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FACTORS ASSOCIATED WITH ESTIMATE OF HIGH TERATOGENIC RISK IN FEMALES EXPOSED TO ANTI-INFECTIVE AND ANTI-INFLAMMATORY DRUGS DURING PREGNANCY

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Abstract: Considering that a small number of drugs are completely safe for use during pregnancy, the right choice and adequate risk assessment are extremely important. The aim of this study was to analyze factors associated with the estimation of high teratogenic risk (as judged by clinical pharmacologist) in pregnant females who were prescribed anti-infective drugs or mild analgesics. A cross-sectional study included 284 pregnant women who came for an advice about teratogenic risk to clinical pharmacologist in Clinical Centre Kragujevac, Serbia during the period from 1997 to 2012. All of the included pregnant women were prescribed mild analgesics and/or anti-infective drugs during the first 3 months of pregnancy. The data were collected from patient files and by phone interviews. Clinical pharmacologists estimated the risk of teratogenicity as "high" in pregnant females who were using tetracyclines or propionic acid derivatives. Disorders of development reported by mothers during phone interviews were associated with cephalosporin use during the first 3 months of pregnancy, while miscarriages or abortions happened more often in women who used a tetracycline. Estimate of risk from congenital anomalies after use of drugs during pregnancy, which makes clinical pharmacologists as part of their routine healthcare services, depends on the amount of published data about previous experiences with specific drugs during the first 3 months of pregnancy.

Keywords: pregnancy, drugs, risk of teratogenicity, risk estimation

Almost all drugs used during pregnancy, eventually get access to fetal circulation, because placenta is not behaving as significant barrier for drug transfer. Putting it this way, all drugs are potentially, and some definitely, teratogen and/or toxic to fetus (1, 2). Approximately 2-3% of cases of intrauterine development disorders are caused by drugs prescribed during pregnancy (3, 4, 5). A study has shown that around 86% of all pregnant women take at least one drug during pregnancy and 36% of them do that in the first trimester (6).

The safest scenario for pregnant woman is to avoid medical treatment, if possible. In case of acute or chronic condition, certain principles of drug use during pregnancy should be followed (1, 4, 5). FDA had only roughly categorized drugs in five groups (A, B, C, D, and X) according to their potential to caused fetal damage (1, 4, 5). Considering that a small number of drugs are completely safe for use during pregnancy (group A), the right choice and risk assessment are extremely important. In this process, clinical pharmacologists (CPs) are often consulted. However, only a few studies dealt with risk estimate that was made by CPs. In one of them, results have shown a great discrepancy in assessment between general physicians or specialists other than CPs, who just followed FDA recommendations, and clinical pharmacologists. Risk estimate was similar in only 28% of pregnant women, including 9% of those with high risk (FDA category X) (7).

The risk assessment must be made on individual bases considering dose, route of administration, length of therapy, drug's pharmacokinetics and pharmacodynamics, as well as the period of gestation when the drug was used. FDA classification is rather imprecise and of little help to practicing physicians when they have to give concrete advice. Clinical pharmacologists are the most adequate health care professionals for this job, although they are few in numbers (7).

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Anti-infective drugs and mild analgesics are frequently prescribed to pregnant females. Apart from beta-lactams and acetaminophen (7, 8), all other drugs from these two groups bear certain teratogenic risk and should be used with caution, only when it is absolutely necessary (9, 10, 11, 12, 13). Anti-infective drugs and mild analgesics are generally used for acute pain and infection during the first trimester when patients usually don't know that they are pregnant. Studies have shown that 37% of pregnant women in the first 36 weeks take acetaminophen, while 23% of them use ibuprofen (14). Use of anti-infective drugs is also frequent: 37% of pregnant women take oral anti-infective agents once or several times during the pregnancy. Twenty-one percent of them use this drug for urinary tract infection and 21% for respiratory infections (15).

The aim of this study was to analyze factors associated with estimation of high teratogenic risk (as judged by the CPs) in pregnant females who were prescribed anti-infective drugs or mild analgesics.

