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RESEARCH ARTICLE

A study to analyze the pattern, causality, severity, predictability and preventability of adverse drug reactions among patients attending department of obstetrics and gynecology at a tertiary care hospital

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ABSTRACT

Background: Adverse drug reactions (ADRs) in women demand a special care due to altered physiology. Despite lingering safety questions, studies on vulnerable groups such as pregnancy, lactation, peri- and post-menopausal women are lacking. Hence, the assessment of ADRs is essential for early risk detection and its management. **Aims and Objectives:** To analyze the pattern, causality, severity, predictability and preventability of occurrence of ADRs in the Obstetrics and Gynecology (OBG) Department. **Materials and Methods:** An observational study was conducted from June 2012 to 2016 to analyze the ADRs reported spontaneously from the Department of OBG to ADR Monitoring Center, Bangalore Medical College and Research Institute. Causality of each ADR was assessed by the WHO-ADR scale, severity by Hartwig and Siegel scale and preventability by modified Schumock and Thornton scale. **Results:** A total of 100 ADRs were reported over 48 months; a maximum number of ADRs were observed in the age group of 21–40 years (81%) and majority of them during pregnancy (62%). The highest number of ADRs was associated with iron therapy (42%) followed by antimicrobials (31%). Gastrointestinal system (51%) was affected predominantly. Gastritis (25%) followed by allergic reactions (18%) was most commonly observed ADRs. The WHO-UMC criteria showed that 61% were "probable" and 57% were "mild" in nature. Preventability assessment showed that 56% were "probably preventable" ADRs. Furthermore, 72% of the ADRs were predictable in nature. 43% of the ADRs required additional medical treatment, while causative drug was withdrawn in 44% of cases. **Conclusion:** This study provides a database of ADRs in the OBG Department and most of the ADRs were predictable and probably preventable with no severe ADRs, which highlights the appropriate management of ADRs at our center.

KEY WORDS: Adverse drug reactions; Causality; Severity; Predictability; Preventability

INTRODUCTION

Adverse drug reaction (ADR) is defined by the World Health Organization (WHO) as "a response to a medicine which is noxious and unintended and which occurs at doses normally used in man."[1] In the 1960s, the WHO launched the Pharmacovigilance Program for monitoring of ADRs in the wake of "Thalidomide disaster". Currently, more than 70 countries worldwide have established drug-monitoring systems for early detection and prevention of possible drug-related morbidity and mortality.[2]

The overall incidence of ADRs leading to emergency admissions ranges from 0.2% to 41.3% globally, while 28.9% are preventable.[1] ADRs are the fourth leading cause of death ahead of AIDS, diabetes mellitus, pulmonary disease,

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and automobile accidents, thereby contributing to increased health-care costs to the patients.[3] 30% of hospitalized patients experience an ADR, of which 0.3% accounts for the cause of death. Among the known risk factors such as age, polypharmacy, and patients with hepatic and renal disease, the female gender is found to have a stronger association in developing ADRs.[4]

Various studies demonstrated that women have 1.5 to 1.7-fold higher risk of ADRs than men, and this difference was relatively consistent and found to be significant among adults across all age groups.[4] Response to the drugs is clearly multifactorial, encompassing a wide range of aspects of sex steroid hormones and organ physiology to psychology and sociocultural factors, gender-related differences in pharmacokinetic and immunological factors as well as differences in the use of medications by females compared with males.[5,6] Furthermore, underreporting of ADRs is still a matter of concern, which could be identified through voluntary reporting as it contributes significantly to the success of Pharmacovigilance Program. Therefore, there is a need to create and enhance physicians' awareness about detection, management, prevention and reporting of ADRs.[2]

All the drugs have beneficial effects and none of them are absolutely devoid of adverse effects. Hence, careful monitoring of drugs is essential with a satisfactory risk: benefit ratio.[7] Usually studies exclude the participation of women of childbearing age group due to fear of teratogenicity, and hence, the data regarding the safety of drugs are limited in Obstetrics and Gynecology (OBG). The present study was planned to gain a comprehensive safety profile of medicines currently prescribed and related ADRs in a tertiary care center. Our hospital is one of the regional centers for ADR monitoring and reporting through the Pharmacovigilance Program of India. In India, pharmacovigilance activities are still in infancy stage due to the lack of well-structured and effective way of monitoring drug safety and thus initiatives to be taken for spontaneous reporting of ADR.[8]

The primary objective of this study was to analyze the pattern of ADRs and the drugs associated with it. The secondary objectives were to analyze the causality, severity, predictability, and preventability of ADRs reported from the Department of OBG at Vani Vilas Hospital, Bangalore Medical College and Research Institute.

