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Gender Differences in Adverse Drug Reactions Among Adult Patients Reported to the Iraqi Pharmacovigilance Center

Areej A. Abdulrazaq[*,1], Dheyaa J. Kadhim[*] and Manal M. Younus[**]

[*] Department of Clinical Pharmacy, College of Pharmacy, University of Baghdad, Baghdad, Iraq.
[**]Head of Iraqi Pharmacovigilance Center, Directorate of Technical Affairs, Ministry of Health, Iraq.

Abstract

For many years it was argued that there may be a gender differences in adverse drug reactions (ADRs). This assumption was based on many possible factors such as hormonal or behavior differences, and it was not clearly identified since the female gender was not preferred to be enrolled in many clinical trials. The primary aim of this study was to assess the extent of possibly relevant gender differences in drug – ADRs regarding causality, severity, preventability, seriousness, expectedness and outcome. While the secondary aim was to assess for which group of drugs and for which ADRs gender differences are identified most often. The study was a retrospective one that depends on processing a specially selected group of data obtained from the Iraqi Pharmacovigilance Center database. The data included consisted of 3833 individual case safety reports sent during the period from 1st January 2017 to 31st December 2019. It was found that the reported adverse drug reactions for females (60.84 %) were much more than males (39.16 %). In addition, significant differences in age group distribution of adverse drug reactions were found in which females in their reproductive age had more adverse drug reactions while the older adult males were more likely to suffer adverse drug reactions if compared with the same age groups from the opposite gender. The highest type of adverse drug reactions for both genders were those that fall in the skin and subcutaneous tissue disorders (26.4 % in females) and (22.6 % in males) with statically significant difference between the two genders. While the highest group to cause adverse drug reactions was the systemic anti-infective agents with a greater chance 'statistically significant' in females to suffer a side effect from this group of medications (40.8 %) compared to male gender (35.5 %). The frequency of serious adverse drug reactions was significantly more prevalent in females (45.4 %) than for males (41.3 %) while the fatal outcome was significantly more observed in males (0.8 %) as compared with females (0.2 %). The expectedness analysis gave the finding that for each gender, the chances to get an expected ADR were nearly equal.

Keywords: Pharmacovigilance, Adverse drug reactions, Iraqi pharmacovigilance center, Gender differences, Iraq.

اختلافات الجنسين في الاعراض الجانبية للأدوية لدى البالغين والتي تم الابلاغ عنها للمركز العراقي لليقظة الدوائية

أريج أثير عبد الرزاق *[،1]، ضياء جبار كاظم * و منال محمد يونس **

*فرع الصيدلة السريرية ،كلية الصيدلة، جامعة بغداد، بغداد، العراق.
**مدير المركز العراقي لليقظة الدوائية، دائرة الامور الفنية، وزارة الصحة، العراق.

الخلاصة

لطالما كانت إحتمالية وجود إختلافات في الاعراض الجانبية بين الجنسين محل جدل لدى الدارسين لسنوات عديدة. هذه الفرضية قد تولدت بسبب وجود اختلافات متعددة كالهورمونية او السلوكية و غيرها. و لم يتم الكشف عن هذا التباين بشكل واضح بسبب عدم إشراك الإناث بصورة كافية أثناء التجارب السريرية السابقة على الادوية. إن الغاية الرئيسية من هذه الدراسة هو بيان إمكانية وجود إختلافات محتملة بين الجنسين خاصة بالأعراض الجانبية للأدوية متمثلة في إختلافات في قياس السببية والشدة و إمكانية الوقاية و الجدية و توقع الحصول و النتيجة، أما الهدف الثانوي فهو تقييم لأي المجاميع الدوائية و لأي الأعراض الجانبية يعود الإختلاف بين كلا الجنسين. هذه الدراسة تمت بأثر رجعي على بيانات منتقاة بصورة خاصة من قاعدة بيانات مركز اليقظة الدوائي العراقي. و قد شملت التقارير المرسلة الى المركز خلال ٣ سنوات للفترة الزمنية من الأول من كانون الثاني لعام ٢٠١٧ ولغاية الحادي والثلاثين من كانون الأول لعام ٢٠١٩. خلال دراسة العينة البحثية تمت ملاحظة أن التقارير المرسلة لحالات من الإناث كانت تشكل ٦٠,٨٤ % من المجموع الكلي للعينة بينما شَكّلت تقارير الرجال ٣٩,١٦ % فقط. بالإضافة الى ذلك، وجدت إختلافات كبيرة في توزيع الفئات العمرية وكانت نسبة النساء البالغات في سن الخصوبة إحصائيا هي الأكثر عرضة للإصابة بالأعراض الجانبية، بينما كان الرجال البالغين من الأعمار الأكبرسناً هم الأكثر عرضة للمعاناة من الأعراض الجانبية فيما إذا ما قورنت النسبة بالفئة العمرية المماثلة من الجنس الآخر. هذا وقد كانت الأعراض الجانبية الواقعه ضمن فئة الجلد و إضطرابات أنسجة تحت الجلد هي الأعلى و بنسبة ٢٦,٤ % في الإناث و ٢٢,٦ % في الذكور مع وجود إختلاف ذو دلالة إحصائية بين هذه النسب. في حين أن أعلى مجموعة دوائية تسبيباً للأعراض الجانبية هي المضادات الحيوية المخصصة للاستخدام الجهازي العام مع وجود فرصة أكبر "ذات دلالة إحصائية" لدى الإناث لحصول الأعراض من هذه الأدوية ٤٠,٨% مقارنة بجنس الذكور ٣٥,٥ %. و كان تواتر الأعراض الجانبية الجدية او الخطيرة أكثر إنتشارا بين الاناث ٤٥,٤ % مقارنتا بالذكور ٤١,٤ % في حين أن النتيجة المميتة كانت أكثر إنتشارا لدى الذكور ٠,٨ % بالمقارنة مع الإناث ٠,٢ %. وقد بين تحليل التوقعات أنها كانت متساويا تقريبا بالنسبة لكل من الجنسين.

