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Fetal Safety of Macrolides

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Macrolide antibiotics are largely used in pregnancy for different bacterial infections. Their fetal safety has been studied by several groups, yielding opposing results. In particular, there have been studies claiming an association between macrolides and cardiovascular malformations. Exposure in early infancy has been associated with pyloric stenosis and intussusception. This has led to an avoidance in prescribing macrolides to pregnant women in several Scandinavian countries. The Objectives of the present study was to investigate the fetal safety of this class of drug by linking a large administrative database of drug dispensing and pregnancy outcome in Southern Israel. A computerized database of medications dispensed from 1999 to 2009 to all women registered in the Clalit health maintenance organization in southern Israel was linked with two computerized databases containing maternal and infant hospitalization records. Also, medical pregnancy termination data were analyzed. The following confounders were controlled for: maternal age, ethnicity, maternal pregestational diabetes, parity, and the year the mother gave birth or went through medical pregnancy termination. First- and third-trimester exposures to macrolide antibiotics as a group and to individual drugs were analyzed. During the study period there were 105,492 pregnancies among Clalit women that met the inclusion criteria. Of these, 104,380 ended in live births or dead fetuses and 1,112 in abortion due to medical reasons. In the first trimester of pregnancy, 1,033 women were exposed to macrolides. There was no association between macrolides and either major malformations [odds ratio (OR), 1.08; 95% confidence interval (CI), 0.84 to 1.38)] or specific malformations, after accounting for maternal age, parity, ethnicity, prepregnancy diabetes, and year of exposure. During the third trimester of pregnancy, 959 women were exposed to macrolides. There was no association between such exposure and perinatal mortality, low birth weight, low Apgar score, or preterm delivery. Similarly, no associations were demonstrated with pyloric stenosis or intussusception. Use of macrolides in the first trimester of pregnancy is not associated with an increased risk of major malformations. Exposure in the third trimester is not likely to increase neonatal risks for pyloric stenosis or intussusception in a clinically meaningful manner.

Macrolide antibiotics are widely used for a variety of bacterial infections in pregnancy, including chlamydia, gonorrhea, Gram-positive upper respiratory infections, and premature rupture of membranes, and in cases of beta-lactam allergies (1–8). The macrolides cross the placenta, and their clearance rate in pregnancy is faster in late pregnancy (9, 10). Several studies conducted over the last 50 years failed to show an association between the use of erythromycin in the first trimester of pregnancy and the risk of major malformations for the most part (11–13). In contrast, a widely publicized Swedish study reported increased risk of cardiovascular malformations, leading several Scandinavian countries to avoid prescribing the drug to pregnant women (14). Data concerning the fetal safety of clarithromycin, azithromycin, and roxithromycin have been limited but failed to show increased fetal risks (15–20).

Recently, exposure to macrolides in very early infancy has been associated with increased risk of pyloric stenosis (21, 22) and intussusceptions (23).

Most studies to date have had small samples sizes and failed to include data on induced abortion, the exclusion of which may lead to bias toward the null (24).

The objectives of the present study were to investigate the fetal safety of this class of drugs in large administrative databases of drug dispensing and pregnancy outcome in southern Israel.

MATERIALS AND METHODS

A population-based retrospective cohort study was conducted, including all women 15 to 49 years of age who were registered in Clalit Health Services and had a delivery or a pregnancy termination due to medical reasons at Soroka Medical Center (SMC) between 1 January 1999 and 30 December 2009. Clalit Health Services is the largest health maintenance organization in the country, in which 70% of the women in the southern district of Israel 15 to 49 years of age are insured. SMC is the regional hospital, where 98% of the deliveries take place (25, 26).

Almost 70% of the population in southern Israel are Jewish and 25.4% are Bedouin Muslim. The Bedouin population composes only 3.5% of the total population of the state of Israel; however, they account approximately half of the births in southern Israel due to a high birth rate (total fertility rate of 7.5 for the Bedouin population versus 2.7 for the Jewish population) (25).

Compared to central Israel, which is the most populated and well-developed area of the state, most settlements in the southern district are ranked at low to average socioeconomic levels (27). The Israeli Central

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TABLE 1 Distribution of macrolides dispensed during the first and third trimesters of pregnancy

	No. of prescriptions dispensed in:	
	First trimester	Third trimester
Macrolide	1,033	959
Erythromycin	325	446
Roxithromycin	535	476
Clarithromycin	141	9
Azithromycin	46	34

Bureau of Statistics (CBS) uses a socioeconomic scale of clusters ranked from 1 to 10, in which clusters 1 to 3, clusters 4 to 7, and cluster 8 to 10 represent low, average, and high socioeconomic ranks, respectively. Data published by the CBS show, for example, that 86% of the Jewish settlements in the southern district are ranked in clusters 4 and 5, while only 13% of the Jewish settlements in central Israel are ranked within those clusters. Similarly, 42% of the Jewish settlements in central Israel are ranked in clusters 6 and 7, whereas only 2% of the Jewish settlements in the south are ranked at that level. Furthermore, 42% of the Arabic settlements in central Israel are ranked in the low socioeconomic clusters (clusters 1 to 3), while 100% of the Bedouin settlements in the south are ranked in the low socioeconomic clusters (27).

