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Research Article
Characteristics of Adverse Drug Reactions and Related Risk Factors among Female Patients

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Abstract

Background and Objective: Previous studies have demonstrated that Gender-associated Adverse Drug Reactions (ADRs) were one of the leading causes of harm and/or death among patients during medical treatments. However, the ADRs focusing the female patients are very rare. This study aimed at exploring characteristics of ADRs and related risk factors among female patients in obstetrics and gynaecology hospital. **Materials and Methods:** A retrospective analysis was performed on 357 hospitalizations and outpatients from January, 2010-October, 2015 in our hospital. The ADRs that happened in the female patients were strictly monitored and reported by doctors after drug administration. ADRs were evaluated based on the WHO-Uppsala Monitoring Center criteria. Regression analysis via the Cox proportional hazards model was performed to assess independent predictive variables against the latency of ADR. **Results:** The most frequently ADRs were rash, vulvar, vaginal discomfort or nausea. The latency of ADR's onset in patients ranged from several seconds to a couple of days and 0.5-24 hrs was the most frequently (n = 190, 53.22%) in general. Both age and allergy histories were positively correlated with the duration period of ADRs (hazard ratio HR 2.919, 95% CI 1.049-8.124 and HR 4.107, 95% CI 1.478-11.410). **Conclusion:** These data demonstrate the characteristics of the ADRs in female patients, to provide an increasing number of female-patient based ADR database and valuable data to study pharmacovigilance.

Key words: ADRs, risk factor, pharmacovigilance, sex hormones, maternal, obesity, patient safety

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Effective medications can offer better therapeutics for improving patients' conditions, with which unpleasant responses to these drugs were usually accompanied. ADRs could influence individuals' healthcare and also remain a major cause of readmitting hospitalization, which makes the patients bear an increasing burden of health care expenditure[1-3]. ADRs are frequent, undesirable and unpredictable effect mainly due to the off-target effect of drug activity[4].The overall incidence of ADRs ranges from 0.15-30%, but the hospital admission rate due to ADRs is over 20% in China[5-7]. Detecting and establishing preventive strategies against ADRs is crucial for patient safety. Previous studies have shown that gender, age and drug combinations might be considered as the risk factors for ADRs[6, 8-11]. Increasing studies are focusing on the relationship between gender and ADRs because female appears to be more risk for many medications[9,12,13]. Hormone-related physiological changes lead to increase sensitivity to drug effects and limited evidence of drug effectiveness and safety in female patients[14,15]. However, drug safety in female individuals remained unclear.

So this paper based on a retrospective study aims to address the question that what specific characteristics of female-gender-based ADRs happened in gynaecology and obstetrics hospital, concerning risk factors such as subjects' age, kinds of prescribed drugs, especially traditional Chinese medicine, a combination of drugs and interventions.

MATERIALS AND METHODS

Setting and study patients: A retrospective analysis of ADRs was performed at the Obstetrics and Gynecology Hospital of Fudan University from January, 2010-October, 2015. Informed consent of participants was not required as the retrospective study design did not affect the healthcare of included patients. This study was carried out at the 840-bed academic, tertiary level women's hospital nationwide. So the source of female patients was stable and the patterns of ADRs were always concerned with multiformity. This study has been approved by the Ethics Committee of Obstetrics and Gynecology Hospital, Fudan University.

Data collection: All data, which have been collected and reported to the national spontaneous ADR reporting system, were recorded by a trained medical team including two experienced pharmacists and ten experienced doctors. The practice training was based on the principle that pharmacists and doctors learned most and made them realistic by practical assignments[16,17]. These made sure that once the suspected

