Evaluation of Drugs Exposure in Pregnancy According to Different Risk Categories: Do FDA-Based Decisions Lead to More Curettage?

Farklı Risk Kategorilerine Göre Gebelikte İlaca Maruz Kalımın Değerlendirilmesi: FDA Esaslı Kararlar Daha Fazla Küretaja Neden mi Oluyor?

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ABSTRACT Objective: The aims of the study were to compare the risk levels of exposed drugs during pregnancy with regard to United States Food and Drug Administration (FDA), Australian Drug Evaluation Committee (ADEC) and Teratogen Information System (TERIS) risk categories, and to determine the outcomes of FDA risk category based decisions on the course of pregnancy in pregnant women who applied to Dokuz Eylul University (DEU) Teratogenity Information Service (TIS). **Material and Methods:** In this cross-sectional study, 220 pregnant women were enrolled who referred to DEU TIS for a teratogenity risk evaluation due to drug exposure during their pregnancies. Demographics, medical history, time and duration of the exposed drugs were recorded. Drugs exposed during pregnancy were divided into two categories as high or low risk. A drug that was exposed during pregnancy of the highest risk according to FDA was taken into consideration for the evaluation of the outcomes of the pregnancy. Additionally, FDA, TERIS and ADEC risk categories which were classified as "low", "unknown" or "high" risk were compared with each other to evaluate the agreement of the pregnancy risk categories. **Results:** The voluntary or medical curettage ratio was higher in pregnant women with high-risk drug exposure compared to low risk drug exposure, regarding FDA teratogenity risk categories (OR: 2.32, CI: 1.13-4.77, p=0.032). Fair or moderate agreements were demonstrated among FDA, ADEC and TERIS risk categories. The kappa coefficients of FDA-ADEC, TERIS-ADEC and TERIS-FDA were 0.379, 0.454 and 0.221, respectively. **Conclusion:** Although exposure of pregnant women to high risk drugs according to FDA risk categories was found to be associated with increased voluntary or medical curettage rates, results of epidemiologic studies should be taken into consideration in the assessment of teratogenic risks due to the poor agreements among pregnancy risk categories.

Key Words: United States Food and Drug Administration (FDA); teratogens; congenital abnormalities; abnormalities, drug-induced; catalogs, drug; drug toxicity; drug toxicity

ÖZET Amaç: Çalışmanın amaçları, Amerika Birleşik Devletleri Gıda ve İlaç Dairesi (FDA), Avustralya İlaç Değerlendirme Komitesi (ADEC) ve Teratojen Bilgi Sistemi (TERIS) risk kategorilerine göre gebelikte ilaçlara maruz kalımın riskini karşılaştırmak ve Dokuz Eylül Üniversitesi (DEU) Teratojenite Bilgi Servisi (TBS)'ne başvuran gebelerin, gebeliklerinin seyrinde FDA risk kategorileri esas alınarak verilen kararların sonuçlarını saptamaktır. **Gereç ve Yöntemler:** Bu kesitsel çalışmada, ilaç maruz kalımına bağlı teratojenite riski için TBS'ye yönlendirilen 220 gebenin demografik verileri, tıbbi özgeçmişleri, ilaca maruz kalma zaman ve süreleri kaydedildi. Gebelik sırasında maruz kalınan ilaçlar FDA'ye göre yüksek ve düşük riskli olarak sınıflandırıldı. Gebelik sırasında maruz kalınan ilaçlardan en yüksek risk düzeyine sahip ilaç, gebeliğin sonuçlarını değerlendirmek üzere göz önünde bulundurduldu. Ayrıca, FDA, TERIS ve ADEC gebelik risk kategorileri, düşük, yüksek ve bilinmeyen risk gruplarına ayrılarak, uyumluluklarını değerlendirmek için birbirleriyle karşılaştırıldı. **Bulgular:** FDA teratojenite risk kategorilerine göre yüksek riskli ilaca maruz kalımı olan gebelerde, düşük riskli ilaca maruz kalanlara göre, gönüllü ya da tıbbi küretaj oranı daha yüksek bulundu (OR: 2,32, CI: 1,13-4,77, p=0,032). FDA, ADEC ve TERIS risk kategorileri arasında az ya da orta derecede uyum saptandı. FDA-ADEC, TERIS-ADEC ve TERIS-FDA kappa katsayıları sırasıyla 0,379, 0,454 ve 0,221 idi. **Sonuç:** FDA risk kategorilerine göre gebelerin yüksek riskli ilaçlara maruz kalması, gönüllü ya da tıbbi küretaj oranlarında artış ile ilişkili olduğu bulunmasına karşın, teratojenite riski değerlendirmesinde, gebelik risk kategorileri arasındaki zayıf tutarlılık nedeniyle, epidemiyolojik çalışma sonuçları dikkate alınmalıdır.