MATERIALS AND METHODS

An observational study was carried out for 48 months from June 2012 to June 2016 to analyze the ADRs reported spontaneously from the Department of OBG at a tertiary care hospital to the ADR Monitoring Center of Bangalore Medical College and Research Institute. The study protocol was assessed and approved by the Institutional Ethics Committee before starting the study. Patient's demographics, clinical and drug data, details of ADRs, onset time, causal drug details, outcome, and severity were collected as per the Central Drug Standard Control Organization adverse drug event reporting form. Confidentiality of data was maintained.

Assessment Tools

Causality assessment

The causality relationship between suspected drug and reaction was established using the WHO-ADR causality assessment scales.[9] Categorized into certain, probable, possible, unassessable/unclassifiable, unlikely and conditional/unclassified.

Assessment of severity

The severity of reported reactions was assessed using Hartwig and Siegel scale and was categorized into mild, moderate, and severe.[10]

Assessment of predictability

The predictability of the reported ADRs was assessed using developed criterion for determining the predictability of an ADR and was categorized as type A (dose-dependent and predictable form) and type B (idiosyncratic, no clear dose-response relationship, and not predictable form) ADRs according to the system introduced by Rawlins and Thompson.[11]

Assessment of preventability

The preventability of each ADRs was assessed using modified Schumock and Thornton scale and was categorized as definitely preventable, probably preventable, and not preventable.[12]

Statistical Analysis

Data were entered and analyzed in Microsoft Office Excel 2010. Variables such as age, suspected drug, drug class, systems involved, temporal relation of ADR, type of ADR and its management, causality, severity, predictability, and preventability were expressed as frequencies and percentages.

RESULTS

A total of 100 ADRs were reported spontaneously, of which 81% of ADRs were among patients 21–40 years of age. The age range was 18–64 years [Figure 1].

Sixty-two ADRs occurred during pregnancy, of which gastrointestinal system (51%) was predominantly affected. Gastritis (25%) was the most common ADR, followed by allergic reaction (18%). Table 1 represents the organ-system wise distribution of ADRs in the study.

Most commonly used medications that contributed to ADRs were hematinics - 42% (ferrous sulfate + iron sucrose), followed by antimicrobials (31%), analgesics (9%), hormones (6%), uterine stimulants (5%), and miscellaneous such as antifibrinolytics (3%), uterine relaxants (2%), mineral (1%), and antihypertensive drugs (1%) [Figure 2].

Causality assessment by the WHO-ADR scale revealed that, of 100 ADRs, 61% were probable and 39% were possible. None of the ADRs were certain, unlikely, un-assessable or unclassifiable and conditional or unclassified [Table 2].

Severity assessment by Hartwig and Siegel scale showed 57% as mild, 43% as moderate, and no severe ADRs [Table 3].

Predictability assessment by Rawlins and Thompson indicated that 72% were predictable (type A), while 28% were not predictable (type B) ADRs [Figure 3].

