Coll. Antropol. **32** (2008) 3: 919–925
Original scientific paper

Teratogenicity of Antibacterial Agents

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A B S T R A C T

The aim of our study was to study the possible correlation between use of antibacterial drugs in pregnancy and occurrence of congenital malformations. Among 6099 investigated pregnant women, 392 (6.43%) used antibacterial drugs. The most frequently used antibacterials belonged to category B (75.77%), while 14.54% antibiotics belonged to category D and 1.02% to category X. The most often used antibiotics were cephalexin (22.19%), amoxicillin (20.66%) and ampicillin (14.29%). In 14 embryos exposed to effects of beta-lactams in utero, malformations were detected. The results of this study show possible teratogenic potential even with those antibacterials which are considered safe, but as those are usually minor malformations, they often pass undetected. Because of that and because of frequent use of antibacterials during pregnacy, detailed examinations concerning their safety should be made.

Key words: *antibiotics, adverse effects, pregnancy+drug effects, pregnancy complications, fetus+drug effects, teratogens, abnormalities*

Introduction

An International multicentric study entitled Collaborative Study on Drug Use in Pregnancy (DUP) was initiated in 1987 by the Mario Negri Institute (Milano) and co-sponsored by the WHO Regional Office for Europe (Copenhagen). There were 22 countries involved in 4 continents, among which two centers from former Yugoslavia: Zagreb and Novi Sad. The study covered drug use in pregnancy and puerperium. Novi Sad participated with 296 questionnaires performed on pregnant women, who were admitted to the Clinic for delivery. The prescription of some medicines in the Centre of Novi Sad was found to be at the extreme, mainly in the postpartum period. Therefore educational efforts were made in order to improve prescribing habits, and 10 years later, considerable improvements were seen. However, this sample was limited in number, covering only 100 pregnent women[1,2]. Therefore, in 2001 year, the study about drug use in pregnancy was repeated on all pregnant women who were admitted to the Department of Obstetrics and Gynecology for delivery and to Genetics Counseling Department at the Institute for Child and Youth Health Care.

Administration of antibacterials during pregnancy is very common[3,4]. It is well known that pharmacoepidemiological studies dealing with prescription of drugs in pregnancy are numerous[5–7]. Results showed, that only exceptionally drugs that are used in pregnancy have been proven teratogenic. However, little is known about subtle effects of drugs on fetal development, particularly when dealing with old drugs[8–13].

According to the Food and Drug Administration all drugs can be classified in 5 risk groups. Risk factors (A, B, C, D and X) have been assigned to all drugs on the level of risk the drug poses to the fetus. Risk factors are designed to help the reader to classify quickly a drug for use during pregnancy. They do not refer to breast feeding risk. Drugs from category A and B are safe, drugs from category C should be given only if the potential benefit justifies the potential risk to the fetus, drugs from category D should be given only in a life-treatening situation or for a serious disease for which safer drugs cannot be used or are ineffective. The risk of the use of the drugs from category X in pregnant women clearly outweighs any possible benefit[14].

Penicillins and cephalosporins, according to FDA classification of drugs based on safety for the fetus belong to category B. Therefore they belong to the most often used drugs in pregnancy[10,14–17]. Nevertheless, some recent papers report presence of teratogenic potential of these

Received for publication June 20, 2007

drugs[18–22]. Therefore the aim of our study was to establish the possible correlation between use of antibacterial drugs in pregnancy and occurrence of congenital malformations.

Materials and Methods

The data for this study were collected as a part of the study analysing the teratogenicity of drugs used in pregnancy, a longitudinal study performed in Novi Sad district, designed to investigate the potential teratogenicity of the drugs.

The independent Ethics Committee of the Faculty of Medicine, Novi Sad, approved the study. Pregnant women attending the Clinics of University Teaching Centre in 2001 were eligible to be involved.

The study was performed from Jan 1st – Dec 31st 2001 and involved the women who terminated pregnancy for medical reasons or delivered during the observed period. Only women willing to participate in the study who signed informed consent forms were included. All participating women were interviewed.

The sources of the data were:

- the questionnaires for pregnant women given by the doctor during the hospitalization at the Department of Gynecology and Obstetrics or at Genetics Counseling Department
- detailed physical examination of newborn babies in order to establish the presence of major or minor malformations, examination performed according to a standard protocol, done by trained pediatricians
- pathophysical examination of fetuses performed according to a standard protocol, done by trained pathologists.