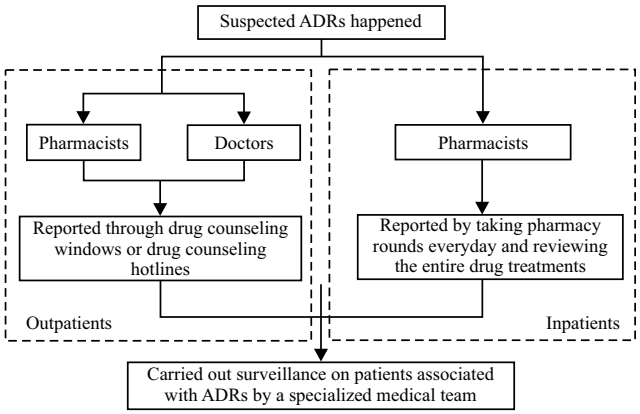

Fig. 1: Procedures of the ADRs' surveillance

ADRs happened in inpatients or spontaneous reported by outpatients in the gynaecology and obstetrics hospital, pharmacovigilance studies could be started in time. Specialized assessments were performed by well-trained pharmacists and doctors. If there was a discrepancy, a high level of physicians and pharmacists would be consulted to reach a coincidence. We set up drug counselling windows and telephone hotlines to monitor the outpatients' ADRs that happened in the clinics or communities. As to the hospitalizations, pharmacists reviewed the entire drug treatments when taking pharmacy rounds every day (Fig. 1). Each patient with suspected ADRs has put intimately observed and updated daily until recovery from the ADR, including information on patient characteristics (age, allergic history, physical status, etc.). ADRs were evaluated based on the WHO-Uppsala Monitoring Center criteria[18]. Subject markers of ADRs through patient notes (named according to the Adverse Reaction Terminology (ART) of the WHO ADR Monitoring Register in Uppsala (WHO-ART), the latency of ADR's onset (calculated from the beginning of suspected medication to the immediate occurrence of ADRs), medical interventions and the duration of ADR(counted from the immediate occurrence of ADRs to the point of recovery from ADRs).

Statistical methods: Results are given in terms of the Hazard Ratio (HR) for a particular factor with an accompanying 95% confidence interval (95% CI). Regression analysis via the Cox proportional hazards model was performed to assess independent predictive variables against the latency of ADR as the outcome variable. STATA (version13) statistical software was used for the Cox proportional hazards model analysis. In addition, the Kaplan-Meier survival curve was performed to evaluate patient survival of ADR recovery. A $p<0.05$ was considered as a statistical significance.

RESULTS

Patient characteristics and ADRs: A total of 357 ADRs were enrolled and 134(37.54%) patients experienced at least one ADR. The subject variables such as age, allergy histories, source of the patients and other presentations are overviewed in Table 1. The younger female patients were more likely to experience ADRs (n = 221, 61.91%). The most frequent ADRs were rash, perineum, vulva or vaginal uncomfortable and nausea, which affected the digestive system (29.1%), skin and appending system (26.37%) and female reproductive system (12.89%) (Table 2). The four classes of drugs followed-up were patent medicines of TCM which were responsible for over one-half of all ADRs (55.74%), antimicrobial agents (20.45%), female reproductive system agents (12.32%) and anti-tumour agents (11.49%) (Table3). *Bao Fu Kang* suppository (26 ADRs), *Xiao Jin* pill (21 ADRs) and *KunTai* capsule (16 ADRs) were chosen for categorizing as patent medicines of TCM because they were reported as the most frequent causative drugs to ADRs.

Latent periods of ADRs: The latency of ADR's onset in patients ranged from several seconds to a couple of days and0.5-24 hrs was the most frequently (n = 190, 53.22%) in general. In the four groups of medicine categories as indicated, followed up data indicated that the mean latency period in a group of anti-tumour agents with a maximum was 53.06±16.85 hrs and a minimum of 20.89±3.20 hrs was observed in a group of patent medicines of TCM. The Group of antibiotics was 29.34±11.98 hrs and the group of female reproductive system agents was 44.95±13.47 hrs, respectively (Table 4), which offer us the crucial period to attend the ADR of different medicine.

Then we investigated the relationship between ages, source of patients, previous allergy histories, medications (single medication or multi-medications), course of medications and a group of suspected drugs in female patients and the duration period of ADRs. We found that both age and allergy histories were positively correlated with the duration period of ADRs (hazard ratio HR 2.919, 95% CI 1.049-8.124 and HR 4.107, 95% CI 1.478-11.410). In addition, we detected a significantly and inversely association between suspected drugs and increased duration of ADR (HR 0.365, 95% CI 0.159-0.834) (Table 5).