We linked 3 computerized databases which draw information directly from original sources—two from Soroka Medical Center (SMC) and one from Clalit Health Services. The SMC's Department of Obstetrics and Gynecology deliveries database includes maternal demographic information, including mother's age and ethnic group (Jewish or Bedouin Muslim), parity, health status during pregnancy and delivery, self-reported smoking status during pregnancy, gestational age at delivery, and delivery results (perinatal death, infant's 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.

Information regarding major malformations diagnosed in newborns or infants until the age of 12 months was collected from the Demog-ICD9 database, which includes demographic and medical information for patients admitted to SMC. Information on drugs dispensed to mothers during the first trimester of pregnancy was collected from the Clalit Health Services medication database, which includes information on the date the drug was dispensed, the anatomical therapeutic chemical (ATC) classification codes of the drugs (including the commercial and generic names), the dose schedule, and the dose dispensed, in terms of the defined daily dose (DDD) (28) (i.e., the assumed average maintenance dose per day). A fourth database, which included data on medical pregnancy terminations, was assembled manually from the registry of the Committee for Termination of Pregnancies at Soroka Medical Center.

The four databases were encoded and linked by personal identification numbers (numbers that are given at birth by the Interior Ministry and used throughout life) to create a registry of medications dispensed during the first trimester of pregnancy and of pregnancy outcomes. We used the unique identification number of the hospitalization given at SMC to the mother and to the newborn to link the mother and the infant's identification number.

The study was approved by the local institutional ethics committee in accordance with the principles of the Declaration of Helsinki. In accordance with Ministry of Health regulations, the institutional ethics committee did not require written informed consent because the data were obtained anonymously from medical files, with no participation of patients.

Study design. The exposure groups were defined as exposure to any macrolide (erythromycin, azithromycin, clarithromycin, or roxithromycin) during the first trimester of pregnancy, or during the third trimester of pregnancy. The unexposed groups were infants or fetuses that were not exposed to any macrolide during the first or third trimester, respectively. The analysis also investigated specific macrolide drugs. An infant or fetus was defined as "exposed" if a macrolide was dispensed to the mother during the first 13 weeks of pregnancy (first trimester group) or during the last 12 weeks of pregnancy (third trimester group). The first day of the last menstrual period was defined as the first day of gestation.

First-trimester exposure to macrolide was also characterized by the total number of defined daily doses (DDD) dispensed. The DDD for macrolides is as follows (28): erythromycin, 1 g; erythromycin ethyl succinate, 2 g; azithromycin, 0.5 g; clarithromycin, 1 g; roxithromycin, 0.3 g. The total defined daily doses dispensed during the first trimester were stratified into three categories: 1 to 5, 6 to 10, and 11 and more.

We investigated the risk of major malformations after exposure to macrolides during the first trimester of pregnancy for live births and stillbirths and for pregnancy terminations due to medical reasons. We used the definitions of major and minor congenital malformations developed by the Metropolitan Atlanta Congenital Defects Program of the Centers for Disease Control and Prevention (CDC) (29–31). Chromosomal diseases were excluded. In subclass analyses of major malformations, the following specific defects were examined (ICD9 codes are in parentheses): anencephaly (740); spina bifida (741); other anomaly of the nervous system (742); anomalies of the eye (743; anomalies of the ear, face, and neck (744); bulbus cordis anomalies and anomalies of cardiac septal closure (745); other anomalies of the heart (746); other anomalies of the circulatory system (747); anomalies of the respiratory system (748); cleft palate and lip (749); other anomalies of the upper alimentary tract (750); other anomalies of the digestive system (751); genital anomalies (752); anomalies of the urinary system (753); musculoskeletal deformities (754); other anomalies of the limbs (755); other musculoskeletal anomalies (756); and anomalies of the integument (757).