Anahtar Kelimeler: Birleşik Devletler Gıda ve İlaç Dairesi (FDA); teratojenler; doğumsal anomaliler; anormallikler, ilaç bağımlı; katologlar, ilaç; ilaç toksisitesi; ilaç bilgilendirme servisleri

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Congenital abnormalities attributable to drug exposure during pregnancy represent about 1% of congenital defects of known etiology.[1,2] Studies from France and Netherlands reported that 99% and 85.6% of the women, respectively, were prescribed for at least one drug during their pregnancy.[3,4] Epidemiologic research on the risk of teratogenity is very important because of the avoidable nature of birth defects caused by drugs. Food and Drug Administration (FDA), Teratogen Information System (TERIS) and Australian Drug Evaluation Committee (ADEC) are the main pregnancy risk categories that standardize the drug-related teratogenic risks in pregnancy. Some other pregnancy risk categories are also being used in some countries such as Germany, Netherlands, Denmark, Switzerland and Sweden (Farmaceutiska Specialiteter i Sverige; FASS).[5,6] It is reported that there is a poor agreement among the FDA, FASS and ADEC pregnancy risk categories.[7] However, to our knowledge, FDA, TERIS and ADEC pregnancy risk categories have not been compared previously in the literature.

Insufficient investigation about teratogenic effects of new medicines and lack of extrapolation of the results of animal studies to the human increase the importance of Teratology Information Services (TIS) established in the United States and Europe.[8,9] Dokuz Eylul University (DEU) School of Medicine Drug and Poison Information Center, Karadeniz Technical University School of Medicine Department of Pharmacology and Izmir Ataturk Training and Research Hospital are the three of well known TIS in Turkey.[10] TIS not only write consultation reports for pregnant women who exposed to drugs, but also perform epidemiologic research studies about the risk assessment of drug exposure during pregnancy.[11]

The aims of our study were to compare the risk levels of exposed drugs during pregnancy with regard to FDA, ADEC and TERIS risk categories, and to determine the influence of FDA risk category-based decisions on the progress of pregnancies that referred to DEU TIS.

MATERIAL AND METHODS

The women who referred to DEU TIS between January 1, 2005 and June 30, 2007 due to drug exposure during their pregnancies were evaluated in this cross-sectional study. This study was approved by the local ethics committee of Dokuz Eylul University School of Medicine.

Demographic data (age, number of previous pregnancies, presence of consanguineous marriage, smoking and alcohol habits, working status, educational status of both women and their partners), medical history (previous stillbirth or miscarriage) and exposed drugs (duration, number of drugs, number of active substances and time of exposure) were recorded after a face to face interview with the pregnant woman.

The patients were called to learn the outcomes of their pregnancies between March and May 2008. Verbal informed consents were obtained from all patients during the telephone call. Data about the outcomes of pregnancies (healthy delivery, premature birth, congenital malformations, miscarriage, medical or voluntary curettage, and stillbirth) were recorded. The pregnant women younger than 19 years of age or older than 35 years of age were accepted as high risk group.[12,13]

Our independent variables were age [low risk (20-34 y); high risk (<19 y and >35y)], the number of pregnancies (first or more than one), consanguineous marriage (yes or no), duration of drug exposure (1-10 days, >11 days), presence of stillbirth/miscarriage in previous pregnancies (yes or no), smoking (yes or no), occupation (working, not working), educational status of women/husband [low (illiterate, literate, primary school, middle school), high (high school, university, PhD)], the number of drugs used (one or more than one) and their pregnancy risk categories (FDA, TERIS and ADEC) as shown in Table 1.

For the evaluation of pregnancy outcomes, after taking most risky drug according to FDA classification into consideration, all exposed drugs were classified as “low risk” or “high risk” according to FDA, TERIS and ADEC (Table 1). The drugs

TABLE 1: Risk levels of medicines according to FDA, TERIS and ADEC.

