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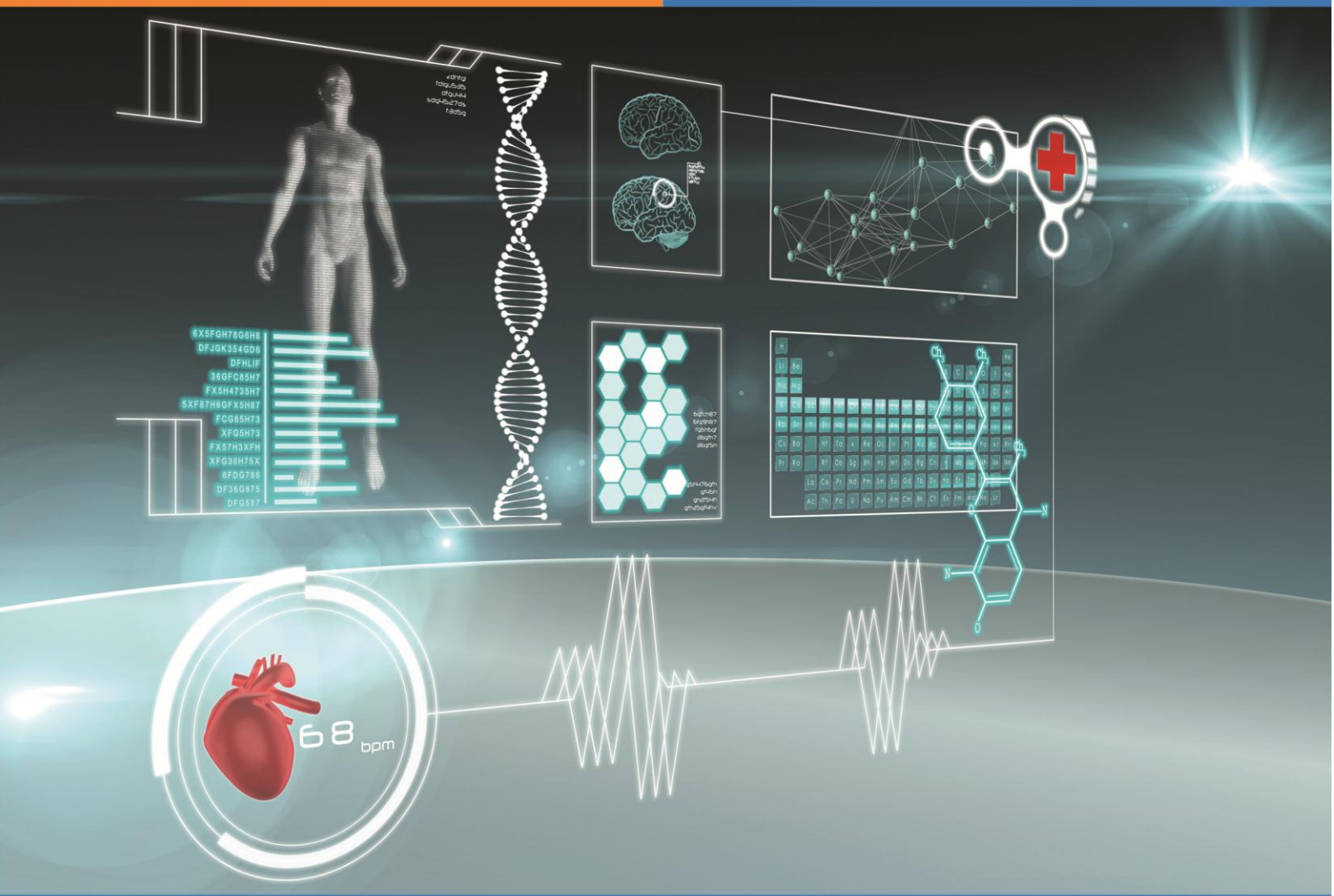

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Address: Al-Razi University - College of Medical Sciences

Telefax: +9671406760 P.O. Box:1152 Sana'a – Yemen

Email: nabilalrabeei@hotmail.com

Designed by Eng. Osama Al-Moaina
Ossamah245@yahoo.com

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Distribution of Therapeutic and FDA Pregnancy Categories among Drugs Prescribed for Pregnant Women in Sana`a, Yemen

Anes A. M. Thabit [1*] and Nabil Ahmed Al-Rabeei [2]

[1]Department of Pharmacy, College of Medical Sciences, Al-Razi University, Yemen[2]

[2]Department of Applied medical sciences, College of Medical Sciences, Al-Razi University, Yemen.

