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ORIGINAL ARTICLE

The safety of amoxicillin and clavulanic acid use during the first trimester of pregnancy

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Aims: The goal of the current study was to assess the risk for major congenital malformations following first-trimester exposure to amoxicillin, or amoxicillin and clavulanic acid (ACA).

Methods: A population-based retrospective cohort study was conducted, by linking 4 computerized databases: maternal and infant hospitalization records, drug dispensing database of Clalit Health Services in Israel and data concerning pregnancy terminations. Multivariate negative-binomial regression was used to assess the risk for major malformations following first-trimester exposure, adjusted for mother's age, ethnicity (Bedouin *vs* Jewish), parity, diabetes mellitus, lack of perinatal care, and the year of birth.

Results: The study included 101 615 pregnancies, of which 6919 (6.8%) were exposed to amoxicillin: 1045 (1.0%) to amoxicillin only and 6041 (5.9%) to ACA. No significant association was found, in the univariate and multivariate analyses, between first-trimester exposure to amoxicillin or ACA and major malformations in general (crude relative risk, 1.05 95% confidence interval 0.95–1.16; adjusted relative risk 1.09, 95% confidence interval 0.98–1.20), or for major malformations according to organ systems. No dose–response relationship was found between exposure in terms of the defined daily dose and major malformations.

Conclusion: Exposure to amoxicillin and ACA during the first trimester of pregnancy was not associated with an increased risk of major congenital malformations.

KEYWORDS

amoxicillin, congenital malformation, drug safety, drugs in pregnancy, teratology

1 | INTRODUCTION

Penicillins are widely used during pregnancy for various bacterial infectious indications. Amoxicillin, a small-sized penicillin, rapidly crosses the placenta following absorption to the bloodstream[1,2] It is prescribed both as a sole medicine as well as in combination with clavulanic acid mostly for the treatment of urinary tract and respiratory infections. A recent report found that 18% of pregnant women who were insured by Medicaid in the USA were prescribed amoxicillin during pregnancy.[3]

Although 3 case–control studies found amoxicillin to be associated with cleft palate[4-6], 3 cohort studies[7-9] and a case–control study[10] did not detect an association between exposure to amoxicillin or amoxicillin combined with clavulanic acid (ACA) during the first trimester of pregnancy and major malformations. Furthermore, recent studies have suggested that antibiotic induced changes in the microbiome may affect the pregnancy outcomes.[11,12]

The primary goal of the current study was to assess the risk for major malformations following exposure to either amoxicillin or ACA using a large population-based cohort study.

Sharon Daniel and Maya Doron have contributed equally to this study.

2 | METHODS

We conducted a population-based retrospective cohort study including all pregnancies of women aged 15–45 years, registered with the *Clalit* health services maintenance organization in southern Israel in the years 1998–2009. The cohort included all pregnancies which resulted in delivery or pregnancy termination due to medical indications. Pregnancies with multiple foetuses, pregnancies that resulted in chromosomal defects and pregnancies exposed in utero to anti-folic acid medicines were excluded from the study. *Clalit* health services is the leading health maintenance organization in the southern district, where 70% of the childbearing-aged women are insured[13]. Soroka Medical Center (SMC) is the only tertiary medical centre in the region, in which 98% of the deliveries take place.[14]

What is already known about this subject

- Penicillins are widely used during pregnancy for various infectious indications. Recent studies have suggested that changes in the microbiome induced by antibiotics, may affect the pregnancy outcome.

What this study adds

- First-trimester exposure to amoxicillin and amoxicillin combined with clavulanic acid is not associated with increased risk for major congenital malformations in general, or with specific major congenital malformations related to organ systems.

2.1 | Databases

To create the cohort, we linked 4 computerized databases: the births' medical record computerized database of the division of Obstetrics and Gynecology that contains information regarding all deliveries that took place at SMC, including demographic information, medical diagnoses during and before pregnancy, self-report of tobacco use, delivery results and adverse birth outcomes. A trained medical secretary reviews the data before entry to the database.