PATIENTS AND METHODS

We conducted a cross-sectional study of the population which included 751 pregnant women who came for an advice to clinical pharmacologist in Clinical Centre Kragujevac, Serbia during the period from 1997 to 2012, and were recorded in archive of the Clinical Pharmacology Department. We included in our study only those pregnant women who were taking mild analgesics and/or anti-infective drugs (n = 284). Among the included women, those who agreed were interviewed by phone (n = 91), at least three years after the delivery. The following data were collected from the interviews: employment status, level of education, outcome of the pregnancy when they were advised by a clinical pharmacologist (artificial abortion, spontaneous abortion or delivery), the child weight at birth, time and mode of delivery, number of spontaneous and artificial abortions, number of children, prophylaxis with folic acid, presence of congenital anomalies or any kind of development disorder. The data about drugs used during pregnancy, week of gestation when the drugs were used, their dosage and duration of therapy and advice given by clinical pharmacologists (advice to change therapy, assessment of basal, moderate or high risk, or else) were collected from the patient files archived in Clinical pharmacology department, Clinical Centre Kragujevac. Pregnant females who came for advice before taking a drug were excluded from our study.

The study was approved by the Ethics Committee of Clinical Center Kragujevac, and it was conducted according to the principles of the Declaration of Helsinki on human experimentation.

Statistics

Standard descriptive statistics were used to describe the study population, its characteristics, and exposure to anti-infective drugs and mild analgesics. Mean and standard deviation was calculated for all continual variables, while percentages were used to express the values of categorical variables. Difference between subgroups in values of continues variables was tested by nonparametric Man-Whitney U test, while differences in frequencies were tested by Chi-square test. The differences were considered significant if $p < 0.05$. Logistic regression was used to analyze the influence of independent and confounding variables on the study outcomes. At first, univariant logistic regression was performed for each variable and the multivariant logistic regression model was then constructed assessing the influence of each variable after adjustment for other variables.

RESULTS

Between 1997 and 2012, in total 751 pregnant women came to Clinical Pharmacology Department in Clinical Center Kragujevac for advising after taking drug therapy during pregnancy. Out of that population, 284 patients (38%) were taking some mild analgesic or anti-infective drug (during the study 91 of them were interviewed by phone and 193 were analyzed based on the file data only).

Mean age was similar ($p = 0.1$) in both groups, 28.0 ± 5.5 years in the interviewed group (n = 91) and 27.8 ± 5.0 years in the non-interviewed group (n = 193). Gestational age in the moment of taking an analgesic and/or anti-infective was 10.5 ± 7.3 weeks for the non-interviewed group and 10.6 ± 7.1 weeks for the phone-interviewed group; $p = 0.988$. One or more anti-infective drugs was taking 85% of women in the study, and one or more analgesics was taking 15% of participants.

Among the females who were phone-interviewed, 91.2% of prescribed drugs were taken for infections (mostly respiratory and urinary) and 8.8% for analgesia. In the non-interviewed group 95.8% of drugs were prescribed for infection and 4.2% for analgesia.

In total 67% of study participants were using anti-infective drugs and/or mild analgesics during teratogenic period. Average length of the prescribed therapy was 5.7 ± 3.7 days in the phone-interviewed

group and 11.5 ± 7.3 days in the non-interviewed group, (p = 0.188). Pregnant women came for advice and risk assessment after taking one (65%) or more drugs (35%). Table 1 shows which anti-infective and anti-inflammatory drugs were used.

Phone-interviewed women

Multivariate logistic regression was made to analyze the effects of variables on probability that clinical pharmacologist would assess the risk of congenital anomalies or fetal toxicity as "high" in the group of phone-interviewed women (n = 91). Backward Stepwise Deletion method was used to find the optimal model (Cox Snell R squarev= 0.056, Nagelkerke R Square= 0.113). The logistic regression model described the decision with the following equation: log(odds) = -1.466 + 3.285*tetracycline + 20.888*teratogenic period.

The other analyzed outcome in the group of 91 phone-interviewed pregnant women was presence of any developmental disorder in the offspring. The analysis showed that among the included variables only use of cephalosporins had a significant influence on this outcome. Backward Stepwise Deletion method was used to find the optimal model (Cox Snell R square = 0.056, Nagelkerke R Square = 0.113). The logistic regression model described the developmental disorder probability with the following equation: log(odds)= 0.693 + 1.806*cephalosporins.