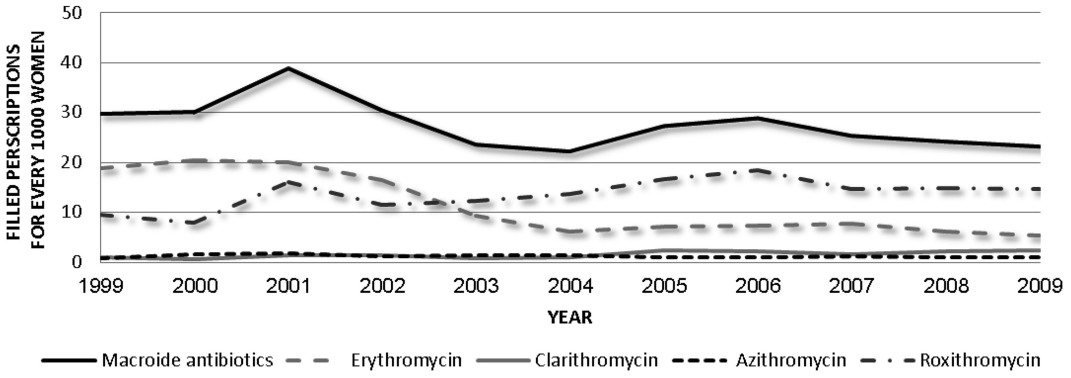

FIG 1 Annual trend of macrolides dispensed to pregnant women in the study.

TABLE 2 Comparison of the characteristics of women exposed and unexposed to macrolides during the first trimester of pregnancy

Characteristic	No. (%) of women		*P* value
	With exposure to macrolides (n = 1,033)	Without exposure to macrolides (n = 104,459)	
Ethnicity			
Jewish	339 (32.8)	37,461 (35.9)	0.044
Bedouin	693 (67.2)	66,988 (64.1)	
Pregestational diabetes	23 (2.2)	1,054 (1.0)	<0.001
Maternal smoking during pregnancy	26 (2.5)	2,074 (2.0)	0.224
Maternal age (yr) (mean ± SD)	29.77 ± 5.92	28.68 ± 5.85	<0.001
Parity (mean ± SD)	2.21 ± 0.72	2.08 ± 0.72	<0.001

In a separate analysis we investigated the risk of pyloric stenosis (ICD9 code 7505) or intussusception (ICD9 code 5600) in infants exposed to macrolides during the last 12 weeks of pregnancy.

Statistical analysis. We used the SPSS program, version 17 (IBM SPSS; Somers, NY), for statistical analysis. Characteristics of mothers from the exposed and unexposed groups were compared by the chi square or Fisher exact test for categorical variables and the Student *t* test for continuous variables. We used a multivariate logistic-regression model to determine whether exposure to macrolides was independently associated with an increased risk of major congenital malformations adjusting for maternal age, parity, ethnic group (i.e., Jewish versus Bedouin Muslim), pregestational diabetes mellitus, and year of birth or medical pregnancy termination. A categorical multivariate logistic-regression model was constructed to determine whether greater exposure in terms of defined daily dose (DDD) was associated with an increased risk for major congenital malformations. Odd ratios and 95% confidence intervals were computed. Similar methods were used to estimate the risks of pyloric stenosis or intussusceptions after third-trimester exposure to macrolides.

RESULTS

There were 105,492 births and 1,112 pregnancy terminations at SMC between 1999 and 2009. Overall, 1,033 fetuses were exposed to macrolides during the first trimester of pregnancy, and 959 during the third trimester. Table 1 presents the distribution of the different macrolide antibiotics in these two groups. The use of macrolides by women during pregnancy remained stable during the study period (Fig. 1).

TABLE 3 Multiple logistic regression analysis for the risk of major malformations among infants born to women exposed during the first trimester to macrolides vs the unexposed

Variable	Major malformation OR (95% CI)[a]	*P* value
Macrolide exposure	1.074 (0.839–1.376)	0.57
Maternal age	1.019 (1.013–1.025)	<0.001
Pregestational diabetes	1.678 (1.370–2.055)	<0.001
Parity	0.959 (0.946–0.972)	<0.001
Ethnicity (Bedouin/Jewish)	1.453 (1.362–1.550)	<0.001
Year of birth/pregnancy termination	1.025 (1.017–1.033)	<0.001

[a] OR, odds ratio; CI, confidence interval.

TABLE 4 Multiple logistic regression analysis for the risk of cardiovascular malformations among women exposed to macrolides during the first trimester of pregnancy

Variable	Cardiovascular malformation OR (95% CI)	*P* value
Macrolide exposure	0.953 (0.649–1.400)	0.81
Maternal age	1.019 (1.010–1.028)	<0.001
Pregestational diabetes	1.945 (1.487–2.544)	<0.001
Parity	0.991 (0.971–1.011)	0.39
Ethnicity (Bedouin/Jewish)	1.246 (1.133–1.372)	<0.001

[a] OR, odds ratio; CI, confidence interval.