الكلمات المفتاحية: اليقظة الدوائية ، التفاعلات الدوائية الضارة ، مركز اليقظة الدوائية العراقي ، إختلافات الجنسين ، العراق.

[1]Corresponding author E-mail: pharmacologicaleffect@gmail.com
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Introduction

From the very early beginning of the human history, human noticed that there were undesirable effects accompanied the benefits while using medications. Many events such as the tragic disaster of thalidomide urged for the development of a well-defined and organized system to monitor drug safety and detect any possible harm to ensure that similar events will never be repeated in the future[1], therefore pharmacovigilance science was developed. Pharmacovigilance (PV) is "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem" as defined by the World Health Organization (WHO)[1]. Adverse drug reaction (ADR) is defined by the later as "any noxious or unintended response to a drug, which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function"[2]. The spontaneous reporting system which depends on the physician, pharmacist, any health care provider or any other person is the greatest source of newly defined ADRs in recent years. The reasons behind its importance are; its immediate availability after the drug is released to the market[2] and its great ability of detecting rare ADRs that may be missed during the clinical trials[3]. This system has its limitations such as the under reporting by health care providers and the high percentage of false positive reports in addition to the low quality of some information reported[2]. Other sources of information includes clinical studies, observational studies and the randomized controlled trials[2]. Vigiflow which represents the WHO international database of the ADRs reported to the Uppsala monitoring center by the means of spontaneous reports or so called the Individual Case Safety Reports (ICSR) is considered a rich mine of raw information that could be processed in countless ways to obtain various important information[4]. In Iraq, there are very small number of studies that make use of the Vigiflow database belonging to the Iraqi Pharmacovigilance Center (IPhvC) that could enrich the Iraqi individuals in addition to the world knowledge about ADRs.

Many studies have found that female gender suffers more ADRs than male gender without any distinct clear reasons[5–8]. These variances may be related to hormonal, pharmacodynamics and pharmacokinetic reasons[7,9–11] or may be simply because female gender is consuming more drugs and different medication groups than those used by males [7,9,12–14] or even due to behavioral causes[6,15]. The pharmacovigilance parameters and demographic patient's characteristics inspection may give a better idea about ADRs differences between male and female.

The primary aim of this study was to assess the extent of possibly relevant sex differences in drug–ADRs reported to the Iraqi Pharmacovigilance center regarding causality, severity, preventability, seriousness, outcome and expectedness. While the secondary aim was to assess for which drugs and for which ADRs sex differences are identified most often.

Subjects and Method

This is a pharmacovigilance retrospective study that deals with the data obtained from the online World Health Organization-Uppsala Monitoring Center (WHO-UMC) database known as (Vigiflow) which contain individual case safety reports (ICSRs). Only ICSRs that belong to the Iraqi Pharmacovigilance Center (IPhvC) were accessed after taking the required legal permissions. Reports in the period of three years (from the 1st of January 2017 to the 31st of December 2019) concerning adult patients (≥ 18 years) -which were found to be (7080) reports- were collected and analyzed.

General exclusion criteria that applied were: Reports that not specify the patient's gender (217 reports), reports in which the reporter didn't describe if the ADR was serious or not (311 reports) and reports that didn't mention the action taken to deal with the reported ADR (2487 reports).

