Annals of Medical Research
DOI: 10.5455/annalsmedres.2018.12.279 2019;26(4):646-52

Original Article

Maternal antibiotic exposure and fetal outcomes: Is there evidence for teratogenicity?

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Abstract

Aim: During pregnancy, untreated infections may be associated with low birth weight, preterm birth, and spontaneous abortion. Thus, use of antibiotics are commonly seen in pregnancy. In this study, we aimed to evaluate the possible teratogenic risks related to the maternally exposed antibiotics during pregnancy.

Material and Methods: Data from pregnant women, who used antibiotics for several infectious diseases between 2014 and 2018, and admitted to our Teratology Information Service for drug analysis, were collected. Data concerning their medication, concomitant drugs and co-morbidities were documented. The possible teratogenic risks related to the drugs were evaluated. A follow-up was conducted with the women after delivery to obtain whether any major or minor congenital malformations occurred in the infants.

Results: The maternal use of doxycycline between 3-6th weeks, and acyclovir between 1-2nd weeks of pregnancy resulted in elective termination. The maternal use of cefazoline between 3-4th weeks of pregnancy, and the use of amoxicillin-clavulanate between 3-6th weeks of gestation resulted in spontaneous abortion. In the outcome of one pregnancy, the concomitant exposure of miconazole, metronidazole, ciprofloxacin, ornidazole and isoconazole in the first two weeks of pregnancy resulted in hypothyroidism in the infant.

Conclusions: Antibiotics presented no major teratogenic effects. However, their use in pregnancy should be used only when indicated. Pregnant women should have access to the information and specific advice on the use of medications with proven safety in pregnancy through counseling with the Teratology Information Services.

Keywords: Anti-bacterial Agents; Pregnancy; Teratology.

INTRODUCTION

Clinical features of infectious diseases in pregnant women, diagnosis and treatment regimen are generally similar to those in nonpregnant patients (1). However, there is little direct information about the safety of many antibiotics during pregnancy. The reliable use of certain antibiotics generally derives from indirect evidence of animal studies or observational studies that may have numerous confounders. Teratogenic drugs, when used shortly before or during pregnancy, can irreversibly modify growth, structure or function of the developing embryo or fetus. The safest way is to use the antibiotics that have well-established safety profiles during pregnancy (2).

Some certain points should be considered in pregnant women. These are the teratogenicity potential of the agent used in the infection control, maternal physiological changes, susceptibility to infection during pregnancy, and the effects of the infective agent on the mother and fetus (3). Pregnant women should have access to the information and specific advice on the use of medications with proven safety in pregnancy through counseling with the Teratology Information Service (TIS) worldwide. TIS provides evidence-based information for drugs and fetal safety to the pregnant women who are exposed to drugs at any time during pregnancy. The European Network of Teratology Information Services (ENTIS) and MotherToBaby (Organization of Teratology Information Specialists, OTIS) are well-established networks of TIS which counsel thousands of patients in developed countries every year (4). However, in Turkey, this issue is very new in Clinical Pharmacology, and unfortunately

Received: 10.12.2019 **Accepted:** 07.02.2019 **Available online:** 19.02.2019
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pregnant women have limited access to these kinds of specialized information sources.

In this study, we aimed to evaluate the possible teratogenic risks related to the maternally exposed antibiotics during pregnancy.

MATERIAL and METHODS

A number of 20 pregnant women, who had admitted to our Clinical Pharmacology Teratology Information Service (TIS) of University Hospital between the years 2014 and 2018 for antibiotics consumption, were included in this retrospective observational study. The study was approved by the Ethics Committee of Clinical Trials of the Faculty of Medicine (Approval Date: 24.10.2018; Approval No: 2018/19/13).

The demographic data for maternal drug exposure was obtained by admitting of pregnant women to our TIS unit, and filling out our registration form. All relevant data concerning medication, exposure to other agents and co-morbidities were documented by face to face interview with the women. Obstetric and medical history, treatment indications and details of drug or other exposures, timing in pregnancy, duration, dose and concomitant medications, social or illicit drug use, smoking, ionized radiation exposure, herbal consumption, and symptoms of maternal toxicity related to one of the agents of exposure were obtained at the first contact with TIS. The gestational week was calculated based on ultrasonography (USG) or the last menstrual period. Subsequently, risk assessment for teratogenicity was performed for each case individually based on the literature. At the end of this procedure, we represented a risk analysis score for each case on a written structured form and gave to the patient, in order to inform both the patient and her obstetrician.