Risk levels	FDA	TERIS	ADEC
Low risk medicines	A, B, C, unidentified	None, minimal, unlikely, undetermined, unidentified	A, B1, B2, B3, C, unidentified
High risk medicines	D, X	Small, moderate, high	D, X

FDA: United States Food and Drug Administration; ADEC: Australian Drug Evaluation Committee; TERIS: Teratogen Information System.

that were named as "unidentified" were accepted as "low risk" if there were no data regarding their pregnancy risk categories and/or teratogenic effects. Anatomical Therapeutic and Chemical (ATC) Index was used to classify for all exposed drugs.

FDA, TERIS and ADEC risk categories were compared with each other in order to evaluate the agreement of the pregnancy risk categories (Table 2).[14,15] All exposed drugs were classified as "low", "unknown" or "high" risk according to FDA, TERIS and ADEC classifications. To compare the agreements, we only used the drugs that were included in all three categories.

TABLE 2: Comparing the FDA, TERIS and ADEC risk classifications.

FDA	TERIS	ADEC
A, B	None, minimal, unlikely	A, B1, B2,
D, X	Small, moderate, high	D, X
C, unidentified	Undetermined, unidentified	B3, C, unidentified

FDA: United States Food and Drug Administration; ADEC: Australian Drug Evaluation Committee; TERIS: Teratogen Information System.

STATISTICAL ANALYSIS

All data were recorded using Statistical Package for the Social Sciences (SPSS) version 11.0.1. Odds ratio with 95% confidence interval was calculated to compare the results according to FDA risk evaluation, and logistic regression models were constructed for the multivariable analysis. Agreements between FDA, TERIS and ADEC pregnancy risk categories were evaluated by the Kappa statistical analysis. Results were considered significant when $p<0.05$.

RESULTS

The number of pregnant referred to DEU TIS was 309. Women who could not be reached (n=83, 26.9%), or did not use any drug during their pregnancies (n=4, 1.3%) or did not want to give verbal informed consent (n=2, 0.6%) were excluded from the study. The response rate was 71.2% (n=220).

DEMOGRAPHICS

Of the patients, 78.2% (n=172) were between 20 and 34 years of age. The mean age was 29.1±5.6 years (range= 15-43 years) and mean pregnancy week on presentation to TIS was 8.2±4.4 weeks (range= 3–28 weeks, Table 3). High risk teratogenic drug exposure according to FDA classification was 29.1% (n=64). Of the study group, 71.4% (n=157) were nonsmokers and none of the patients used alcohol. The consanguineous marriage rate was 12.7% (n=28). The majority of the pregnant women were exposed to drug(s) in the first trimester (87.3%, n=192) followed by the second (11.8%, n=26) and the third trimesters (0.9%, n=2). The most risky drugs were mostly in category C (58.6%, n=129), followed by D, X and B, respectively (17.7%, n=39; 11.4%, n=25; 3.2%, n=7). For the 9.1% (n=20) of the drugs, risk categories could not be defined. None of the reported drugs were in category A. Exposure to the drugs for more than 10 days during pregnancy was 52.3% (n=115, Table 3).

Although most pregnant women (74.1%, n=163) completed their pregnancies with an alive baby (healthy delivery, preterm delivery and delivery with congenital anomaly), four (1.8%) of them had newborns with birth defects (Table 3 and 4). Medical or voluntary curettage ratio and spontaneous abortion ratio were 17.3% (n=38) and 8.6% (n=19), respectively.

DISTRIBUTION OF EXPOSED DRUGS

Pregnant women (n=220) were found to be exposed to 265 different active substances in total. About a quarter of all pregnant women (26.4%,

TABLE 3: Demographics according to FDA risk classification of pregnant women.

