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Pregnancy Outcome Following Gestational Exposure to Fluoroquinolones: a Multicenter Prospective Controlled Study

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Concerns regarding the teratogenicity of fluoroquinolones have resulted in their restricted use during gestation. This is despite an increasing need for their use due to emerging bacterial resistance. The objectives of the present investigation were to evaluate pregnancy and fetal outcomes following maternal exposure to fluoroquinolones and to examine whether in utero exposure to quinolones is associated with clinically significant musculoskeletal dysfunctions. We prospectively enrolled and followed up 200 women exposed to fluoroquinolones (norfloxacin, ciprofloxacin, ofloxacin) during gestation. Pregnancy outcome was compared with that for 200 controls matched for age and for smoking and alcohol consumption habits. Controls were exposed to nonteratogenic, nonembryotoxic antimicrobial agents matched by indication, duration of therapy (±3 days), and trimester of exposure. Rates of major congenital malformations did not differ between the group exposed to quinolones in the first trimester (2.2%) and the control group (2.6%) (relative risk, 0.85; 95% confidence interval, 0.21 to 3.49). Women treated with quinolones had a tendency for an increased rate of therapeutic abortions compared with the rate among women exposed to nonteratogens (relative risk, 4.50; 95% confidence interval, 0.98 to 20.57), resulting in lower live-birth rates (86 versus 94%; $P = 0.02$). The rates of spontaneous abortions, fetal distress, and prematurity and the birth weight did not differ between the groups. Gross motor developmental milestone achievements did not differ between the children of the mothers in the two groups. We concluded that the use of fluoroquinolones during embryogenesis is not associated with an increased risk of major malformations. There were no clinically significant musculoskeletal dysfunctions in children exposed to fluoroquinolones in utero. The higher rate of therapeutic abortions observed in quinolone-exposed women compared to that for their controls may be secondary to the misperception of a major risk related to quinolone use during pregnancy.

Fluoroquinolones are a class of antibiotic agents that act by inhibiting bacterial DNA gyrase. Different factors combine to raise teratogenic and fetotoxic concerns regarding their use during pregnancy. Mammalian DNA shares similar topoisomerases with micropathogens. Together with the fact that fluoroquinolones cross the human placenta (5), they can theoretically have mutagenic and carcinogenic effects on the developing fetus. Furthermore, the quinolones have a high affinity for cartilage. Studies with beagle dogs and guinea pigs have demonstrated arthropathy of weight-bearing joints after the administration of 200 and 1,000 mg of pipemidic acid and oxolonic acid, respectively (6). This observation was further supported by human case reports (2, 3). A recent study suggested a high malformation rate (11.9%) among children who had been exposed to ofloxacin in utero (11). Moreover, 5 reported cases of abdominal wall malformations are an alarming sign in light of the published background rate of these malformations: 2 to 5/10,000 population. Finally, higher rates of fetal distress and delivery by cesarean section were reported for a cohort of 38 women exposed to quinolones compared to the rates for controls exposed to nonteratogenic drugs (1).

In light of the increasing levels of resistance of many micropathogens to the antibiotics commonly prescribed during pregnancy, the clinical use of fluoroquinolones has been increasing substantially. Together with the fact that half of the pregnancies in North America are unplanned (12), the safety of fluoroquinolones during pregnancy is an increasing concern.

Presently, the available data regarding the use of quinolones during pregnancy are very limited: only the results of one prospective controlled study with a very limited sample size ($n = 38$) (1) and an uncontrolled survey (11) have been reported. Therefore, we initiated a multicenter, prospective controlled study to evaluate the potential teratogenic and fetotoxic concerns related to the use of fluoroquinolones during human pregnancy.

MATERIALS AND METHODS

We enrolled 200 women who called one of four teratogen information services to obtain information about the potential risks of drug use during pregnancy. These centers included Motherisk (Toronto, Ontario, Canada), Teratogen Information Service (Tampa, Fla.), Philadelphia Pregnancy Healthline (Philadelphia, Pa.), and Centro Regionale d'Informazione sul Farmaco (Milan, Italy). The data collection and follow-up methods were consistent among the centers, which used a structured questionnaire.