The third outcome analyzed in the phone-interviewed women was composite of miscarriage or artificial abortion. It was under significant influence of both tetracycline prescribing and assessing teratogenic risk as "high". Backward Stepwise Deletion method was used to find the optimal model (Cox Snell R square = 0.089, Nagelkerke R Square = 0.16). The model of logistic regression was described with the equation: log(odds) = 0.431 + 0.353*tetracycline + 1.658 * assessing teratogenic risk as "high".

Non-interviewed women

In the group of 193 pregnant women who were not phone-interviewed assessing the risk of congenital anomalies as "high" by CPs was also analyzed as categorical outcome using logistic regression. The variables included in the regression were the use of tetracycline, aminoglycoside, a quinolone, propionic acid derivative, and any drug use during teratogenic

Table 1. Use of anti-infective drugs and mild analgesics in the study sample.

Drug group or individual drug	All pregnant women (n = 284	Pregnant women interviewed by phone (n = 91)
Penicilins	34 (17.9%)	12 (13.2%)
Cephalosporins	39 (20.5%)	12 (13.2%)
Tetracyclines	31 (16.3%)	21 (23.1%)
Macrolides	27 (14.2%)	12 (13.2%)
Clindamycin and lincomycin	11 (5.8%)	8 (8.8%)
Aminoglycosides	50 (26.3%)	16 (17.6%)
Quinolones	21 (11.1%)	11 (12.1%)
Glycopeptide antibiotics	1 (0.5%)	0 (0%)
Metronidazole	18 (9.5%)	4 (4.4%)
Sulfonamides	11 (5.8%)	3 (3.3%)
Fosfomycin	2 (1.1%)	7 (7.7%)
Antivirals	0 (0%)	1 (1.1%)
Antifungals	16 (8.4%)	7 (7.7%)
Anti-parasitic drugs	3 (1.6%)	0 (0%)
Acetylsalicylic acid	10 (5.3%)	2 (2.2%)
Propionic acid derivates	25 (13.2%)	13 (14.3%)
Acetaminophen	6 (3.2%)	8 (8.8%)
Acetic acid derivates	13 (6.8%)	9 (9.9%)
Oxicams	3 (1.6%)	1 (1.1%)
Pirazolones	7 (3.7%)	4 (4.4%)
Nimesulide	0 (0%)	1 (1.1%)

period. Backward Stepwise Deletion method was employed to find the optimal model (Cox Snell R square = 0.215, Nagelkerke R Square = 0.323). The model was described with the following equation: log(odds) = -3.505 + 2.013*tetracycline + 1.113*aminoglycoside + 1.355*quinolones + 1.117*propionic acid derivate + 1.179*drug use in teratogenic period.

In Table 2 the adjusted odds ratios from logistic regressions for the study variables according to the three major outcomes are listed – assessing teratogenic risk as "high", disorders of development and composite of abortion or miscarriage. The included variables were preterm delivery, previous spontaneous miscarriage or abortion, use of anti-infective and anti-inflammatory drugs during pregnancy, drug use during teratogenic period, use of folic acid for prevention of neural tube defects, pregnancy outcomes and assessing teratogenic risk as "high" by the CPs (only when developmental disorders and composite of abortion or miscarriage are considered as outcome i.e. dependent variables). The odds ratios for assessing teratogenic risk as "high" as the outcome were high in pregnant females who were using tetracyclines (even higher in phone-interview group) and quinolones (higher in non-interviewed group). The most surprising result was very high odds ratio (OR = 13.23 (2.07 – 84.64)) for disorders of development while taking cephalosporins during pregnancy.

DISCUSSION AND CONCLUSIONS

Our study showed that rating of teratogenic risk as "high" by the CPs was associated with use of

Table 2. The adjusted odds ratios for variables grouped according to the study outcomes. The cells are left empty if the value could not be calculated due to small numbers. Some of the variables were omitted completely from the table, because they were either of rare occurrence (e.g. preterm delivery) or present in all women (e.g. use of folic acid), so it was not possible to calculate ORs and include them in logistic regression.