In the Department of Gynecology and Obstetrics and in Genetics Counseling Department of Novi Sad, 6099 questionnaires were filled by pregnant women during 2001. The questionnaire, based on the questionnaire of the year 1987, was designed at the Department of Pharmacology, Toxicology and Clinical Pharmacology, Faculty of Medicine in Novi Sad. Maternal data were collected retrospectively by interviewing the participating women before delivery. Questionnaires were fulfiled by a trained, highly qualified medical doctor. Information requested on the questionnaire included mother's data (age, education, obstetrical history), and drug therapy, as well as use of alcohol, caffeine, nicotine and narcotics during pregnancy. Only the women who took antibiotics during pregnancy were analysed. Altogether, 392 pregnant women were included in final analysis. After delivery or abortion, newborn and fetuses were analysed in order to establish existence of minor or major malformations.

The use of antibacterials was analysed according to their use in first, second or third trimester of pregnancy. Antibacterials used by pregnant women were categorized by risk of harmful effect on fetus in 5 categories according to FDA.

Results

Out of the total number of pregnant women 2013 (33.00%) of them used medications (Figure 1).

All drugs used during pregnancy, and malformations which were detected in their fetuses or newborns are presented in Table 1.

Out of the total number of pregnant women that used medications during pregnancy (2013 pregnant women) 392 (19.5 %) used antibacterial drugs (Figure 2). Malfor-

TABLE 1
MEDICATIONS USED DURING THE PREGNANCY AND CONGENITAL MALFORMATIONS IN FETUSES OR NEWBORN BABIES

Class of drugs	number of pregnant women N	number of malformed fetuses or newborn n	(n/N)%	(N/6099)%	(n/6099)%
J	392	20	5.10	6.43	0.33
G	289	13	4.50	4.74	0.21
A	449	18	4.01	7.36	0.30
B	442	15	3.39	7.25	0.25
N	166	12	7.23	2.72	0.20
C	102	5	4.90	1.67	0.08
R	23	1	4.35	0.38	0.02
H	2	0	0	0.03	0
G*	536	28	5.22	8.79	0.46
D	5	0	0	0.08	0
M	22	1	4.55	0.36	0.02

J – drugs for infections, G – drugs for genitourinary disorders, A – drugs for alimentary tract disorders and metabolism, B – drugs for blood disorders, N – drugs for CNS disorders, C – drugs for cardiovascular disorders, R – drugs for respiratory disorders, H – drugs for hormonal disorders, G* – drugs for delivery and it's complications (Tocolitics), D – drugs for dermatological disorders, M – drugs for musculosceletal disorders

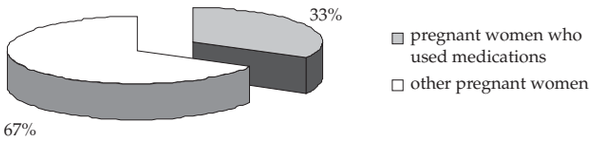

Fig. 1. Usage of medications during pregnancy.

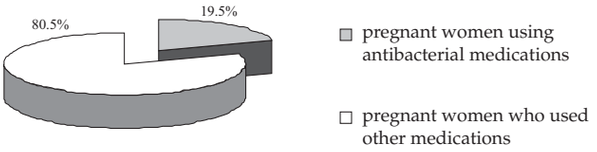

Fig. 2. Usage of antibacterial medications during pregnancy.

mations were detected in 20 (5.1%) cases. The prevalence of malformations in newborns whose mothers did not take antibiotics in pregnancy was 5.4% (5707 pregnant women; 306 newborns with malformations).

The use of antibacterial drugs in each trimester of pregnancy was as follows: 44.6% in the first trimester, 21% in the second trimester and as much as 37.9% in the third trimester (Figure 3).

The most frequently used antibacterial medications were from category B (75,8%), while 14.5% antibiotics belonged to category D and 1.0% to category X (Figure 4).

The most often used antibiotics were cephalexin (87 pregnant women), amoxicillin (81 pregnant women) and ampicillin (56 pregnant women), all belonging to group

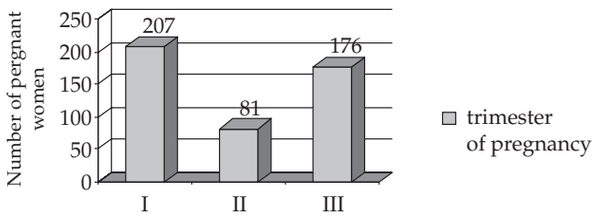

Fig. 3. Usage of antibacterial drugs in pregnancy by trimesters.