The birth results of our patients who were exposed to drugs were obtained by contacting with the families after birth. After delivery, a follow-up was conducted with a structured telephone interview with the women. Data on prenatal diagnostics, course and complications of pregnancy and delivery, gestational age at delivery and neonatal outcome parameters such as birth weight, minor and major congenital anomalies and postnatal disorders were obtained. This is the only valid way in all TIS worldwide to achieve the results of maternal drug exposure on the fetus (4). Birth defects were categorized as major and minor congenital defects according to Malformation Coding Guides of European Surveillance of Congenital Anomalies (EUROCAT) (5).

Statistical analysis

The data were analyzed using the SPSS 17.0 program. Continuous variables were expressed as median (range).

RESULTS

Between 2014 and 2018, a number of 20 cases with exposure to antibiotics during pregnancy were identified. The antibiotics had been reciped for the following indicationsin women: Upper respiratory infection (n=5), vaginitis (n=5), dental abscess (n=3), urinary tract infection (n=3), acne vulgaris (n=2), brucellosis (n=1), gastroenteritis (n=1), dermatosis (n=1), cellulitis (n=1), and inflammatory bowel diseases (n=1), given that one pregnant woman may have one or more diagnosis. The ages of pregnant women range between 18 and 45 years. Their gestational age at the first contact to TIS range between 5 and 11 weeks. We found that 17 women used the drugs in the first trimester, and three women in the preconception period. All pregnancies were treated at therapeutic and standard doses. The administration routes were per oral (p.o), intravaginal, intramuscular (i.m) or topically to the skin. Antibiotic subtypes used by the pregnant women in this study were doxycycline (1x100 or 2x100 mg p.o), rifampicin (1x600 mg p.o), cefprozil (2x500 mg p.o), ciprofloxacin (1x500, 2x500 or 2x750 mg p.o), miconazole / metronidazole (1x200/750 mg intravaginal), ornidazole (2x500 mg p.o), cefazolin (2x1000 mg i.m), amoxicillin-clavulanate (1x1000 or 2x1000 mg p.o), azithromycin (1x500 mg p.o), metronidazole (2x500 mg p.o), ampicillin (4x1000 mg, i.m), ampicillin-sulbactam (2x1000 mg), fucidic acid (2x1 topical), isoconazole (3x1 topical), gentamicin (1x160 mg i.m), clindamycin (1x150 mg p.o), penicillin G benzathine (1x1.2 IU i.m), fluconazole (1x200 mg p.o), acyclovir (5x800 mg p.o), and methenamine (1x1000 mg p.o). Pregnant women may have used several antibiotics concomitantly. Exposed antibiotics and concomitant drugs are shown in Table 1.

There was no exposure to cigarette, alcohol, or herbal. The gestational age at the beginning of antibiotic use range between zero and seven weeks, and expiry week range between one and eight weeks. Patterns of antibiotic exposure are presented in Table 2.

The maternal use of doxycycline between 3-6th weeks, and that of acyclovir between 1-2nd weeks of pregnancy resulted in elective termination. Both of their diagnoses were acne vulgaris, and they, additionally, had used well-established teratogenic medications, isotretinoin, and lithium. The maternal use of cefazoline between 3-4th weeks of pregnancy, and the use of amoxicillin-clavulanate between 3-6th weeks of gestation resulted in spontaneous abortion. Their diagnoses were dental abscess, and co-exposed medications were modafinil and nonsteroidal anti-inflammatory drugs (NSAIDs). The concomitant use of miconazole, metronidazole, ciprofloxacin, ornidazole, and isoconazole between 0-2nd weeks in one pregnancy resulted in hypothyroidism in the infant. Another case, whose mother had Crohn disease, was exposed to ciprofloxacin for the first six gestational weeks in utero and was born small for gestational age at the 36 weeks (2600 g). Maternal drugs had additionally included azathioprine, mesalazine, and prednisolone.