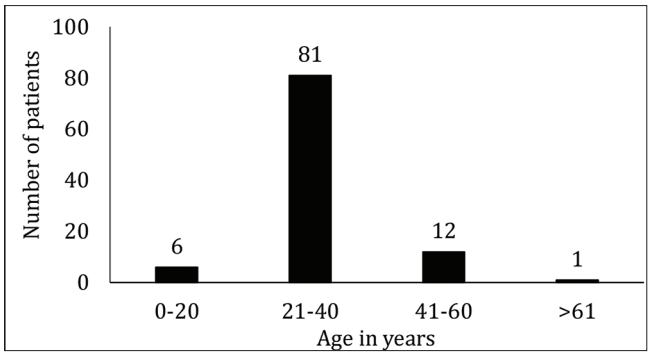

Figure 1: Age distribution of adverse drug reactions reported

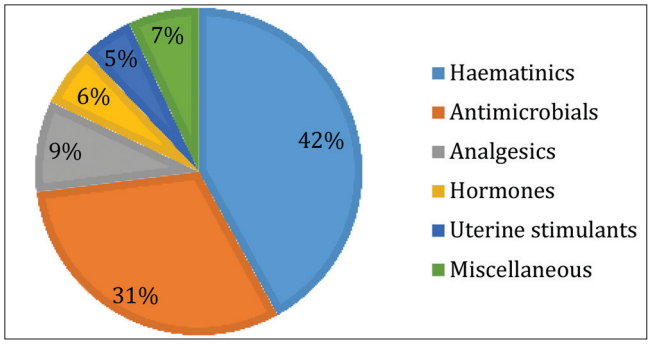

Figure 2: Spectrum of drugs causing adverse drug reactions

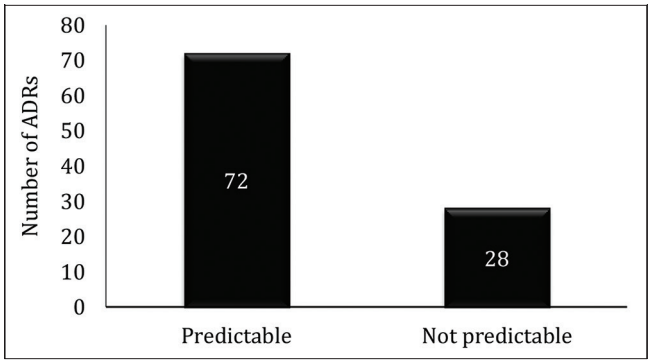

Figure 3: Assessment of the predictability of adverse drug reactions

Preventability assessment by modified Schumock and Thornton scale showed that 56% was probably preventable and 44% was not preventable. None of the ADRs was definitely preventable [Figure 4].

Management of ADRs is as follows: 43% of the ADRs managed by additional medical treatment, non-medical in 36%, and 21% required no treatment [Figure 5].

Action taken: Causative drug was withdrawn in 44%, dose not changed in 39%, and dose was reduced in 17% [Table 4].

Table 1: Organ-system wise distribution of ADRs (*n*=100)

Systems involved	ADRs	Frequency (%)
Gastro intestinal system (*n*=51)	Gastritis	25
	Diarrhoea	10
	Vomiting	07
	Constipation	03
	Nausea	02
	Anorexia	01
	Abdominal pain	01
	Heart burn	01
	Taste alteration	01
Immune system (*n*=20)	Allergic reaction	18
	Chills	02
Dermatological system (*n*=19)	Rash	11
	Dermatitis	03
	Urticaria	02
	Fixed drug eruption	01
	Alopecia	01
	Skin pigmentation	01
Haematopoietic system (*n*=5)	Post-menopausal bleeding	03
	Thrombophlebitis	01
	Menorrhagia	01
Cardio vascular system (*n*=4)	Hypertension	01
	Postural hypotension	01
	Bradycardia	01
	Palpitation	01
Central nervous system (*n*=1)	Headache	01

ADRs: Adverse drug reactions

Table 2: WHO causality assessment of ADRs (*n*=100)

Causality assessment	ADRs
Certain	0
Probable	61
Possible	39
Unlikely	0
Unclassifiable	0
Unclassified	0

