

β -lactam antibiotics during pregnancy: a cross-sectional comparative study Zagreb-Novi Sad

M. ERIC¹, M. LEPPÉE², A. SABO³, J. CULIG^{2,4}

¹Department of Anatomy, School of Medicine, University of Novi Sad, Novi Sad (Serbia)

²Department of Pharmacoepidemiology, Andrija Stampar Institute of Public Health, Zagreb (Croatia)

³Department of Pharmacology, Toxicology and Clinical Pharmacology, School of Medicine, University of Novi Sad, Novi Sad (Serbia)

⁴Department of Pharmacology, School of Medicine, Josip Juraj Strossmayer University Osijek, Osijek (Croatia)

Abstract. – Background and Objectives: During pregnancy, a number of changes occur in women's body, and some medications are safe and some are not. The aim of our study was to establish the possible correlation between use of β -lactam antibiotics in pregnancy and occurrence of congenital malformations.

Material and Methods: The study included 893 pregnant women from Zagreb and 6099 pregnant women from Novi Sad. 527 pregnant women used β -lactams. First part of the study (one month study) was performed at four maternity hospitals in Zagreb, Croatia. Second part were collected as a part of the study analysing the teratogenicity of drugs used in pregnancy, a longitudinal study performed in Novi Sad district.

Results: Pregnant women most frequently used antibacterial agents in the first trimester of pregnancy. They used 15 different antibacterial medications, most often β -lactams. In Zagreb arm, out of the total number of pregnant women that used medications during pregnancy (859), 231 (26.9%) used β -lactam antibiotics. Malformations were detected in 8 (3.5%) cases. The prevalence of malformations in newborns whose mothers did not take β -lactam antibiotics in pregnancy (662) was 2.7% (18 newborns with malformations). In Novi Sad arm, out of the total number of pregnant women that used medications during pregnancy (2013), 296 (14.7%) used β -lactam antibiotics. Malformations were detected in 14 (4.7%) cases. The prevalence of malformations in newborns whose mothers did not take β -lactam antibiotics in pregnancy (5803) was 1.7% (99 newborns with malformations).

Discussion: The results show possible teratogenic potential even with those antibacterials which are considered safe (amoxicillin) but as those are usually minor malformations they often pass undetected. International pharmacoepidemiological studies of drug use in pregnancy could substantially contribute to the improvement of pharmacotherapy, and could be of great help in assessing the fetal risks.

Key Words:

β -lactam antibiotics, Pregnancy, Congenital malformations, Zagreb, Novi Sad.

Introduction

During pregnancy, a number of changes occur in women's body, and some medications are safe and some are not. Some require a higher than usual dose, and some doses change with the advancing pregnancy. Prescribing drugs during pregnancy poses a challenge to the physician to balance optimal treatment of the maternal symptoms and disease against possible harm to the foetus^{1,2}.

Pharmacoepidemiological studies dealing with prescription of drugs in pregnancy are numerous^{1-2,4,5}. Epidemiological studies of pregnancy outcome after specific drug exposures are often superficially reassuring, but most are severely limited in their power to detect adverse outcomes⁶. 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 drugs⁷⁻⁸. Controlled studies of drug use during pregnancy cannot be performed for ethical reasons. Therefore, data can only be obtained from animal experiments, general databases, professional literature, and individual reports on sporadic use of drugs in pregnancy⁹.

According to the Food and Drug Administration (FDA) all drugs can be classified in five 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-threatening 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 benefit¹⁰.

An International multicentric study entitled Collaborative Study on Drug Use in Pregnancy (DUP) was initiated in 1987 by the Mario Negri Institute (Milan, Italy) and co-sponsored by the WHO Regional Office for Europe (Copenhagen). There were 22 countries involved in four continents, among which two centers from former Yugoslavia: Zagreb and Novi Sad. 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 pregnant women¹¹.

