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Original Research Article

Adverse Drug Reaction Monitoring of Commonly Prescribed Medicines in Gynaecology Patients in a Tertiary Care Hospital in North India

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ABSTRACT

Introduction: The prevalence of gynecological disorders is quite high which warrants more number of prescribed drugs. Females are also at an increased risk of developing ADRs as compared to men. Present study focuses on the Adverse Drug Reactions (ADRs) monitoring of drugs commonly prescribed to gynaecological patients.
Materials and Methods: Gynaecological patients who were on drugs for various gynaecological disorders were observed prospectively in a cross-sectional, non-interventional manner and ADRs were collected by spontaneous/solicited monitoring. ADRs were coded according to the MedDRA classification, were assessed for their seriousness, severity, causality and preventability and were managed accordingly. The seriousness of adverse events was assessed according to the type of outcome as mentioned in the CDSCO ADR proforma. Severity was assessed using modified Hartwig scale, causality assessment was done using WHO-UMC scale and preventability of ADRs was done by using modified Schumock and Thornton criteria.
Results: 235 patients, who were being treated for various gynaecological disorders, were observed of whom 163 patients reported ADRs. A total of 181 ADRs were collected and eighteen patients reported more than one ADR. Antibiotics were the most common group of drugs implicated in the causation of ADRs. The most commonly affected organ class was the gastrointestinal system. Majority of the reactions (81.77%) were 'mild' in nature and no serious reactions were reported. Causality assessment by WHO-UMC scale revealed most of the reactions as 'probable' (72.93%) while 27.07% were classified as possible. Preventability assessment determined that 47.51% of ADRs were 'not preventable' and only 7.74% were labelled as definitely preventable. Majority (59.68%) of the ADRs were managed by withdrawing the suspected drug.
Conclusion: Overall, drugs for gynaecological disorders appear to be a safe option for patients but they still have potential to cause ADRs, so for better patient safety, probability of ADR should be kept in mind before prescribing any drug.
Key Words: Gynaecology, Adverse Drug Reactions, WHO UMC, MedDRA

INTRODUCTION

Pharmaceutical industry is growing at a very fast rate and there are more effective drugs in the market than ever before. These drugs can do good and can also do harm. But for a medicine to be considered safe its expected benefits should be greater than any associated risks of harmful reactions. WHO defines an adverse drug reaction as "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis,

diagnosis or therapy of disease, or for modification of physiological function", [1] Adverse drug reactions are one of the major causes of morbidity and account for nearly 5% of all hospital admissions all over the world. Over two million ADRs occur yearly that result in 5% fatality annually. [2] Adverse drug reactions are the fourth leading cause of death ahead of pulmonary disease, diabetes mellitus, AIDS, pneumonia and automobile deaths. [3] They also contribute to excessive health care costs through increased patient morbidity and mortality. [4]

A number of studies clearly suggest that ADRs are 50 to 75% more likely in women than men. [5] In an analysis of 48 community-based cohort studies, the overall incidence of suspected ADRs in males was 12.9 per 10000 patient-months of exposure, and in females, was 20.6 per 10 000 patient-months of exposure. [6] The overall age-standardized odds ratio of an ADR in females compared with males was 1.6. This gender difference was significant in all age groups above 19 years of age, and was relatively consistent across all age groups. In a Spanish study, 60% of adverse reactions to nonsteroidal anti-inflammatory drugs were in women (odds: 1.67). [7] In a Canadian study, 74.1% of ADRs were in women. [8] In a study done on a population of over 20 million people in Italy, female is to male ratio for ADRs was found to be 1.58. [9] So, there is clearly an increased risk for developing an ADR in women.

The reasons for this increased risk are not entirely clear but include gender-related differences in pharmacokinetic, immunological and hormonal factors. Generally, females weigh less than males, have a higher percent body fat and a lower lean body mass which lead to different pharmacokinetic of a drug in women than men. [5] Female also faces certain specific issues when compared with men like menstruation, menopause, lactation etc which are associated with physiological changes, which in turn affect the response to drugs. [10] Women also use significantly different range of drugs than men, like contraceptives and hormonal preparations which can affect the metabolism of the body and are themselves affected by a wide range of therapeutic agents and thus have a greater potential to cause ADRs. [10,11]

As the data regarding the safety of drugs used in various gynaecological disorders available in India is limited. So, to gain a comprehensive safety profile of gynaecological medicines, the present study was planned to actively generate data on the safety profile of currently prescribed drugs for gynaecological disorders in a tertiary care centre.