[*]Correspondent author: aneesalabsi1973@gmail.com

Abstract

Background*: The concern of using medicines in pregnancy is due to the threat of potential teratogenic effects of the drug and physiologic adjustments in the mother in response to the pregnancy.* ***Aim****: to determine the distributions of therapeutic categories and FDA pregnancy categories among drug prescribed for pregnant women in Sana`a-Yemen.* ***Methods****: A sample of 924 medications orders prescribed for pregnant women in Sana`a-Yemen, was analyzed in this study. The sample was divided into two groups: Hospital and clinic prescriptions. Within each group, drugs were categorized according to their therapeutic effects and then according to the FDA system of classification for drugs in pregnancy.* ***Results****: The overall distributions of GIT drugs (29.2 %,), systemic antibacterials (18.3%) and vitamins hematinics (17%), among the prescribed drugs, were larger than the other categories. Based on the FDA system, the overall distributions of FDA categories A, B, C, D, X and the non-classified category among the prescribed drugs were 8.2%, 40.9 %, 20.3 %, 4.6 %, 0.7 % and 25.3 %, respectively. There were no significant variations (P > 0.05) in the distribution of therapeutic or FDA categories between the hospital and clinic prescriptions.* ***Conclusions****: Majority (64.5 %) of drugs prescribed for pregnant women in Sana`a-Yemen belongs to the GIT drugs, systemic antibacterials, vitamins and hematinics categories. In another respect, the distribution of risky drugs belonging to FDA categories (D and X) and the non-classified category comprises 30.6 % of all drugs prescribed for pregnant women.*

Keywords*: Therapeutic categories; FDA categories; prescribed drugs; Pregnancy; Yemen*

Introduction

The use of medicines during pregnancy still represents a challenge for medicine, since the majority of drugs cross the placental barrier[1]. The concern of using medicines in pregnancy is due to the threat of potential teratogenic effects of the drug and physiologic adjustments in the mother in response to the pregnancy[2].

Current evidence suggests that between 65%-94 % of women take at least one prescription drug during pregnancy[3,4]. Nearly 70% of women are taking a drug in the first trimester during organogenesis[3]. The substances that may cause birth defects via a toxic effect on an embryo or fetus are called teratogens[5]. Many drugs, such as. Tetracycline, phenytoin, diethylstilbestrol, synthetic vitamin A and cytotoxic antitumors are well-known teratogens. Besides the risk of using certain medicines, miscarriage and modifications in the maternal organism during pregnancy may interfere in the extension of fetal exposure to the drug administrated to the mother. This effect depends on different factors, particularly the mother-fetus elimination mechanism and placenta permeability, in addition to the reduction of plasmatic carrying proteins and increase of cardiac work, which reflects an increased level of glomerular filtration and kidney clearance of the drug[6, 7].

In Yemen, birth defects were found to be the third cause of premature death in 2005 and the 4th cause in 2016. Furthermore, they were s also the 7th cause of all death cases in 2016 with a total number of 1295 deaths (5.8 % of all death cases). This number is significantly higher than the corresponding number of 766 and 477 death cases estimated in Saudi Arabia and Oman, respectively[8].

The first regulations of drug labeling during pregnancy were implemented in the USA in 1962 after the exposure of over 10,000 children to thalidomide[7]. The 5-letter classification system (A,B,C,D,X) of drugs use during pregnancy was then introduced in 1979 by the Food and Drug Administration (FDA). The interpretation of these letters is shown in table 1[9].