Data concerning pregnancy terminations due to medical indications were collected from the Committee for Termination of Pregnancies' files.

The Clalit Health Services' drug dispensation computerized database comprises data regarding medicines dispensed to all residents of the southern district that are registered with Clalit Health Services, including the Anatomical Therapeutic Chemical classification codes of the drugs, generic and commercial names, the date of dispensing and the amount of defined daily dose dispensed.

Information concerning major malformations diagnosed in newborns or infants until age 12 months was retrieved from the Soroka Medical Center hospitalization database, including demographic data and medical diagnoses coded by the International Classification of Diseases-9 (ICD-9). Board-certified neonatologists and paediatricians diagnose all major malformations for newborns and infants.

The data have been previously used.[15,16] All pregnancy records were successfully linked with newborn and children's records except for cases of foetal death before or during delivery. There was only 1 woman who had 1 record of a pregnancy in the cohort, in which we did not find dispensing of any drug in the medication database.

2.2 | Definitions of exposure, potential confounders and major malformations

Three exposure groups were created: pregnancies exposed at least once to amoxicillin during the first trimester (from the first day of the last menstrual period until the end of the 13th gestational week), were classified as the amoxicillin-only exposure group, whereas pregnancies exposed at least once to amoxicillin combined with clavulanic acid were considered as the ACA exposure group. We created a third group, combining all exposures to either of the drugs. The 3 exposure groups were compared with pregnancies that were not exposed to either of the drugs.

The definitions of major congenital malformations developed by the Metropolitan Atlanta Congenital Defects Program of the Centers for Disease Control and Prevention were used to define major malformations by systems for both live births and pregnancy terminations (12).

The following subclasses of birth defects were examined: cardiovascular malformations (ICD-9 codes 745–747); central nervous system malformations (ICD-9 codes 740–743); gastrointestinal malformations (ICD-9 codes 750–751); and genitourinary malformations (ICD-9 codes 752–753). We also examined the risk for specific malformations: cleft palate (ICD-9 code 749) and spina bifida (ICD-9 code 741).

The following potential confounders were accounted for: maternal age, smoking during pregnancy, ethnic group (Jewish *vs* Bedouin Muslim), birth order, parity, lack of perinatal care, obesity and the diagnosis of diabetes mellitus and gestational diabetes. Women that are insured by Clalit Health Services are followed during pregnancy by either *Clalit* obstetrics' clinics, or the pregnancy clinics at the Israeli ministry of health. A woman was considered as having insufficient perinatal care if she had <3 follow-up visits during pregnancy. This variable was found to be associated with both exposure to amoxicillin and major malformations, and distinguishes, we believe, a group of pregnancies with unique characteristics.

2.3 | Statistical analysis

We used the SPSS software, version 18 (IBM SPSS, Somers, NY, USA) and R software for statistical analyses. Maternal characteristics were compared between exposed and unexposed pregnancies using the χ^2 test for categorical variables and the Student *t* test for continuous variables. Multivariate Negative Binomial Regression models were used to examine the independent risk for major congenital malformations following exposure to amoxicillin and ACA.

Because 7 different models were performed to assess the association with the different groups of malformation, a Bonferroni correction was used in order to account for multiple comparisons. Only associations with a *P*-value of <.007 were counted as statistically significant.

All multivariate models were adjusted for mother's age, ethnicity (Bedouin *vs* Jewish), parity, diabetes mellitus, lack of perinatal care and the year of birth.

To consolidate the results, we performed a dose–response analyses, between the defined daily dose of amoxicillin and ACA dispensed during the first trimester of pregnancy and the rate of major malformations. The amount of defined daily dose for amoxicillin is 1 g.[17]

We also performed several subanalyses. To overcome possible indication bias due to differences in the proportion of infectious diseases between the exposed and unexposed groups, a secondary analysis was performed, by comparing exposed pregnancies with pregnancies that were exposed to amoxicillin during the 60 days preceding pregnancy.