Administration of antibacterials during pregnancy is very common^{12,13}. Beta-lactam antibiotics represent the oldest class of antibiotics used in the treatment of infections, and they are the most widely-used group of antibiotics in pregnancy. Beta-lactam antibiotics are bactericidal antibiotics that inhibit the synthesis of cell walls of sensitive bacteria¹⁴. There are a broad class of antibiotics that include penicillin derivatives (penams), cephalosporins (cephems), monobactams, and carbapenems¹⁵ that is, any antibiotic agent that contains a β -lactam nucleus in its molecular structure.

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^{16,17}. Nevertheless, some recent papers report presence of teratogenic potential of these drugs¹⁸. 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

First part of the study (one month study) was performed at four maternity hospitals in Zagreb, Croatia: University Department of Gynecology

and Obstetrics, Zagreb University Hospital Center; University Department of Gynecology and Obstetrics, Sestre Milosrdnice University Hospital; University Department of Gynecology and Obstetrics, Merkur University Hospital; and University Department of Gynecology and Obstetrics, Sveti Duh General Hospital (part 1).

Second part 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.

This part of the study (one year study) was performed at the Genetic Counseling Unit, Institute for Children and Adolescents, University Department of Gynecology and Obstetrics, and Department of Pathology and Histology, Clinical Center in Novi Sad, Serbia, included pregnant women presenting to the Genetic Counseling Unit for risky pregnancy and pregnant women hospitalized at University Department of Gynecology and Obstetrics for delivery or abortion (part 2).

The study included 893 pregnant women from Zagreb and 6099 pregnant women from Novi Sad. An informed consent on their participation in the study was obtained from all study subjects.

Data were collected from the following sources:

1. Questionnaire for pregnant women, filled in by a physician, containing two types of data: hospital records and information obtained by interview;
2. Thorough physical examination of the neonate, performed by a neonatologist according to standard protocol; and
3. Thorough pathologic examination of the fetus, performed by a pathologist according to standard protocols.

The questionnaire, based on the validated questionnaire of the year 1987, was designed. Maternal data were collected retrospectively by interviewing the participating women before delivery. Questionnaires were fulfilled by a trained, highly qualified medical doctor. Information requested on the questionnaire included mother's data (age, education, obstetrical history), and drug therapy, use of contraception, ultrasound (US) studies, x-rays, as well as use of alcohol, caffeine, nicotine and narcotics during pregnancy. Only the women who took beta-lactam antibiotics during pregnancy were analysed. Altogether, 527 (231 from Zagreb and 296 from Novi Sad) 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 beta-lactams 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. Vital data on the newborns and maternal data on previous deliveries and on medication taken between hospital admission and delivery were collected from hospital records.

The independent Ethics Committees of the School of Medicine, Zagreb and Faculty of Medicine, Novi Sad, approved the study. Student's *t*-test and Chi-square test with a significance level of $p \leq 0.05$ were used when appropriate for the evaluation of the results.

Statistical Analysis

All analysis were performed with SigmaStat 3.0 for Windows (SPSS Science software products, Chicago, IL, USA).

Results

Zagreb Arm

Out of the total number of pregnant women (893), 859 (96.2%) of them used medications. Out of the total number of pregnant women that used medications during pregnancy (859), 231 (26.9%) used β -lactam antibiotics. Malformations were detected in 8 (3.5%) cases. The prevalence of malformations in newborns whose mothers did not take β -lactam antibiotics in pregnancy (662) was 2.7% (18 newborns with malformations). The most frequently used β -lactam antibiotics were from FDA category B (146; 63.2%), while 85 (36.8%) β -lactam antibiotics belonged to category C.

Novi Sad Arm

Out of the total number of pregnant women (6099), 2013 (33.0%) of them used medications. Out of the total number of pregnant women that used medications during pregnancy (2013), 296 (14.7%) used β -lactam antibiotics. Malformations were detected in 14 (4.7%) cases. The prevalence of malformations in newborns whose mothers did not take β -lactam antibiotics in pregnancy (5803) was 1.7% (99 newborns with malformations). All β -lactam antibiotics used in

Novi Sad were from FDA (Food and Drug Administration) category B (296; 100%).

