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Clinical Pharmacology Consultation: A Better Answer to Safety Issues of Drug Therapy during Pregnancy?

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Abstract

Purpose: Drug safety classifications give a very basic estimation of risk and should only be used as general guideline when assessing risk of pregnancy-related drug exposure or planning treatment. We conducted a study to assess the strength of association between both the clinical pharmacologists' risk assessment and the FDA risk categorization, and adverse pregnancy outcomes. Methods: We retrospectively reviewed records of 1076 patients consecutively referred to the clinical pharmacology outpatient clinic for pregnancy-related drug exposures (2000-2008). Clinical pharmacologists' risk assessments were reviewed in relation to FDA drug categorization and available pregnancy outcomes. Results: Overall, clinical pharmacologists' risk estimation was in agreement with the FDA risk categorization system in only 28% of consulted women, and in only 9% of women with high risk exposure (FDA DX). Clinical pharmacologists' risk assessment confirming high risk drug exposure had a better positive predictive value for adverse pregnancy outcomes than the FDA DX categorization (25% vs. 14%, respectively), while the negative predictive values were similar (92% vs. 94%, respectively). Clinical pharmacologists' risk assessment was a better predictor of adverse pregnancy outcomes when compared to FDA risk categorization [OR 2.11 (95%CI 1.5-3.1; p<0.001) vs. OR 1.52 (95%CI 1.1-2.1; p=0.014), respectively]. Conclusions: Additional evaluation beyond the FDA drug classification is essential for safer and more rational drug use in pregnancy. Clinical pharmacologists who have undergone rigorous medical training are ideally placed to consult on administration of medicines in pregnant women, thus making the prescribing of treatments in that patient category substantially safer and more rational.

Key words: pregnancy-related drug exposure, FDA, drug safety classifications, clinical pharmacology, risk assessment, drug safety

Introduction

The estimated prevalence of birth defects in general population is 2-4% [1]. It is claimed that this prevalence is mainly independent of drug use in pregnancy, with less than 1% of birth defects thought to be attributable to maternal drug use [2]. Nevertheless, there is much fear about prescribing drugs in pregnant women, making underprescribing as much a concern as overprescribing. Several studies have explored the prevalence of drug prescription in pregnant women, with a wide range of results from 19% to more than 90% of pregnant women receiving at least 1 drug during pregnancy [3-6]. As approximately 50% of pregnancies are unplanned, often drug exposure occurs in the early and most vulnerable stage of pregnancy [7]. Therefore, risk classification systems have been set up to summarise the available data on drug safety during pregnancy and to help in assessment of risks of pregnancy-related drug exposures and balancing of benefits and risks when prescribing drugs in pregnant women. One of the most frequently used is the US Food and Drug Administration (FDA) pregnancy risk categorisation which places the drug in one of five categories (A, B, C, D and X) according to the level of risk to the infant [8]. However, it is important to understand that drug safety classifications give a very basic estimation of risk and should only be used as general guidelines when planning treatment [9], and that there are inconsistencies between various drug classifications which can be a source of great confusion among users of drug safety classification systems [10]. Although the FDA has announced the replacement of the present risk classification system with a narrative framework in order to ease informed counselling on drug safety in pregnancy, the pregnancy risk categories are still in effect and are still being used by physicians [11]. Since Croatia has not established its own risk classification system, the FDA risk classification system is still the most used system in Croatia, due to its accessibility to prescribers through the Croatian Drug Registry [12] and the Croatian Pharmacotherapeutic Formulary [13].

However, risk assessments must always be made on an individual basis, and the dose, route, duration, and gestational timing of the exposure must also be taken into consideration in each case. Both underestimation and overestimation of risk must be avoided, and

pregnant women with conditions requiring treatment must be treated adequately. Although their medical training predisposes clinical pharmacologists to a significant role in the area of drug use during pregnancy, this is probably the least developed area of clinical pharmacology.

