First trimester exposure to cefuroxime: a prospective cohort study

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Aims There are no published studies on the safety of cefuroxime use during pregnancy. We therefore investigated prospectively the possible teratogenic effect of intrauterine exposure to cefuroxime.

Methods One hundred and six women who received cefuroxime during the first trimester of pregnancy were recruited from three teratogen information centres in Israel. Exposed women were paired for age, smoking habits and alcohol consumption with references being exposed to nonteratogenic antibiotics administered for the same indications.

Results Maternal history, birthweight, gestational age at delivery, rates of live births, spontaneous abortions and fetal distress were comparable among the two groups. Rates of major malformations in the cefuroxime group (3.2%) did not differ from references (2%) ($P=0.61$, relative risk = 1.56, 95% confidence interval 0.27–9.15). There was a significantly higher rate of induced abortions among the cefuroxime exposed women as compared to the references ($P=0.04$, relative risk = 3.33, 95% confidence interval 0.94–11.77).

Conclusions Our data may suggest that exposure to cefuroxime during the first trimester is probably not associated with an increased risk for malformations or spontaneous abortions; however, in light of the small sample size and the broad confidence limits, larger studies are needed to confirm these findings.

Keywords: cefuroxime, pregnancy, teratogenicity

Introduction

Since the thalidomide disaster of the early 1960s, there has been much concern over maternal drug administration and the risk of adverse effects on the developing fetus. Nevertheless, the number of women who receive drug treatment during pregnancy is surprisingly high. According to the World Health Organization, the incidence of drug use in pregnancy in Europe is approximately 80% [1]. The use of anti-infectives among pregnant women in Europe was reported to be 12.3% [2].

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.

Second and third generation cephalosporins are prescribed today to pregnant women, although there are no appropriate data on their safe use during pregnancy, and particularly during embryogenesis. When given to rats at doses one and a half to eight times the human dose, the cephalosporins containing the *N*-methylthiotetrazol (MTT) side chain resulted in testicular toxicity, the consequences of which for the human fetus are unknown at this time [3]. Cephalosporins may also cause adverse effects in the mother, such as hypersensitivity reactions, haematologic toxicity and bleeding dyscrasias [3, 4].

Cefuroxime is a second generation cephalosporin prescribed for various infections such as pneumonia, otitis, sinusitis and urinary tract infection [5, 6]. It has bactericidal activity against *Streptococcus pneumoniae,*

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Klebsiella pneumoniae, Staphylococcus aureus, Group A beta haemolytic *Streptococcus,* and Gram negative bacteria [5, 6].

In humans, cefuroxime is known to cross the placenta during pregnancy [7–9].

According to the manufacturer there is no information on cefuroxime use during pregnancy, no information on its embryopathic or teratogenic risk, and therefore, the current recommendation is that the drug should not be used in pregnant women, especially during the first trimester.

We have not been able to locate controlled studies on possible human reproductive effects of cefuroxime. The aim of our study was to prospectively evaluate the safety of cefuroxime during the first trimester.

Methods

From June 1997 through March 1999 we enrolled 109 women who called one of three teratogen information services to obtain information about the potential risks of cefuroxime use during pregnancy. Women called the teratogen information services (TIS) at the time of exposure. All women in the study who eventually had a spontaneous abortion called before abortion had occurred. They were taking the drug at the time of or after calling the TIS.

The centres included Assaf Harofeh Teratogen Information Center (Zerifin, Israel), The National Teratogen Information Center (Jerusalem, Israel), and Beilinson Teratogen Information Center (Petach Tikva, Israel).

The data collection and follow-up methods were consistent among the centres, which used a structured questionnaire.

Data were collected at the time of exposure and before pregnancy outcome was known and included maternal age, gravidity, parity, number of past spontaneous and induced abortions, smoking and alcohol consumption habits, cefuroxime dose, timing, indication, duration of therapy and maternal history.

All women were called after the expected date of delivery for a follow-up telephone interview and information was collected regarding the outcome of the pregnancy, perinatal complications, birth weight, physical findings, any birth defects, and gross motor developmental milestone achievements according to the Denver Developmental Scale [10].

As a reference group, we recruited 106 pregnant women who were counseled at Assaf Harofeh Teratogen Information Center for the use of antibiotics that are known to be nonteratogenic and nonembryotoxic. References were matched for indication of antibiotic therapy, maternal age (± 2 years), smoking and alcohol consumption habits.

