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First-trimester exposure to amoxycillin/clavulanic acid: a prospective, controlled study

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Aims
The number of published studies on the use of amoxycillin/clavulanic acid during pregnancy is small and so is the number of pregnancies investigated in those studies. In this study we wished to investigate prospectively the safety of intrauterine exposure to amoxycillin/clavulanic acid in a relatively large cohort of women.

Methods
Women treated (n = 191) with amoxycillin/clavulanic acid during the first trimester of pregnancy were recruited from two teratogen information centres in Israel. Exposed women were matched for age, smoking habits and alcohol consumption with 191 controls exposed to amoxycillin only for similar medical indications.

Results
Maternal age, birth weight, gestational age at delivery, rates of live births and abortions were comparable between the two groups. Rates of major malformations in the amoxycillin/clavulanic acid group (3/158, 1.9%) did not differ significantly from controls (5/163, 3%) (P = 0.49, relative risk = 0.62, 95% confidence interval 0.15, 2.55), and were within the expected baseline risk for the general population.

Conclusion
These data suggest that exposure to amoxycillin/clavulanic acid during pregnancy is unlikely to be associated with an increased risk of malformations.

Introduction

Amoxycillin/clavulanic acid (A/C) is a broad-spectrum antibiotic prescribed for various infections such as tonsillitis, pneumonia, otitis, sinusitis and urinary tract infection [1, 2]. Clavulanic acid is a β-lactamase inhibitor produced by *Streptomyces clavuligerus* [3]. The combined drug has been shown to inhibit staphylococcal β-lactamases [3, 4] and numerous β-lactamases produced by Gram-negative organisms [2, 5–7].

Since the thalidomide disaster of the early 1960s, there has been much concern about the risk of adverse effects of maternal drug exposure on the developing fetus. Nevertheless, the number of women who receive drug treatment during pregnancy is high. According to the World Health Organization, the incidence of drug

use by pregnant women in Europe is approximately 80% [8]. The use of anti-infectives among pregnant women in Europe was reported to be 12.3% [9]. Patients frequently take drugs before becoming aware of their pregnancy, while in some cases the therapeutic benefit of drug treatment outweighs any risk of adverse effects on the fetus. Several studies have described the use of A/C for various infections in pregnant women [10, 11]. No adverse effects in the fetus or newborn attributable to this treatment were observed. However, these studies and another recent study by Czeizel *et al.* [12] on first-trimester exposure to A/C included only a small number of patients. We therefore aimed to evaluate prospectively the safety of A/C during pregnancy in a large cohort of women.

Methods

Recruitment of cases and controls

From June 1999 through March 2001, we enrolled 191 women who called one of two teratogen information services (TIS) in Israel to obtain information at the time of exposure about the potential risks of A/C use during pregnancy. The centres included Assaf Harofeh Teratogen Information Service, Zerifin ($n = 81$ women), and the Israeli Teratogen Information Service, Jerusalem ($n = 110$ women). The study was approved by Assaf Harofeh ethics committee.

Data collection was done via a structured telephone questionnaire that was the same in both centres. Data were collected at the time of exposure, which was before pregnancy outcome was known. The data included maternal age, gravidity, parity, number of past spontaneous and induced abortions, smoking and alcohol consumption habits, use of other medications, A/C dose, timing, indication, duration of therapy and maternal history.

Exposed women were matched for age (±2 years), smoking habits and alcohol consumption with 191 women exposed to amoxycillin for similar medical indications, who were counselled at the same two TISs.

Both cases and controls were called after the expected date of delivery for a follow-up telephone interview. At that time, information was collected from the mother, regarding the outcome of the pregnancy, perinatal complications, birth weight, physical findings, and any birth defects. The time between delivery and follow-up interview was 3–18 months in both groups. Major anomalies were identified through the telephone interview with the mother and verified from medical records or by the family physician.

Our primary outcome of interest was the rate of major malformations, i.e. structural abnormalities of surgical, medical, or cosmetic importance [13]. Secondary outcomes of interest were live birth rates, the number of spontaneous and induced abortions, the number of fetal deaths, gestational age at delivery, birth weight and the presence of meconium and/or abnormal fetal heart rate monitoring during delivery, or the need for neonatal intensive care.