There is lack of organized information services on drug safety during pregnancy in Croatia; information is mostly available through some hospital Departments of Paediatrics, Gtynaecology or Clinical Pharmacology. There is only one office in Croatia (Genetic Counselling with Teratogen Information Service) that is a part of European Network of Teratology Information Services (ENTIS), which includes 12 European and 2 non-European countries with the objective to coordinate the activities of different Teratology Information Services [14]. Similarly, councelling of patients and health care providers about exposures related to pregnancy and breastfeeding in North America is provided through the Organization of Teratology Information Services (OTIS) [15].

Consultations on drug use during pregnancy have a 20-year tradition at our unit. When consulting women on risks of drug exposure or therapy planning during pregnancy, we too use the FDA risk categorization system as well as the Australian Drug Evaluation Committee's categorization [16]; however, only as a general guidance. To the best of our knowledge, there are no studies that examine the proportion of agreement between a classification system and a clinical pharmacologist's (or other experts') risk assessment on pregnancy-related drug exposure which also includes the evaluation of these differences in relation to pregnancy outcomes. In one study that similarly compared the differences in advice on drug safety in pregnancy between product monographs and Drug Information Centres in Norway, no data on pregnancy outcomes were available [17].

With these objectives in mind we conducted this study hoping to provide a clearer assessment of value of the FDA risk classification and clinical pharmacologists' consultation in relation to adverse pregnancy outcomes caused by medication use.

Methods

Study Design and Patient Population

The Division of Clinical Pharmacology at the University Hospital Zagreb comprises a ward (11 beds), clinical research unit and outpatient clinic. The clinical pharmacology outpatient clinic serves patients with various pharmacotherapeutical problems. Approximately 20% of patients at the outpatient clinic are referred for consultation on drug use in pregnancy. During the first patients' visit, demographic data, data on concomitant diseases, reasons for referral, habits (smoking, alcohol consumption), previous pregnancies, prescribed medications and indications for their prescription, are collected by the use of a structured questionnaire. For every patient advised, a written clinical pharmacologist's expert opinion is prepared with a risk estimation concerning the individual patient's characteristics and indications for drug treatment, and sent by post within 2-3 days to the referring physician or/and the patient's home address (when requested). Where appropriate, a final risk assessment is made with recommendations for the continuation, reassessment or discontinuation of therapy. Approximately 9-12 months after the consultation counselled patients are contacted by phone or post (where telephone number was not available) in order to obtain information on the pregnancy outcomes.

We retrospectively reviewed records of 1144 consecutively referred patients during a 9-year period (2000-2008). Clinical pharmacologists' risk assessments of patients were reviewed in relation to the FDA drug categorization and available pregnancy outcomes. This study included only patients referred for consultation on pregnancy-related drug exposures. Pregnancy outcomes were available for 516 patients. Prior to data analysis of adverse pregnancy outcomes, we excluded cases of induced abortions (46 cases) and exposures to medications not classified by FDA risk classification system (5 cases); 465 pregnancy outcomes were available for further analysis. Adverse pregnancy outcomes included were: spontaneous abortion, malformations, and other complications during pregnancy (preterm birth, perinatal complications possibly related to medication use).

FDA pregnancy risk classification and risk assessment

All drugs prescribed to a patient during pregnancy were classified according to the FDA risk classification. Since the FDA categorization scheme classifies drugs in one of five major categories according to the potential fetal risk (A, B, C, D and X), we converted it into a numeric rating scale (NRS; 1, 2, 3, 4 and 5). Similarly, final clinical pharmacologists' risk assessments were also converted into the same numeric scale thus allowing further comparisons and analysis (Table 1). Literature data on the use of specific drugs during pregnancy, gestational age of the embryo or fetus during the exposition to the drug, route of drug administration, absorption rate of the drug, whether the drug crosses the placenta, indication for the treatment, etc., were taken into account for each patient prior to final risk assessment. In compiling the clinical pharmacologists' expert opinion following sources were used: British National Formulary [18], AHFS Drug Information [19], Briggs' Drugs in pregnancy and lactation [20], Micromedex Database [21], PubMed [22] search on latest articles published on specific topic. The FDA and ADEC categorization are used as a general guideline, which was followed by extensive literature search on drug safety of a specific drug, with the remark that all clinical pharmacologists working as consultants have more than 5 years experience in the area of drug safety in pregnancy and have in-depth knowledge in this field of clinical pharmacology.