Furthermore, to address possible selection bias, we performed a propensity score matching analysis for total major malformations following exposure to both amoxicillin and ACA using R, the MatchIt package. Selection bias might occur when the sample selected for the study has different characteristics from the study's population. A propensity score analysis enables the selection of a sample, such that the exposed and unexposed observations are similar in characteristics that are relevant for the association with exposure, i.e. their probabilities of being assigned to the exposure group, based on individual characteristics, are similar. The variables that were used to create the propensity model were maternal age, ethnic group, diabetes mellitus and obesity. The matching was performed such that the propensity for drug exposure for every exposed pregnancy was as close as 0.1 standard deviation from the propensity of the matched unexposed pregnancies.

Since >1 pregnancy for 1 woman could have been included in the study, a clustering effect might exist, which could alter the results. To address this potential clustering effect, a secondary analysis was performed using a mixed model, clustered by the women's identification number.

A relatively small number of pregnancies were diagnosed with maternal obesity. Since we assumed this is an underestimation of the actual proportion of maternal obesity in our cohort, this variable was not included in the multivariate analysis. Nonetheless, we performed a secondary analysis using obesity as an additional confounder.

Because the southern district of Israel contains the unique Bedouin population, previously reported as having higher rates of major malformations, we performed a subanalysis, stratified by the women's ethnic group.

2.4 | Ethics

The study was approved by the institutional Ethics Committee of Soroka Medical Center.

3 | RESULTS

There was a total of 114 987 pregnancies for women insured by *Clalit* health services at SMC between 1999 and 2009. The study included 101 615 pregnancies, which matched the inclusion criteria, of which

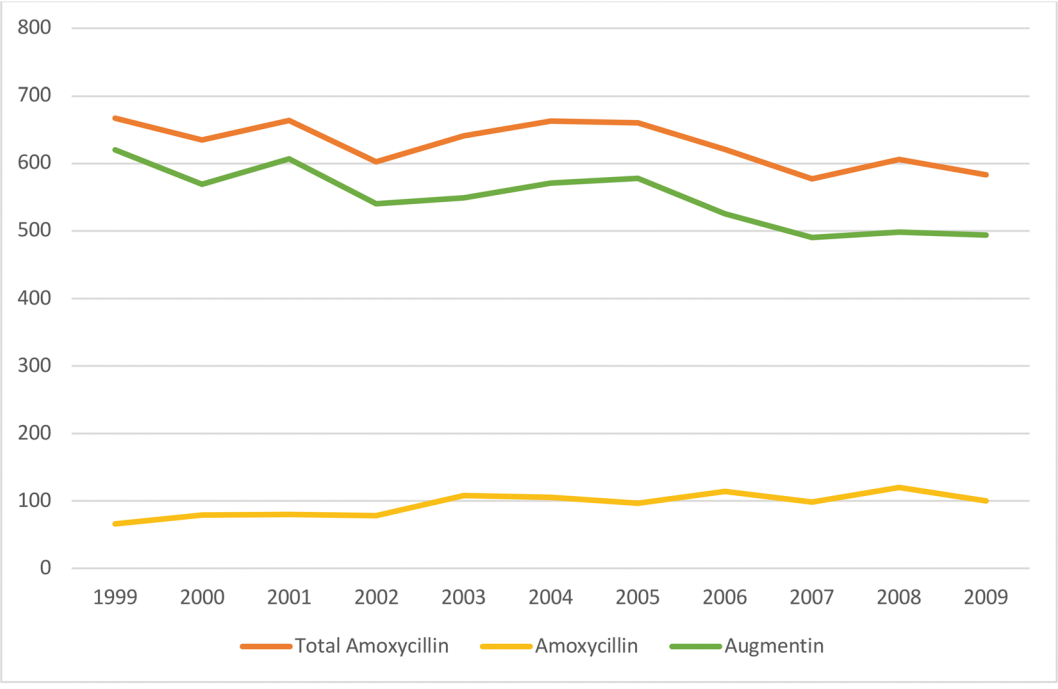

FIGURE 1 The proportion of pregnancies exposed to amoxicillin and amoxicillin and clavulanic acid during the first trimester among unexposed pregnancies, according to the birth year of the offspring or year of pregnancy termination

100 520 (98.9%) pregnancies ended with delivery, and 1095 (1.1%) pregnancies ended with a pregnancy termination due to medical indications.