Additional specific exclusions were done manually while processing each ICSR separately which were: duplicated reports (32 reports), gender specific ADRs that cannot be compared between both sexes such as vaginal bleeding in female or male impotence (19 reports). gender specific drugs that prescribed for a specific condition related to one gender only such as oral contraceptives (54 reports), reports including vaccines as a suspect of causing the ADR (9 reports), reports that did not include the name of the suspect drug (13 reports), reports that didn't contain the details of the ADR, but only mentioned that there was an ADR that took place (16 reports), reports about blood and auxiliary products such as plasma and packed RBCs (40 reports), reports about the local reactions that appears after doing the allergy tests (44 reports), reports about the intentional over dose or suicidal attempts (2 reports), 3 reports that were excluded because it contained counterfeit medicine and product quality issues. In addition to that, in ICSRs that contain multiple drug suspects or multiple ADRs, some of their drug-ADR combinations (26 combination) were omitted for missing action taken to deal with a drug suspect or for being a gender specific ADR. The resulted study sample was consisted of (3833) reports that have (3972) drugs as suspects, (6153) ADRs and (6407) Drug-ADR combinations to be processed and statistically analyzed.

The differences in the total number of ICSRs, the total number of suspect drugs and the total number of ADRs are due to the fact that in a single ICSR,

there may be more than one suspect or more than one ADR. The number of Drug-ADR combinations is expected to be the largest number among them because in ICSRs containing several suspects or ADRs, each combination was recorded and analyzed seperatedly.

For each ICSR that included in this study, patient's gender was recorded as it is the most important parameter in this study since the study is depending on finding the differences between the two sexes. For the age of patients, it was recorded and grouped into 3 intervals so that it would be easier to compare and study. These age groups were 18-45 years, >45-65 years and above 65 years' intervals representing female reproductive age, post-menopausal age and elderly age groups respectively.

Adverse drug reactions classification

The ADRs were classified using the highest level of hierarchy in the Medical Dictionary for Regulatory Activities (Med DRA) which is called the System Organ Classes (SOC) that contain 27 major classes[16].

Suspected drugs classification

The drugs mentioned in the extracted data were classified according to the Anatomical Therapeutic Chemical (ATC) Classification system, which classify all the medical compounds depending on its different characteristics, it consists of 5 levels. This study concentrates on the 1st level which has fourteen anatomical /pharmacological groups [17].

For the drug combinations that were suspected to cause an ADR, it was recorded and dealt with as a single suspect and it was left without any distinct ATC code, but referred to as 'combination' while doing the drug suspect calculations.

Causality assessment

Using the WHO-UMC algorithm [18], a causality assessment was done to predict the certainty of association between the administration of a suspected drug in a specific report and the ADR that took place. (Table 1) illustrate the descriptions of each level in the used causality assessment. For this criteria, Drug-ADR combinations were compared between both genders.

Table 1. The WHO-UMC criteria for causality assessment [18]

Causality term Assessment	Criteria
Certain	Event or laboratory test abnormality with plausible time relation to exposure _ Cannot be explained by diseases or other drugs _ Response to withdrawal plausible (pharmacologically, pathologically) _ Event definitive pharmacologically or phenomenological. _ Challenge causes definite recurrence.
Probable/likely	_ Event or laboratory test abnormality with reasonable time relation to exposure _ Unlikely to be explained by diseases or other drugs _ Response to withdrawal clinically reasonable _ Rechallenge not required or possible.
Possible	_ Event or laboratory test abnormality with reasonable time relation to exposure _ Could also be explained by diseases or other drugs _ Information on withdrawal may be lacking or unclear.
Unlikely	_ Event or laboratory test abnormality with time relation to exposure that makes an association improbable (but not impossible) _ Diseases or other drugs provide plausible explanations.
Conditional/ unclassified	_ Event or laboratory test abnormality _ More data for proper assessment needed, or _ Additional data being examined.
Unassessable/ unclassifiable	_ Report suggesting an adverse reaction _ Cannot be judged because information is insufficient or contradictory _ Data cannot be supplemented or verified.

Severity

The modified Hartwig and Seigel criteria were used to assess the severity of the Drug-ADR combinations by categorizing them into 7 ascending levels starting from (level 1) which is mild and requires no interpretations to (level 7) that describes a lethal ADR [19]. These levels are explained clearly in (Table 2).

Table 2，Hartwig's Severity Assessment Scale[19]

Level of severity	The criteria
Level 1	An ADR occurred but required no change in treatment with the suspected drug
Level 2	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment requirement was required. No increase in length of stay (LOS)
Level 3	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. AND/ OR an Antidote or other treatment was required. No increase in LOS
Level 4	Any Level 3 ADR which increases length of stay by at least 1 day. OR The ADR was the reason for the admission
Level 5	Any Level 4 ADR which requires intensive medical care
Level 6	The adverse reaction caused permanent harm to the patient
Level 7	The adverse reaction either directly or indirectly led to the death of the patient 2

Expectedness

It was evaluated by reviewing the summery of product characteristics (SmPC or SPC). Drug-ADR combinations were categorized into two groups: either 'expected' if the ADR is mentioned previously or 'unexpected' if it is not recorded previously in the SmPC[20].