Statistical Methods

Standard descriptive statistics were used to describe the study population, referral characteristics and pregnancy exposures. Means and Standard Deviations (SD) were calculated for continuous variables. For categorical data proportions were calculated and analyzed using the M-L Chi-square test. Statistical significance was set at $p<0.05$.

Associations with adverse pregnancy outcomes for FDA categorization and clinical pharmacologists' risk assessment (on a NRS), age, parity, number of spontaneous abortions, and number of prescribed drugs were evaluated using multiple logistic regression for continuous predictors, with adjusted odds ratios and its 95% confidence intervals as the association measures, or where appropriate (for categorical variables: smoking, age group, previous pregnancies, and previous history of spontaneous abortions) by calculating odds

ratios and its 95% confidence intervals for a 2x2 contingency table, using Chi-square test of association. Positive and negative predictive values for adverse pregnancy outcomes were calculated for both FDA DX (NRS 4 and 5) categorization and clinical pharmacologists categorization (NRS 4 and 5).

All tabulations and statistical analysis were done using Statistica for Windows, Version 8.0, StatSoft, Inc. (2008).

Results

Between 2000 and 2008, we advised 1144 pregnant women, aged 16-47 years (mean age 30 years) referred to the clinical pharmacology outpatient clinic for consultations on 2244 drug exposures and 81 radiological diagnostic procedures.

Most consultations were regarding drug exposure during pregnancy (95%); other consultations included therapy planning during this or future pregnancies, partners' drug exposure, diagnostic procedures, and other exposure-related problems during pregnancy. For the purpose of this study, we further analyzed only data on patients referred for consultations on pregnancy-related drug exposure (N=1076). Patients were mostly referred due to drug exposure during the 1st trimester of pregnancy (95%) and 84% of them were advised in their 2nd month of pregnancy.

Most of the women were referred by a gynaecologist (89%), followed by general physicians (5%) and other specialists (4%; mostly neurologists and psychiatrists), and 2% of patients came self-initiatively.

Similar proportions of patients were consulted on drugs prescribed for the treatment of an acute condition (45%) and a chronic condition (41%). The mean number of drugs taken during pregnancy was 2.1 (range 1-9), and more than 50% of women were prescribed ≥2 drugs. For more than 40% women this was their first pregnancy. The patients' demographic and referral characteristics are shown in Table 2.

Drug exposure and risk assessment

When exposure to individual drugs was taken into account most women were exposed to FDA category C (56%) and category B drugs (41%). When the highest FDA drug category among drugs prescribed to an individual patient was taken into account, most women were exposed to at least FDA category C (39%), followed by category D (30%) drugs. The exposure to high risk FDA drugs (FDA DX) drugs was high; 34% (466 women) of pregnant women were prescribed at least one FDA category D or X drug. When the FDA categorization system was converted to a numeric scale (NRS 1-5), the mean risk assessment value in the studied population was 3.4 (Std.Dev. ± 0.96). Fifty-seven women

(5.4%) were exposed to medications with unknown pregnancy categories. Data on pregnancy-related drug exposure are summarized in Table 2.

The clinical pharmacologists' risk assessment was available for all patients consulted on drug exposure during pregnancy. Estimation of high risk exposure was recorded for 95 women (9%). On a numeric rating scale, the mean risk assessment value was 2.3 (Std.Dev. ±0.71).

Clinical pharmacologists' risk assessment was agreeable with FDA risk categorization in only 17% of FDA D drug exposures and 14% of FDA X drug exposures. In all other cases the clinical pharmacologists' risk assessment was lower; with the highest mean point difference of 2.2 within the FDA X group (Table 3).

Clinical pharmacologists' risk assessment vs. FDA classification in regard to available pregnancy outcomes

Due to the high rate of patients lost for follow-up, pregnancy outcomes were available only for 516 pregnancies (48%). Starting in 2004, we more thoroughly organized the collection of follow-up data of advised patients using a more active approach (repeated phone calls and search for potentially changed phone numbers or address in case of failure, etc). The most patients that were lost to follow-up were advised in the previous period, and were lost to follow-up due to the lack of information on, or changes in, patient's phone numbers, home address, etc.