B. They were all used throughout pregnancy. Tetracyclines, sulfonamides, aminoglycosides and quinolones, which belonged to groups C (sulfonamide-trimethoprim combinations, erythromycin estolate, ciprofloxacin, norfloxacin) and D (doxycycline, streptomycin, gentamicin), were used in the first trimester of pregnancy. This period is not harmful as the goal organs as not developed yet (Table 2).

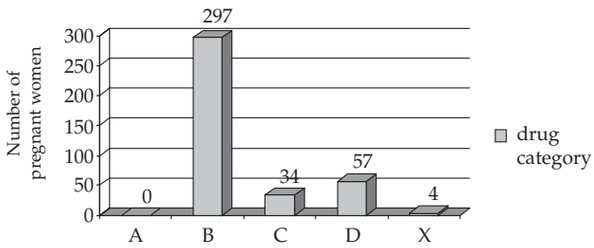

Fig. 4. Usage of antibacterial drugs during pregnancy and risk from harmful effects on the fetus.

TABLE 2
ANTIBACTERIAL AGENTS USED BY PREGNANT WOMEN

Type of antibacterial drugs	Name of drug	Pharmacotherapeutic subgroup (ATC)	Number of pregnant women using the drug	Trimester of pregnancy		
				I	II	III
TETRACYCLINES	doxycycline	J01AA02	41	41	–	–
PENICILLINS	ampicillin	J01CA01	56	18	12	32
	amoxicillin	J01CA04	81	32	27	43
	penicillin G	J01CE	43	10	17	21
	amoxicillin, clavulanic acid	J01CR02	12	8	3	4
CEPHALOSPORINS	cephalexin	J01DA01	87	34	18	69
	cefaclor	J01DA08	10	8	1	4
	ceftriaxone	J01DA13	7	2	2	3
SULFONAMIDES	sulfonamide- trimethoprim combinations	J01EE01	13	13	–	–
MACROLIDE ANTIBIOTICS	erythromycin estolate	J01FA01	11	11	–	–
AMINOGLYCOSIDE ANTIBIOTICS	streptomycin	J01GA01	1	1	–	–
	gentamicin	J01GB03	15	15	–	–
QUINOLONES	ciprofloxacin	J01MA02	9	9	–	–
	norfloxacin	J01MA06	1	1	–	–
NITROIMIDAZOLES	metronidazole	J01XD01	5	4	1	–

Malformations which were detected on fetuses exposed to antibacterial drugs and trimester of exposure are shown in Table 3. We detected one major malformation (hypospadias) in newborn exposed to amoxicillin during the first trimester after conception. In this case, additional teratogens were not detected.

The use of antibiotics together with another potential teratogen during pregnancy is shown in Table 4.

Discussion

Stages of pregnancy that are critical with respect to possible harmful effects of medications on the developing fetus are still inexplicitly defined and potential risks of drugs for mother and the fetus are faintly understood, thus question of medication use during pregnancy still remains a chronic and everlasting problem. A comprehensive monitoring of the use of medicines in a particular environment over a long period of time can decrease the risk of harmful effects of drugs during pregnancy through proper evaluation of pharmacotherapy during pregnancy, and if necessary, through appropriate educational measures towards improvement of pharmacotherapeutical practice.

Drug prescribing for pregnant women has been monitored in Novi Sad since 1987, when, in the framework of international Collaborative Study on Drug Use in Pregnancy (DUP), the investigation included 296 pregnant women. The second pilot study, encompassing 100 pregnant women was conducted in 1999, and in 2001 the third, by now the longest study performed, which lasted during the whole year 2001[1,2,26].