Data were collected at the time of exposure and before pregnancy outcome was known and included maternal age, gravity, parity, number of past sponta-

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neous and therapeutic abortions, smoking and alcohol consumption habits, drug exposure of interest (i.e., quinolone dose, timing, and indication for and duration of therapy), and maternal and genetic history.

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

As a control group, we recruited 200 pregnant women who were counseled at Motherisk for the use of antibiotics that are known to be nonteratogenic and nonembryotoxic to account for the potential adverse effects of the infections themselves. Controls were matched for maternal age (±3 years), smoking and alcohol consumption habits, indication for and duration (±3 days) of therapy, and trimester of exposure. All women in the control group were followed up in a similar manner.

Our primary outcome of interest was the rate of major malformations, as defined by Marden et al. (9). Secondary outcomes of interest were live-birth rates, the numbers of spontaneous and therapeutic abortions, the numbers 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 malformations, fetal organogenesis was defined as the period between the 4th and 13th weeks of gestation (10).

Each of the participating centers received ethics approval locally.

Statistical analysis. Data for the two groups are presented as means ± standard deviations. Continuous data between groups were compared by the Student *t* test and the Mann-Whitney rank sum test, as appropriate. Categorical data were compared by χ^2 analysis. The rates of major malformations were analyzed by the Fisher extract test. Relative risk and the 95% confidence interval were also calculated. Multiple linear regression analysis was used to study the effects of the daily dose and duration of quinolone therapy, indication for therapy, trimester of exposure, and smoking and alcohol consumption habits on gestational age. Multiple logistic regression analysis was used to investigate the effects of these variables on live-birth rates.

TABLE 1. Characteristics of mothers exposed to fluoroquinolones compared to those of mothers exposed to nonteratogenic antibacterials

Characteristic	Quinolone group (n = 200)	Nonteratogenic antibiotic group (n = 200)	P value
Maternal age (yrs)	30.8 ± 5.2	30.6 ± 4.7	0.12[a]
Gravity (no.)	2.2 ± 1.3	2.1 ± 1.3	0.10[a]
Parity (no.)	0.9 ± 1.0	0.7 ± 0.9	0.83[a]
Spontaneous abortion (no.)	0.2 ± 0.5	0.3 ± 0.7	0.02[a]
Therapeutic abortion (no.)	0.1 ± 0.4	0.1 ± 0.4	0.55[a]
Nonsmoking status (%)	86.2	85.7	0.96[b]
No alcohol consumption (%)	99.2	94.7	0.07[b]
Concurrent drug therapy (%)			
Antiemetic or antipeptic agents	16.5	18.0	0.69[b]
Analgesics	10.0	12.0	0.52[b]
Antidepressants	1.0	1.5	0.97[b]
Folic acid supplementation	24	20	0.62[b]

[a] Mann-Whitney rank sum test.
[b] χ^2 test (with Yates correction).

RESULTS

Data for a total of 200 women exposed to fluoroquinolones during pregnancy were collected. Seventy-six (38%) of the women were from Toronto, 52 (26%) were from Philadelphia, 40 (20%) were from Tampa, and 32 (16%) were from Milan.

To exclude the possibility of selection bias, maternal characteristics were compared by using a cross-center analysis: maternal age, gravity, parity, the rate of previous spontaneous and therapeutic abortions, and smoking and alcohol consumption habits were not statistically different among the women at the participating centers.

One hundred five women (52.5%) were exposed to ciprofloxacin, 93 (46.5%) were exposed to norfloxacin, and 2 (1%) were exposed to ofloxacin. Information on treatment indication was given for 154 of the women: 69.4% of the women were treated for urinary tract infections, 24% were treated for respiratory tract infections, and the other 6.4% were treated for skin infections (n = 6), osteomyelitis (n = 2), breast abscess (n = 1), and a ruptured ovarian cyst (n = 1).

One hundred thirty-six women were exposed to quinolones during the period of organogenesis (4 to 13 weeks of gestation), 34 women were exposed during the second trimester (13 to 26 weeks of gestation), and 30 women were exposed during the third trimester (26 weeks to delivery). The treatment doses ranged from 400 to 800 mg for norfloxacin, 500 to 1,000 mg for ciprofloxacin, and 200 to 400 mg for ofloxacin.