There were no significant differences in age, referring physician, previous pregnancy, parity, history of spontaneous or induced abortions, number of prescribed drugs, FDA's and clinical pharmacologists' risk classification, between women with available outcomes and women that were lost to follow-up. The only confounder that was more present in the group of women with available pregnancy outcomes was smoking (30% vs. 23%; p=0.012, respectively). Nevertheless, we conclude that women with available pregnancy outcomes are representative for the whole sample of 1076 patients advised on pregnancy-related drug exposure

Four hundred and thirty-five healthy babies were delivered in 428 pregnancies, there were 46 cases of induced abortions, and 31 cases of spontaneous abortions, 8 women suffered other complications during pregnancy and there were 3 cases of observed congenital malformations (1 major, 2 minor). After excluding induced abortions (46 cases) and exposures to medications not classified by the FDA (5 cases), 465 pregnancy outcomes were available for further analysis. We did not include cases of induced abortions, since they do not represent adverse pregnancy outcomes in the narrow sense, i.e. adverse outcome directly attributable to the use of a medication.

Both FDA and clinical pharmacologists' risk classification were revealed as significant predictors for adverse pregnancy outcomes. However, calculation of odds ratios (OR) confirmed a more significant association of clinical pharmacologists' risk assessment as compared to FDA risk categorization, both when using a NRS or proportions of those exposed to high risk medications (Table 4). Clinical pharmacologists' categorization of pregnancy-related drug exposure to a high risk group (NRS 4 and 5), had a better positive predictive value for adverse pregnancy outcomes as compared to the FDA categorization (25% vs. 14%, respectively), while the negative predictive values were similar (92% vs. 94%, respectively). Overall, clinical pharmacologists' risk estimation for studied drug exposures was lower as compared to the FDA risk categorization.

Other risk factors associated with adverse pregnancy outcomes

Clinical pharmacologists' risk assessment was the strongest predictor of adverse pregnancy outcomes, whereas the number of drug exposition was not significantly related to adverse pregnancy outcomes. Other risk factors significantly associated with adverse pregnancy outcomes were age, concomitant diseases, previous pregnancies, and parity. Cigarette smoking and number of drug exposures were not significantly associated with adverse pregnancy outcomes. Although the history of previous spontaneous abortions was not significantly related to adverse pregnancy outcomes, the number of previous spontaneous abortions increased the odds for an adverse pregnancy outcome. The calculated ORs for all evaluated risk factors and their confidence intervals are shown in Table 4.

Discussion

This study confirms significant differences in risk estimation between the FDA classification system and the clinical pharmacologists' risk assessment for pregnancy-related drug exposures, with an overall agreement in only 28% of cases.

The FDA categorization system gives only limited guidance to the prescribing physician, and many clinicians feel that despite the intent of the new labelling requirements to facilitate drug prescribing for pregnant patients, it has not lived up to original expectation in this regard [9]. It has been claimed that the FDA system is too simple and exerts confusion concerning gradation of risk across the categories. The second criticism of these categories is that they create an incorrect impression that the drugs within a given category present similar reproductive risk. Among the drugs listed in the Physicians' Drug Reference, only 0.7% of drugs carry an FDA category A classification; 19% are in category B; 66% are in category C; 7% are in category D and 7% are in category X [23]. In response to these objections, the FDA made an announcement in May 2008, stating that they will replace the current A, B, C, D, and X classification system with a narrative framework consisting of 3 major information parts: risk summary, clinical consideration and data. These changes were designed to facilitate informed counselling about and prescribing of medicines for women who are pregnant, breastfeeding, or of childbearing potential [11]. However, to date, the pregnancy risk categories are still in effect and are still being used by physicians.

Whether to prescribe a drug to a pregnant woman is a decision that must be made on an individual basis and includes a critical assessment of the available data from studies done in animals and humans. Furthermore, there are numerous factors that should be taken into consideration: gestational age of the embryo or fetus during the exposition to the drug, route of drug administration, pharmacokinetic and pharmacodynamic characteristics of the drug [24].