All drugs used during pregnancy and number of malformations detected in their fetuses or newborns are presented in Table I.

The most often used β -lactam antibiotics in Zagreb were cephalexin (55 pregnant women), amoxicillin (47 pregnant women). Cefuroxime-axetil and amoxicillin-clavulanic acid combination (38 pregnant women) were used throughout pregnancy too.

The most often used β -lactam antibiotics in Novi Sad were cephalexin (87), amoxicillin (81) and ampicillin (56). Penicillin G (43) and amoxicillin-clavulanic acid combination (12) were used throughout pregnancy too (Table II).

Malformations which were detected on fetuses exposed to β -lactam antibiotics and trimester of exposure are shown in Table III. We detected eight malformations in Zagreb arm (three malformations of osteomuscular system, two of cardiovascular and the same number of the head and neck malformations and one of urogenital system). In Novi Sad arm, 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. In this part of the study we detected 13 minor malformations.

The use of β -lactam antibiotics together with another potential teratogen during pregnancy is shown in Table IV.

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 Zagreb and Novi Sad since 1987, in the framework of International Collaborative

Table I. Medications used during pregnancy and congenital malformations in fetuses or newborn babies (Zagreb and Novi Sad).

Class of drugs	Nr. of pregnant women (N)		Nr. of malformed fetuses or newborn (n)		(n/N) %		(N/893) % Zagreb	(N/6099) % Novi Sad	(n/893) % Zagreb	(n/6099) % Novi Sad
	Zagreb	Novi Sad	Zagreb	Novi Sad	Zagreb	Novi Sad				
A	736	449	16	18	2.17	4.01	82.42	7.36	1.79	0.30
B	310	442	12	15	3.87	3.39	34.71	7.25	1.34	0.25
J	289	392	8	20	2.77	5.10	32.36	6.43	0.90	0.33
G	386	289	8	13	2.07	4.50	43.23	4.74	0.90	0.21
N	382	166	6	12	1.57	7.23	42.78	2.72	0.67	0.20
C	132	102	3	5	2.27	4.90	14.78	1.67	0.34	0.08
R	30	23	0	1	0.00	4.35	3.36	0.38	0.00	0.02
M	8	22	0	1	0.00	4.55	0.90	0.36	0.00	0.02
D	136	5	0	0	0.00	0.00	15.23	0.08	0.00	0.00
H	32	2	0	0	0.00	0.00	3.58	0.03	0.00	0.00

Study on Drug Use in Pregnancy (DUP). In Novi Sad the second pilot study, encompassing 100 pregnant women was conducted in 1999¹⁹.

In the meantime, usage of medications in pregnancy becomes more rational, including antimicrobials. Rationalization of the antimicrobial usage in pregnancy is very important to reduce fetal risk of congenital malformation and, on the other hand, reduces antimicrobial resistance²⁰⁻²².

A multicenter trial of the prevalence and spectrum of urinary infection agents, their resistance to beta-lactame antibiotics in pregnant women in Russia was conducted in two stages. Stage 1 (2001) included microbiological studies, stage 2 (2005-2006) pharmacoepidemiological ones. Most frequent uropathogens in the examinees were *Escherichia coli* (62.9%) and *Klebsiella spp* (9.7%). Their most common strains were often resistant to ampicillin, amoxicillin. Therefore, these drugs are often ineffective against urinary infections in pregnant women. Drugs of choice are oral cephalosporins of the third generation (cephoxim), inhibitor-protected aminopenicillins, for parenteral administration-parenteral cephalexim, cephtriaxon followed by oral (cephisim) cephalosporins of the second-third generation²³.

Reassuringly, penicillins, erythromycins, and cephalosporins, although used commonly by pregnant women, were not associated with many birth defects²⁴.