There were no differences in characteristics among the women in the study and control groups (Table 1) except for a higher reported rate of previous miscarriages in the control group. Concurrent drug therapy did not differ between the study and the control groups: 16.5% of the women in the quinolone group used antiemetic or antipeptic agents (antihistamines, pyridoxine, H_2 blockers, antacids), whereas 18.0% of the women in the control group used such agents (P = 0.69). Analgesics (acetaminophen, nonsteroidal anti-inflammatory agents) were used by 10.0% of the women in the quinolone group, whereas they were used by 12.0% of the women in the control group (P = 0.52), and antidepressants were taken by 1% of the women in the quinolone group and 1.5% of the women in the control group (P = 0.97). In addition, four women in each group reported the use of salbutamol inhaler to control mild asthmatic attacks. One patient in the quinolone group used verapamil throughout pregnancy to control her essential hypertension, and one patient in the control group had used bromocriptine to treat her prolactin-secreting pituitary microadenoma.

There was a trend toward a higher rate of therapeutic abortions among the quinolone-exposed women (9 of 200 versus 2 of 200 for the control group; P = 0.06). This is reflected in a lower live-birth rate among the quinolone-exposed women (173 of 200 versus 188 of 200 for the control group; P = 0.02). However, of all the potential drug-related factors (i.e., daily dose, duration, trimester of exposure, and indication) analyzed by multiple logistic regression, none had a statistically significant predictive value on the live-birth rate. Gestational age at delivery was significantly lower among the quinolone-exposed women: 39.3 ± 2.0 weeks versus 39.8 ± 2.0 weeks among the women in the control group (P = 0.02). However, there were no differences in rates of prematurity. Similarly, there were no differences in pregnancy outcome with respect to the rates of spontaneous abortions, birth weight, and fetal distress (Table 2). Multiple regression analysis demonstrated no significant predictive effect of each of the potential risk factors on gestational age at delivery.

We found no differences in the rates of major malformations between children exposed to fluoroquinolones during organogenesis and children of mothers in the control group: 3 of 133 versus 5 of 188 (P = 0.54; relative risk = 0.85; 95% confidence interval, 0.21 to 3.49).

The major malformations noted in the quinolone group were two cases of ventricular septal defect and one case of patent ductus arteriosus. Among the controls, the major malformations included two cases of ventricular septal defect, one case of atrial septal defect with pulmonic valve stenosis, one

TABLE 2. Pregnancy outcome for women exposed to fluoroquinolones during pregnancy compared to that for controls exposed to nonteratogenic antibiotics

Outcome or characteristic	No. of women with the following outcome/ total no. of women:		Relative risk (95% confidence interval)	*P* value
	Quinolone group	Nonteratogenic antibiotic group		
Live births	173/200	188/200	0.92 (0.86–0.98)	0.02[a]
Spontanous abortion	18/200	10/200	1.80 (0.85–3.80)	0.17[a]
Therapeutic abortion	9/200	2/200	4.50 (0.98–20.57)	0.06[a]
Vaginal delivery	145/173	148/188	1.06 (0.96–1.18)	0.27[a]
Premature birth	11/173	13/188	0.92 (0.42–2.00)	0.99[a]
Birth weight, <2,500 g	7/173	9/188	0.85 (0.32–2.22)	0.93[a]
Fetal distress	22/173	27/188	0.89 (0.52–1.49)	0.76[a]
Delivery by cesarean section	28/173	40/188	0.83 (0.61–1.13)	0.21[a]
Gestational age	39.3 ± 2.0[b]	39.8 ± 2.0[b]		0.02[c]
Birth weight	3,452 ± 537[d]	3,477 ± 608[d]		0.92[c]

[a] χ^2 test (with Yates correction).
[b] Units are in weeks of gestation.
[c] Mann-Whitney rank sum test.
[d] Units are in grams.

case of hypospadias, and one case of displaced hip. The maternal reports of all major malformations were confirmed by their physicians in writing, and the confirmation included the specific diagnosis.

