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The Outcomes of Pregnancy in Women Exposed to the New Macrolides in the First Trimester

A Prospective, Multicentre, Observational Study

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Abstract

Background: Macrolides are a group of commonly prescribed antibiotics. There is some doubt surrounding the use of the newer macrolides in pregnancy.

Objective: The present study aimed to compare outcomes of pregnancies exposed to the new macrolides clarithromycin, azithromycin and roxithromycin with non-teratogenic preparations.

Methods: In this prospective, multinational, multicentre, controlled, observational study, information was obtained either from pregnant women or their healthcare professionals who contacted their local teratogen information services in Italy, Israel, the Czech Republic, the Netherlands and Germany seeking information after exposure to macrolides. The comparison group included women or their healthcare professional who contacted these centres with questions regarding known non-teratogenic preparations.

Information on obstetric and other background parameters was collected at enrollment; after delivery, subjects or their healthcare professionals were contacted to ascertain pregnancy outcome parameters and other exposures through the remainder of the pregnancy.

Results: A total of 608 women exposed to macrolides during pregnancy were enrolled; 511 of the exposures occurred during the first trimester. The comparison group comprised 773 women exposed to non-teratogenic preparations during the first trimester of pregnancy. No significant difference in the rate of major congenital malformations was found between the study group and the comparison group (3.4% vs 2.4%; p = 0.36; odds ratio (OR) 1.42; 95% CI 0.70, 2.88) or in the rate of cardiovascular malformations (1.6% vs 0.9%; p = 0.265; OR 1.91; 95% CI 0.63, 5.62).

No significant differences were found between subgroups of macrolides in the rates of major congenital malformations or cardiac malformations, although for azithromycin this was of borderline significance.

Conclusions: This study, in agreement with earlier smaller studies, suggests that the new macrolides do not pose a significantly increased risk of major congenital malformations or cardiac malformations.

Background

Macrolides are a group of commonly prescribed antibiotics. Numerous indications exist, including Gram-positive lower and upper respiratory infections, soft tissue infections, and *Helicobacter pylori* peptic ulcer disease. Furthermore, they are the main treatment alternative in penicillin-allergic patients. Urogenital infections caused by chlamydia or mycoplasma are common in women of reproductive age and are frequently treated with macrolides. Erythromycin, the first macrolide introduced, has been extensively studied in the past,[1-3] and the drug is considered by most authors as appropriate for use during pregnancy.[2,4] However, Källén et al.[2,3] reported an association between erythromycin use during pregnancy and cardiac malformations in offspring. The newer macrolide antibiotics clarithromycin, azithromycin and roxithromycin are better tolerated than erythromycin, but there are limited data available regarding the teratogenicity of these antibiotics.[1,2,4-15] The issue of whether these antibiotics have a teratogenic effect when taken in the first trimester of pregnancy remains unclear. Since many pregnancies are unplanned, it is not an uncommon occurrence for women to be prescribed macrolides before they are aware of their pregnancy.[16,17]

Three Israeli centres recently published a small multicentre study encompassing 118 women exposed to one of three macrolide antibiotic preparations in the first trimester of pregnancy.[12] This study group was compared with two control groups for pregnancy outcomes: women reporting exposure to other antibiotics, and women reporting exposure to non-teratogenic medications. Although not statistically significant, the use of roxithromycin was associated with higher rates of major and cardiac malformations when comparing the various macrolides, but the number of participants limited the statistical power of this outcome. A similar trend was reported by Paulus et al.,[15] but not in a study by Chun et al.[13]

As mentioned, in the previous study conducted in Israel, small numbers of study participants precluded informative comparison of the various macrolides. In the present, larger scale study, we aimed to compare the outcomes of pregnancies exposed to clarithromycin, azithromycin and roxithromycin with a control group of women, for major congenital and cardiovascular malformations, and to add further information about the

safety of administering these medications during pregnancy.

Materials and Methods

We conducted a prospective, multinational, multicentre, observational study, utilizing data collected retrospectively. The study group comprised of pregnant women who contacted the local teratogen information service (TIS), either directly or through their healthcare providers, seeking information after exposure to macrolide preparations, including clarithromycin, azithromycin, and roxithromycin, in the first trimester of pregnancy. Participating TIS centres were located in Israel (two centres), Italy (three centres) and one centre each in the Czech Republic, the Netherlands and Germany. There was no overlap in participants or data acquisition between the previously published study[12] and the current study, either in the exposure group or in the control group. TIS centres are units dedicated to providing evidence-based clinical information to patients and healthcare professionals about exposures during pregnancy and lactation.