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 placenta²⁵. From previous data, it is unlikely that penicillins and cephalosporins are teratogenic²⁶. 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^{27,28}. According to Briggs et al¹⁰, the use of ampicillin in early pregnancy was associated with a prevalence ratio estimate of 3,3 for congenital heart disease in a retrospective study. 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 be-

Table II. β -lactam antibiotics used by pregnant women (Zagreb and Novi Sad).

ATK	β -lactam antibiotics	Zagreb	Novi Sad			
		Total	Trimester			Total
			I	II	III	
J01CA	Ampicillin	10	18	12	32	56
	Amoxicillin	47	32	27	43	81
J01CE	Penicillin G		10	17	21	43
	Benzilpenicillin	11				
	Benzatin fenoximetilpenicillin	9				
J01CF	Cloxacillin	4				
J01CR	Amoxicillin+clavulanic acid	38	8	3	4	12
J01DA	Cephalexin	55	34	18	69	87
	Cefaclor		8	1	4	10
	Ceftriaxone		2	2	3	7
	Cefazolin	5				
J01DC	Cefuroksim	13				
	Cefuroximaxetil	38				
J01DD	Ceftibuten	1				

cause 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 used²⁹. 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 gestation³⁰. 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.

In the study of Novi Sad 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 two and right ear flap in one newborn were detected. Out of the three newborns which were born with minor malformations, one 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^{31,32}. None of these have linked the use of cephalosporins with congenital defects or toxicity in the newborn³³.

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.

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

Table III. Detected malformations on fetuses which were exposed to β -lactam antibiotics (Zagreb and Novi Sad).

Name of drug	Risk category	Number of fetuses with malformations		Type of malformation		Trimester of pregnancy					
						I		II		III	
		Zagreb	Novi Sad	Zagreb	Novi Sad	Zagreb	Novi Sad	Zagreb	Novi Sad	Zagreb	Novi Sad
Ampicillin	B	1	3	Cardiovascular system	Short lingual frenulum (2x), right ear flap	-	1	-	-	1	2
Amoxicillin	B	1	4	Urogenital system	Short lingual frenulum, hypospadias, talipes valgus, micrognathia	-	1	-	1	1	2
Penicillin G	B	2	3	Head and neck	Syndactyli of the 2nd and 3rd toe in both feet, four fingers line, cyst of choroid plexus right ear flap	-	2	2	-	-	1
Amoxicillin, clavulanic acid	B		1				1		-		-
Cephalexin	B	4	2	Osteomuscular system, cardiovascular system	Cyst of choroid plexus, short lingual frenulum	1	1	4	-	1	1
Cefaclor	B	1			Syndactyli of the 2nd and 3rd toe of the left foot		1		-		-

Table IV. Exposure of pregnant women to effects of β -lactam antibiotics together with another potential teratogen (Novı Sad).

Name of drug	Trimester of pregnancy	Use with another potential teratogen	Findings on fetuses and newborns
Ampicillin	II	1 woman with pneumonia, 1 woman older than 35 years	Negative
Penicillin G	I	1 woman exposed to X-ray	Right ear flap
	III	2 women who smoked up to 10 cigarettes per day	Negative
	II	1 woman with pneumonia	Negative
Cephalexin	I, III	2 women older than 35 years	Negative
	I	1 woman exposed to X-ray	Short lingual frenulum
	III	Contact with varicella (chickenpox)	Negative
Ceftriaxone	III	2 women older than 35 years	Negative
	I	1 woman exposed to X-ray	Negative

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 three-fold, 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. They used 15 different antibacterial medications, most often beta lactam antibiotics. The most frequently used antibacterial were drugs from category B according to harmful effects to the fetus. The results of this study show possible teratogenic potential even with those antibacterials which are considered safe (amoxicillin) but as those are usually

minor malformations they often pass undetected. International pharmacoepidemiological studies of drug use in pregnancy could substantially contribute to the improvement of pharmacotherapy, and could be of great help in assessing the fetal risks, especially when using new drugs.

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