Preventability: For evaluation of preventability, the modified Schumock and Thornton criteria were applied to each Drug-ADR combination, the criteria depend on answering 7 questions that discuss several points about the drug safety and conditions of administration with a simple answer of Yes or No[21]. If any of these questions was answered with 'Yes', the ADR would be considered to be preventable. While if all the 7 answers were 'No' it will be recorded as a non-preventable ADR. In case of having any questions with unclear answer while assessing an ICSR, this will be labeled as a possibly preventable ADR (Table 2-3).

Table 3. Schumock and Thornton preventability assessment criteria[21]

	Question	Yes	No
1	Was there a history of allergy or previous reaction to the drug?		
2	Was the drug involved inappropriate for patient's Clinical Condition?		
3	Was the dose, route, or frequency of administration inappropriate for the patient's age, weight or disease?		
4	Was there any required therapeutic drug monitoring, or other laboratory tests not performed?		
5	Was a drug interaction involved in the ADR?		
6	Was poor compliance involved in the ADR?		
7	Was a toxic serum concentration or a laboratory? monitoring test documented?		

Seriousness

The seriousness was covered depending on the ICSR seriousness assessment method, which is adopted by the Iraqi pharmacovigilance center (Figure 1)[3]. Relying on the judgment of the person that made the spontaneous report, the ADR that took place was categorized as serious or not.

III. MANAGEMENT OF ADVERSE DRUG REACTION:	
Drug (s) discontinued [ ] Yes [ ] No	Improvement on discontinuation [ ] Yes [ ] No
Hospitalization (following the ADR)	[ ] Yes [ ] No [ ] Already hospitalized
Do you consider the reaction to be serious?	[ ] Yes [ ] No
If yes, please tick (✓) to indicate why the reaction is considered to be serious: [ ] Patient died due to the reaction [ ] Involved or prolonged in patient hospitalization [ ] Life threatening [ ] Involved persistent or significant disability of incapacity [ ] Congenital anomaly [ ] Medically significant, please give details:----------	
Treatment given: [ ] No [ ] Yes, please specify ----------	

Figure 1.Seriousness assessment in the Iraqi ICSR [3]

Action taken

Information regarding the action taken found in the original Iraqi ICSR (Figure 1) was very important in this study for the identification of the severity level that previously discussed in this paper.

Outcome: It can be found on the original Iraqi ICSR on (section II) as shown in (Figure 2) this section will tell the reader if the ADR happened recovered or not, and if the outcome was unknown or fatal. The comparison of this property can give an idea of which gender has better odds in its ADR experience.

Ethical approval

This study has been approved by the scientific committee of the University of Baghdad/ College of Pharmacy and the Iraqi Ministry of Health (MOH)/ Department of Research and Development before it was started.

II. DETAILS OF ADVESE DRUG REACTION (ADR)			
Onset Date: ----/----/---- dd/mm/yy	Outcome:	[ ] Recovered (date): ----------	[ ] Not recovered yet
		[ ] Fatal (date of death) -------	[ ] unknown
End Date: ----/----/----- dd/mm/yy	Duration:	----------	Min, Hour, day, week, month, year

Figure 2. The outcome recording in the Iraqi ICSR [3]

Statistical analysis

All the data were tabulated and organized using Microsoft Excel 2016. IBM Statistical Package for the Social Sciences (SPSS) program version 26 was used in the statistical calculations. Descriptive statistics such as counting the percentages and frequencies were done. Chi-square test was applied to compare between both genders and search for any significance. Yate's Chi square test was adopted in case of having small values that is below 5 to compare. P values which is less than 0.05 was considered to be statistically significant.

Results

From the total of 3833 ICSRs, females had 2332 reports (60.84%) while males had 1501 (39.16%). Age group distribution demonstrated in (Table 1) shows that for younger adults that having an age in the array of (18-45 years), the possibility of having an ADR in the female (63.6 %) is more than that of the male gender (55.5 %) of the total specific gender population, and this was found to be statistically significant with a P value of (0.0000005). While for the older age group of (>45-65 years) the chances of males to have an ADR is more (30.8 %) compared to (25.9 %) in females, the same was found in the next age group that contains adults of (> 65 years) which shows greater chance in male (13.7 %) than female (10.5 %) with a P value of (0.001 and 0.002) respectively.