The comparison group comprised of pregnant women, or their healthcare professionals, who contacted the TIS centres with queries regarding exposures to non-teratogenic compounds during the first trimester (included compounds were paracetamol (acetaminophen), penicillins, cephalosporins, hair dye or levothyroxin), provided by four of the participating TIS centres (one each in Israel, Germany, the Netherlands and Italy).

At the first contact with the TIS, participants were asked to enroll in the study and were interviewed (either by phone or by written questionnaire) for demographic background parameters, general medical and obstetric histories, details of the present pregnancy and details of exposure to macrolides, as well as any other exposures or risk factors (such as smoking, alcohol use, etc.). After delivery, the women or their healthcare professionals were contacted within 2 months to ascertain pregnancy outcome parameters and details of macrolide or other exposures throughout the remainder of the pregnancy. A follow-up call was made 1 year after delivery to assess for any previously unidentified malformations. Enrollment took place between 2005 and 2008, with the last follow-up calls conducted in 2009.

The definition used for major malformations was based on the list of malformations published by the Centers for Disease Control and Prevention Metropolitan Atlanta Congenital Defects Program coding manual.[18]

Statistical Analysis

The main outcome was the prevalence of congenital malformations; secondary outcomes were rate of abortions, rate of preterm deliveries and birthweight. Subgroup analyses were performed for the rate of cardiovascular malformations.

Student's *t*-test was applied to normally distributed, continuous variables; the Mann-Whitney U-test was applied to non-normally distributed continuous variables, and categorical variables were analysed with the Chi-squared and Fisher's exact tests where appropriate. Results are expressed as mean and standard deviation. Logistic regression modelling was employed to examine possible correlations between the rate of major structural cardiovascular anomalies and various parameters, including macrolide exposure, smoking, alcohol consumption, previous abortions, previous child with structural anomaly, and maternal age.

Statistical analysis was performed using SPSS version 14 for Windows (SPSS Corporation, Chicago, IL, USA).

Results

A total of 608 women contacted the participating TIS centres during the study period, having reported exposure to macrolides in the course of their pregnancy. Of these, 511 exposures occurred in the first trimester (255 women were exposed to clarithromycin, 156 to azithromycin and 100 to roxithromycin; of all exposures, 215 individuals were from Italy, 179 from Germany, 80 from the Netherlands, 32 from Israel and 5 were from the Czech Republic) and 392 of the women were exposed in the critical period (4th-13th week of pregnancy), 192 (49%) were exposed to clari-

thromycin, 119 (30%) to azithromycin and 81 (21%) to roxithromycin. Indications for use were upper respiratory tract infections, *Helicobacter pylori*, urogenital infections and pneumonia. Mean daily dose of azithromycin was 500 mg (range 100–1000 mg), roxithromycin 300 mg (100–900 mg) and clarithromycin 500 mg (100–1500 mg). Duration of treatment ranged from 3 to 7 days.

As a comparison group, 773 women who were exposed to non-teratogenic preparations during the first trimester of their pregnancy were enrolled.

The mean gestational age at first call to the TIS was 6.7 ± 4.2 weeks (median 6 weeks) for the study group and 9.4 ± 5.6 weeks (median 8 weeks) for the comparison group.

Maternal Characteristics

Maternal characteristics of the study and comparison groups are summarized in table I. Maternal age, number of previous pregnancies (gravidity) and previous number of births (parity) were significantly lower in the study group than in the control group. Smoking rates and alcohol consumption were significantly higher in the macrolide-exposed group than in the comparison group ($p < 0.001$).

No significant differences were found in the rates of previous elective terminations of pregnancy [ETOP] ($p = 0.8$), previous spontaneous abortions ($p = 0.17$) and having a previous child with major malformations ($p = 0.18$), between the groups.

Significant differences were found among the various subgroups of macrolides in gravidity ($p < 0.001$) and parity ($p < 0.001$). No differences were found in maternal age ($p = 0.096$), smoking habits ($p = 0.382$), the rate of previous ETOP ($p = 0.43$), previous spontaneous abortions ($p = 0.333$) or previously giving birth to a child with major malformations ($p = 0.105$).