Table 1: Interpretation of FDA classification system of drugs in pregnancy

FDA Pregnancy category of drugs	Interpretation	Recommendation of use or not in pregnancy
A	No risk in controlled human studies: Adequate and well-controlled human studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy and there is no evidence of risk in later trimesters.	The drug is safe during pregnancy.
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR Animal studies have shown an adverse effect, but adequate and well-controlled studies in human pregnant women have failed to demonstrate a risk to the fetus in any trimester.	The drug is relatively safe and therefore can be used if necessary and when there is no alternative to category A drugs.
C	Animal reproduction studies have shown an adverse effect on the	Risk-not ruled out**:** the drug should be avoided unless

	fetus and there are no adequate and well-controlled studies in humans.	potential benefits may warrant its use despite potential risks.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans.	Positive-evidence risk **:** The drug should not be used unless there is a life-threatening on pregnant women if not used
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience.	Contraindicated in pregnancy: The drug is not used because the risks involved in the use of the drug in pregnant women clearly outweigh potential benefits

In 2015, FDA replaced the former pregnancy risk letter categories on prescription and biological drug labeling with new information to make them more meaningful to both patients and healthcare providers. The new labeling system allows better patient-specific counseling and informed decision making for pregnant women seeking medication therapies. While the new labeling improves the old format, it still does not provide a definitive "yes" or "no" answer in most cases. Clinical interpretation is still required on a case-by-case basis. The Pregnancy and Lactation Labeling Final Rule (PLLR) went into effect on June 30, 2015; however, the timelines for implementing this new information on drug labels (also known as the package insert) is variable. Prescription drugs submitted for FDA approval after June 30, 2015, will use the new format immediately, while labeling for prescription drugs approved on or after June 30, 2001, will be phased in gradually. Medications approved prior to June 29, 2001, are not subject to the PLLR rule[10,11].

Studies concerning the use of inappropriate drugs in pregnancy have been conducted in many countries. For instance, measured rates of use of contraindicated medicines (category X) in pregnancy ranged from 0.9% (Denmark; 1991–1996) to 4.6% (USA; 1996–2000). The use of medicines with positive evidence of risk (category D) was 2.0% in Italy, 2004[12]. In Taiwan, a study, conducted in 2014, revealed that 1.1 % of drugs prescribed for pregnant women were of category D or X [13]. In Oman, 2016, a study conducted on 204 prescriptions for pregnant women revealed that the distribution of categories prescribed for pregnant women was B (30.0%), C (27.14%), D (1.43%) and X (0%)[14]. In Egypt, a study revealed that the distribution of categories (D) and (X) among drugs used by/prescribed for pregnant women were 0.5% and 0.9 %, respectively[15].Another study conducted in Ethiopia, 2017, revealed a distribution of only 0.5% of category D[16].

Aim of the study

The aim of this study was to determine the distribution of therapeutic and the FDA pregnancy categories among drug prescribed for pregnant women in Sana`a-Yemen.

Subjects and Methods

A descriptive, cross-sectional study was done in public and private hospitals and community pharmacies. A total of 924 medication orders prescribed by physicians in Sana`a for

pregnant women during the period from 2nd August/2017 to 3rd February 2018, were analyzed in this study. Photocopies of prescriptions were obtained, after oral consent of the patients. The sample was collected randomly from different public and private hospitals and from community pharmacies located in different areas in Sana`a. The number of hospitals and clinic prescriptions collected, were 484 and 440, respectively.

The collected prescriptions were divided initially according to the source of prescriptions into 2 groups: hospital and clinic prescriptions. In each group, the prescribed drugs were inputted (as generic names) into suitable table sheets. Some drug products contained more than one generic name e.g. cough preparations. In such cases, only the drug having higher risk according to the FDA system of classification was inputted, but if the drugs had the same FDA categorization, each drug was then inputted individually. In other cases, if the same drug had different strengths, dosage forms or route of administration, the drug was inputted as just one entity.

In each group of prescriptions, the individual frequency of prescribing a drug and the total frequency of prescribing all drugs were also calculated. The overall total of frequencies of all drugs in the two groups was then calculated.