ADRs' outcome: We also performed two weeks follow-up to assess the relationship between intervention-positive patients and intervention-negative patients after ADRs happened.

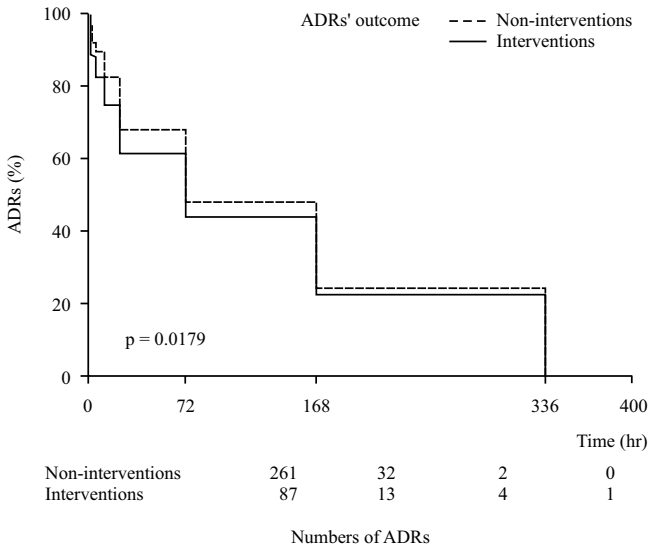

Fig. 2: Kaplan-Meier curve for ADR-free survival in the presence of medical intervention
p = 0.018 presence of medical interventions vs. absence of medical interventions

Table 1: Distribution of the 357 cases according to age, source of the patients, allergies, medications and ADRs severity

	Frequency of ADRs (n)	Percent (%)
Age		
<44	221	61.91
45~59	109	30.53
>60	27	7.56
Source of the patients		
Outpatient	286	80.11
Inpatient	71	19.89
History of allergy		
Yes	65	18.21
No	240	67.23
Unknown	52	14.56
Medications		
Single	276	77.31
Combination	81	22.69
Severity of ADRs		
General	349	97.76
Severe	8	2.24

Among all 348 patients, 261 patients have received no treatments except drug withdrawal (non-intervention group), while 87 patients took additional ADR-related treatments (intervention group), such as antihistamines, glucocorticoids, NSAIDs or other medical therapies to recover (Table 6). There was statistical significance in the ADR duration between the non-intervention group and intervention group (Chi-square 5.6, p = 0.018), which indicated that medical treatments for ADRs were effective for earlier recovery compared with no intervention patients (Fig. 2).

Table 2: Variety body system involved in ADRs

System impairment	Adverse drug reactions (number of ADRs)	Total frequency of ADRs n (%)
Digestive system	Nausea (36), vomiting (35), abdominal pain (19), gastrointestinal disorders (19), diarrhoea (17), flatulence (6), oral ulcer (5), mouth dryness (3), others† (9)	149 (29.10)
Skin and appending system	Rash(88), itching (35), sweating (3), erythema (2), others† (7)	135 (26.37)
Systemic reactions	Fever (27), chilly (10), confusion (8), anaphylactic reaction (7), anaphylactic shock (3), others† (8)	63 (12.30)
Female reproductive system	Perineum, vulva or vagina burning, itching, irritation or pain(45), vaginal bleeding (4), vaginal discharge (3), others† (14)	66 (12.89)
Central and peripheral nervous system	Headache (21), dizziness (15), numbness (3), others† (1)	40 (7.81)
Respiration system	Chest tightness (13), dyspnea (5), others† (5)	23 (4.49)
Cardiovascular system	Palpitation (9), others† (5)	14 (2.74)
Application-site	Application site pain (7), others† (2)	9 (1.76)
Hepatobiliary system	Transaminase elevation (5), bilirubin concentrations elevation (2)	7 (1.37)
Musculoskeletal system	Muscle soreness (4), others† (2)	6 (1.17)
Other systems*	Others† (22)	22
Total		534 (100)