Characteristics of mothers exposed and unexposed to macrolides are presented in Table 2.

The adjusted risk for major congenital malformations following exposure to macrolides during the first trimester of pregnancy was 1.074 (0.839 to 1.376) (Table 3). Macrolide exposure was not associated with increased risk for cardiovascular malformations (Table 4) or central nervous system, musculoskeletal, gastrointestinal, or urogenital malformations. Similar results were obtained for each macrolide separately In addition, there was no significant dose response in the association between macrolides and major malformations in univariate analyses or after adjustment using a categorical multiple logistic regression (Table 5).

Exposure to macrolides in the third trimester was not associated with increased risk of either pyloric stenosis or intussusception (Table 6). However, due to the very small numbers of observations in the exposed group, no attempt was made to perform multivariate logistic regression.

DISCUSSION

Macrolides are widely used in pregnancy, and therefore establishing their fetal safety is critical in ensuring evidence-based safe use during fetal development. In the study period, the dispensing of macrolides to pregnant women stayed stable between 20 and 40 prescriptions for 1,000 women in the study region. Starting in 2003, we saw an increase in use of the newer macrolides, led by roxithromycin (Fig. 1).

Our large population-based study failed to show an association between first-trimester macrolide exposure and either overall ma-

TABLE 5 Categorical multiple logistic regression analysis for the effect of macrolide dose on the risk for major malformations

Variable	Major malformation OR (95% CI)[a]	*P* value
DDD[b]		
Unexposed	Reference	
1–5	0.928 (0.287–2.999)	0.9
6–10	1.095 (0.282–4.246)	0.89
>10	1.322 (0.365–4.790)	0.78
Maternal age (yr)	1.019 (1.013–1.025)	<0.001
Pregestational diabetes	1.712 (1.398–2.097)	<0.001
Parity	0.959 (0.945–0.972)	<0.001
Ethnicity (Bedouin/Jewish)	1.451 (1.360–1.549)	<0.001
Year of birth or pregnancy termination	1.025 (1.017–1.033)	<0.001

[a] OR, odds ratio; CI, confidence interval.
[b] DDD, defined daily dose. For a description, see the text.

TABLE 6 Crude odds ratio for pyloric stenosis and intussusception after third trimester exposure to macrolides

Diagnosis	OR (95% CI)[a]	No. (%) of subjects		*P* value
		With exposure to macrolides ($n = 952$)	Without exposure to macrolides ($n = 101,879$)	
Pyloric stenosis	—[b]	0	50 (0.0)	—[b]
Intussusception	1.049 (0.146–7.528)	1 (0.1)	102 (0.1)	0.61

[a] OR, odds ratio; CI, confidence interval.
[b] Due to zero cases in the exposed, OR could not be calculated.

jor malformations or specific malformations. In particular, our study could not confirm the Swedish study claiming an increase in cardiovascular malformations in connection with macrolides (14). Similarly, we did not detect risks for any other adverse fetal outcome. Moreover, by calculating the dose of exposure, we could rule out a dose response relationship between macrolides and any of these risks.

Our study is unique in using one of very few administrative databases that also capture malformations among the subgroup undergoing pregnancy termination. Our recent study showed that not including data on induced abortion creates bias toward the null, which may be critical when the results do not suggest an increased risk in the exposed group (24).

Our attempts to verify fetal risks for pyloric stenosis were limited by an absence of pyloric stenosis cases among the 952 exposed infants/fetuses, compared to 50 cases out of the 101,879 unexposed infants/fetuses. There was one case of intussusception among the exposed infants/fetuses, compared to 102 cases among the unexposed infants/fetuses, suggesting no increased risk. In both cases, our observed rates of these adverse outcomes were lower in the exposed than among the unexposed infants/fetuses, suggesting that a clinically meaningful increased risk is highly unlikely.

Our study has several limitations that need to be acknowledged:

Similar to all administrative database studies, our study assumed that a medication being dispensed is also a drug being taken. In previous studies of our databases, it has been shown that in cases of deep vein thrombosis and familial Mediterranean fever, there was close agreement between dispensing records and women's reports on adherence in pregnancy (32). It is conceivable that infection in pregnancy would be similarly associated with high adherence rates. In addition, our study population represents well the unique nature of southern Israel, but it has a limited ability to generalize the socioeconomic distribution of the Israeli population.

In conclusion, our study strengthens the rational for using macrolides when needed in pregnancy, by providing data on fetal safety based on a large cohort. There are high levels of anxiety among prescribers and pregnant women, often leading to suboptimal drug therapy even in life-threatening maternal conditions (33). By empowering the use of macrolides in pregnancy, it is hoped that the present study contributes to rational drug use in pregnancy.

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