ADRs: Adverse drug reactions

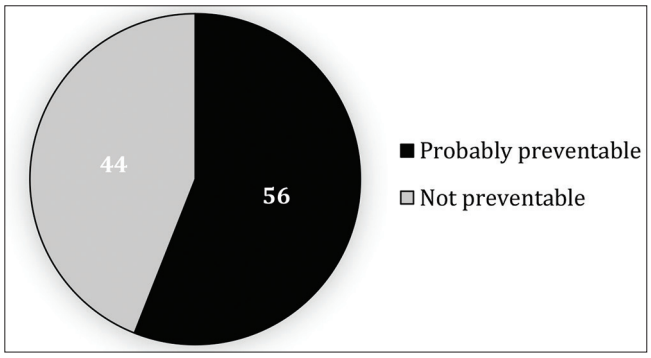

Figure 4: Assessment of the preventability of adverse drug reactions

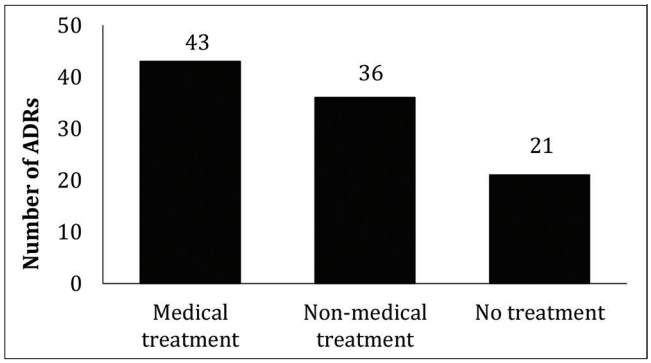

Figure 5: Management of adverse drug reactions

Table 3: Severity assessment of ADRs (*n*=100)

Severity assessment	ADRs
Mild	57
Moderate	43
Severe	0

ADRs: Adverse drug reactions

Table 4: Action taken after ADRs (*n*=100)

Action taken	ADRs
Drug withdrawn	44
Dose of the drug not changed	39
Dose of the drug reduced	17

ADRs: Adverse drug reactions

DISCUSSION

India is one of the fourth largest producers of pharmaceuticals in the world. It is introducing many new drugs every year and so knowledge about the importance of ADR monitoring is essential for every health-care professional.[13]

The majority of the patients belonged to the age group of 21–40 years which is similar to the previous study done by Sanjay Gaur *et al*.[14] presented the most common age group was 18–39 years that could probably be due to the increased use of medicines, more incidence of diseases such as diabetes and hypertension in this population.

In our study, 62 ADRs occurred during pregnancy which is similar to the study by Dhar *et al*.[6] which reported 63 ADRs, of which 40 occurred during pregnancy. A higher rate of ADRs were detected due to the physiological changes in pharmacokinetic, immunological, and hormonal factors occurring during pregnancy.

The present study showed the most common ADRs in women with anemia (37%), bacterial infection (8%), pelvic pain (3%), postpartum hemorrhage (3%), and eclampsia (2%) and showed the most common ADRs in non-pregnant women with dysmenorrhea (7%), urinary tract infection (6%), and candidiasis treatment (4%). However, different spectra were seen in a study done by Dhar *et al*.[6] and the most common ADR was breathlessness and palpitation (19.04%), while others were cough (14.28%) and rash and pruritus (12.69%). More than half of the pregnant women (58%) in India suffer from anemia, and the primary cause is found to be iron deficiency. Iron requirement of pregnant women is higher which is apparently more than the amount of iron storage in the body, and the iron deficiency leads to adverse health consequences both for mother and fetus.[15]

In our study, most commonly affected organ system was the gastrointestinal system (51%) followed by immune system (20%), dermatological system (19%), hematopoietic system (5%), cardiovascular system (4%), and central nervous system (1%). In a study done by Dhar *et al*.,[6] the most commonly affected organ class was cardiovascular system (19.04%) followed by respiratory system (14.28%). The reason could be that spectrum of drugs used in our study had most common side effects affecting gastrointestinal system.

Gastritis (25%) was the most common ADR, followed by allergic reaction (18%), rash (11%), and diarrhea (10% of patients). Majority of ADRs were due to hematinic (42%), followed by antimicrobials (31%), analgesics (9%), hormones (6%), uterine stimulants (5%), and miscellaneous such as antifibrinolytics (3%), uterine relaxants (2%), and antihypertensive drugs (1%). This is at par with the study conducted by Dhar *et al*.[6] where the most common therapeutic class involved in ADRs was antimicrobials in 33.33% of patients.