Table 1. Age group distribution of ADRs

Age group (years)	Number and percentage of ICSR	Freq. and percentages in female	Freq. and percentages in male	Gender difference (P value)
18-45	2316 (60.4 %)	1483 (63.6 %)	833 (55.5 %)	**0.0000005***
>45-65	1068 (27.9 %)	605 (25.9 %)	463 (30.8 %)	**0.001***
> 65	449 (11.7 %)	244 (10.5 %)	205 (13.7 %)	**0.002***
Total	3833 (100.0 %)	2332 (100.0 %)	1501 (100.0 %)	

*Significant (P-value <0.05) according to Chi square test.

ADRs: Adverse drug reactions, ICSR: Individual Case Safety Report

Comparing the ADR classes' distribution between both genders depending on the SOC system classification shown in (Table 2) gave the picture that the highest type of ADRs for both genders were those that fall in the skin and subcutaneous tissue disorders (26.4 % in females) and (22.6 % in males) with a statically significant difference between the two genders. The second one was found to be the gastrointestinal disorders but without any statistical significant difference. Respiratory, thoracic and mediastinal disorders came in the third place with (11.9 %) in females and (10.1 %) in males which make it a statistically significant difference (P value 0.037). The group of disorders that came in the fourth stage is those that fall under the general disorders with the following percentages for female and male (10.5 % and 11.2%) respectively, with no significant differences. The nervous system ADRs were having statistically significant differences (P value 0.02), with higher values for the male gender (10.3 %) while females were (8.6 %). Other classes had less percentages and no statistically significant differences between both genders.

A statistically significant gender differences were found (Table 3), while testing which medication group -by using the ATC classification- is suspected to be responsible for making the highest number of ADRs in both genders. By taking a deeper look, it was found that the highest group to cause ADRs was the systemic anti-infective agents with a greater chance 'statistically significant' in females to suffer a side effect from this group of medications (40.8 %) compared to male gender (35.5 %), the cardiovascular group was in the second place with a statistically significant difference toward the male gender (13.9 %) more than females (8.5 %). The third was the alimentary tract group with approximately equal chances for both male (9.4 %) and female (9.2 %). The nervous system came in the next place with males having (9.3 %) and females (8.8 %) so relatively equal chances is present. The fifth group that responsible for making high numbers of ADRs was the antineoplastic and immune-modulating agents, this group was found to cause ADRs in females (9.7 %) more than males (5.8 %) with statistically significant differences (P value 0.00001).

Another important finding that was recorded in this study is that, males are more prone to have an ADR due to a drug-drug interaction with a statistically significant difference (P value 0.03). Other groups shown in (Table 3) are participating in less extent in the overall percentage of causing ADRs and has no statistically significant differences, except for a group that has low participation but a statistically significant difference which was the systemic hormonal agents that was clearly causing more ADRs in males (4.1 %) than females (2.9 %) (P value 0.047).

Table 2. Distribution of ADR according to the SOC system in both genders.

SOC system	Freq. and percentage of total reports	Freq. and percentage in female	Freq. and percentage in male	Gender differences (P value)
Blood and lymphatic system disorders	39 (0.6 %)	25 (0.7 %)	14 (0.6 %)	0.769
Cardiac disorders	253 (4.1 %)	150 (3.9 %)	103 (4.4 %)	0.396
Ear and labyrinth disorders	38 (0.6 %)	20 (0.5 %)	18 (0.8 %)	0.241
Eye disorders	118 (1.9 %)	65 (1.7 %)	53 (2.3 %)	0.128
Gastrointestinal disorders and Hepatobiliary disorders	1251 (20.3 %)	755 (19.8 %)	496 (21.1 %)	0.229
General disorders and administration site conditions	663 (10.8 %)	400 (10.5 %)	263 (11.2 %)	0.402
Immune system disorders	246 (4.0 %)	155 (4.1 %)	91 (3.9 %)	0.696
Infections and infestations	55 (0.9 %)	34 (0.9 %)	21 (0.9 %)	1.000
Injury, poisoning and procedural complications	34 (0.6 %)	17 (0.4 %)	17 (0.7 %)	0.154
Investigations	89 (1.4 %)	53 (1.4 %)	36 (1.5 %)	0.656
Metabolism and nutrition disorders and Endocrine disorders	116 (1.8 %)	72 (1.9 %)	44 (1.9 %)	0.956
Musculoskeletal and connective tissue disorders	103 (1.7 %)	62 (1.6 %)	41 (1.7 %)	0.731
Neoplasms benign, malignant and Unspecified and Congenital, familial and genetic disorders	10 (0.2 %)	5 (0.2 %)	5 (0.2 %)	0.441
Nervous system disorders	568 (9.2 %)	326 (8.6 %)	242 (10.3 %)	**0.022***
Psychiatric disorders and Social circumstances	92 (1.5 %)	61 (1.6 %)	32 (1.3 %)	0.372
Renal and urinary Disorders and Reproductive system and breast disorders	49 (0.8 %)	29 (0.8 %)	20 (0.8 %)	0.702
Respiratory, thoracic and mediastinal disorders	689 (11.2 %)	451 (11.9 %)	238 (10.1 %)	**0.037***
Skin and subcutaneous tissue disorders	1537 (25.0 %)	1005 (26.4 %)	532 (22.6 %)	**0.00089***
Vascular disorders	203 (3.3 %)	119 (3.1 %)	84 (3.6 %)	0.339
Total	6153 (100.0 %)	3804 (100.0 %)	2349 (100.0 %)	