Variables	Assessing teratogenic risk as "high" (phone-interviewed women) ($OR_{adjusted}$)	Assessing teratogenic risk as "high" (non-interviewed women) ($OR_{adjusted}$)	Disorders of development (phone-interviewed patients) ($OR_{adjusted}$)	Composite of abortion or miscarriage (phone-interviewed patients) ($OR_{adjusted}$)
Previous miscarriage(s)	0.538 (0.054 – 5.35)	/	0.487 (0.045 – 5.324)	0.809 (0.083 – 7.923)
Previous abortion(s)	0.211 (0.015 – 3.008)	/	1.986 (0.296 – 13.323)	1.999 (0.307 – 12.998)
Use of penicillin	/	0.670 (0.204 – 2.199)	3.294 (0.448 – 24.202)	/
Use of cephalosporine	1.896 (0.343 – 10.485)	1.609 (0.569 – 4.548)	**13.235* (2.069 – 84.639)**	1.101 (0.19 – 6.39)
Use of tetracycline	**16.405* (4.71 – 57.132)**	**9.905* (3.807 – 25.768)**	0.985 (0.15 – 6.483)	2.671 (0.716 – 9.966)
Use of aminoglycoside	1.759 (0.299-10.356)	**2.649* (1.155 – 6.075)**	0.977 (0.156-6.13)	0.351 (0.038 – 3.269)
Use of quinolones	0.403 (0.031 – 5.294)	**4.448* (1.457 – 13.573)**	2.07 (0.168 – 25.477)	1.747 (0.277 – 11.017)
Use of propionic acid derivates	0.169 (0.011 – 2.602)	1.785 (0.671 – 4.749)	0.754 (0.092 – 6.162)	2.706 (0.346 – 21.158)
Use of paracetamol	0.456 (0.029 – 7.182)	0.307 (0.028 – 3.307)	2.058 (0.241 – 17.613)	0.372 (0.022 – 6.152)
Use of acetic acid derivatives	2.392 (0.353 – 16.206)	0.965 (0.236 – 3.95)	2.408 (0.328 – 17.658)	/
Use of pyrazolone	6.722 (0.24 – 83.188)	1.29 (0.217 – 7.653)	2.662 (0.154 – 46.134)	4.559 (0.273 – 76.079)
Any drug use during teratogenic period	/	**4.379* (1.595 – 12.018)**	2.14 (0.358 – 12.785)	1.005 (0.145 – 6.975)
Assessing teratogenic risk as "high"	/	/	0.555 (0.055 – 5.585)	**5.728* (1.114 – 29.466)**

*significant adjusted OR according to logistic regression at $p < 0.05$

certain anti-infective drugs with known teratogenic effects (tetracycline, aminoglycoside and quinolones), especially when used early in pregnancy (i.e. during teratogenic period), while use of mild analgesics (non-steroid anti-inflammatory drugs) was not considered to generate "high" teratogenic risk. Rating of teratogenic risk as "high" by the CPs (and consequent communication of the risk to pregnant women) significantly increased chances of artificial abortion or miscarriage. Besides, our study also showed a significant association of cephalosporin use during pregnancy with increased chances of disorders of development.

Discrepancy in teratogenic risk assessment between CPs and general practitioners (or specialists other than CPs) who rely only on FDA classification was found in several studies. In the work of Erdeljic et al. the risk assessment made by clinical pharmacologists had much better positive predictive value than the FDA classification, especially within the high-risk group. Negative predictive values were similar for both FDA classification and advise by a CPs (7).

This was a reason why in our study we used risk assessment by adequately trained healthcare professionals like CPs, instead relying only on the FDA classification. Many other studies also pointed that this classification oversimplifies the decision-making process, is often misinterpreted or misused, (16) and in combination with lack of information or not being aware of reliable sources of information, it may lead to overestimation of the risk by healthcare professionals other than CPs. In one study, e.g. majority of participants believed that more than 30% of drugs were teratogen or toxic to the fetus. Main reason for overestimation of risk was probably fear of litigation but unrealistic estimate of risk will influence decision-making of pregnant woman and may generate unnecessary worrying. Pregnant females in this scenario may choose to discontinue an essential drug or terminate perfectly normal pregnancy [16]. Our study confirmed that rating risk of teratogenicity after drug use during pregnancy as "high" increases chances that pregnant woman will decide to terminate pregnancy artificially. Therefore, estimating the risk of teratogenicity as precise as possible is absolutely essential, and clinical pharmacologists should be certainly involved.