Majority of ADRs were due to hematinic drugs such as oral ferrous sulfate accounting for 26% and intravenous iron sucrose for 16%. The proposed mechanism of oral ferrous sulfate inducing gastritis involves iron oxidation and subsequent damage to the esophagus and stomach. More specifically, when iron is oxidized from ferrous to ferric form, an epithelial injury occurs. [16] Iron sucrose is associated with adverse effects in 38 per million population, typically administered as a slow push injection or a 15–30 minute infusion in doses of 100–200 mg. Hypersensitivity reactions to iron sucrose involve generalized pruritus, burning

sensation, and peribuccal hyperesthesia because even small amounts of corresponding allergens are able to trigger a mediator release when the patient is simultaneously exposed and this is managed by corticosteroids and antihistamines.[17]

Antimicrobial drugs accounted for 31% of ADRs, namely cefotaxime (9%), fluconazole (4%), ceftriaxone (3%), ofloxacin (3%), and others (norfloxacin, ampicillin, amoxicillin, metronidazole, and cotrimoxazole). Allergic reactions are the major threat in the use of antibiotics, especially penicillin group of drugs. There is partial cross-sensitivity between cephalosporins; although the risk of an allergic reaction to cephalosporins in those with an established IgE-mediated allergy to penicillin may be low, it was up to 10% due to the sharing of the beta-lactam ring. Such mild allergic reaction can be treated with an antihistaminic like diphenhydramine, which helps relieve itching and skin rash.[18]

Causality assessment by the WHO-ADR scale showed that 61% were probable and 39% were possible in our study with no cases as certain because rechallenge of offending drug was not done. Severity assessment by Hartwig and Siegel scale indicated 57% as mild, 43% as moderate, and no severe ADRs. This shows that, in our center, there are no severe adverse reactions accounting for the use of safe profile medicines during pregnancy with no banned drugs. Predictability assessment by Rawlins and Thomson indicated that 28% were not predictable (type B) ADRs, while 72% were predictable (type A). Preventability assessment by modified Schumock and Thornton scale showed that 56% was probably preventable, 44% was not preventable, and none of the ADRs were definitely preventable. Majority (43%) of the ADRs required additional medical treatment. Causative drug was withdrawn in 44%, dose not changed in 39%, and dose was reduced in 17%.

As some of the ADRs were preventable, this calls for the urgent need to reinforce the monitoring of adverse reactions to drugs, public education, inclusion of reaction monitoring, and an introduction to drug-safety in the curriculum of medical undergraduates, as well as systemic and periodic medical education of health professionals.

Strengths and Limitations

This study provides a database of ADRs of prescribed drugs in the OBG Department in our hospital, which will help the doctors for their optimum and safe usage of drugs. A sincere attempt has been made to assess the pattern, causality, severity, predictability, and preventability with validated questionnaire which adds to the strength of our study. The main limitation of this study is that it represents only the ADRs reported to the Department of Pharmacology and not the complete picture of ADRs occurring in the tertiary care hospital reason being under-reporting of ADRs. The duration of hospital stay of the study participants due to ADRs and the related costs of ADRs were not calculated as there was no follow-up of the patients. Thus, a prospective study with larger sample size would have helped to analyze the predictors of ADRs.

CONCLUSION

Iron therapy accounting for maximum ADRs has risks as well accompanying clinical benefits. A wide spectrum of ADRs affecting the gastrointestinal, CNS, cardiovascular, immune, and hematopoietic system was reported. Most of the ADRs are predictable and probably preventable with no severe ADRs, which highlights the appropriate management of ADRs at our center.

Reporting of ADRs has become an important component of monitoring and evaluation activities performed in hospitals. This information will be useful for identifying and minimizing preventable ADRs while generally enhancing the ability of prescribers to manage ADRs more effectively.

This study will be useful as a preliminary study in initiating a culture of ADR reporting among health-care professionals in the hospital. Reporting programs are necessary to educate and increase awareness about reporting of ADRs among the health-care professionals in the developing countries.

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