ADRs: Adverse drug reactions, **SOC**: System Organ Classes**.**

*****Significant (P-value <0.05) according to Chi square test.

Table 3. Drug ATC group in both gender

ATC group	Frequencies and percentage	Freq. and percentage in female	Freq. and percentage in Male	Gender difference (P value)
A	368 (9.3 %)	222 (9.2 %)	146 (9.4 %)	0.853
B	292 (7.4 %)	173 (7.2 5%)	119 (7.6 %)	0.578
C	423 (10.6 %)	206 (8.5 %)	217 (13.9 %)	0.00000007*
Comb. †	33 (0.8 %)	14 (0.6 %)	19 (1.2 %)	0.030*
D	35 (0.9 %)	24 (1.0 %)	11 (0.7 %)	0.342
G	24 (0.6 %)	15 (0.6 %)	9 (0.6 %)	0.862
H	135 (3.4 %)	71 (2.9 %)	64 (4.1 %)	0.047*
J	1537 (38.7 %)	984 (40.8 %)	553 (35.5 %)	0.00087*
L	324 (8.2 %)	234 (9.7 %)	90 (5.8 %)	0.00001*
M	264 (6.6 %)	158 (6.5 %)	106 (6.8 %)	0.749
N	358 (9.0 %)	213 (8.8 %)	145 (9.3 %)	0.603
P	5 (0.1 %)	1 (0.0 %)	4 (0.3 %)	0.153‡
R	137 (3.4 %)	79 (3.3 %)	58 (3.7 %)	0.447
S	23 (0.6 %)	12 (0.5 %)	11 (0.7 %)	0.396
V	14 (0.4 %)	8 (0.3 %)	6 (0.4 %)	0.780
Total	3972 (100.0 %)	2414 (100.0 %)	1558 (100.0 %)	

ATC; Anatomical Therapeutic Chemical. **A**; Alimentary tract and metabolism. **B**; Blood and blood forming organ. **C;** Cardiovascular system. **D**; Dermatological agents. **G**; Genitourinary system and sex hormones. **H**; Systemic hormonal preparations. **J**; Anti-infective for systemic use**. L**; Antineoplastic and immune modulating agents. **M**; Musclo-skeletal system**. N;** Nervous system**. P;** Antiparasitic agents, insecticides and repellants**. R**; Respiratory system**. S**; Sensory organs**. V**; Various**.**

* Significant (P-value <0.05) according to Chi square test.

† Comb. Refers to the ADRs caused by drug combinations (Drug-Drug interactions)

‡ Yates' Chi square test was adopted because of the small values (below 5).

When comparing the seriousness of ADRs between both genders (Table 4), a statistically significant difference (P value 0.001) was found which indicate that the reported ADRs were considered to be more serious in female (45.4 %) than for males (41.3 %) according to the initial reporter judgment.

Table 4. Seriousness of ADR in both gender

Seriousness	Freq. and percentage in total ICSR	Female frequency and percentage	Male frequency and percentage	Gender difference (P value)
No	3456 (56.2 %)	2076 (54.6 %)	1380 (58.7 %)	**0.001***
Yes	2697 (43.8 %)	1728 (45.4 %)	969 (41.3 %)	
Total	6153 (100.0 %)	3804 (100.0 %)	2349 (100.0 %)	

***** Significant (P-value <0.05) according to Chi square test.

Studying the outcome of ADRs in both genders shown in (Table 5), demonstrates that there were statistically significant differences. The fatal outcome was more observed in male gender (0.8 %) as compared with females (0.2 %). The recovery was more detected in females (77.1 %) than males (74.1 %) while the unknown outcome was recorded more frequently in males (13.2 %) than female (10.4 %). Other outcome subgroups that include the recovery with sequelae, ADRs that not recovered till the time of reporting and the ADRs that still under the recovery phase were without any statistically significance differences.