The prevalence of exposure to both amoxicillin and ACA is presented in Figure 1. A total of 6919 (6.8%) pregnancies were exposed to amoxicillin during the first trimester of pregnancy: 1045 (1.0%) pregnancies were exposed to amoxicillin and 6041 (5.9%) pregnancies to ACA. Of the 1095 pregnancy terminations, 536 (48.9%) were diagnosed by perinatal sonography with major malformations. In 10 160 pregnancies (9%), the woman purchased folic acid supplements during the first trimester of pregnancy.

A comparison of maternal characteristics between exposed and unexposed pregnancies are presented in Table 1. Exposed women were older (mean of 29.2 *vs* 28.5 y among unexposed women), had higher parity (mean 4.1 *vs* 3.6,), higher rates of smoking during pregnancy (2.4 *vs* 1.9%) and pregestational diabetes (1.5 *vs* 1.0%) and a lower rate of insufficient perinatal care (6.0 *vs* 9.3%). Furthermore, most of the exposed women were of Bedouin–Muslim ethnicity (67.2 *vs* 64.2% among unexposed pregnancies). Most of the differences that were found between the exposed and unexposed groups were clinically unimportant, but due to the relatively large sample size, these differences were statistically significant.

Overall, 6166 (6.1%) pregnancies resulted in major malformations: 2384 (2.3%) with cardiovascular malformations, 180 (0.2%) with central nervous system malformations, 825 (0.8%) with genitourinary malformations, 319 (0.3%) with gastrointestinal malformations, 131 (0.1%) with cleft palate and spina bifida occurred in 76 (0.1%) pregnancies.

No significant associations were found, in the univariate and multivariate analyses, between first trimester exposure to either total amoxicillin (crude relative risk [RR] 1.05, 95% confidence interval [CI] 0.95–1.16; adjusted RR 1.09, 95% CI 0.98–1.20), amoxicillin alone (crude RR 1.00, 95% CI 0.78–1.28, adjusted RR 1.03, 95% CI 0.80–1.32), or ACA (crude RR 1.06, 95% CI 0.95–1.17, adjusted RR 1.09, 95% CI 0.98–1.21) and major malformations in general (Table 2).

TABLE 2 The risk for major malformation in infants or foetuses following intra-uterine exposure to amoxicillin/amoxicillin and clavulanic acid (ACA) during the first trimester

			Major congenital malformations	
			Relative risk*; 95% confidence interval	
	Exposed	Exposed cases	Crude	Adjusted*
Total amoxicillin + ACA	6919	440	1.05 (0.95–1.16)	1.08 (0.98–1.2)
Amoxicillin	1045	63	1.00 (0.78–1.28)	1.03 (0.8–1.32)
ACA	6041	386	1.06 (0.95–1.17)	1.09 (0.98–1.21)

*The relative risks are adjusted for maternal age, birth order, ethnic group, presence or absence of pregestational diabetes mellitus, insufficient perinatal care, smoking during pregnancy, and year of birth or pregnancy termination.

Also, no significant associations were found between exposure and subclasses of major malformations or specific malformations. For exposure to total amoxicillin—cardiovascular malformations: adjusted RR 1.13, 95% CI 0.98–1.31, central nervous system malformations: adjusted RR 1.02, 95% CI 0.77–1.36; gastrointestinal malformations: adjusted RR 1. 01, 95% CI 0.66–1.54; genitourinary malformations: adjusted RR 1.10, 95% CI 0.85–1.43; cleft palate: adjusted RR 1.34, 95% CI 0.74–2.44; neural-tube malformations: adjusted RR 0.85, 95% CI 0.34–2.11 (Figure 2).

No dose–response relationship was found between the amount of defined daily doses of amoxicillin alone, or ACA dispensed throughout the first trimester of pregnancy and major malformation (Table 3).