All women in the reference group were followed up in a similar manner. The timespan between delivery and follow-up interview was 3–18 months in both groups.

Our primary outcome of interest was the rate of major malformations, as defined by Marden *et al.* [11]. 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 fetal distress defined as the presence of meconium and/or abnormal fetal heart rate monitoring during delivery, or the need for neonatal intensive care.

For the analysis of major malformation, the period of fetal organogenesis was defined as the period up to the 13th week of gestation [12].

Each of the participating centres obtained ethics approval locally.

Statistics

Continuous data, such as maternal age, gestational age at delivery, and birth weight, were compared using Student's *t*-test and are presented as mean $\pm$ s.d. Categorical data such as pregnancy outcome, fetal distress, malformations and method of delivery are presented by risk estimates and 95% confidence intervals.

Results

We prospectively enrolled and followed 109 women exposed to cefuroxime during the first trimester. The indications for prescribing the drug were sinusitis (20%), otitis media (15%), otitis externa (15%), pneumonia (20%), and urinary tract infection (30%). Three women refused to participate in the survey.

The mean daily dose of cefuroxime was 750 ± 250 (500–1000) mg; duration of therapy was 7.5 ± 2 (5–10) days.

The antibiotics used among the reference group were amoxycillin (30%), penicillin (30%), cephalexin (20%), cloxacillin (15%). Five percent of the women used paracetamol (acetaminophen). The indications for treatment were sinusitis (21%), otitis media (17%), otitis externa (15%), pneumonia (23%), and urinary tract infection (29%).

There were no differences in characteristics among the women in the exposed and reference groups with regard to maternal age, gravidity, parity, number of previous miscarriages or induced terminations (Table 1).

Eight of the 106 women (7.5%) had an X-ray examination during the first trimester; four had chest X-rays and four had frontal sinus X-rays, while none of the women in the reference group underwent X-ray exposure.

Table 1 Characteristics of mothers exposed to cefuroxime compared with those of mothers exposed to nonteratogenic antibiotics.

	Cefuroxime	*References*	P
Maternal age (years)	30 ± 5.2 (17–41)	30 ± 4.5 (20–41)	0.9
Gravidity	2.5 ± 1.8 (1–10)	2.5 ± 1.3 (1–9)	0.8
Parity	1.1 ± 1.5 (0–8)	1.2 ± 1(0–5)	0.9
Spontaneous abortion (*n*)	0.2 ± 0.6 (0–5)	0.17 ± 0.6 (0–4)	0.4
Induced abortion (*n*)	0.15 ± 0.5 (0–3)	0.08 ± 0.3 (0–2)	0.2
Alcohol use	4/106 (3.9%)	4/106 (3.9%)	1
Cigarette smoking	8/106 (7.5%)	9/106 (8.4%)	0.8

Pregnancy outcome

There was a significantly higher rate of induced abortions among the cefuroxime exposed women (10 out of 106 *vs* 3 of 106 for the control group; $P=0.04$, relative risk = 3.33, confidence interval = 0.94–11.77); however, this was not reflected in a significantly lower live birth rate among the cefuroxime exposed women (93 of 106 *vs* 97 of 106 for the control group; $P=0.36$)(Table 2).

One woman in the cefuroxime-exposed group had an induced abortion due to multiple fetal anomalies (anencephaly and hypoplastic left heart) observed on routine ultrasonography. Five other women had an induced abortion between the 8th and 11th weeks of pregnancy because of anxiety after becoming aware of their pregnancy and cefuroxime use in the early stages. Two other women in the cefuroxime group and three women in the reference group refused to explain the reason for the induced abortion. The aborted fetuses were presumably not examined by a pathologist.

There was no significant difference between the two groups with regard to gestational age at birth, prematurity, birth weight, fetal distress and delivery method (Table 2).

Malformations (major and minor)

The major malformations in the cefuroxime group were one case of ventricular septal defect and one case of penile hypospadias. The minor malformations in the cefuroxime group were as follows: one case of mild brachycephaly without clinical significance (exposed to cefuroxime and promethazine), two cases of undescended testis, one case of a small hole in the inferior part of the auricle (cefuroxime and garamycin), one case of an absent fingernail, one case of metatarsus adductus, one haemangioma, one minor syndactyly, one umbilicial hernia and one case of cafe au lait spot on the back.