*Other systems related system impairment with ≤5 ADRs' reports. †Others represent the total of each ADRs with = 1 report

Table 3: Frequency of reports by medicine categories and suspect drugs

Medicine categories	No (%) ADRs	Drugs (numbers of ADRs for each drug)
Patent medicines of TCM	199 (55.74)	*Bao fu kang* suppository (26), *xiaojin* pill (21), *kun tai* capsule (16)
Antimicrobial agents	73 (20.45)	Nifuratel and nysfungin (12), ornidazole (7), metronidazole (7), nifuratel (7), compound of metronidazole (6)
Female reproductive system agents	44 (12.32)	Ethinylestradiol and cyproterone (3), desogestrel and ethinylestradiol (2), dydrogesterone (2)
Anti-tumour agents	41 (11.49)	Methotrexate (13), paclitaxel (3), exemestane (2), carboplatin (2), dactinomycin (2)
Total	357 (100)	

Table 4: Latency of ADR's onset

	Frequency of ADRs (n (%)				Latency of ADRs (hr)	
Class of suspected drugs	T≤0.5 hrs	0.5<T≤24 hrs	T>24 hrs	Total	Mean	Std. dev
Antibiotics	22 (30.14)	38 (52.05)	13 (17.81)	73 (100)	29.34	11.98
Anti-tumor agents	18 (43.90)	5 (12.20)	18 (43.90)	41 (100)	53.06	16.85
Female reproductive system agents	3 (6.82)	31 (70.46)	10 (22.72)	44 (100)	44.95	13.47
Patent medicines of TCM	48 (24.12)	116 (57.79)	35 (17.59)	199 (100)	20.89	3.20
Total	91 (25.49)	190 (53.22)	76 (21.29)	357 (100)	75.22	3.98

T refers to the latency periods, which was calculated from the beginning of medication to the onset of ADRs

Table 5: Risk factors contributed to latency periods of ADRs assessed by multivariate analysis

Covariate	HR (95% CI)	p-value
Age	2.919 (1.049, 8.124)	0.040*
Sources of patients	2.405 (0.486, 11.896)	0.282
History of allergy	4.107 (1.478, 11.410)	0.007*
Medications	2.413 (0.429, 13.577)	0.317
Course of medications	0.016 (0.000, 2.023)	0.094
Group of suspected drugs	0.365 (0.159, 0.834)	0.017*

*p-value indicated statistical significance. ADRs, Adverse drug reactions, CI: Confidence interval, HR: Hazard ratio

Table 6: Medical interventions associated with ADRs

	Frequency of ADRs (n)	Percentage
Self-treated or clinic-treated ADRs	30	8.4
Drug withdrawal after ADRs with additional treatments	87	24.37
Drug withdrawal after ADRs without additional treatments	261	73.11
Continue as before	9	2.52

DISCUSSION

This study was conducted by doctors and pharmacists' intensively monitoring to report ADRs to explore the specific characteristics and the duration period of ADRs of side effects of medications that happened in female patients. Previous studies have shown that many factors involved in ADRs, including self-perceived health status, gender, age, sex, as well as drug-related factors[19-21]. In our present study, the most frequent ADRs were rash, perineum, vulva or vaginal discomfort, as well as nausea, consistent with previous reports. Ranked from least to most likely of side effects were as follows:

anti-tumour agents, female reproductive system agents, antimicrobial agents and patent medicines of TCM, respectively. There are some different aspects: (1) we focused on female due to the different genes, genetics, hormone variations, biological rhythms and other physical conditions between male and female[21,22]. Furthermore, the uses of specific medications for female patients, such as oral contraception, the herbal remedy which can conversely influence body endocrine environment[23]. In addition, it has been revealed that women were more prone to ADRs than male[24]. (2) The latency periods of ADR in selected drugs. ADRs were classified as type A and type B according to drugsdose[18]. Therapeutic agents and the treatment period were reported to be associated with the latency and acuity of ADRs onset[25]. However, very little was known about the latency of ADRs' of different medications. Our results have shown that about 55.74% of patients got ADRs due to the administration of Patent medicines of TCM. Further analyses showed that Patent medicines of TCM also had the shortest mean latency of ADRs. These data indicated that we should take more attention to the ADRs caused by Patent medicines of TCM. Our data also showed that both age and allergy histories were positively correlated with the latent periods of ADRs. (3) We emphasized the outcome of ADRs patients with or without intervention. A previous study suggested that the average length of hospital stay ranged from 8-17 days because of ADRs[6]. So we performed two weeks follow-up since ADRs happened to the end of ADRs with or without interventions.