In a secondary analysis, performed to overcome possible indication bias, a total of 6458 pregnancies that were exposed to amoxicillin during the first trimester of pregnancy were compared with 5125 pregnancies that were exposed during the 60 days preceding pregnancy. No significant association was found for major malformations in general (RR 1.01 95% CI 0.87–1.17).

TABLE 1 Characteristics of women exposed to amoxicillin or amoxicillin/clavulanic acid (ACA) compared with unexposed pregnancies

Variable	Amoxicillin (*n* = 1045)	ACA (*n* = 6041)	Total amoxicillin + ACA (*n* = 6919)	Unexposed (*n* = 94 696)
Mother's age (y) mean ± SD	29.18 ± 5.6 (*P* = .001)	29.31 ± 5.7 (*P* < .001)	29.28 ± 5.7 (*P* < .001)	28.59 ± 5.8
Pregestational diabetes mellitus, *n*; %	19; 1.8% (*P* = .006)	91; 1.5% (*P* < .001)	106; 1.5% (*P* < .001)	922; 1.0%
Smoker *n*; %	22; 2.1% (*P* = .717)	145; 2.4% (*P* = .015)	165; 2.4% (*P* = .012)	1,846; 1.9%
Birth order mean + SD	4.07 ± 2.7 (*P* < .001)	4.16 ± 2.7 (*P* < .001)	4.14 ± 2.7 (*P* < .001)	3.67 ± 2.6
Ethnic group* *n*; %				
Bedouin	732; 70.6%	4031; 66.7%	4649; 67.2%	60 761; 64.2%
Jewish	307; 29.4% (*P* < .001)	2010; 33.3% (*P* < .001)	2270; 32.8% (*P* < .001)	33 924, 35.8%
Birth year median	2004 (*P* = .32)	2004 (*P* < .001)	2004 (*P* < .001)	2004
Insufficient perinatal care *n*; %	56; 5.4% (*P* < .001)	366; 6.1% (*P* < .001)	412; 6.0% (*P* < .001)	8755; 9.3%
Obesity *n*; %	7; 0.7% (*P* = .012)	21; 0.3% (*P* = .224)	29; 0.4% (*P* = .052)	250; 0.3%