The prescribed drugs, in each group, were classified therapeutically into 19 therapeutic categories. Then, they were classified according to the FDA system of classification for drugs in pregnancy, into 5 categories: A, B, C, D, and X. The FDA categorization was carried out by using the website of Medscape[17]. This website, which has a partnership with FDA[18] was used instead of the FDA website due to the ease of information. An extra category (designated as non-classified) was set to include all drugs that have not yet been classified by FDA.

For both therapeutic or FDA categories, the distribution a category in the hospital or clinic prescription groups was calculated as follows:

$$D_c = 100 \times fc / f_g$$

, where f_c was the frequency of drugs belonging to that category in the group of prescriptions and f_g was the sum of all drugs frequencies in that group. The overall average distribution ($Do_{average}$) of each category in all analyzed prescriptions was calculated as follows

$$Do_{average} = 100 \times D_{c1}/D_{c2}$$

Where D_{c1} and D_{c2} were the distributions of the category in the hospital and clinic prescriptions, respectively. In order to test the variation in distributions of categories within each group (hospital or clinic), the relative standard deviation (RSD %) was calculated as follows:

$$RSD\% = 100 * a / b$$

Where (a) was the average of all D_c within the group and (b) was the standard deviation of those data. If RSD% was greater than 15%, the variation was considered significant[19].

To assess the variation in the distribution of categories between the two groups (hospital, clinic), Student Paired t-test was used to analyzed numerical variables with normal distribution [20]. Chi-square test was used to test the variation in categorical data of analyzed prescriptions[19]. In both methods, the variation was considered significant if *P*- value) was <0.05. Lists of risky drugs prescribed for pregnant women in the analyzed sample of prescriptions were established. The listed drugs included drugs belonging to the categories D, X as well as the "non-classified" category.

Results

Drugs prescribed for pregnant women

As demonstrated in table 2, 52.7 % and 47.7 % of the prescriptions sample analyzed in this study were obtained from hospitals and clinics, respectively. The sample included a total of 376 drugs. The total frequency of drugs in the hospital and clinic prescriptions were 661 and 655, respectively, with an overall frequency of 1316 for all prescribed drugs. There was no significant variation between data of hospital and clinic prescriptions (P>0.05).

Table 2: Drugs prescribed for pregnant women in hospitals and clinics.

Data of prescriptions		Hospital prescriptions	Clinic Prescriptions	Total
No/(%) of prescriptions		484(52.4 %)	440 (47.6 %)	924(100%)
No. of drugs	**Different**	102	92	376
	Similar	182		
***f_t* (Total of all drugs)**		661	655	1316 *
Chi-square (P- value)		0.063$^{\lozenge}$		

**: ∑f =The total frequency of all drugs in the two group, $^{\lozenge}$: insignificant variation (P >0.05)*

Distribution of therapeutic categories

Table 3 demonstrates the distributions of 19 therapeutic categories among the drugs prescribed for pregnant women in the two groups: hospital and clinic prescriptions. The results revealed that GIT drugs in both hospitals and clinics had the largest distributions among other categories with a distribution (%) of 22.819% and 35.552%, respectively. The overall Mean distribution of that category ± SD was 29.185 ± 9.003 and its 95% C.I was 27.421-56.606%. The other categories that showed the considerable distribution in the hospital and clinic prescriptions, respectively, included systemic antibacterial (23.356% and 13.135%) and vitamins and hematinics. No intergroup significant variation in the distribution of therapeutic categories was observed between the hospital and clinic prescriptions (P<0.05). On the contrary, intragroup variation was significant among the categories in both hospital and clinic prescriptions with RSD > 15%.

Table 3: Distribution of therapeutic categories among the drugs prescribed for pregnant women in Sana'a-Yemen.