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

DISCUSSION

The association between fluoroquinolones and arthropathy, although observed in immature animals and rarely reported in humans, has resulted in the restricted use of fluoroquinolones during pregnancy. Data from recent reports suggest that quinolone administration to children and adolescents with cystic fibrosis is safe on the basis of both clinical and magnetic resonance imaging assessments (4). However, since these observations have focused on children and adolescents, it is unclear whether in utero exposure to quinolones and their potential deposition in fetal cartilage are associated with any long-term musculoskeletal dysfunctions. Our data, which we obtained using the Denver Developmental Scale, suggest that in utero exposure to quinolones is not associated with clinically significant major musculoskeletal dysfunctions. This tool is very limited in evaluating subtle joint changes that would have been detected only by sensitive methods. Magnetic resonance imaging of weight-bearing joints of children exposed to quinolones in utero is in progress in our attempt to address this concern.

In designing this study, we aimed at controlling for the indication for the drug so that the putative effects of the infections would not be attributed to the quinolones. The prospective nature of this study aimed at obviating recall and selection bias.

The rate of major malformations in among children born alive and exposed to quinolones during the first trimester was within the expected normal range (1 to 5%) and was numerically identical to that among children in the control group. Importantly, we did not observe any major or minor abdominal wall malformations. The sample size of our study has a power to detect a 3.5-fold increased risk of major malformations, assuming a baseline risk of 3% with a power of 80% and an α value of 0.05. These data suggest that despite the limited strength of this study to detect a minimal increased risk above the baseline, it is very unlikely that fluoroquinolones are a major human teratogen.

The shorter length of gestation observed in the quinolone group is probably of no clinical significance because the other parameters such as birth weight and the rates of occurrence of birth weights below 2,500 g did not differ between the two groups. Moreover, multiple regression analysis indicated that quinolone therapy-related factors such as the daily dose, the duration of and indication for therapy, and the trimester of exposure probably do not explain the shorter length of gestation age in this group. The higher rate of therapeutic abortions observed in the quinolone-exposed women compared to that observed in their controls may be secondary to misinformation and misperception of a major risk related to their use during pregnancy. However, other medical and especially nonmedical reasons can also account for this finding. The possible high misperceived risk related to quinolone use during gestation probably stems from several statements found in the literature: the Compendium of Pharmaceuticals and Specialties (1a) states that "ciprofloxacin should not be used in pregnant women unless the likely benefits outweight the possible risk to the fetus." Another recent publication (11) claims that "quinolones should still be regarded as contraindicated during pregnancy," although these data were from an uncontrolled study. It is our experience that such information often leads to excess anxiety and unnecessary therapeutic 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 (7). Moreover, early intervention has been shown to prevent unnecessary pregnancy terminations by correcting misinformation, thus de-

TABLE 3. Acquisition of milestones defined by the Denver Developmental Scales

Milestone	Age (mo) at which milestone was acquired		*P* value[a]
	Quinolone group	Nonteratogenic antibiotic group	
Lifting	2.2 ± 1.0	2.3 ± 1.1	0.21
Sitting	5.9 ± 1.7	5.8 ± 1.2	0.24
Crawling	7.2 ± 1.6	7.2 ± 1.4	0.40
Standing	8.7 ± 1.8	8.7 ± 1.8	0.45
Walking	11.2 ± 1.7	12.0 ± 2.3	0.41

[a] Student *t* test.

creasing the high misperceived risk by women exposed to nonteratogens (8).

In the era of increasing resistance of many micropathogens to different antibacterial agents, quinolones should not be prescribed as first-line agents for the treatment of uncomplicated urinary tract infections and should definitely not be prescribed for upper respiratory tract infections. However, in cases of infections with resistant micropathogens or complicated urinary tract infections during pregnancy, when the use of quinolones is mandatory, or in cases of inadvertent fetal exposure to fluoroquinolones (unplanned pregnancies), our data indicate that their benefits outweigh the risks to the fetus and that therapeutic abortions due to fetal exposure to these agents is unjustified.

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