Table 1. Data about pregnant women

Age	Indication	USG (week)	Exposed antibiotics	Concomitant drugs
-	Brucellosis	5	Doxycycline Rifampicin	-
-	Upper respiratory infection	6	Cefprozil	NSAID Butamirate Biperiden
40	Vaginitis	6	Ciprofloxacin Miconazole+ metronidazole Ornidazole	-
-	Dental abscess	6	Cefazolin	Modafinil NSAID
-	Vaginitis+ Urinary tract infection	5	Doxycycline Miconazole+ metronidazole Amoxycillin clavulanate	-
-	Upper respiratory infection	6	Azithromycin	-
-	Acne vulgaris	7	Doxycycline	Olanzapine Lithium Quetiapine
37	Gastroenteritis	11	Metronidazole	Hyoscine Betahistine Metoclopramide
36	Dermatosis	6	Doxycycline	-
-	Cellulitis	6	Ampicillin Fucidic acid	NSAID
34	Dental abscess	7	Amoxycillin clavulanate	NSAID
30	Acne vulgaris	7	Acyclovir Fucidic acid	Isotretinoin Vitamin B
27	Vaginitis	6	Miconazole+metronidazole Ciprofloxacin+ornidazole Isoconazole	Trazodone Duloxetine Bismuth Metoclopramide Pantoprazole NSAİD
26	Dental abscess	6	Amoxycillin clavulanate	NSAID Ulipristal
37	Vaginitis	7	Gentamicin Clindamycin	Escitalopram Triamcinolone
-	Vaginitis+ Urinary tract infection+ Upper respiratory infection	7	Fluconazole Ciprofloxacin Amoxycillin clavulanate	NSAID Desloratadine
45	Upper respiratory infection	6	Penicillin G benzathine	Citalopram Vitamin B12 Ca dobesilate
-	İnflammatory bowel diseases	8	Ciprofloxacin	Azathioprine Mesalazine Prednisolone
18	Upper respiratory infection	7	Ampicillin sulbactam	NSAID
24	Urinary tract infection	6	Ciprofloxacin Methenamine Gentamicin	NSAID

USG: Ultrasound NSAID: non-steroidal anti-inflammatory drugs

Table 2. Patterns of antibiotic exposure

Exposed antibiotics	Doses	Route	Startweek	Expiry week	Exposed period
Doxycycline	2x100 mg	p.o	2	3	1st trimester
Rifampicin	1x600 mg	p.o	2	3	1st trimester
Cefprozil	2x 500 mg	p.o	4	5	1st trimester
Ciprofloxacin	2x500 mg	p.o	4	5	1st trimester
Miconazole+ Metronidazole	1x200/750 mg	intravaginal	4	5	1st trimester
Ornidazole	2x500 mg	p.o	4	5	1st trimester
Cefazolin	2x1000 mg	i.m	3	4	1st trimester
Doxycycline	2x100 mg	p.o	2	3	1st trimester
Miconazole+ Metronidazole	1x200/750 mg	intravaginal	2	3	1st trimester
Amoxycillin Clavulanate	2x1000 mg	p.o	4	5	1st trimester
Azithromycin	1x500 mg	p.o	4	5	1st trimester
Doxycycline	1x100 mg	p.o	3	6	1st trimester
Metronidazole	2x500 mg	p.o	7	8	1st trimester
Doxycycline	2x100 mg	p.o	2	3	1st trimester
Ampicillin	4x1000 mg	i.m	6	7	1st trimester
Fucidic Acid	2x1	topical	6	7	1st trimester
Amoxycillin Clavulanate	2x1000 mg	p.o	3	6	1st trimester
Acyclovir	5x800 mg	p.o	1	2	Before conception
Fucidic Acid	2x1	topical	1	2	
Miconazole+Metronidazole	1x200/750 mg	intravaginal	0	2	Before conception
Ciprofloxacin+Ornidazole	2x500 mg	p.o	0	2	Before conception
Isoconazole	3x1	topical	0	2	Before conception
Amoxycillin Clavulanate	1x1000 mg	p.o	3	4	1st trimester
Gentamicin	1x160 mg	i.m	2	3	1st trimester
Clindamycin	1x150 mg	p.o	2	3	1st trimester
Fluconazole	1x200 mg	p.o	4	5	1st trimester
Ciprofloxacin	2x750 mg	p.o	5	6	1st trimester
Amoxycillin Clavulanate	2x1000 mg	p.o	6	7	1st trimester
Penicillin G Benzathine	1x 1.2 IU	i.m	0	1	Before conception
Ciprofloxacin	1x500 mg	p.o	0	6	1st trimester
Ampicillin Sulbactam	2x1000 mg	p.o	6	7	1st trimester
Ciprofloxacin	2x750 mg	p.o	4	5	1st trimester
Methenamine	1x1000 mg	p.o	4	5	1st trimester
Gentamicin	1x160 mg	i.m	4	5	1st trimester