Pregnancy Outcomes

Table II summarizes pregnancy outcomes in the study and comparison groups. The rate of live births was significantly lower in the macrolide-exposed group (86.3%) than in the comparison group (91.2%) owing to the higher rate of ETOP in the study group (6.1% vs 2.1%). Taking out the ETOPs, there was no significant difference between the two groups in the proportion of live births (91.8% in the study group and 93.1% in the comparison group; $p = 0.48$). There were no significant differences between the groups in the rates of spontaneous abortions ($p = 0.579$), mode of delivery, premature births ($p = 1$), gestational age at birth ($p = 0.266$), birthweight ($p = 0.963$), and 1- and 5-minute Apgar scores ($p = 0.385$ and 0.405, respectively).

When subgroups of different macrolides were compared, no statistically significant differences were found among the three macrolides in the rate of live births, spontaneous abortions and ETOP, rate of multiple gestations, premature birth, mode of delivery, gestational age at birth, birthweight, or 1- and 5-minute Apgar scores.

Table I. Maternal characteristics of the first-trimester macrolide exposure and comparison group

	Study group (N = 511)	Comparison group (N = 773)	p-Value
Maternal age [y]	30.4 ± 5.7 (16–44)[a]	31.9 ± 5.1 (17–48)[a]	<0.001
Prior gravidity	0.82 ± 1.2 (0–5)[a]	1.5 ± 1.2 (0–10)[a]	0.018
Prior parity	0.9 ± 0.9 (0–9)[a]	1.1 ± 1.2 (0–10)[a]	<0.001
Smoking	47/359 (13.1)[b]	48/728 (6.4)[b]	<0.001
Any alcohol consumption	26/363 (7.1)[b]	19/749 (2.5)[b]	<0.001
Previous ETOP	22/359 (6.1)[b]	52/763 (6.8)[b]	0.8
Previous spontaneous abortions	44/353 (12.5)[b]	123/763 (16.1)[b]	0.17
Previous malformations	3/505 (0.6)[b]	12/764 (1.5)[b]	0.18

a Mean ± SD (range).

b n (%).

ETOP = elective termination of pregnancy.

Table II. Pregnancy outcomes of first-trimester macrolide exposure and comparison group

	Study group (N = 511)	Comparison group (N = 773)	p-Value	OR (95% CI)
Live birth	441 (86.3)[a]	705 (91.2)[a]	0.006	0.60 (0.15, 2.35)
Spontaneous abortion	39 (8.1)[a]	52 (6.8)[a]	0.611	1.15 (0.57, 1.34)
ETOP	31 (6.1)[a]	16 (2.1)[a]	<0.001	3.06 (0.17, 6.03)
Multifetal gestation	2/440 (0.5)[a]	17/705 (2.4)[a]	0.015	5.39 (1.24, 23.46)
Prematurity	37/435 (8.5)[a]	61/705 (8.7)[a]	1.000	1.01 (0.64, 1.51)
Gestational age [wk]	39.07 ± 2.17 (22–43)[b]	39.21 ± 2.16 (25–43)[b]	0.266	
Birth weight [g]	3287 ± 536 (1000–4840)[b]	3289 ± 588 (490–5120)[b]	0.963	
Apgar 1	8.74 ± 1.09 (4–10)[b]	8.8 ± 1.19 (1–10)[b]	0.385	
Apgar 5	9.63 ± 0.9 (7–10)[b]	9.7 ± 0.8 (1–10)[b]	0.405	

a n (%).

b Mean ± SD (range).

ETOP = elective termination of pregnancy; **OR** = odds ratio.

Major Congenital Malformations

No significant difference was found in the rate of major congenital malformations among live births between the study group and the comparison group (15/441; 3.4% vs 17/705; 2.4%; p = 0.36; odds ratio (OR) 1.42; 95% CI 0.70, 2.88) [table III]. Although higher in the study group, the difference in the rate of cardiovascular malformations between the study group and the comparison group was not statistically significant (7/441; 1.6% vs 6/705; 0.9%; p = 0.265; OR 1.91; 95% CI 0.63, 5.62).

When the subgroups exposed to different macrolides were compared (table IV), no statistically significant differences were found among the various macrolides in the prevalence of major congenital malformations (5.2% for azithromycin, 4.5% for roxithromycin, 1.8% for clarithromycin; p = 0.191). The proportion of cardiovascular malformations was higher in the azithromycin subgroup (3.0%) compared with roxithromycin (2.2%) and clarithromycin (0.5%) [p = 0.157].