The evaluation of population characteristics in our study revealed a population under increased basal risk for adverse pregnancy outcomes, mainly due to the increased age, high prevalence of chronic conditions and exposure to high-risk drugs (FDA DX). The mean

number of drugs prescribed to pregnant women in our study was similar or even lower than in studies exploring drug use during pregnancy [25] and comparable to a cross-sectional study that evaluated the drug use in pregnant women of 4 Zagreb's maternity hospitals (mean 2.6 drugs) [26]. However, the exposure of pregnant women included in our study to FDA category DX drugs was significantly higher when compared with the exposure in general population of pregnant women (34% vs. approximately 6-7%) [6,27]. These findings were not surprising, and could be attributable to the tendency of other specialists to refer patients exposed to high risk drugs to a clinical pharmacologist for further consultations, while patients exposed to drugs carrying lower risk categories are consulted within their own clinics. The prevalence of other risk factors was as well considerable within the studied population; 51% of pregnant women were older than 30 years and 52% were suffering from a chronic condition. The percentage of women older than 30 years was higher than the Croatian average age of parturient women (40.4% in 2008) [28]. No data on the prevalence of chronic conditions among women of childbearing-age was available for Croatia, but data for the US report 9.9% of women of childbearing-age with a chronic condition [29]. Twenty seven percent of women were smoking, which is in agreement with Croatian statistics (approximately 30% of smokers among women) [30]. Approximately 40 % of advised women were in their first pregnancy which is a slightly lower rate as compared with the Croatian average (48% of first pregnancies) [31].

Overall, clinical pharmacologists' risk estimation was in agreement with the FDA risk classification system in only 28% of consulted cases. Although 34% of patients were exposed to FDA category DX drugs, high risk exposure according to a clinical pharmacologist's assessment was recorded in only 9% of patients (NRS 4 and 5). Percentages of A-X risk assessments by FDA risk classification and a clinical pharmacologist are shown in Chart 1. The found rate of disagreement in estimation of risk of pregnancy-related drug exposures in our study (72%) was higher than recorded in one similar study that compared the differences in advice on drug safety in pregnancy between product monographs and five Drug Information Centres in Norway. The authors found a 47%

difference in advices given on drug safety in pregnancy between these two sources of information, with information from the product monographs being significantly more restrictive [17]. This could be explained by the possibility of more accurate risk estimation in our study due to available data on all relevant risk factors, timing and dosage of drug exposure. Furthermore, the mentioned study did not include pregnancy outcomes. Subsequently, the question may be raised if the less restrictive advice on drug safety in pregnancy was an understatement of risk and possibly resulted in more adverse pregnancy outcomes.

Due to known difficulties associated with assessments of the benefits and risks of drug therapy during pregnancy, there is a concern among prescribers about underestimating the risks of drug exposure especially during early pregnancy. The exclusive use of the FDA classification system could lead to overestimation of the risk which may result in unnecessary withholding of beneficial therapy or in the termination of otherwise wanted pregnancies. This thesis is supported by our own experience; pregnant women are in some cases referred from other specialists for consultation with the aim to ease the decision for therapy cessation or patients' decision for pregnancy termination.

Despite the fact that in 72% of women included in our study the risk estimation was lower as compared to the FDA risk classification system, adverse pregnancy outcomes in this group were not more frequent when compared with the group with the same risk estimation (7.9% vs. 11.8%, respectively; p=0.211; and 12.7% vs. 20.0% in FDA DX group, p=0.304).

The potential impact of differences in risk estimations can be illustrated by evaluating the distinctions in risk assessments within the FDA category X. The clinical pharmacologists' risk assessment was in agreement with the FDA risk classification system for only 21 out of 150 women with FDA category X exposure. In all other cases the risk estimation was lower. In everyday clinical practice, this difference could mean a significant decrease in numbers of potentially unnecessary induced pregnancy terminations. Indeed, after obtaining the clinical pharmacologists' expert opinion, only 10 out of 78 women with available outcomes (13%) exposed to FDA category X drugs considered the risk high enough to undertake an induced

pregnancy termination. We can only assume that this number would be higher without the risk reassessment done by a clinical pharmacologist.