		FDA pregnancy risk classification					
		Low risk n=156 (70.9%)		High risk n=64 (29.1%)		Total n=220 (100.0%)	
		n	%	n	%	n	%
Age (mean±SD)		28.9±5.5 (15-43)	--	29.5±5.6 (19-41)	--	29.1±5.55 (15-43 age)	--
Smoking	Yes	46	70.5	17	26.6	63	28.6
	No	110	29.1	47	73.4	157	71.4
Occupational status	Working	91	58.3	42	65.6	133	60.5
	Not working	65	41.7	22	34.4	87	39.5
Educational status	Low	64	41.0	33	51.6	97	44.1
	High	92	59.0	31	48.4	123	55.9
Consanguineous marriage	Yes	22	14.1	6	9.4	28	12.7
	No	134	85.9	58	90.6	192	87.3
Number of live delivery	D=0	74	47.4	24	37.5	98	44.5
	D=1	52	33.3	24	37.5	76	34.5
	D≥2	30	19.3	16	25.0	46	20.9
Time of the exposure	1. Trimester	140	89.7	52	81.3	192	87.3
	2. Trimester	15	9.6	11	17.2	26	11.8
	3. Trimester	1	0.6	1	1.6	2	0.9
Pregnancy week (mean±SD)		8.0±4.1 (3-28)	--	8.7±5.1 (3-28)	--	8.2±4.4 (3-28 week)	--
Number of pregnancies according to	1-10 day	80	51.3	25	39.1	105	47.7
duration of medicine use	≥11 day	76	48.7	39	60.9	115	52.3
Presence of stillbirth/miscarriage	No	111	71.2	45	70.3	156	70.9
	Yes	45	28.8	19	29.7	64	29.1
Distribution according to	Single	37	23.7	21	32.8	58	26.4
number of medicine	A lot of	119	76.3	43	29.7	162	73.6
Distribution of	A	--	--	--	--	--	--
most risky medicine according to	B	7	4.5	--	--	7	3.2
FDA	C	129	82.7	--	--	129	58.6
	No code	20	12.8	--	--	20	9.1
	D	--	--	39	60.9	39	17.7
	X	--	--	25	39.1	25	11.4
Outcomes of pregnancies	Healthy delivery	100	64.1	37	57.8	137	62.3
	Preterm delivery	18	11.5	4	6.3	22	10.0
	Medical or voluntary curettage	21	8.3	17	9.4	38	17.3
	Miscarriage	13	13.5	6	26.6	19	8.6
	Congenital malformation	4	2.6	--	--	4	1.8

FDA: United States Food and Drug Administration.

n=58) were exposed to only one drug and 22.7% (n=50) were exposed to only one drug and a single active substance. The most frequently exposed active substances were anti-infective drugs (24.6%, n=216) and nervous system drugs (24.1%, n=212) according to ATC Index (Figure 1).

VOLUNTARY OR MEDICAL CURETTAGE RATIO ACCORDING TO DEMOGRAPHICS OF THE PREGNANT WOMEN

There were 38 women with voluntary or medical curettage. Of these, seven had curettage after 11 weeks of gestation. Of these seven women, four patients were exposed to high risk drugs (Table 5).

TABLE 4: Types of congenital anomalies.

No	Anomalies	Medicine name and its category of pregnancy risk classification systems (FDA/TERIS/ADEC)
1	Cleft lip palate	Ampicillin/sulbactam (B/Unlikely/A), dimenhydrinat (B/Unlikely/A), triamcinolone (C/Undetermined/B3), ambroxol (No code/No code/No code)
2	Pes varus, exotropia, hypermetropia	Ampicillin/sulbactam (B/Unlikely/A), cefprozil (B/No code/No code), ornidazole (No code/No code/No code), amoxicillin (B/None/A), fosfomycin (B/No code/No code), caffeine (C/None/A), povidone iodine (No code/No code/No code), paracetamol (No code/None/A)
3	Heart valve defect and hypothyroid	Lansoprazole (B/undetermıned/B3), amoxicillin (B/None/A), famotidine (B/Unlikely/B1), clarithromycin (C/undetermıned/B3), alginate (No code/No code/No code)
4	Hypospadias	Meloxicam (C/No code/No code), diosmin (No code/No code/No code), hesperidin (No code/No code/No code), thiocolchicoside (No code/No code/No code), dipyrone (No code/Undetermined/No code)

FDA: United States Food and Drug Administration; ADEC: Australian Drug Evaluation Committee; TERIS: Teratogen Information System.