Considering the critical period only, the prevalence of major malformations in the macrolides group was 3.3% (11/334) and the rate of cardiac malformations was 1.8% (6/334).

When the subgroups exposed to different macrolides were compared with the comparison group (table V), no statistically significant differences were observed in the prevalence of major congenital malformations (5.2% vs 2.4%; p = 0.09) or cardiovascular malformations (3% vs 0.9%; p = 0.06) between azithromycin and the comparison group, although the result was of borderline significance, with a trend toward a higher rate of malformations in the study group.

No statistically significant differences were observed in the prevalence of major congenital malformations (4.5% vs 2.4%; p = 0.28) or cardiovascular malformations (2.2% vs 0.9%; p = 0.22) between roxithromycin and the comparison group.

No statistically significant differences were observed in the prevalence of major congenital malformations (1.8% vs 2.4%; p = 0.80) or cardio-

Table III. Major congenital malformations and cardiac malformations in the macrolide exposure and comparison groups after first-trimester exposure

	Study group (N = 511) [n (%)]	Comparison group (N = 773) [n (%)]	p-Value	OR (95% CI)
Major congenital malformations	15/441[a] (3.4)	17/705[a] (2.4)	0.359	1.42 (0.70, 2.88)
Cardiac malformations	7/441[a] (1.6)	6/705[a] (0.9)	0.265	1.91 (0.63, 5.62)

a Denominator is total live births as no malformations were identified in the ETOPs and spontaneous abortions.

ETOP = elective termination of pregnancy; **OR** = odds ratio.

Table IV. Congenital malformations and cardiac malformations by macrolide subgroup

	Azithromycin (n = 134) [n (%)]	Roxithromycin (n = 89) [n (%)]	Clarithromycin (n = 218) [n (%)]	p-Value
Major congenital malformations	7 (5.2)	4 (4.5)	4 (1.8)	0.191
Cardiac malformations	4 (3.0)	2 (2.2)	1 (0.5)	0.157

vascular malformations (0.5% vs 0.9%; p = 0.99) between clarithromycin and the comparison group.

Table VI summarizes the detailed congenital malformations reported in the study and comparison groups.

Discussion

The primary objective of this study was to determine the prevalence of major congenital malformations and cardiac malformations in patients treated with the new macrolides in the first trimester of pregnancy. We observed no significant difference between the groups in prevalence of malformations, which was found to be no greater than the 3–4% seen in the general population. Although higher in the study group, the difference in the rate of cardiovascular malformations between the study group and the comparison group was not statistically significant (7/441; 1.6% vs 6/705; 0.9%; p = 0.265; OR 1.91; 95% CI 0.63, 5.62).

Women in the study group were slightly younger than the comparison group. Although increased risk of malformations is associated with older maternal age, the rate of malformations was higher in the macrolides group. However, the difference between the mean ages of 30 and 32 years can be considered clinically insignificant. There was no difference in the rates of gestational diabetes and hypertension between the groups. Another difference in pregnancy characteristics between the groups was the higher rate of mutifetal pregnancies in the comparison group. However, when comparing these pregnancies with single-fetus pregnancies, there was no difference in the rate of prematurity or congenital malformations.

Our results are in accordance with previous publications. Including the latest study conducted in Israel,[12] there are reported pregnancy outcomes for about 131 azithromycin,[6,9,12] 316 clarithromycin[10-12] and 200 roxithromycin exposed cases[12-15] during organogenesis. All these studies conclude that the new macrolides do not pose an increased risk for major malformations.

However, there are some conflicting results concerning the use of erythromycin, the first and oldest macrolide, during pregnancy. Källén et al.[2,3] reported an association between erythromycin use during pregnancy and cardiac malformations in offspring. In a recent study on antibacterial medication use during pregnancy and the risk of congenital malformations,[19] although no increased risk for major birth defect was observed among 202 women treated with erythromycin during the first trimester, elevated adjusted ORs (AORs) were observed for anencephaly (AOR 2.4; 95% CI 1.1, 5.3) and transverse limb deficiency (AOR 2.1; 95% CI 1.0, 4.2).[19] We did not observe any pregnancy with anencephaly or transverse limb deficiency in the study group.