A number of pregnant women taking medications more than doubled over the past 30 years. Statistics nowadays shows that approximately nine out of ten women take at least one medication during pregnancy (16). In several studies, the most frequently used drugs during pregnancy were anti-infective drugs, analgesics, drugs for gastrointestinal problems and drugs used for the treatment of psychiatric disorders (17, 18). Uncontrolled use of OTC drugs during pregnancy is also a problem, as it seems that more than 90% of pregnant women take either a prescription or over-the-counter medication (19, 20).

Our results did not show that non-steroid anti-inflammatory drugs were associated with the assessment of teratogenic risk as "high". In the study of Nezvalova-Henriksen et al. ibuprofen used in the second trimester was associated with low birth weight, and when used in second and third trimester it was significantly associated with asthma in an 18-month-old child (21). Also, non-aspirin NSAIDs (diclofenac, naproxen, celecoxib, ibuprofen alone or in combination) used during pregnancy were associated with an increased risk of spontaneous abortion (22), and intake of ibuprofen in late pregnancy was linked to development of persistent pulmonary hypertension of the newborn, suggesting the need for further investigation (23). Although some studies showed that neither ibuprofen nor naproxen increased the risk of spontaneous abortion, it was only proven when they were used in the first six weeks of pregnancy (24). More recent data shows the potential association between NSAID use and dextro-transposition of the great arteries (25), and link naproxen use with orofacial clefts, especially in the first trimester (26).

However, considering group of anti-infective drugs, our study showed significant association between the use of tetracycline, aminoglycoside and quinolones and assessment of teratogenic risk as "high". This result is in agreement with the available published data. Tetracycline is teratogen, hepatotoxic and can be deposited in the fetal bones; streptomycin leads to fetal hearing damage and quinolones can damage fetal articular cartilage (1). As the CPs were well aware of these literature data, it is not surprising that they rated risk of congenital anomalies after maternal use of these antibiotics as "high". Association between the use of tetracycline and assessing risk as "high" was particularly strong in both groups. As already mentioned, tetracyclines have documented teratogen risk, especially during the second month of pregnancy.

They were associated with a higher rate of neural tube defects, cleft palate and other major congenital anomalies (27, 28, 29). On the other hand, the most recent data are pointing to satisfactory safety of doxycycline, when compared to other tetracyclines during pregnancy (30).

The most intriguing result of our study was significant association of cephalosporin use in preg-

nancy and disorders of development (asthma in childhood, allergies, obesity, etc). Although there are no definite proofs of safety of cephalosporins during pregnancy, they are often prescribed for pregnant patients to treat various infections, such as pneumonia, otitis, sinusitis and urinary tract infections (31). When given to rats at doses which were one and a half to eight times the human dose, the cephalosporins containing the N-methylthiotetrazol side chain resulted in testicular toxicity (32). This was not the case with other cephalosporins (33). Berkovitch et al. tried to investigate possible teratogenic effects of cefuroxime after intrauterine exposure, but definitive conclusion was not reached.

Although from June 2015 the FDA implemented new format of pregnancy and lactation labeling rule, with more details for medical practitioners, experts like CPs are still needed to make the comprehensive and more reliable estimate of teratogenic risk after inadvertent drug use in early pregnancy (16).

In conclusion, our study showed that clinical pharmacologists mostly made correct assessment of teratogenicity risk after use of either mild analgesics or anti-infective drugs in early pregnancy, as their rating of "high" risk was associated only with drugs for which considerable data about teratogenic effects could be found in medical literature. Communicating "high" risk of teratogenicity after drug use to pregnant women was associated with increased probability of miscarriage or abortion, i.e. it could influence pregnant women to decide to abort pregnancy.

Conflicts of interest

The authors declare that no conflicts of interest exist.

Ethical approval

This study was conducted according to ethical principles and was approved by The Ethics Committee of Clinical Centre Kragujevac in 2012, reference number 01-4989.

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