Table 5. Outcome of the ADR for each gender.

Outcome	Freq. and percentage in total	Freq. and percentage in female	Freq. and percentage in male	Gender difference (P value)
Fatal	24 (0.4 %)	6 (0.2 %)	18 (0.8 %)	0.00019*
Not recovered	524 (8.5 %)	324 (8.5 %)	200 (8.5 %)	1.000
Recovered	4673 (75.9 %)	2933 (77.1 %)	1740 (74.1 %)	0.006*
Recovered with sequelae	20 (0.3 %)	14 (0.4 %)	6 (0.3 %)	0.451
Recovering	208 (3.4 %)	132 (3.5 %)	76 (3.2 %)	0.620
Unknown	704 (11.4 %)	395 (10.4 %)	309 (13.2 %)	0.0009*
Total	6153 (100 %)	3804 (100 %)	2349 (100 %)	

***** Significant (P-value <0.05) according to Chi square test..

The causality assessment (Table 6) showed that the major category found in the study sample was the probable which counted for (66.1 %) of the total number of Drug-ADR combinations followed by the possible category (28 %). There were significant differences in the probable and the possible categories only. Females ADRs, according to these findings, are more obvious and related easier to the suspect drug because the probable category has higher percentage in the female gender (68.5 %) compared with male gender (62.2 %), while the possible category has higher male findings (31.4 %) compared with the females (25.8 %). For other categories, values were closely the same without any statistically significant differences.

Table 6. Causality assessment of ADR.

Causality by WHO method	Freq. and percentage in total reports	Female frequency and percentage	Male frequency and percentage	Gender difference (P value)
Certain	15 (0.2 %)	9 (0.2 %)	6 (0.2 %)	0.882
Conditional	265 (4.1 %)	161 (4.1 %)	104 (4.3 %)	0.710
Possible	1791 (28.0 %)	1023 (25.8 %)	768 (31.4 %)	**0.0000012***
Probable	4234 (66.1 %)	2714 (68.5 %)	1520 (62.2 %)	**0.0000002***
Unlikely	102 (1.6 %)	55 (1.4 %)	47 (1.9 %)	0.097
Total	6407 (100 %)	3962 (100 %)	2445 (100 %)	

*Significant (P-value <0.05) according to Chi square test.

The evaluation of severity criteria shows that most of the reported ADRs were considered to be from Level 2 of the Hartwig's severity assessment scale which represents ADRs that needs only to discontinue administrating of the suspect agent as a management to the harm ensued. There were statistically significant differences between both genders in two levels of severity only. These were the third level which refers to the ADRs that need to stop giving suspect drugs in addition to the use of a drug or an antidote for treating the resulted harm, this level was significantly higher in female gender (9.2 %) compared to male (7.2 %). The other level that also showed a statistically significant difference was the seventh level, ADRs that cause death of the patient directly or indirectly, which was found to be higher in male gender (0.8 %) than female (0.2 %) (Table 7).

Table 7. Severity of ADR in both gender

Severity level	Freq. and percentage in all ICSR	Female freq. and percentage	Male freq. and percentage	Gender difference (P value)
Level 1	791 (12.3 %)	474 (12.0 %)	317 (13.0 %)	0.236
Level 2	4211 (65.7 %)	2600 (65.6 %)	1611 (65.9 %)	0.826
Level 3	540 (8.4 %)	364 (9.2 %)	176 (7.2 %)	**0.0053***
Level 4	785 (12.3 %)	481 (12.1 %)	304 (12.4 %)	0.727
Level 5	40 (0.6 %)	26 (0.7 %)	14 (0.6 %)	0.680
Level 6	12 (0.2 %)	9 (0.2 %)	3 (0.1 %)	0.520 ‡
Level 7	28 (0.4 %)	8 (0.2 %)	20 (0.8 %)	**0.0002***
Total	6407 (100 %)	3962 (100 %)	2445 (100 %)	

*Significant (P-value <0.05) according to Chi square test.
‡ Yates' Chi square test was adopted because of the small values (below 5).

Females and males had no statistically significant differences in the preventability patterns of ADRs in both possibly preventable and preventable ADRs, while the non-preventable subgroup were totally not found in the study population because some of the important information needed to mark the cases as a non-preventable ADR were not recorded in the ICSRs. The resulted findings are recorded in (Table 8).

Table 8. Preventability of ADR in both sex.

Preventability of ADR	Total report freq. and percentage	Female freq. and percentage	Male freq. and percentage	Gender difference (P value)
Possibly preventable	6170 (96.3 %)	3823 (96.5 %)	2347 (96.0 %)	0.303
Preventable	237 (3.7 %)	139 (3.5 %)	98 (4.0 %)	
Total	6407 (100 %)	3962 (100 %)	2445 (100 %)	

The expectedness analysis showed in (Table 9) gave the finding that for each gender the expectedness of ADRs were nearly equal.