Table V. Major congenital malformations and cardiac malformations in each macrolide subgroup compared with the comparison group

		Study group [n (%)]	Comparison group [n (%)]	p-Value	OR (95% CI)
Azithromycin	Major congenital malformations	7/134 (5.2)	17/705 (2.4)	0.09	2.23 (0.91, 5.50)
	Cardiac malformations	4/134 (3)	6/705 (0.9)	0.06	3.59 (0.99, 12.88)
Roxithromycin	Major congenital malformations	4/89 (4.5)	17/705 (2.4)	0.28	1.90 (0.63, 5.79)
	Cardiac malformations	2/89 (2.2)	6/705 (0.9)	0.22	2.68 (0.53, 13.48)
Clarithromycin	Major congenital malformations	4/218 (1.8)	17/705 (2.4)	0.80	0.76 (0.25, 2.27)
	Cardiac malformations	1/218 (0.5)	6/705 (0.9)	0.99	0.54 (0.06, 4.48)

OR = odds ratio.

Table VI. Congenital malformations in the macrolide exposure and comparison groups[a]

Major malformation	Exposure	Indication	Wk of exposure (GA)	Trimester of exposure	Comments	Additional information
Macrolide group						
VSD – small, without haemodynamic relevance	Roxithromycin	Bronchitis	Before wk 10	First	PDA – spontaneous closure of the ductus	Gabapentin, smoker, no surgery
ASD secundum	Roxithromycin	Tonsillitis	5	First	Aneurysm of cardiac septum	
VSD	Azithromycin	Bronchitis	11	First	Maternal HIV	Lamivudine, nevirapine, stavudine through whole pregnancy, zidovudine 34–36 wk
VSD	Azithromycin	Bronchitis	9	First		
VSD	Azithromycin		5–6	First		Ibuprofen Paracetamol
Tetralogy of Fallot	Azithromycin		11–12	First	Preterm delivery. Died	Gestodene 4–11 wk
ASD	Clarithromycin		11	First		
Pyloric stenosis	Roxithromycin	Tonsillitis	4	First	Hernia inguinalis, prematurity, IUGR	Cefpodoxime 2–3 wk Norfloxacin 2–3 wk Ciprofloxacin 3–4 wk
Polydactyly	Roxithromycin	Bronchitis	2	First	Sixth digits in all four extremities	Doxycycline 3–4 wk, abdomen x-ray 12 wk, smoker
Cleft lip	Azithromycin	Bacterial infection, not specified	3	First	Cheilochisis of both sides	
Malformation of urinary tract	Azithromycin	Bronchitis	5	First	Epispadias	
Hydronephrosis grade III	Clarithromycin		7	First	Hypoglycaemia, laryngotracheomalacia	Oxazepam 0–18 wk, terbinafine 1–2 wk
Sacrococcygeal teratoma	Azithromycin	Bacterial infection, not specified	2–3	First		
Malformation of lung CCAM type III	Clarithromycin		4	First		Methylprednisolone 1–3 wk
Multiple face angiomas	Clarithromycin		12	First		Smoker
Comparison group						
ASD secundum					No clinical implications	
Tetralogy of Fallot					Cyanosis, operated at 3 months of age	
ASD					Preterm, wk 35	
ASD					Facial dysmorphism	
Corpus callosum agenesis					Hypoplasia of cerebellum, contraction of the big toes on both sides with sandal's gap	

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Table VI. Contd

Major malformation	Exposure	Indication	Wk of exposure (GA)	Trimester of exposure	Comments	Additional information
Limb malformation					Proximal defect of femur with longitudinal defect of lower leg and foot on one side	
Pyloric stenosis						
Anal atresia						
Dysplasia of right ear					Enlargement of left kidney	
Pulmonary valve stenosis						
Esophageal atresia						
Hypospadias						
Potter sequence						
Hip dysplasia						
Hydronephrosis						
Accessory kidney						

a Blank cells indicate not applicable.

ASD = atrial septal defect; **CCAM** = congenital cystic adenomatoid malformation; **GA** = gestational age; **IUGR** = intrauterine growth retardation; **PDA** = patent ductus arteriosus; **VSD** = ventricular septal defect.

In addition, we specifically looked for cardiac malformations.