Penicillins and cephalosporins were the most frequently used antibiotics during pregnancy. Beta-lactam antibiotics are widely used because of their lack of toxicity in humans. However, during pregnancy, exposure of the fetus is likely to occur because beta-lactam antibiotics cross the placenta[18]. From previous data, it is unlikely that penicillins and cephalosporins are teratogenic[14]. Only one reference has linked the use of penicillin G with congenital abnormalities: an examination of hospital records indicated that in three of four cases the administration of penicillin G had been followed by birth of a malformed baby. However, due to uncompleted analysis of the data no causal relationship to penicillin G could be shown[19,20]. According to Briggs (1998), the use of ampicillin in early

TABLE 3
DETECTED MALFORMATIONS ON FETUSES WHICH WERE EXPOSED TO ANTIBACTERIAL DRUGS

Name of drug	Risk category	Number of fetuses with malformations	Type of malformation	Trimester of pregnancy		
				I	II	III
doxycycline	D	1	diastasis of rectal abdominal muscle	1	–	–
ampicillin	B	3	short lingual frenulum (2x), right ear flap	1	–	2
amoxicillin	B	4	short lingual frenulum, hypospadias, talipes valgus of the right foot, micrognathia	1	1	2
penicillin G	B	3	syndactyli of the 2nd and 3rd toe in both feet, four fingers line, cyst of choroid plexus	2	–	1
amoxicillin, clavulanic acid	B	1	right ear flap	1	–	–
cephalexin	B	2	cyst of choroid plexus, short lingual frenulum	1	–	1
cefaclor	B	1	syndactyli of the 2nd and 3rd toe of the left foot	1	–	–
ceftriaxone	B	0	–	–	–	–
sulfonamide-trimethoprim combinations	C (D in 3/3)	2	hydronephrosis of both kidneys, cyst of choroid plexus	2	–	–
erythromycin estolate	C	0	–	–	–	–
streptomycin	D	0	–	–	–	–
gentamicin	D	2	cyst of choroid plexus, talipes valgus of both feet	2	–	–
ciprofloxacin	C	1	cyst of choroid plexus	1	–	–
norfloxacin	C	0	–	–	–	–
metronidazole	B (X in 1/3)	0	–	–	–	–

TABLE 4
EXPOSURE OF PREGNANT WOMEN TO EFFECTS OF ANTIBACTERIALS TOGETHER WITH ANOTHER POTENTIAL TERATOGEN

Name of drug	Trimester of pregnancy	Use with another potential teratogen	Findings on fetuses and newborns
doxycycline	I	3 women older than 35 years	negative
	II	1 HB positive woman	jaundice precocious
ampicillin	II	1 woman with pneumonia, 1 woman older than 35 years	negative
	I	1 woman exposed to X-ray	right ear flap
	III	2 women who smoked up to 10 cigarettes per day	negative
penicillin G	II	1 woman with pneumonia	negative
	I, III	2 women older than 35 years	negative
	I	1 woman was exposed to X-ray	short lingual frenulum
cephalexin	III	contact with varicella (chickenpox)	negative
	III	2 women older than 35 years	negative
ceftriaxone	I	1 woman was exposed to X-ray	negative
erythromycin estolate	I	1 woman was exposed to X-ray	negative
streptomycin	I	1 woman was exposed to X-ray	negative
gentamicin	I	1 woman who smoked up to 10 cigarettes per day	cyst of choroid plexus
ciprofloxacin	I	1 woman was exposed to X-ray	negative

pregnancy was associated with a prevalence ratio estimate of 3.3 for congenital heart disease in a retrospective study[14]. A specific defect, transposition of the great arteries, had a risk of 7.7 based on exposure in 2 of the 29 infants with anomaly. The investigators did note that the results had to be viewed cautiously because the data were subject to recall bias (drug histories were taken by questionnaire or telephone up to one year after presumed exposure) and the study could not distinguish between the fetal effects of the drug versus those of the infectious agent for which the drugs were used[21]. The prenatal administration of amoxicillin on fetuses of mice at doses of 500 or 650 mg/kg body weight resulted in both teratogenic and toxic effects on fetuses of treated mothers. Such effects comprised the development of abnormal hindlimbs and tails. The drug was safe to treated dams at all dose levels and at all times during gestation[22]. In young rats exposed to ampicillin and amoxicillin in utero, a mild oligonephronia was present and cystic tubule dilation was observed in newborn and in young animals as well[18].

In our study 192 pregnant women used penicillins. Malformations were detected in 11 fetuses (5.7%). In newborns exposed to ampicillin activity in utero short lingual frenulum in 2 and right ear flap in 1 newborn were detected. Out of the 3 newborns which were born with minor malformations, 1 was exposed to X-rays during the preconception period. However, this X-ray exposition is probably not the cause of minor malformation that we detected. In newborns exposed to amoxicillin activity in utero short lingual frenulum (1 newborn), hypospadias (1 newborn), talipes valgus of the right foot (1 newborn) and micrognathia (1 newborn) were detected. These newborns were not exposed to another potential teratogens. The results show possible teratogenic potential of amoxicillin. In newborns exposed to penicillin G activity in utero syndactyli of the 2nd and 3rd toe in both feet (1 newborn), four fingers line (1 newborn) and cyst of choroid plexus (1 newborn) were detected.