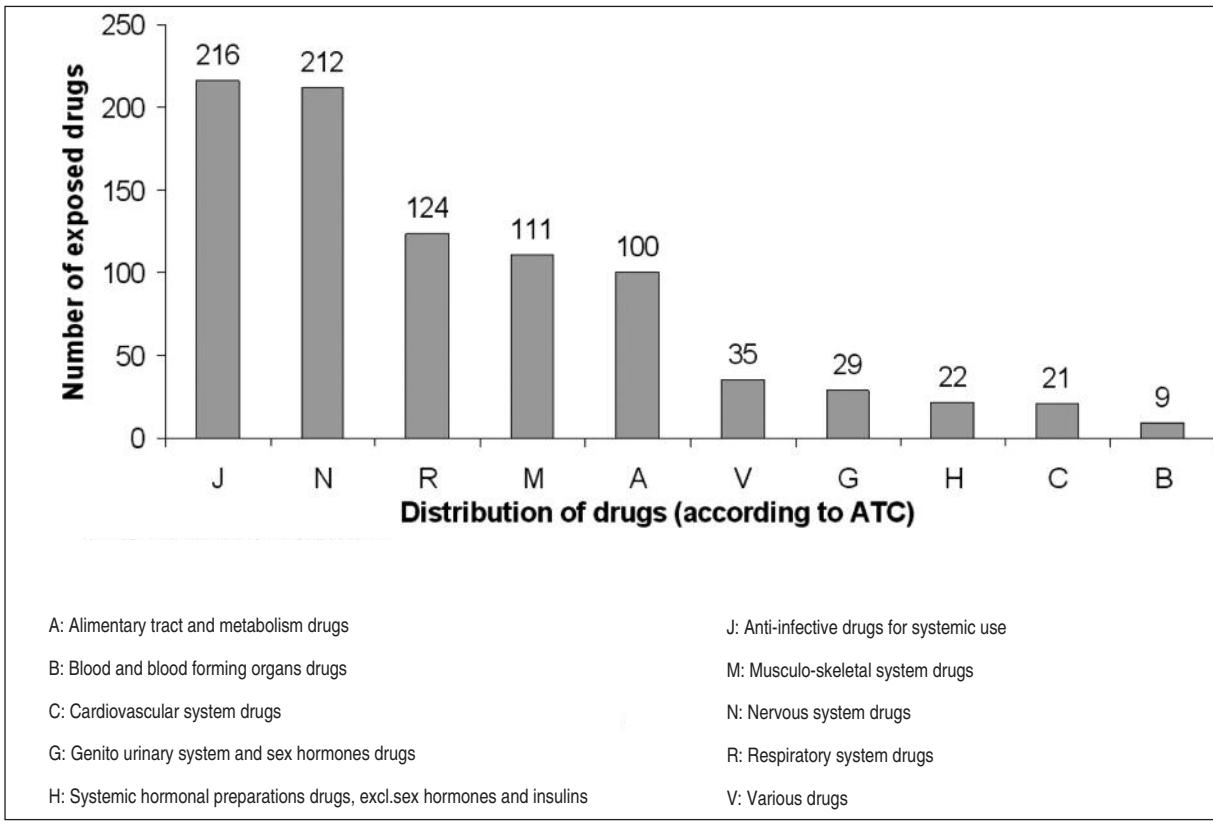

FIGURE 1: Distribution of the exposed drugs according toAnatomical Therapeutic and Chemical (ATC) Index.

TABLE 5: Number of voluntary or medical curettage according to FDA classification and time of curettage.

		FDA pregnancy risk classification		
		Low risk n=21 (55.3%)	High risk n=17 (44.7%)	Total n= 38
Time of curettage	Before 10 weeks	18	13	31
	After 11 weeks	3	4	7

FDA: United States Food and Drug Administration.

TABLE 6: Distribution of voluntary or medical curettage according to FDA, TERIS and ADEC.

		Voluntary or medical curettage					
		No		Yes		Total	
		n=182	%	n=38	%	n=220	OR (%95 CI)
The group of most risky medicine in FDA	Low risk	135	86.54	21	13.46	156	2.33 (1.13-4.78)
	High risk	47	73.44	17	26.56	64	p=0.032*
The group of most risky medicine in TERIS	Low risk	163	83.16	33	16.84	196	1.30 (0.45-3.73)
	High risk	19	79.17	5	20.83	24	p=0.839
The group of most risky medicine in ADEC	Low risk	147	85.47	25	14.53	172	2.18 (1.02-4.69)
	High risk	35	72.92	13	27.08	48	p=0.69

OR: Odds ratio; CI: Confidence interval.

The voluntary or medical curettage rate was higher in pregnant women with high risk drug exposure than that of low risk drug exposure, regarding FDA teratogenity risk categories (OR: 2.32, CI: 1.13-4.77, p=0.032, Table 6). However, the voluntary or medical curettage ratio did not differ significantly between high and low risk drugs regarding TERIS and ADEC classifications (Table 6, p>0.05).