Therapeutic category	Distribution (%)			
	Hospital Prescriptions	Clinic Prescriptions	Do $^{\lozenge}$	
			Mean ± SD	95 % C.I
CNS drugs	1.879	0.701	1.290 ±0.83	1.127 -2.41
CVS drugs	0.805	0.701	0.753 ± 0.07	0.738 - 1.49
Antihemorrhogics	3.221	1.401	2.311 ± 1.28	2.059 - 4.37
Respiratory drugs	2.148	1.751	1.94 ± 0.28	1.895 - 3.84
Renourinary drugs	3.087	5.254	4.171 ± 1.53	3.870 - 8.04
Systemic antihistamines	0.537	0	0.268 ± 0.38	0.194 - 0.46
Systemic corticosteroids	0.268	0	0.134 ± 0.19	0.097 - 0.23
GIT drugs	22.819	35.552	29.185 ± 9.00	27.421-56.60
Endocrine drugs	2.550	5.954	4.252 ± 2.40	3.781 - 8.03
Non-opioid Analgesics	5.235	4.378	4.807 ± 0.60	4.688 - 9.49
Opioid analgesics	0.134	09	0.067 ± 0.09	0.049 - 0.11

Systemic. Antibacterials	23.356	13.135	18.245 ± 7.22	16.829- 35.07
Systemic Antifungals	1.342	0.701	1.021 ± 0.45	0.932 - 1.95
Anti-TB drugs	0.268	0	0.134 ± 0.19	0.097 - 0.23
Antiprotozoals	3.758	0.175	1.967 ± 2.53	1.470 - 3.43
Anthelmintics	0	0.175	0.088 ± 0.12	0.063- 0.15
Vitamins & hematinics	16.913	17.163	17.038± 0.17	17.003- 34.04
Antiinfective and cleansing vaginal drugs	7.651	11.734	9.692 ± 2.88	9.127- 18.81
Dermal, otic oromucosal and ophthalmic preparations.	4.027	1.226	2.626 ± 1.98	2.238 - 4.86
RSD* % (Intragroup) variation	140.2 ▲	169.5 ▲		
t- test (P -value) (Intergroup variation)	0.33 □			

◊: Overall Mean distribution of the category ± SD *: Relative standard deviation;
▲: Significant intragroup variation (RSD > 15 %) □: Insignificant intergroup variation (P >0.05)

Distribution of FDA Pregnancy categories

Table 4 shows the distributions of FDA-pregnancy categories among drugs prescribed for pregnant women in hospital and clinic prescriptions. The largest distribution (39.79 % and 42.008%), in the two groups, respectively, was observed in the category (B) with an overall Mean ± SD of (40.899 ± 1.568) and 95 % C.I. of (40.592 - 81.491 %). The category that demonstrated the second rank of distribution was the "Non-classified" category.

The distributions of this category were 24.957 % and 25.762 %, respectively, in the hospital and clinic prescription groups with an overall Mean ± SD of (25.360±0.569) and 95% C.I. of (25.248-50.607%). Similar to that observed in therapeutic categories, there was no intergroup significant variation in the distribution of FDA categories ($P<0.05$), while the intragroup variations of categories distribution in the hospital and clinic prescription groups were both significant categories RSD > 15%.

Lists of risky and non-classified prescribed drugs

Table 4 demonstrates the lists of risky drugs prescribed for pregnant women. In addition to 13 "non-classified" drugs, the lists included 4 drugs of category (D) and 3 drugs of category (X).

Table 4: Distribution of FDA pregnancy categories among drugs prescribed for pregnant women in Sana'a-Yemen.

FDA pregnancy Category	Distribution %			
	Hospital Prescriptions	Clinic Prescriptions	Do ◊	
			Mean ± SD	95 % C.I.
A	11.476	4.814	8.145 ± 4.71	7.222 - 15.367
B	39.79	42.008	40.899 ± 1.56	40.592 - 81.491
C	19.265	21.42	20.343 ± 1.52	20.044 - 40.386

D	3.457	5.737	4.597 ± 1.61	4.281 - 8.878
X	1.055	0.259	0.657 ± 0.56	0.547 - 1.204
Non-classified	24.957	25.762	25.340 ± 0.56	25.248 - 50.607
RSD* % (Intragroup)variation	87.2 ▲	95.9 ▲		
t-test (P-value); (Intergroup variation)	0.5 □			

◊: Overall Mean distribution of the category ± SD *: Relative standard deviation;
▲: Significant intragroup variation (RSD > 15 %) □: Insignificant intergroup variation (P >0.05)

Table 5: Lists of risky and non-classified drugs prescribed for pregnant women in Sana'a-Yemen.