Several published reports have described the administration of cephalosporins to pregnant patients in various stages of gestation[23,24]. None of these have linked the use of cephalosporins with congenital defects or toxicity in the newborn[14,25,26].

In our study 104 pregnant women used cephalosporins. Malformations were detected in 3 newborns (2.9%). In newborns exposed to cephalexin activity in utero, cyst of choroid plexus (1 newborn) and short lingual frenulum (1 newborn) were detected. One newborn with short lingual frenulum was exposed to X-rays during the first trimester after conception. X-ray exposure could theoretically contribute to appearance of the malformation. In 1 newborn exposed to cefaclor activity in utero, syndactyli of the 2nd and 3rd toe of the left foot was detected. This newborn was not exposed in utero to other potential harmful factors.

Tetracyclines are a class of antibiotics that should be used with extreme caution, if at all, in pregnancy. Problems attributable to the use of the tetracyclines during the gestational period can be classified into four areas: adverse effects on fetal teeth and bones, maternal liver toxicity, congenital defects and miscellaneous effects. Tetracycline forms a complex with calcium orthophosphate and becomes incorporated into bones and teeth undergoing calcification. In the latter structure, this complex

causes a permanent discoloration, as remodeling and calcium exchange do not occur after calcification is completed. Because the deciduous teeth begin to calcify at around 5 or 6 month in utero, use of tetracycline after this time will result in staining. They belong to category D, regarding harmful effects on the fetus[14,27].

In our study 41 pregnant women used tetracyclines, most of them in the first trimester. Malformations were detected in 1 newborn (2.4%). It was a minor malformation, diastasis of rectal abdominal muscle and the newborn was not exposed in utero to another known potential teratogen.

Sulfonamides belong to category B regarding harmful effects on the fetus during the first and second trimester and to category D during the third trimester. Sulfonamides are teratogenic in some species of animals, a finding that has prompted warnings of human teratogenicity. Investigators associated in utero sulfonamide exposure with tracheoesophageal fistula, cataracts, ductus arteriosus persistens, hypoplasia of limb, miscellaneous foot defects, urethral obstruction, hypoplasia or atrophy of adrenals, hypospadias[28–30]. Combination of sulfonamide and trimethoprim, co-trimoxasole (category C), shouldn't be used during pregnancy due to the activity of trimethoprime in the metabolism of folates[31,32].

In our study 13 pregnant women used sulfonamides. Malformations were detected in 2 fetuses (15.4%). We detected hydronephrosis of both kidneys in 1 fetus and cyst of choroid plexus in 1 newborn. In these cases exposition to other potential teratogens during pregnancy was not detected.

Aminoglycosides may cause side effects in the fetus and in mother when given in pregnancy, so they should be used in pregnancy only in exceptional situations when other antibiotics are not efficient or cannot be applied. They belong to category D regarding harmful effects on the fetus. Eighth cranial nerve toxicity in the fetus is well known following exposure to aminoglycosides like streptomycin and may potentially occur with gentamicin[14].

In our study 16 pregnant women used aminoglycosides. All examined pregnant women used gentamicin and streptomycin in the first weeks of pregnancy, which is not a harmful period. Malformations were detected in 2 newborns (12.5%). In newborns exposed to gentamicin activity in utero, a cyst of choroid plexus (1 newborn) and talipes valgus of both feet (1 newborn) were detected. The newborn with the cyst of choroid plexus was exposed to nicotine (his mother smoked up to 10 cigarettes per day during the first trimester).

The use of quinolones during pregnancy does not appear to be associated with an increased risk of major congenital malformations. Although a number of birth defects have occurred in the offspring of women who had taken this drug during pregnancy, the lack of a pattern among the anomalies is reassuring. However, a causal relationship with some of the birth defects cannot be excluded. A 1993 review on the safety of fluoroquinolones confirmed that these antibacterials should be avoided during pregnancy because of the difficulty in extrapolating animal mutagenicity results to humans and because interpretation of this toxicity is still controversial[33]. The authors of this review were not convinced that fluoroquinolones induced fetal cartilage damage and subsequent arthropathies were a major concern, even though this effect had been demonstrated in several animal species after administration to both pregnant and immature animals and in occasional human case reports involving children. Others have also concluded that fluoroquinolones should be given with extreme caution, because safer alternatives are usually available[34].