In the study, the majority of outpatients' ADRs were typically related to patent medicines of TCM mainly it was difficult to classify, extract and standardise. Pharmacovigilance in TCM safety surveillance is still facing many challenges in China. There are some limitations to our study. Further studies are needed to evaluate the frequency of patients administrated with Patent medicines of TCM.

CONCLUSION

By analysis of 357 female patients' ADRs, it demonstrates that there is a correlation between suspected ADRs and the class of drugs or an individual's history of allergy. To the specific patient such as using a drug that is apt to induce ADRs or a patient with prior allergies, it will be valuable for the medical team to draw attention to the entire course of medication. Furthermore, the population in intervention-positive groups is considerable, so we propose that actively medical therapies are necessary for particular ADR-exposed patients, which could have potentially positive consequence, such as cutting down the medical expenses, reducing the injury of body status, etc.

SIGNIFICANCE STATEMENT

This study discovers the characteristics of the ADRs in female patients that can be beneficial for providing an increasing number of female-patient based ADR database and valuable data to study pharmacovigilance. This study will help the researcher to uncover the critical areas of the characteristics of the ADRs in female patients that many researchers were not able to explore. Thus, a new theory on the correlation between suspected ADRs and the class of drugs or an individual's history of allergy may be arrived at.

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REFERENCES

1. van Der Hooft, C.S., M.C. Sturkenboom, K. van Grootheest, H.J. Kingma and B.H.C. Stricker, 2006. Adverse drug reaction-related hospitalisations: A nationwide study in the Netherlands. Drug Saf., 29: 161-168.
2. Wolf, R., E. Orion, B. Marcos and H. Matz, 2005. Life-threatening acute adverse cutaneous drug reactions. Clin. Dermatol., 23: 171-181.
3. Dormann, H., A. Neubert, M. Criegee-Rieck, T. Egger and M. Radespiel-Tröger *et al*., 2004. Readmissions and adverse drug reactions in internal medicine: The economic impact. J. Intern. Med., 6: 653-663.
4. McNeil, B.D., P. Pundir, S. Meeker, L. Han, B.J. Undem, M. Kulka and X. Dong, 2015. Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions. Nature, 519: 237-241.
5. Deng, Q., X. Fang, Q. Zeng, J. Lu, C. Jing and J. Huang, 2017. Severe cutaneous adverse drug reactions of Chinese inpatients: A meta-analysis. Anais Brasileiros Dermatol., 92: 345-349.
6. Giardina, C., P.M. Cutroneo, E. Mocciaro, G.T. Russo and G. Mandraffino *et al*., 2018. Adverse drug reactions in hospitalized patients: Results of the FORWARD (facilitation of reporting in hospital ward) study. Front. Pharmacol., Vol. 9. 10.3389/fphar.2018.00350
7. Geer, M.I., P.A. Koul, S.A. Tanki and M.Y. Shah, 2016. Frequency, types, severity, preventability and costs of adverse drug reactions at a tertiary care hospital. J. Pharmacol. Toxicol. Methods, 81: 323-334.
8. Priyadharsini, R., A. Surendiran, C. Adithan, S. Sreenivasan and F.K. Sahoo, 2011. A study of adverse drug reactions in pediatric patients. J. Pharmacol. Pharmacother, 2: 277-280.