SD, standard deviation

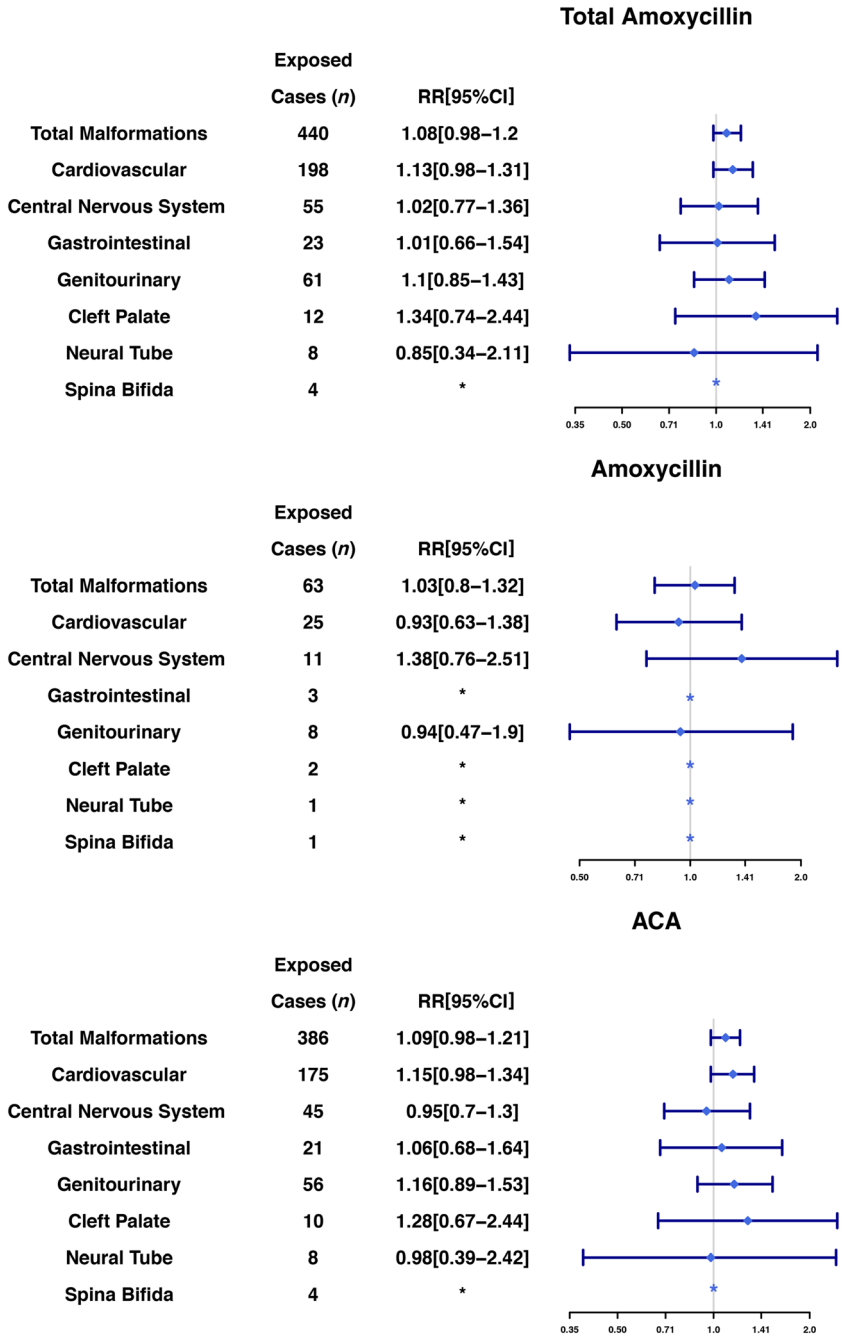

FIGURE 2 The risk for major malformations according to organ systems and specific malformations following exposure to amoxicillin/amoxicillin and clavulanic acid (ACA) during the first trimester of pregnancy. *Relative risk (RR) was not calculated due to <5 exposed cases. CI, confidence interval

In a propensity score analysis, a sum of 6919 pregnancies that were exposed to amoxicillin during the first trimester of pregnancy was matched by the propensity to be exposed to amoxicillin with 34 593 unexposed pregnancies. The relative risk for total major malformations was similar (RR 1.05 95% CI 0.95–1.16).

The mean and median number of pregnancies for each woman in the cohort was 2.29 and 2, respectively. In a mixed model, clustered by the women's identification number, no significant association between exposure to amoxicillin major malformations was found (RR 1.09, 95% CI 0.98–1.20).

In a stratified subanalysis according to the women's ethnic group, exposure to amoxicillin was not associated with major malformations for both Jewish (RR 0.90, 95% CI 0.72–1.10) and Bedouin (RR 1.17, 95% CI 0.98–1.30) women.

4 | DISCUSSION

The current study did not detect an association between exposure to amoxicillin or clavulanic acid and major malformations in general, nor for subclasses of malformation or for specific defects. The dose–response analyses showed a preventive effect against major malformations with increasing DDD of both amoxicillin and ACA. Previous studies suggested an association between maternal fever

TABLE 3 Relative risks and 95% confidence interval for major malformations following exposure to amoxicillin/amoxicillin and clavulanic acid (ACA) according to levels of defined daily dose

	Adjusted hazard ratio** (95% confidence interval)		
Total number of defined daily doses *	Total amoxicillin + ACA	Amoxicillin	ACA
None	1 (reference category)	1 (reference category)	1 (reference category)
1–7	0.87 (0.70–1.07)	0.93 (0.72–1.20)	0.74 (0.49–1.11)
8–14	0.97 (0.87–1.09)	0.95 (0.84–1.08)	1.07 (0.43–1.37)
15 and more	0.74 (0.57–0.95)	0.75 (0.56–0.99)	0.72 (0.42–1.45)

*Defined daily dose is the assumed average maintenance dose per day for a drug when it is used in adults for its main indication.