In our study 10 pregnant women used quinolone antibiotics. All examined pregnant women used medications from this group in the first weeks of pregnancy. Malformations were detected in 1 newborn (10%). In newborns exposed to ciprofloxacin activity in utero, a cyst of choroid plexus (1 newborn) was detected. The newborn was not exposed to another teratogen in pregnancy.

The available reports have arrived at conflicting conclusions on the safety of metronidazole in pregnancy[35].

In our study 5 pregnant women used nitroimidazoles. Malformations were not detected in their fetuses.

Analysis of antibiotic prescribing in the period 1989–2002 revealed a distinct decreasing tendency. Such trends of reduction of drugs during pregnancy strongly suggest that healthcare providers, as well as their patients, are aware of potential risks of medications for pregnancy and development of the fetus. It is well established that first-trimester exposure to drugs is critical for the fetus. At advanced stages of pregnancy most of the drugs may result in individual minor malformations. Thus, abandonment of particular medication after first or second trimester does not necessarily imply ceasing of its potential harmful effects on the fetus, mother or pregnancy course. All this emphasized the need for urgent educational efforts aimed at instructing medical professionals, as well as the women in reproductive period. The scope of such education is threefold, i.e.: 1. the pregnancy should be planned whenever possible 2. in all cases when monthly period is late, if possible within the »all-or-nothing« period (the first 21 days of pregnancy) it is necessary to confirm pregnancy, and if so, withdraw the use of all medications; and 3. healthcare providers should take into account that all their patients may be pregnant, thus the therapy of choice should include medications from the group B or at least C, as well as continuous monitoring of the patient's health status.

Conclusions

According to our investigation pregnant women most frequently used antibacterial agents in the first trimester of pregnancy (207 pregnant women; 52.8 %). They used 15 different antibacterial medications, most often beta lactam antibiotics: cephalexin – 87 pregnant women (22.2 %); amoxicillin – 81 pregnant women (20.7 %); ampicillin – 56 pregnant women (14.3 %); penicillin G – 43 pregnant women (11.0 %). The most frequently used

antibacterial were drugs from category B according to harmful effects to the fetus (297 pregnant women; 75.8 %). The prevalence of malformations in newborns whose mothers did not take antibiotics in pregnancy was 5.4% and the prevalence of malformations in newborns whose mothers did take antibiotics in pregnancy was 5.1%. In 20 embryos exposed to effects of antibacterials *in utero* malformations were detected (19 minor, 1 major malformations). Ten fetuses/newborns with minor malformations and one with a major malformation were exposed *in utero* to penicillins, that is 5.7% of the total number of fetuses exposed to penicillins. Short lingual frenulum was detected in 3 cases, additional teratogens were not detected. In publications up to now, these malformations have not been described as a result of the use of penicillins in pregnant women. The results of this study show possible teratogenic potential even with those antibacterials which are considered safe (amoxicillin-hypospadias), but as those are usually minor malformations they often pass undetected. Because of that and because of frequent use of antibacterials during pregnancy, detailed examinations concerning their safety should be made.

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TERATOGENOST ANTIBAKTERIJSKIH LIJEKOVA

SAŽETAK

Cilj naše studije bio je utvrditi moguću povezanost između uporabe antibakterijskih lijekova u trudnoći i učestalosti kongenitalnih malformacija. Od 6099 ispitivanih trudnica, 392 (6,43%) su koristile antibakterijske lijekove. Najčešće su rabljeni antibakterijski lijekovi koji pripadaju kategoriji B (75,77%), dok je 14,54% antibiotika pripadalo kategoriji D, a 1,02% kategoriji X. Najčešće rabljeni antibiotici bili su cefaleksin (22,19%), amoksicilin (20,66%) i ampicilin (14,29%). Malformacije su dijagnosticirane kod 14 plodova koji su *in utero* bili izloženi djelovanju beta-laktamskih antibiotika. Rezultati ove studije ukazuju na moguć teratogeni potencijal antibakterijskih lijekova koji se smatraju sigurnim, ali kako se većinom radi o minor malformacijama, one često ostaju nezapažene. Zbog toga i zbog česte uporabe antibakterijskih lijekova u trudnoći, potrebno je sprovesti detaljna istraživanja o sigurnosti njihove primjene.