A good example is the use of oral contraceptives in early pregnancy. Although oral contraceptives are categorized as FDA category X drugs, available evidence does not support such high risk estimation for exposure during early pregnancy. There is no firm evidence linking oral contraceptives with any fetal anomalies except possible masculinization of the female external genitalia. Exposure after 8 weeks of gestation would presumably be required for this effect to occur [32]. Out of 64 pregnancies with documented exposure to oral contraceptives during the 1st trimester of pregnancy with available outcomes, there were 52 pregnancies (81%) that resulted in delivery of a healthy child, 5 spontaneous abortions (8%), 4 induced abortions, 1 pregnancy complication (1.6%; a case of a preterm delivery) and 2 congenital anomalies (1 major and 1 minor congenital malformation). Both the rate of congenital malformations and the rate of spontaneous abortions in women exposed to oral contraceptives during the first trimester in our study were within expected rates (3% and 8%, respectively).

The overall rate of congenital malformations in our study was 0.6% (3/465) which is lower than the expected rate of congenital malformations within general population of pregnant women in Europe (2.3%) acording to data from the European Surveillance of Congenital Anomalies [23]. We have no obvious explanation for such a low rate of congenital malformation recorded in our study. The rate of spontaneous abortions in our study was 6.2% (32/465), which is as well lower than the expected rates of 10-15% [34,35]. The rate of spontaneous abortions in Croatia is 15.9% [36]. This finding could be explained with the fact that most women were referred to us during the 2nd or 3rd month of pregnancy at a time point when some of the spontaneous abortions might have already occured. The rate of women with previously legal abortion (9%) was also lower as compared with the general population (19%) [35] . This could likely be attributed to underreporting due to unwillingness to provide information on previous induced abortions.

We assessed the strength of association between both the clinical pharmacologists' risk assessment and the FDA risk categorization, and adverse pregnancy outcomes. Risk estimation by a clinical pharmacologist was a better predictor for adverse pregnancy outcomes when compared to the FDA risk classification. Despite the mentioned limitations of the FDA risk classification system, our study results confirmed its general usefulness in risk estimation of pregnancy-related drug exposures. Hence with large numbers of false positives and few false negatives, the positive predictive values for adverse pregnancy outcomes were low; 14% for the FDA DX (or NRS 4 and 5) classification and 25% for the high risk estimation by a clinical pharmacologist (NRS 4 and 5). This means that 14% of women exposed to FDA DX drugs during pregnancy will actually ***have*** an adverse pregnancy outcome, as well as 25% of women exposed to drugs classified by a clinical pharmacologist as being hazardous (NRS 4 and 5). The negative predictive value for adverse pregnancy outcome was similar between both methods of risk classification (94% vs. 92%, respectively), which means that 94% and 92% of women classified as being exposed to lower-risk drugs will actually ***not have*** an adverse pregnancy outcome. Due to lack of data from prospective controlled studies, it is rarely possible to precisely assess the risks of medication use during pregnancy, thus the positive predictive value of any available method for risk estimation of pregnancy-related drug exposure is expected to be low. From a legal and ethical point of view, it is often safer for drug manufacturers and prescribers to overestimate than underestimate potential risks. Nevertheless, women must receive accurate and updated information, as unrealistic perception of risk may lead to unnecessary terminations of otherwise wanted pregnancies or inadequate treatment of maternal disease.

Other already established risk factors that were confirmed as significantly associated with the occurrence of adverse pregnancy outcomes in our study were: age [37], concomitant chronic disease [38,39], history of previous pregnancies and number of previous pregnancies [40]. The most reliable information on drug safety in pregnancy is derived from large population based pregnancy registries, like the Norwegian [41] or Swedish Medical Birth Register [42] which includes data on practically all deliveries in Sweden. Although the most important

advantage of such databases is their size, there are some limitations: reporting bias (underreporting of drug use, interviewer's lack of interest to collect all information, etc.), no precise information on dosage and timing of drug use and lack of accurate data on underlying diseases. The most important advantage of our study are accurate information on the drug dosage and timing of drug exposure, data on confounders, and a low reporting bias regarding medication use since the women were referred specifically for that reason. The limitations are the small sample size and a large number of lost to follow-up.