Statistical analysis

For the analysis of major malformation, the period of embryonic organogenesis was defined as the period up to week 13 of gestation [14]. The beginning of pregnancy was defined according to the menstrual date and ultrasound date. Continuous data, such as maternal age, gestational age at delivery, and birth weight, were compared using Student's *t*-test and presented as mean ± SD. Categorical data such as pregnancy outcome, fetal distress, malformations and method of delivery are presented by risk estimates and 95% confidence intervals (CIs). The method used to calculate the *P*-values was χ^2. CIs for the estimated parameters were computed by a general method described elsewhere [15].

Results

We prospectively enrolled and followed 191 women exposed to A/C during the first trimester.

The indications for prescribing A/C to the study group were tonsillitis (23%), otitis (12%), sinusitis (20%), pneumonia (15%), urinary tract infection (10%), skin infection (6%), dental abscess (6%), and other infections (8%). Each tablet of 500 mg A/C contains 500 mg amoxycillin (as trihydrate) and 125 mg clavulanic acid (as potassium salt). The mean daily dose of A/C was 1500 ± 250 (500–3000) mg, for 7.9 ± 3.7 (2–28) days.

The indications for prescribing amoxycillin in the control group were tonsillitis (20%), otitis (10%), sinusitis (15%), pneumonia (15%), urinary tract infection (10%), *Helicobacter pylori* (5%), skin infection (9%), dental abscess (8%), and other infections (8%). The mean daily dose of amoxycillin was 1500 ± 350 (500–3000) mg for 7 ± 2 (2–14) days.

There were no differences in characteristics among the study and the control groups with regard to maternal age, gravidity, parity, and number of elective terminations of pregnancy (Table 1).

Pregnancy outcome

Women in the A/C group had significantly higher rates of spontaneous abortions in previous pregnancies com-

Table 1
Characteristics of mothers exposed to amoxycillin/clavulanic acid (A/C) compared with those of mothers exposed to amoxycillin

	A/C	Amoxycillin	*P*-value
Maternal age (years)	30.7 ± 4.7 (19–45)	30.1 ± 4.5 (21–44)	0.198*
Gravity (*n*)	2.9 ± 1.8 (1–11)	2.7 ± 1.2 (1–7)	0.907†
Parity (*n*)	1.408 ± 1.1 (0–6)	1.4 ± 1.1 (0–6)	0.934†
Previous miscarriage (*n*)	0.408 ± 0.9 (0–6)	0.18 ± 0.43 (0–6)	0.025†
Induced abortion (*n*)	0.188 ± 0.68 (0–5)	0.13 ± 0.4 (0–2)	0.745†
Alcohol use (*n*)	1/191	1/191	1
Cigarette smoking (*n*)	21/191	14/191	0.21

*T-*test.* †*Mann–Whitney test.*

Table 2
Pregnancy outcome for women exposed to amoxycillin/clavulanic acid (A/C) compared with that of women exposed to amoxycillin

Pregnancy outcome	A/C	Amoxycillin	*P*	RR	95% CI
Live births	158/191	162/191	0.67	0.98	0.89, 1.07
Stillbirth	1/191	0/191	0.31		
Spontaneous abortion	14/191	12/191	0.68	1.17	0.55, 2.46
Induced abortion	18/191	16/191	0.71	1.13	0.59, 2.14
Gestational age at birth	39.4 ± 1.6 (34–42)	39.6 ± 1.6 (30–42)	0.294*		
Prematurity (<37 weeks)	6/158	5/163	0.73	1.24	0.39, 3.97
Birth weight (g)	3239 ± 488 (1670–4300)	3232.8 ± 468 (1950–4500)	0.582*		
Birth weight <2500 g	7/158	6/163	0.75	1.2	0.41, 3.5
Fetal distress	5/158	5/163	0.97	1.03	0.3, 3.49
Vaginal delivery	126/158	142/163	0.04	0.92	0.83, 1.01
Caesarean section	33/158	20/163	0.04	1.7	1.02, 2.84
Major malformations	3/158	5/163	0.49	0.62	0.15, 2.55

*T-*test.*

pared with controls ($P = 0.025$, Table 1); however, no significant difference in spontaneous abortion rate was observed between the two groups in the present pregnancy (Table 2).