There were seven (1.6%) cases of cardiac malformations in our study group, compared with six in the comparison group (0.9%). Although the proportion was almost double, the difference was not statistically significant ($p = 0.265$). Taking into account that in two of these pregnancies – one with atrial septal defect, the other one with ventricular septal defect (VSD) – macrolide exposure had taken place before the critical period of embryonic heart formation, a causal relationship to the mothers' medication seems remote. Furthermore, one fetus was affected with a small VSD without hemodynamic relevance, raising some doubt whether this VSD should be considered a major malformation.

The higher rate of major congenital malformations and cardiac malformations in the azithromycin subgroup (5.2% and 3.0%, respectively) reflects the two above-mentioned pregnancies with early exposure,

When comparing the different macrolide subgroups with the comparison group, although the rates of major congenital malformations and cardiovascular malformations were higher in the azithromycin subgroup, no statistically significant differences were found. This finding is in agreement with previous studies but should be looked into in future studies as our study, in itself, does not ascertain the safety of this compound because of the borderline significance of the higher rate of cardiac malformations found in this group.

There were no differences in the rates of major congenital malformations or cardiovascular malformations between the roxithromycin-treated subgroup and the clarithromycin-treated subgroup compared with the comparison group.

The rate of spontaneous abortions did not differ between groups (7.6 vs 6.7%) [table III]. Median gestational age of first contact was 2 weeks earlier in women of the study group. This 'delayed study entry' of the comparison group further diminishes the difference in abortion incidence. Due to spontaneous case reporting in observational investigations, study enrollment occurred at varying stages during (early) pregnancy.

The higher rate of induced abortions in the study group affected the lower rate of live births

in the study group, and it may be secondary to misinformation and misperception of a major risk related to macrolide use during pregnancy. Misinformation often leads to excess anxiety and unnecessary induced abortions. It has been demonstrated that both pregnant women and their physicians tend to assume a high teratogenic risk to a variety of compounds not known to cause harm in humans.[20] Early intervention has been shown to prevent unnecessary pregnancy terminations by correcting misinformation, thus decreasing the misperception of high risk held by women exposed to non-teratogens.[20]

The strengths and limitations of prospective observational cohort studies have recently been described in detail.[21] Our study has a number of limitations. The outcome data were collected by written questionnaire or via telephone interview and, in some cases, came from the mothers. However, mother's reports might have a lower sensitivity for accurately identifying major congenital malformations.[22]

The comparison group was derived of women who contacted four of the eight participating centres, which may have clouded population or ethnic differences. On the other hand, it can be assumed that a comparison group of one Italian TIS can represent the other two Italian centres, and the same applies to the two Israeli centres, thus these unexposed subjects are representative of six of the eight populations. Furthermore, in the study group these centres enrolled 86% of participants. Another point worth considering is that we have no data regarding the severity of illness and maximal measured temperature during the disease that the macrolides were prescribed for. As the comparison group also included compounds used for febrile illnesses, we feel that this should not influence our results.

Our study only has the capacity to identify a very large effect size for all major congenital malformations combined, as shown in the following power calculation:
considering the baseline risk for major congenital malformations in the control group of 2.4% and given a ratio of 1 : 1.6 between the study and comparison group sizes and a statistical power of 80%, a sample size of 441 live births in exposed women would enable us to detect a 2.4-fold rise in the rate of major anomalies.

The sample size of the clarithromycin-exposed group of 219 live births results in a ratio of 1 : 3.2 between the study group and the comparison group, and would enable us to detect a 2.9-fold rise in the rate of major malformations. Similarly, a sample size of 134 live births of the azithromycin-exposed group and a ratio of 1 : 5.3 between the study group and the comparison group would enable us to detect a 3.4-fold rise in the rate of major malformations, while a sample size of 90 live births in the roxithromycin-exposed group and a ratio of 1 : 7.9 between the study group and the comparison group would enable us to detect a 3.9-fold rise in the rate of major malformations. Considering the critical period only, given the ratio of 1 : 2.1 between the study group and the comparison group sizes and a statistical power of 80%, a sample size of 334 live births in exposed women enables us to detect a 2.7-fold rise in the rate of major anomalies.

Conclusions

This study, in agreement with earlier smaller studies, suggests that the new macrolides do not pose a significantly increased risk of major congenital malformations or cardiac malformations. Because of study size limitations, it permits one to rule out a 3-fold risk of major malformations after exposure to macrolides during the first trimester, and a 6-fold risk of cardiovascular malformations.

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