**The relative risks are adjusted for maternal age, birth order, ethnic group, presence or absence of pregestational diabetes mellitus, insufficient perinatal care, smoking during pregnancy, and year of birth or pregnancy termination.

during the first trimester of pregnancy and major malformations. This preventive effect may, in part, be due to decreased burden of infectious diseases on exposed pregnancies.

Our study reports a relatively high rate of major malformations in general when compared with the previous Israeli findings.[18] However, unlike previous studies, our study contains not only malformations diagnosed in newborns by board-certified neonatologists, but also major malformations diagnosed during hospitalizations until the age of 12 months and diagnoses performed on foetuses from pregnancy terminations. Furthermore, the Southern District of Israel contains the unique Bedouin population, previously reported as having higher rates of major malformations compared to the Jewish population.[19,20]

The inclusion of diagnoses on foetuses from pregnancy terminations prevents a bias towards the null hypothesis.[16] We also performed a secondary analysis, excluding pregnancy terminations, and achieved similar results (RR1.08, 95% CI 0.98–1.19 for total amoxicillin and total major malformations).

The SMC databases contain information on alcohol abuse which was previously found to be associated with major malformations. Since most of the women in the Southern district come from religious Jewish or Bedouin–Muslim communities, and because women of childbearing age in those communities rarely consume alcohol, no women in the cohort were diagnosed with alcohol abuse during pregnancy.[21]

Our findings are consistent with a previous population-based case–control and 3 cohort studies.[7-10] In contrast, 3 case–control studies found amoxicillin use to be associated with cleft palate.[4-6] In these 3 studies, exposure was defined by interviews performed with mothers after delivery, and therefore the results were subjected to recall bias.

Our study used information regarding dispensing, rather than prescriptions, of amoxicillin and clavulanic acid from the Clalit Health Services' drug dispensing database. Nonetheless, data regarding adherence to drug therapy were lacking. However, previous studies, performed on the same drug dispensing databases, found the adherence to therapy for both deep vein thrombosis and familial Mediterranean fever to be >90%.[22,23] High rates of adherence to iron supplementation therapy were also found in a previous study, based on the same dispensing database.[24] Furthermore, high rates of concordance were found between medication use and the computerized prescription databases.[25-27]

In recent years, there is accumulating evidence that gestational exposure to antibiotics may have adverse effects on children, probably through changes in the gut microbiome.[28] These findings raise a concern regarding the association between a change in maternal microbiome during pregnancy and major malformations. Our study suggests that the antibiotics studied are not associated with increased risk of birth malformations. However, potential underlying indications for receiving antibiotics, such as childhood asthma, should also be considered.

5 | CONCLUSION

Exposure to amoxicillin and ACA both as a group and for both individual medications was not associated with major malformations in general or with major malformations according to organ systems.

COMPETING INTERESTS

There are no competing interests to declare.

The study received no funding. The study was approved by the ethics committee at Soroka Medical Center according to the declaration of Helsinki.

CONTRIBUTORS

S.D. designed the study, analysed the data and interpreted the results, wrote the manuscript; has given final approval of the version to be published and agreed to be accountable for all aspects of the work. M.D. designed the study, acquired and analysed the data, was involved in drafting the manuscript; has given final approval of the version to be published and agreed to be accountable for all aspects of the work. G.K. designed the study, was involved in drafting the manuscript and revising it for important intellectual content; has given final approval of the version to be published and agreed to be accountable for all aspects of the work. E.L. was involved in drafting the manuscript and revising it critically for important intellectual

content; has given final approval of the version to be published and agreed to be accountable for all aspects of the work. A.L., study supervisor, designed the study, interpreted the results, was involved in drafting the manuscript and revising it critically for important intellectual content; has given final approval of the version to be published and agreed to be accountable for all aspects of the work.

The study received no funding. The study was approved by the ethics committee at Soroka Medical Center according to the declaration of Helsinki.

DATA AVAILABILITY STATEMENT

The data cannot be shared due to the confidentiality policy at Soroka Medical Center and Clalit Health Services.

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