antagonists. As folic acid supplementation reduces the risk of birth defects associated with exposure to folic acid antagonists [21, 22] and many of the women with no recorded folic acid supplementation actually may have received folic acid, the true difference between the rates of birth defects between the groups exposed and unexposed to folic acid antagonists might be even larger. Adherence to folic acid intake in our population has been studied by Greenshpoon [26]. Interviews with 260 pregnant women in Maternal-Child Clinics in the Negev revealed that only 152 (or 58.5%) took folic acid supplements. In comparison, by ethnicity, 104 of 134 Jewish (or 77.6%) and 48 of 126 Bedouin women took folic acid supplements ($P < 0.001$). This was supported by folic acid blood concentrations of 14.8 ng ml^{-1} ($\pm$SD 6.6) and of 9.0 ng ml^{-1} ($\pm$4.6) in women who reported taking and in those who reported not taking supplements, respectively ($P < 0.001$) [26]. These findings corroborate our data that Bedouins may have had lower risk for congenital malformations associated with exposure to folic acid antagonists, possibly due to lower adherence to treatment, leading to lower exposure.

In conclusion, using a large cohort, we have corroborated an increased risk of congenital malformations associated with exposure to folic acid antagonists during the first trimester of pregnancy. Clinicians should try to avoid the use of these drugs in women contemplating pregnancy.

Competing interests

None to declare.

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