Non-classified	Category D	Category X
1. Aceclofeanc 2. Ambroxol 3. Butamirate 4. Diosmin. 5. Drotaverine. 6. Dydrogesterone. 7. Etamsylate. 8. Hexamine. 9. Mebeverine. 10. Nifuroxazide 11. Secnidazole. 12. Sodium Alginate. 13. Tolperisone.	1. Doxycycline. 2. Gentamicin. 3. Fluconazole. 4. Trimethoprim/sulfamethoxazole.	1. Ethinyl estradiol. 2. Norethisterone. 3. Misoprostol.

Discussion

The present study was conducted to determine the distribution of therapeutic and FDA pregnancy categories among drugs prescribed for pregnant women in Sana'a-Yemen. A total of 924 prescriptions, as shown in table 2, were analyzed in this study. The variation in a number of prescriptions and drugs, and in the frequency of prescribing those drugs between the hospital and clinic prescriptions was insignificant (P > 0.05).

As demonstrated in table 3, the absence of intergroup significant variation (P > 0.05) in the distribution of therapeutic categories between the hospital and clinic prescriptions indicated the similarity of prescription pattern between physicians working in hospitals and private clinics. On the other hand, significant intragroup variation in both hospital and clinic prescription groups could be attributed to the presence of therapeutic categories that were more frequently prescribed than other categories. In this respect, the therapeutic categories that demonstrated larger overall distributions than other categories included GIT drug (29.2 %), systemic

antibacterials (18.3%) and vitamins and hematinics (17 %). The total distribution of those 4 categories was 64.5 % which represented the majority of all prescribed drugs. The pattern of distributions of the categories was quite different from those observed

other Asian/African countries: Oman (Multivitamins 30.6 % and analgesics 11.9 %) [14], and Ethiopia (antibiotics 41% and analgesics 23%)[16]. This finding could be attributed to variation in the prevalence of diseases among pregnant women in each country.

With respect to the distribution of FDA pregnancy categories, as shown in table 4, it was found that the overall distributions of relatively safe drugs, Category A and B, were 8.2 % and 40.9 %, respectively. Together, these two categories comprised 49.1 % of all prescribed drugs which indicated that 50.9 % of all prescribed drugs were not relatively safe in pregnancy. However, if the distribution of category (C), which is a risk-not rule out the category that depends on the evaluation of the physician to drug benefit to risk, was excluded from the distribution of risky drugs, it could be estimated that 30.6 % of the prescribed drugs were non-safe for pregnant women. Among the risky prescribed drugs, 4.6 %, 0.7 %, and 25.3 % belonged to categories (D), (X) and "Non-classified" respectively. Compared to other countries, distribution of category (D) observed in this study was greater than that in Italy (2%), Oman (1.43 %), Egypt (0.5%) and Ethiopia (0.5 %)[14,15,16]. The prescribed drugs, as shown in table 4, which belong to that category, included antibacterials (doxycycline, gentamicin and trimethoprim/sulfamethoxazole) and the oral antifungal (fluconazole). Due to the availability of safer alternatives to those drugs, such as cephalosporins (category B) for the antibacterial and itraconazole (category C) for the antifungal, it was irrational to prescribe category (D) drugs for pregnant women. With respect to category (X), the distribution of this category was also greater than those reported in Oman (0%)[14], but smaller than that in Egypt (0.9%)[15]. The prescribed teratogenic drugs, which belong to category (X), included the sex hormones (Ethinyl estradiol, Norethisterone) and the abortion-inducing prostaglandin analog (misoprostol). Another important finding observed in this study was the prescribing of a considerably high percentage (25.3%) of drugs that have not been yet classified by FDA, as listed in table 5.

Conclusions

Based on results obtained from this study, it could be concluded that majority (64.5%) of prescribed drugs for pregnant women in Sana`a-Yemen belongs to the GIT drugs, systemic antibacterials, vitamins & hematinics categories. In addition, the total distribution of risky drugs (FDA Category D, X, and the non-classified category) comprised 30.6 % of all drugs prescribed for pregnant women.

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