The voluntary or medical curettage rate was higher in patients exposed to drugs for more than ten days when compared to the patients whose exposure interval was less than ten days with respect to FDA teratogenity risk categories (OR: 2.26, CI: 1.08-4.76, p=0.044).

The odds ratios adjusted for occupation, presence of stillbirth or miscarriage in previous pregnancies, educational status of women and their partners, being in the risky age group, smoking habits, the number of drugs used and having the first pregnancies were 2.16, CI: 1.04-4.49, p=0.038.

AGREEMENTS OF PREGNANCY RISK CATEGORIES

Low risk, unknown risk and high risk distributions of the active substances were 20.0% (n=53), 68.7% (n=182) and 11.3% (n=30) for FDA; 25.7% (n=68), 64.9% (n=172), 9.4% (n=25) for ADEC and 32.8% (n=87), 62.6% (n=166), 4.5% (n=12) for TERIS, respectively (Table 7). Kappa coefficients of the pregnancy risk categories of drugs were 0.379 (fair agreement), 0.454 (moderate agreement) and 0.221 (fair agreement); between FDA and ADEC, TERIS and ADEC, TERIS and FDA pairs, respectively (Table 8).

TABLE 7: Distribution of the medicines according to FDA, ADEC and TERIS classifications.

	Low risk	Unknown risk	High Risk
FDA	%20.0	%68.7	%11.3
ADEC	%25.7	%64.9	% 9.4
TERIS	%32.8	%62.6	% 4.5

OR: Odds ratio; CI: Confidence interval; FDA: United States Food and Drug Administration; ADEC: Australian Drug Evaluation Committee; TERIS: Teratogen Information System.

TABLE 8: Percents and strength of agreements of pregnancy risk categories.

Compared risk categories	κ (Kappa) coefficients	Strength of agreement	Significance
FDA-TERIS	0.221	Fair	p<0.0001
FDA-ADEC	0.379	Fair	p<0.0001
ADEC-TERIS	0.454	Moderate	p<0.0001

FDA: United States Food and Drug Administration; ADEC: Australian Drug Evaluation Committee; TERIS: Teratogen Information System.

DISCUSSION

In the first part of our study, we evaluated the demographics of the pregnancies. Similar to the previously published studies, most of these pregnant women were between 20 and 34 years of age.[16] Studies from other countries report that an exposure to drugs during pregnancy is a common problem with the rate of 64.1% to 99.0%.[3,9,17,18] In our study, first trimester drug exposure was 87.3 % and consistent with previous studies.[17,19-22] The inadvertent use of drugs because of unexpected or unplanned pregnancy is a possible reason of this increased drug exposure rate in the first trimester.

In our study, the most frequently exposed drugs during pregnancy were anti-infectives, analgesics, psycholeptics and psychoanaleptics. Similar to our results, antibiotics, analgesics, asthma medications and antiemetics were the most frequently exposed drugs in the previous studies by Riley at al. and Lacroix et al.[3,23] Another study by Bakker et al. reported that pregnancy-related medicines (antacids, antiemetics, laxatives, iron preparations, folic acid and derivatives, gynecological anti-infective agents and antiseptics, gonadotropins and other ovulation stimulants, vitamins, gastrointestinal system drugs, dermatologic medicines and analgesics) were the most frequently prescribed drugs during pregnancy.[21] As anxiety and depression are frequently encountered health problems in the reproductive period, the use of central nervous system agents (including analgesics), respiratory agents and recreational medicines (including alcohol, cigarettes, caffeine and illicit drugs) are common in pregnancy.[24,25] No alcohol exposure was detected in our study. This may probably be due to the sociocultural differences and drinking less as a habit in our country, particularly among women.[26,27]

In our study, more than half of the pregnant women (64.2%) were exposed to more than one drug in their pregnancies; this rate was higher (90%) in a previous report by Olukman at al.[19] This finding is probably a result of polypharmacy which is regarded as an irrational drug prescribing problem in our country. Schirm et al. suggest that the teratogenic effect of polypharmacy can be reduced by consulting pregnant women to use safer drug options.[4]