To the best of our knowledge, this is the first study to examine differences between the FDA risk classification and risk assessment done by a clinical pharmacologist (or another expert) that included pregnancy outcomes of advised women.

Consequently, better positive predictive value for adverse pregnancy outcomes of a clinical pharmacologists' risk assessment as compared to the sole use of the FDA risk classification system, suggests the important role of a trained expert as a corrector of drug classification systems and in providing reliable information for other prescribers as well as pregnant women, thus contributing to better resolution of numerous safety issues of drug therapy during pregnancy.

In conclusion, assessing risk of pregnancy-related drug exposure is time consuming and requires good knowledge of drug pharmacokinetics and pharmacodynamics, epidemiology, teratology as well as training and experience in critical assessment of published data. Clinical pharmacologists who have undergone rigorous medical training are ideally placed to consult on administration of medicines in pregnant women, thus making the prescribing of treatments in that patient category substantially safer and more rational.

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Conflict of Interests

The authors declare no conflicts of interest.

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Table 1. Comparison between risk classifications (FDA vrs. clinical pharmacologists' risk assessment).

Risk categorization		FDA	Clinical pharmacologist's risk assessment
FDA	Numeric scale		
A	1	Controlled studies show no risk. Adequate, well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.	No risk to the fetus according to available data (e.g. acetaminophen).
B	2	No evidence of risk in humans. Either animal study shows risk, but human findings do not, or if no adequate human studies have been done, animal findings are negative.	Risk to the fetus unlikely according to available data (e.g. penicillins, cephalosporins).
C	3	Risk cannot be ruled out. Human studies are lacking, and animal studies are either positive for fetal risk or lacking. However, potential benefits may justify potential risk.	Risk cannot be excluded according to available data (e.g. doxycycline in I trimester) or not enough data available for accurate risk assessment (e.g. tianeptine).
D	4	Positive evidence of risk. Investigational or postmarketing data show risk to the fetus. Nevertheless, potential benefits may outweigh the potential risk.	Risk to the fetus significantly higher than in general population according to available data; e.g. expected rate of congenital malformations with sodium valproate aproximately 9% [43].
X	5	Contraindicated in pregnancy. Studies in animals or humans or investigational or postmarketing reports have shown fetal risk, which clearly outweighs any possible benefit to the patient.	Risk to the fetus very likely; e.g. approximately 40% negative pregnancy outcomes with warfarin [44]. Contraindicated drugs in pregnancy.

Table 2. Patient's demographic and referral characteristics (N=1144), and data on pregnancy-related drug exposure.

	Mean (range)	N (%)
ALL PATIENTS		
Maternal Age (yrs) (N=1133)	29.9 (±5.50, 16-47)	
Smoking (N=1116)		305 (27.3)
Consultation on: (N=1143)		
Exposure to drugs during this pregnancy		1076 (94.1)
Therapy planning during this pregnancy		22 (1.9)
Therapy planning for future pregnancy		19 (1.7)
Diagnostic procedure during pregnancy		13 (1.4)
Drugs taken by the partner at the time of conception		7 (0.6)
Other problems*		4 (0.3)
Pregnancy planning, partner on chronic drug therapy		2 (0.2)
Consultation not possible due to inadequate data†		1 (0.1)
First pregnancy (N=1059)		602 (56.8)
- Previous spontaneous abortions		81/602 (13.5)
PATIENTS ADVISED ON DRUG EXPOSURE DURING PREGNANCY (N=1076)		
Pregnancy trimester at the time of consultation (N=967)	Mean (Std.Dev., Range)	N (%)
I		823 (85.1)
II		138 (14.3)
III		6 (0.6)
Concomitant disease present (N=1073)		555 (51.7)
Average number of drugs taken	2.1 (±1.29, 1-9)	
Monotherapy		492 (45.7)
≥2 drugs		584 (54.3)
Indication for drug prescription:		
Acute illness		480 (44.8)
Chronic illness		436 (40.7)
Other indication		120 (11.2)
Acute and chronic illness		22 (2.1)
Acute illness, other indication		10 (0.9)
Chronic illness, other indication		3 (0.3)
Time of drug exposure: (N=2195)		
Before pregnancy		31 (1.4)
I trimester		2084 (94.9)
II trimester		7 (0.3)
III trimester		3 (0.1)
I, II trimester		68 (3.1)
I, II, III trimester		2 (0.1)
FDA category drug exposure/NRS		
A/1		86 (7.9)
B/2		445 (41.2)
C/3		603 (56.0)
D/4		330 (30.5)
X/5		150 (13.9)
NC‡		57 (5.4)