The minor malformations in the reference group were as follows: mild increased head circumference, undescended testis, dilatation of renal pelvis (resolved), metatarsus adductus, small haemangioma on the left hand, and umbilical hernia.

The rate of major malformations in the cefuroxime group (3.2%) did not differ from that of the reference group (2%) ($P=0.61$, relative risk = 1.56, 95% confidence interval 0.27–9.15). The rate of minor malformations in the cefuroxime group (10.7%) also did

Table 2 Pregnancy outcome for women exposed to cefuroxime compared with that of women exposed to nonteratogenic antibiotics.

Pregnancy outcome	*Cefuroxime*	*References*	P	*RR*	*95% CI*
Live births	93/106	97/106	0.36	0.96	0.87–1.05
Spontaneous abortion	3/106	6/106	0.3	0.50	0.13–1.95
Induced abortion	10/106	3/106	0.04	3.33	0.94–11.77
Gestational age at birth (weeks)	39 ± 2.8(23–42)	39 ± 1.7 (34–42)	0.6		
Prematurity (<37 weeks)	4/93	6/97	0.5	0.70	0.20–2.39
Birth weight (g)	3220 ± 539 (560–4420)	3231 ± 530 (1370–4430)	0.9		
Birth weight <2,500g	4/93	6/97	0.5	0.70	0.20–2.39
Fetal distress	10/93	8/97	0.5	1.3	0.54–3.16
Vaginal delivery	83/93	87/97	0.9	1.0	0.9–1.1
Caesarean section	10/93	10/97	0.9	1.04	0.46–2.39
Major malformations	3/93	2/97	0.61	1.56	0.27–9.15
Minor malformations	10/93	6/97	0.25	1.74	0.66–4.59

RR = Relative Risk 95% CI = 95% Confidence Interval.

not differ from that of the reference group (6.2%) ($P=0.25$, relative risk = 1.74. 95% confidence interval = 0.66–4.59) (Table 2).

Gross motor developmental milestone achievement according to the Denver Developmental Scale did not differ between the two groups (Table 3).

Discussion

Cefuroxime is a broad spectrum antibiotic, administered orally or parenterally. The drug is indicated for urinary tract infection, pneumonia, otitis, sinusitis, and other infectious diseases. There are no published studies on the safety of cefuroxime use in pregnancy, particularly in the first trimester [13].

No teratogenic effect was observed among the offspring of pregnant mice or rabbits treated, respectively, with 28–220 mg kg^{-1}, or 2–14 times the maximum dose of cefuroxime used in humans [14, 15].

Furuashi *et al.* administered cefuroxime to rabbits subcutaneously or intravenously on days 6 through 18 of gestation. Doses of up to 150 mg kg^{-1} had no adverse effects on the fetuses [16].

Our prospective cohort study enrolled 106 women to examine the incidence of major malformations after first trimester exposure to cefuroxime.

The higher rate of induced abortions observed in the cefuroxime–exposed women compared with that observed in their references ($P=0.04$) may be secondary to misinformation and misperception of a major risk related to its use during pregnancy. However, other medical and especially nonmedical reasons can also account for this finding. It is our experience that misinformation often leads to excess anxiety and unnecessary induced abortions. It has been demonstrated that both pregnant women and their physicians tend to assign high teratogenic risk to a variety of compounds not known to cause harm in humans [17]. Moreover, early intervention has been shown to prevent unnecessary pregnancy terminations by correcting misinformation, thus decreasing the high misperceived risk by women exposed to nonteratogens [17].

Both cefuroxime exposure cases and their references had major malformation rates within the expected baseline risk for the general population. The incidence of major anomalies recognized at birth among liveborn infants is 2%-3% in most series; an equal number of additional major anomalies will be recognized by 5 years of age [18]. The incidence of minor malformations in both groups was within the expected 20% base line risk for minor malformations for the general population [19]. However, our study has some limitations. The sample size is small, there is a possibility of selection bias, and the confidence limits are broad.

In conclusion, our data suggest that cefuroxime use during the first trimester of pregnancy is probably not associated with an increased risk for malformations or spontaneous abortions. However, in light of the aforementioned limitations larger studies are needed to confirm these findings.