Our study showed that approximately one third (29%) of the pregnant women were exposed to high risk drugs according to FDA (category D or X) and most of them were exposed to these drugs in the first trimester. Previous studies demonstrated that 9.8%-28% of the pregnant women were exposed to high risk drugs.[7,19,20] Conversely, in subsequent studies by Riley et al. and Bakker et al., 56-79% of pregnant women were exposed to at least one drug during their pregnancy, however, high risk medicine exposure was less (1-4%) than that of ours.[21,23]

It is reported that drug-related congenital malformation rate was less than 1% of all birth defects.[1,28] Although congenital malformation rate was 1.8% (n=4) in our study, small number of cases might probably have not permitted a critical evaluation of this finding. Among the congenital anomalies observed in our study, only cleft palate, of which the risk had been shown to be increased with corticosteroid use in previous studies,[29,30] has been found to be associated with triamcinolone use in pregnancy.

In this study, although most of the pregnancies (74.1%) were completed with delivery, 17.3% of them were terminated with voluntary or medical curettage. Occupational and educational status of women and their partners, presence of stillbirth or miscarriage in previous pregnancies, being in the high-risk age group, smoking, number of drugs used and having the first pregnancy did not seem to interfere the medical or voluntary curettage decision.

The voluntary or medical curettage rate was two-folds higher in pregnant women exposed to high risk drugs compared to that of low-risk drugs according to the FDA classification. On the contrary, voluntary or medical curettage rate was not significantly higher in women exposed to high risk drugs according to TERIS and ADEC risk classifications. This finding is important since it suggests the incoherence among different risk classifications. Voluntary or medical curettage rate was also higher in patients exposed to drugs for more than ten days compared to those exposed less than ten days according to FDA classifications. It is known that the risk of teratogenity is well-proportioned by frequency, dose and the period of the drug use and drugs should be given only if the potential benefit justifies the potential risk to the fetus in the pregnancy.[8,31-33]

In our study, low risk, unknown risk and high risk distribution of the active substances were found to be different according to FDA, ADEC and TERIS (Table 7). Moreover, it has been suggested that the currency and adequacy of the classifications is limited since updating the information re-

garding drugs in these risk categories may not be implemented rapidly.[33] Kappa coefficients of the pregnancy risk categories of drugs were also found to be different between FDA and ADEC, TERIS and ADEC, TERIS and FDA pairs (Table 8), highlighting the poor agreements among three pregnancy risk categories. In particular, low consistency was found between FDA and TERIS risk categories.[14] This is probably due to the following reasons: While FDA mostly uses unpublished premarketing animal studies, TERIS is primarily based on published human studies.[14] Additionally, FDA risk categories are assigned with a regulatory process and negotiation with the sponsor, however, TERIS categories are determined by an independent group of experts. Furthermore, FDA risk categories cover both the potential benefits and risks of drugs during pregnancy, thus provide therapeutic guidance in pregnancy as well, yet TERIS ratings are focused only on the drugs' teratogenic effects and not the potential risks or benefits on the treatment of the mother.[14] Lastly, FDA categories include perinatal risks which are not considered in TERIS risk rating.[34] It was also shown in our study that according to the FDA, ADEC and TERIS teratogenity risk classifications, high risk medicines accounted for 11.3%, 9.4% and 4.5% of all medicines recorded in our study, respectively. These data suggest that TERIS generally assumes that drugs are safer in contrary to opinion of FDA.

Our study showed a low consistency among the generally accepted pregnancy risk categories and emphasizes the diversity of risk perception between the categories. Since TERIS categorization generally assumes that drugs are safer in contrary to opinion of FDA, use of TERIS in evaluation of drug exposure in pregnancy might decrease the number medical and voluntary curettages, however it also might lead to an increase in adverse pregnancy outcomes. Further studies should be directed on the outcomes of FDA, TERIS and ADEC-based decisions to draw better and more definite conclusions on the issue.

CONCLUSION

Exposure to high risk drugs according to FDA risk categories were found to be associated with increased voluntary or medical curettage rates in pregnant women. Because of the poor agreements among pregnancy risk categories; not only pregnancy risk categories but also results of epidemiologic studies should be taken into consideration while assessing the teratogenic risks due to exposed drugs.

LIMITATIONS

The first limitation was the lack of data related to hospital records of some pregnant women. The second limitation was the absence of the medical examination of the newborns to verify the congenital malformations. The third limitation was the inability to differentiate medical or voluntary curettage in the first 10 weeks of pregnancy as the tenth week is limit for legal curettage in Turkey.

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