p.o: per oral; i.v: intravenous; NSAID: nonsteroidal anti-inflammatorydrugs

DISCUSSION

TIS is the reproductive toxicology unit of Clinical Pharmacology Departments in hospitals in many countries and also in Turkey. Our work is to evaluate the teratogenic risks of drugs used by the pregnant women advertently or inadvertently during pregnancy. In this study, we evaluated the safety of antibiotics to expand human data about their use during pregnancy. We found that a total number of 20 pregnant women, who had exposed to the various amounts of antibiotics, resulted in two elective terminations, two spontaneous abortions, one hypothyroidism, and one small for gestational age (SGA) infant. The most common infectious diseases among pregnant women in this study were upper respiratory infection, vaginitis, dental abscess, and urinary tract infection, respectively. The most common antibiotics used by pregnant women were ciprofloxacin, amoxicillin-clavulanate, doxycycline, and metronidazole.

Upper respiratory infections include sinusitis, bronchitis, pneumonia, influenza, and the common cold. In respiratory tract infections, treatment is the same as in non-pregnant women. It is recommended to avoid the use of fluoroquinolones and tetracyclines in pregnancy because of their potential adverse effects on fetal cartilage, bones, and teeth due to the adverse outcomes in animal studies (6). However, there are studies reporting their safe use in human pregnancy (7,8). In our study, the women who were treated with fluoroquinolones due to their diagnosis vaginitis, urinary tract infection and inflammatory bowel diseases had no congenital anomalies in their babies. However, one woman under doxycycline treatment had gone to elective termination, particularly because of her concomitant drug lithium. In the present study, the pregnant women with respiratory tract infections used cefprozil, azithromycin, amoxicillin-clavulanate, penicillin G benzathine, and ampicillin-sulbactam, and gave birth to healthy infants. Beta-lactam antibiotics cross the placenta (9). Maternal use of beta-lactam antibiotics has generally not resulted in an increased risk of birth defects (10). Among macrolides, azithromycin has a good safety profile, although adverse pregnancy outcomes after exposure to clarithromycin were reported in animal studies. Gestational exposure to clarithromycin indicates that the drug seems not to increase major malformation rate above the baseline level (11).

In pregnant women with symptomatic candida vulvovaginitis, it is recommended to administer topical imidazole (clotrimazole or miconazole) because of possible risks with oral azole therapy in pregnancy (12,13). Recent studies found that oral fluconazole increased the abortion and malformation risks compared to unexposed women or women receiving vaginal azole therapy (12,14). Case reports described the birth defects after exposure to high-dose fluconazole (400-800 mg/day) in the first trimester (15). In a case-control study, the relationship between firsttrimester fluconazole use and cleft palate cleft lip and d-transposition of large arteries has been reported (16). However, epidemiological studies have reported that use of a single dose of low fluconazole (150 mg) in the first trimester to treat vaginal infection has not increased birth defects (17-19). Because topical therapy is an effective alternative to the oral route, vaginal treatment would be preferred until more data are obtained to support the safety of low-dose oral fluconazole therapy. In our study vaginitis treatment included miconazole, metronidazole, ornidazole, ciprofloxacin, isoconazole, clindamycin, and gentamicin. Vaginal topical azole products (7-day therapies only) are defined as the preferred treatment of vulvovaginal candidiasis in pregnant women as small amounts are absorbed systemically (20). We found that concomitant use of miconazole, metronidazole, ciprofloxacin, ornidazole, and isoconazole between 0-2nd weeks of pregnancy resulted in hypothyroidism in one infant. The newborn was delivered vaginally, had 38 weeks gestational age, and was 3500 gr in weight. The infant is currently treated with levothyroxine 25 µg/day.