Table 3 Acquisition of milestones as defined by the Denver Developmental Scale.

Age (months) at which milestone was acquired			
Milestone	*Cefuroxime*	*References*	P *value*
Lifting	2.1 ± 1	2.2 ± 1.1	0.21
Sitting	5.8 ± 1.7	5.85 ± 1.2	0.23
Crawling	7.2 ± 1.5	7.1 ± 1.35	0.39
Standing	8.8 ± 1.8	8.7 ± 1.7	0.46
Walking	11.3 ± 1.7	11.9 ± 2.2	0.41

References

1 Matheson I, Soderman P. and the Collaborative Group on Drug Use in Pregnancy. Drug use in pregnancy. Preliminary results from Norway and Sweden. *Eur J Clin Pharmacol* 1988; **36**: A111.

2 De Vigan C, De Walle HE, Cordier S, et al. Therapeutic drug use during pregnancy: a comparison in four European countries. OECM Working Group. Occupational exposures and congenital anomalies. *J Clin Epidemiol* 1999; **52**: 977–982.

3 Martens MG. Cephalosporins. *Obstet Gynecol Clin North Am* 1989; **16**: 291–304.

4 Angelli G, Del Favero A, Parise P, *et al.* Cephalosporin-induced hypoprothrombinemia: is the N-methylthiotetrazole side chain the culprit? *Antimicrob Agents Chemother* 1986; **29**: 1108–1109.

5 Brogden RN, Heel RC, Speight TM, Avery GS. Cefuroxime: a review of its antibacterial activity, pharmacological properties and therapeutic use. *Drugs* 1979; **17**: 233–266.

6 Gold B, Rodriguer WJ. Cefuroxime mechanisms of action, antimicrobial activity, pharmacokinetics, clinical applications, adverse reactions and therapeutic indications. *Pharmacotherapy* 1983; **3**: 82–100.

7 Gilstrap LC, 3d Bawdon RE, Burris J. Antibiotic concentration in maternal blood, cord blood, and placental membranes in chorioamnionitis. *Obstet Gynecol* 1988; **72**: 124–125.

8 Dinsmoor MJ, Gibbs RS. The role of the newer antimicrobial agents in obstetrics and gynecology. *Clin Obstet Gynecol* 1988; **31**: 423–434.

9 Craft I, Mullinger BM, Kennedy MR. Placental transfer of cefuroxime. *Br J Obstet Gynecol* 1981; **88**: 141–145.

10 Frankenburg WK, Dodds J, Archer P, Shapiro H, Bresnick B. The Denver II: a major revision and restandardization of the Denver Developmental Screening Test. *Pediatrics* 1992; **89**: 91–97.

11 Marden PM, Smith DW, McDonald MJ. Congenital anomalies

in the newborn infant, including minor variations. *J Pediatr* 1964; **64**: 357–371.

12 Moore Kl and Persand TVN. *The Developing Human* Clinically oriented embryology. W.B. Saunders Company, Philadelphia, Pa, p 111, 1993.

13 Landers DV, Green JR, Sweet RL. Antibiotic use during pregnancy and the postpartum period. *Clin Obstet Gynecol* 1983; **26**: 391–406.

14 Brodgen RN, Heel RC, Speight TM, Avery GS. Cefuroxime: a review of its antibacterial activity, pharmacological properties and therapeutic use. *Drugs* 1979; **17**: 233–266.

15 Caple-Edwards K, Atkinson RM, Pratt DA. Toxicology studies on cefuroxime sodium. *Toxicology* 1979; **13**: 1–5.

16 Furuhashi T, Nomura A, Ikeye E, Nakazawa M. Teratological studies on cefuroxime in rabbits. *Chemotherapy* 1979; **27**: 245–292.

17 Koren G, Bologa M, Long Y, Feldman Y, Henderson K, Shear NH. The perception of teratogenic risk by pregnant women exposed to drugs and chemicals during the first trimester. *Am J Obstet Gynecol* 1989; **160**: 1190–1194.

18 Stevenson RE, Hall JG, Goodman RM. *Human malformations and related anomalies*, I. New York: Oxford University, p 99, 1993.

19 Merlob P, Papier CM, Klinberg MA, Reisner SH. Incidence of congenital malformations in the newborn, particularly minor anomalies. *Prog Clin Biol Res* 1985; **163**: 51–55.