Table 9: Expectedness of ADR for each gender

Expected ADR	Freq. and percentage in total	Freq. and percentage in female	Freq. and percentage in male	Gender difference (P value)
No	2070 (32.3 %)	1277 (32.2 %)	793 (32.4 %)	0.867
Yes	4337 (67.7 %)	2685 (67.8 %)	1652 (67.6 %)	
Total	6407 (100 %)	3962 (100 %)	2445 (100 %)	

Discussion

This study revealed the characteristics of the reported ADRs to the IPhvC. Some of the obtained results were nearly similar to previous readings from different countries and the other findings were unique in the studied population. The predominance of female gender in the total number of ICSRs is an expected result that resembles many previous studies[6,15,22,23]. This is a multifactorial fact with no clear explanation, that may be due to pharmacological, biological, social and behavioral differences between both genders(6–8). During their reproductive age, females are more susceptible to have ADRs than males from the same age group. This finding cannot be explained by female use of extra -gender specific- drugs such as oral contraceptives since cases containing contraceptive suspects were excluded from the study sample, neither could be related to the total number of population of each gender since it is approximately equal in our country according to official publications[24]. This finding is similar to many previous studies such as; the sex related Vigibase global data analysis of the last 50 years(23) and the Tran et al work which analyzed 10 years data collected from "Glaxo Wellcome-Sunnybrook Drug Safety Clinic" records in Canada searching for gender differences[6]. This age group variation could be due to the fact that females during their reproductive age seek more medical attention and had twice more doctor visits than males and are more likely to report any medical concerns and look for medical advice [11,23]. While for older age groups (>45-65 years) and (> 65 years), the male gender was recorded to have more ADRs than females. This could be because males were found to have greater hospital stays in the ages above 44 years which might mean more medications and complications [11]. The biggest group of drugs that found to cause

ADRs were antibiotics for systemic use and it was higher in the females. A possible explanation of this finding is the increasing number of cesarean section operations in Iraq in the last years(25) which has led to the increasing use of antibiotics for prophylactic reasons. While the cardiovascular system agents were higher in the male gender. This could be reasonable if taking in consideration that; males are diagnosed with cardiovascular diseases more often than females[26], and the prevalence of both stroke and heart disease is higher in men worldwide[27]. This will result in more male gender related consumption of cardiovascular agents[28] and as a result, more ADRs will appear and be reported for those agents.

The observed differences in the SOC systems of ADRs distribution in both genders could be explained by the presence of variances in the used medications by each gender (28) which has led to the appearance of different sorts of ADRs. In the current study, the frequency of serious ADRs was significantly more prevalent in females than for males (Table 4), these results contradict the global analysis of the Vigiflow database which found that males had more serious ADRs than females [23]. Also, it was found that females were taking treatments for the ADRs more than males and males had a higher mortality due to ADRs than females. These findings were similar to the global review of Vigiflow database[23]. The higher mortality in male gender could be explained by three reasons identified here which are: males not tend to seek medical help early during their ADR experience as women do [23], they tend to use different classes of medications (28) in addition to that, they suffer from ADRs in older age groups (Table 1). The males had less clear ADRs outcome since more females are reported to be recovered from their ADRs and more males had unknown outcome (Table 5), also the causality assessment for the males are less linked to the use of medications than the female gender (Table 6). The causality assessment may explain, for some extent, the outcome results of the current study where the ADRs are more clearly linked to medications used by females so it is easier to manage these reactions either by giving treatment or by stop giving the causative drugs while in male gender the causality is less obvious. For the expectedness and the preventability, there were no differences between both genders.

Although the current study has a large sample size over a relatively extended period of time, it has several limitations such as its dependence on the spontaneous reports only which means a lot of important ADRs that occur in practice and passed without reporting were not identified here. The study is of a retrospective type that restricted by the available information only which caused the exclusion of numerous reports missing essential data and that may affect the study statistical results. Also, the available reported data did not have the same quality as they are disclosed by different sources and qualifications which may lead to bias.

Conclusions and Recommendations

In conclusion, the current study showed possibly relevant differences between males and females in the ADRs spontaneously reported to the Iraqi Pharmacovigilance Center indicating that gender may be a risk factor for (development of ADRs for some class of drugs, some types of ADRs, seriousness of ADRs, as well as the outcome of these ADRs). Further work is required to elucidate the mechanisms explaining the differences observed between male and female patients. In addition, more efforts should be done by the Iraqi Pharmacovigilance Center to improve the quality of individual case safety reports.

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