It is interesting to note that the mothers who had spontaneous abortions in our study had dental abscesses, and maternally exposed to cefazolin and amoxicillin-clavulanate. Several hypotheses have been proposed to explain the relationship between periodontal disease and adverse pregnancy outcomes such as preterm birth (21-23). Periodontal flora is reported to cause local inflammation in the fetoplacental unit, and inflammatory mediators may cause systemic inflammation. Periodontal disease may result in an exaggerated local or systemic inflammatory response to bacteria in patients with genetic predisposition. In these diseases, periodontal-induced cytokine production increases, and may lead to preterm labor or premature rupture of membranes in these individuals (23). Co-exposed medications of these women with spontaneous abortions in our study were modafinil and nonsteroidal anti-inflammatory drugs (NSAIDs). It should be kept in mind that these spontaneous abortions may be due to early exposure of NSAIDs as well (24).

Untreated bacteriuriais associated with an increased risk of preterm birth, low birth weight and perinatal mortality (25). In our study, the women with urinary tract infections used amoxicillin-clavulonate, doxycycline, ciprofloxacin, methenamine, and gentamicin. The use of trimethoprim-sulfamethoxazole is reported to be avoided, typically in the first trimester and in the near term. Trimethoprim, a folic acid antagonist, is usually abstained for the first trimester, as it causes abnormal embryo development in animal studies, and some case-control studies have reported a possible relationship with various adverse birth outcomes (26,27). Folic acid supplementation may be necessary in trimethoprim exposed women. Sulfonamides should be prevented in the last days before delivery because they can differentiate bilirubin from the plasma binding sites in the newborn. Sulfonamides have also been associated with birth defects in a case-control study (26). Aminoglycosides are associated with ototoxicity following prolonged fetal exposure (28) and should, therefore, be avoided.

The maternal use of doxycycline between the 3-6th weeks of pregnancy and the use of acyclovir between the 1-2nd weeks of pregnancy resulted in elective termination in our study. Both of their diagnosis were acne vulgaris, and they additionally had used teratogenic other medications, isotretinoin, and lithium. In both cases, it is evident that pregnant women had elective abortions because of the known teratogenic effects of their concomitant drugs. One infant, whose mother had Crohn disease, was exposed to ciprofloxacin for the first six gestational weeks and was born SGA (2600 g). Maternal drugs of this case had additionally included azathioprine, mesalazine, and prednisolone. The low birth weight, in this case, may be due to azathioprine, concomitant medications, or the underlying maternal illness.

We have some limitations in this study. In the first application to the TIS, the information of the pregnant women was obtained by the questionnaire conducted face to face. However, delivery results of pregnant women were obtained by structured telephone calls. Follow-up of structured questionnaires and postnatal telephone calls are prerequisite for evaluating birth results in teratogenic drug analysis. These prerequisites are currently the way all TISs implement worldwide. However, the fact that we could not provide patient protocol files at the time of delivery may cause data limitations. Children should have at least 2 years of follow-up to avoid missing congenital anomalies. Abortions should be examined by autopsy or genetic evaluations to investigate causes of death. Finally, we have a limited sample size and lack of a control group as this is a retrospective observational study. However, this study may be considered as a small contribution to the existing pool of knowledge until epidemiological studies on antibiotic use during pregnancy have been completed.

CONCLUSION

The two main goals of medical treatment of pregnant women for infection are to control maternal infection and to maintain the safe well-being of the fetus. The use of unnecessary antibiotic therapy makes an important contribution to the antibiotic resistance, drug-related adverse effects, and fetal adverse outcomes. Thus, these agents in pregnancy should be used only when indicated, choosing those with the narrowest range possible. The problem arising from the lack of data on the use of many antibiotics during pregnancy can only be solved by reporting individual original reports and contributing to the literature pool of teratogenesis in accordance with international teratology services.

Competing interests: The authors declare that they have no competing interest.
Financial Disclosure: There are no financial supports
Ethical approval: The study was approved by the Ethics Committee of Clinical Trials of the Faculty of Medicine (Approval Date: 24.10.2018; Approval No: 2018/19/13).

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