There was no significant difference between the two groups also with regard to the rate of live births, induced abortions, gestational age at birth, prematurity and birth weight (Table 2). There was a significantly higher rate of caesarian section among the A/C-exposed women compared with the control group (33 out of 158 and 20 out of 163, respectively) [$P = 0.04$, relative risk (RR) 1.7, 95% CI 1.02, 2.84]. However, this was not reflected in a significantly higher rate of fetal distress among the A/C-exposed women compared with the control group (five out of 158, five out of 163, repectively, $P = 0.97$) (Table 2).

Major malformations

The rate of major malformations in the study group (3/158, 1.9%) did not differ significantly from that of the control group (5/163, 3%) ($P = 0.49$, RR = 0.62, 95% CI 0.15, 2.55). The major malformations in the A/C and the control groups are listed in Table 3. Two additional children in the A/C group were excluded from Table 3: one with vesico-ureteral reflux which resolved spontaneously, and one with renal pelvis dilatation with duplication of urethral orifice which did not necessitate any intervention. These two children were diagnosed due to renal pelvis dilatation found ultrasonographically during intrauterine life and confirmed after delivery, and were followed up for approximately 2 years. Several malformations were excluded from the control group: umbilical hernia without surgical intervention, short frenulum

Table 3
Major malformations in the amoxycillin and amoxycillin/clavulanic acid (A/C) groups

Type of malformation	Time of exposure during pregnancy, weeks	Additional pregnancy exposures	Follow-up
Control group (amoxycillin)			
1 VSD	9		Spontaneously closed
2 CDH	7	Acetaminophen, metoclopramide, sulfacetamide	
3 Tracheo-oesophageal fistula	8	Dental X-rays at 4 weeks	Operated several times, gastrostomy
4 VSD	7	Metoclopramide	Spontaneously closed
5 VSD	7		Spontaneously closed
Study group (A/C)			
1 Club foot	13	Omeprazole	Bilateral club foot operation at 8 months of age
2 Unilateral hydronephrosis	9	Acetaminophen	Operated
3 VSD and pulmonic stenosis	7	Acetaminophen	Asymptomatic

VSD, Ventricular septal defect; CDH, congenital dislocation of hip.

of tongue, vaginal cyst (resolved spontaneously), and hydronephrosis (resolved spontaneously shortly after birth).

Discussion

The concerns regarding the safety of therapy for unborn babies leads to the exclusion of pregnant women from progress in pharmacotherapy. Since the thalidomide tragedy, the risks of drug therapy have been overestimated, therefore it is important to study the safety of medications that are commonly used. Prior to our study, the safety of clavulanic acid was supported by the animal data and scanty human reports. In most animal studies, the administration of clavulanic acid with amoxycillin did not produce teratogenic effects when tested in rats or pigs [16–18].

In a study using perfused human placental cotyledons, clavulanic acid could not be documented to cross the placenta [19]. This finding was believed by the authors to be due to insensitivity of their assay rather than to lack of placental transfer. The placental transfer of ticarcillin-clavulanic acid has been reported by others [20].

Amoxycillin, which was chosen to be the control for A/C in our study, is a penicillin derivative similar to ampicillin, showing no increase in the rate of congenital malformations, as reported by the Collaborativve Perinatal Project [21].

Indeed, both A/C exposure cases and their amoxycillin controls in our study had major malformation rates within the expected baseline risk for the general population, 1.9% and 3%, respectively. The incidence of major anomalies recognized at birth among live-born infants is 2–3% in most series; an equal number of additional major anomalies will be recognized by 5 years of age [22]. No specific pattern of malformations among the A/C-exposed infants was observed.

However, this study has some limitations. The ascertainment of birth defects by telephone interview of the mother may be incomplete; there is a potential for sampling bias and data verification. Review of medical records of congenital anomalies reported by the mother does not affect this underestimation and a follow-up examination by a study physician blinded to the exposure status was not performed.

In conclusion, our data sugget that A/C use during pregnancy is unlikely to be associated with a greatly increased risk of malformations.

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