FDA risk category drug exposure to at least§:		
A/1		17 (1.6)
B/2		173 (16.2)
C/3		410 (38.5)
D/4		316 (29.6)
X/5		150 (14.1)
Mean point value at the numeric scale	3.4 (±0.96)	
Clincal pharmacologists' risk asesment		
A/1		31 (2.9)
B/2		822 (77.1)
C/3		121 (11.4)
D/4		72 (6.8)
X/5		20 (1.9)
Mean point value at the numeric scale	2.3 (±0.71)	
Available pregnancy outcomes (N=516)		
Normal		428 (82.9)
Arteficial abortion		46 (8.9)
Spontaneus abortion		31 (6.0)
Other complications		8 (1.6)
Major malformation		1 (0.2)
Minor malformations		2 (0.4)

* 1 pt- inhalation of xylene gas; 2 pt- exposition to smallpox; 3 pt- exposition to organic solvents; 4 pt- exposition to a person who reacently underwent therapy with radioactive iodine

† the patient didn't know which medication she was taking & no medical documentation was available

‡ NC- drugs not categorized by FDA

§ 10 FDA NC drugs excluded

Table 3. Differences in risk estimation.

	N (%)
FDA CDX	876 (82.2)
Clinical pharmacologists risk estimation	
Same risk estimation	297 (27.8)
Lower risk estimation	770 (72.2)
Clinical pharmacologists risk estimation by FDA category:	
FDA C	
Same risk estimation	37 (9.0)
Lower risk estimation	373 (91.0)
Mean point difference; mean (±Std.Dev., range)	0.9 (±0.32, 0-2)
FDA D	
Same risk estimation	54 (17.1)
Lower risk estimation	262 (82.9)
Mean point difference; mean (±Std.Dev., range)	1.5 (±0.78, 0-3)
FDA X	
Same risk estimation	21 (14.0)
Lower risk estimation	129 (86.0)
Mean point difference; mean (±Std.Dev., range)	2.2 (±1.1, 0-4)

Table 4. Risk factors associated with adverse pregnancy outcomes.

	OR	±95% CI	p-value
FDA risk classification (numeric scale)	1.52	1.09-2.13	0.014
FDA category DX	2.71	1.39-5.24	0.002
Clinical pharmacologist risk assessment (numeric scale)	2.11	1.46-3.05	<0.001
Clinical pharmacologists' risk assessment (4 and 5; corresponding to FDA DX)	4.05	1.76-9.32	0.002
Number of drug exposures	1.20	0.95-1.51	0.118
Age	1.10	1.14-1.18	<0.001
Age ≥ 30 years	3.87	1.81-8.30	<0.001
Previous pregnancy	2.38	1.16-4.85	0.014
Number of previous pregnancies	1.58	1.15-2.18	0.005
Previous history of spontaneous abortion	1.54	0.58-4.06	0.409
Number of spontaneous abortions	6.38	1.09-37.39	0.033
Concomitant disease present	2.98	1.46-6.08	0.002
Smoking	1.03	0.49-2.19	0.920

OR- odds ratio; CI- confidence intervals

Chart 1. Percentages of A-X risk assessments by the FDA risk classification and a clinical pharmacologist (NRS; numeric rating scale).