9. Drici, M.D. and N. Clément, 2001. Is gender a risk factor for adverse drug reactions? The example of drug-induced long QT syndrome. Drug Saf., 24: 575-585.
10. Li, X., H. Liu, L. Zhao, J. Liu, L. Cai, L. Liu and W. Zhang, 2017. Clinical observation of adverse drug reactions to non-ionic iodinated contrast media in population with underlying diseases and risk factors. Br. J. Radiol., Vol. 90 10.1259/bjr.20160729.
11. Krähenbühl-Melcher, A., R. Schlienger, M. Lampert, M. Haschke, J. Drewe and S. Krähenbühl, 2007. Drug-related problems in hospitals: A review of the recent literature. Drug Saf., 30: 379-407.
12. Camargo, A.L., M.B.C. Ferreira and I. Heineck, 2006. Adverse drug reactions: A cohort study in internal medicine units at a university hospital. Eur. J. Clin. Pharmacol., 62: 143-149.
13. Oertelt-Prigione, S., R. Parol, S. Krohn, R. Preißner and V. Regitz-Zagrosek, 2010. Analysis of sex and gender-specific research reveals a common increase in publications and marked differences between disciplines. BMC Med., Vol. 8. 10.1186/1741-7015-8-70.
14. Hendriksen, L.C., P.D. van der Linden, A.L.M. Lagro-Janssen, P.M.L.A. van den Bemt and S.J. Siiskonen *et al*., 2021. Sex differences associated with adverse drug reactions resulting in hospital admissions. Biol. Sex Differences, Vol. 12. 10.1186/s13293-021-00377-0.
15. Arbuckle, T.E., 2006. Are there sex and gender differences in acute exposure to chemicals in the same setting? Environ. Res., 101: 195-204.
16. Gerritsen, R., H. Faddegon, F. Dijkers, K. van Grootheest and E. van Puijenbroek, 2011. Effectiveness of pharmacovigilance training of general practitioners: A retrospective cohort study in the Netherlands comparing two methods. Drug Saf., 34: 755-762.
17. Figueiras, A., M.T. Herdeiro, J. Polónia and J.J. Gestal-Otero, 2006. An educational intervention to improve physician reporting of adverse drug reactions: An educational intervention to improve physician reporting of adverse drug reactions: A cluster-randomized controlled trial. JAMA, 296: 1086-1093.
18. Edwards, I.R. and J.K. Aronson, 2000. Adverse drug reactions: Definitions, diagnosis and management. Lancet, 356: 1255-1259.
19. Sevilla-Sanchez, D., N. Molist-Brunet, J. Amblàs-Novellas, P. Roura-Poch, J. Espaulella-Panicot and C. Codina-Jané, 2017. Adverse drug events in patients with advanced chronic conditions who have a prognosis of limited life expectancy at hospital admission. Eur. J. Clin. Pharmacol., 73: 79-89.
20. Hakkarainen, K.M., H. Gyllensten, A.K. Jönsson, K.A. Sundell, M. Petzold and S. Hägg, 2014. Prevalence, nature and potential preventability of adverse drug events-a population based medical record study of 4970 adults. Br. J. Clin. Pharmacol., 78: 170-183.
21. Gandhi, M., F. Aweeka, R.M. Greenblatt and T.F. Blaschke, 2004. Sex differences in pharmacokinetics and pharmacodynamics. Annu. Rev. Pharmacol. Toxicol., 44: 499-523.
22. Wang, H., X. Ye, Q. Gao, C. Wu and Y. Qian *et al*., 2009. Pharmacovigilance in traditional Chinese medicine safety surveillance. Pharmacoepidemiol. Drug Saf., 18: 357-361.
23. Franconi, F., S. Brunelleschi, L. Steardo and V. Cuomo, 2007. Gender differences in drug responses. Pharmacol. Res., 55: 81-95.
24. Zopf, Y., C. Rabe, A. Neubert, K.G. Gaßmann and W. Rascher *et al*., 2008. Women encounter ADRs more often than do men. Eur. J. Clin. Pharmacol., 64: 999-1004.
25. Bircher, A.J., 2005. Symptoms and danger signs in acute drug hypersensitivity. Toxicol., 209: 201-207.