MATERIALS AND METHODS

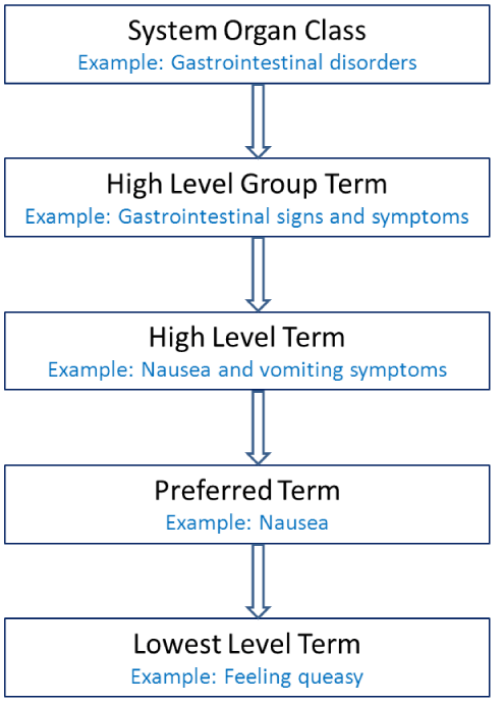
This was a prospective, observational, cross sectional, non-interventional study and involved spontaneous and solicited ADR monitoring of commonly prescribed drugs for gynaecological disorders done in a tertiary care hospital, Pt. B.D. Sharma PGIMS, Rohtak (Haryana). The study was done in accordance with the principles of Good Clinical Practice (GCP) and Declaration of Helsinki with its subsequent amendments.

Outpatients of gynaecology department as well as the inpatients admitted in the gynaecology ward who were on drug treatment for various gynaecological disorders and were known to report some adverse events, were included in the study. Pregnant females, patients with history of drugs abuse or over dose of drug were excluded from the study.

Adverse event monitoring was carried out by Spontaneous/ Solicited reporting. The patient's data was entered into patient's case record form (CRF). The Central Drugs Standard Control Organisation (CDSCO) proforma [12] was used and filled as and when adverse drug reaction was reported and the ADR was assessed for its causality, seriousness, severity, preventability and management.

ADRs were coded according to Medical Dictionary for Regulatory Activities (MedDRA) [13] in which terms for

specific adverse events that are alike or pertain to the same organ system are categorized by System Organ Class (SOC). It is a clinically validated international medical terminology dictionary developed by the International Conference on Harmonization which is used by regulatory authorities in the pharmaceutical industry during the regulatory process. It has 26 broad groups called system organ classes. Adverse events are coded according to the hierarchy system which has five levels, arranged from very specific to very general. "System Organ Classes" (SOCs) are groupings by etiology (e.g. Infections and infestations), manifestation site (e.g. Gastrointestinal disorders) or purpose (e.g. Surgical and medical procedures). [13]



WHO-UMC Scale was used to analyse the causality between the drug and suspected reaction. [14] WHO-UMC Scaleis a combined assessment taking into account the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation. It has categorized ADRs as Certain, Probable, Possible, Unlikely, Conditional/Unclassified, Unassessable/ Unclassifiable. Seriousness of the reaction was determined as per the ADR reporting form which considers the following reactions or reaction outcomes as serious: death, life threatening, hospitalization (initial/prolonged), disability, required intervention to prevent permanent impairment/damage and congenital anomaly. [12] Severity of ADRs was assessed by modified Hartwig scale [15] which categorized ADRs as mild, moderate and severe. Preventability of ADRs was assessed by modified Schumock and Thornton criteria which categorized ADRs as definitely preventable, probably preventable or not preventable. [16] Management of ADRs was also noted.

Descriptive statistical analysis was used with data expressed as numbers and percentages. All statistical analysis was carried out using Microsoft excel and the IBM SPSS statistics version 20.0. The analysis was performed in a step wise manner by suitable categorization of the various observations made.

OBSERVATIONS:

A total of 235 patients were observed, out of which 163 patients reported 181ADRs giving an incidence of 77.02%. Data of 163 patients who reported ADRs was further assessed for various parameters. The mean age of patients who experienced ADRs was 37.28±12.71 (16-71)years. Maximum number of patients who reported ADRs (n=93) were in the age group 30-50 years and least (n=17) were in age group of above 50 years. Weight of the patients who reported ADRs ranged from 40-85 kgs with mean weight being 61.99 ± 12.14 kgs. Majority of the patients were from rural area (63.80%) while 36.20% of patients were from urban area. None of the patient observed had any known drug allergy.

Antibacterials for systemic use were the most common group of drugs implicated in the causation of ADRs followed by drugs prescribed for acid related disorders, anti-inflammatory and anti-rheumatic, antifibrinolytics and antifungal drugs. Among 181 ADRs reported, gastrointestinal

system disorders comprised the maximum number (49.17%) of ADRs followed by nervous system disorder (28.73%), dermatologic system disorder (11.05%), genitourinary system disorder, blood and lymphatic system disorder and body as a whole general disorder each comprised 2.76% ADRs, musculoskeletal system disorder (1.66%) and metabolism and nutrition disorders (1.11%). (Figure 1)

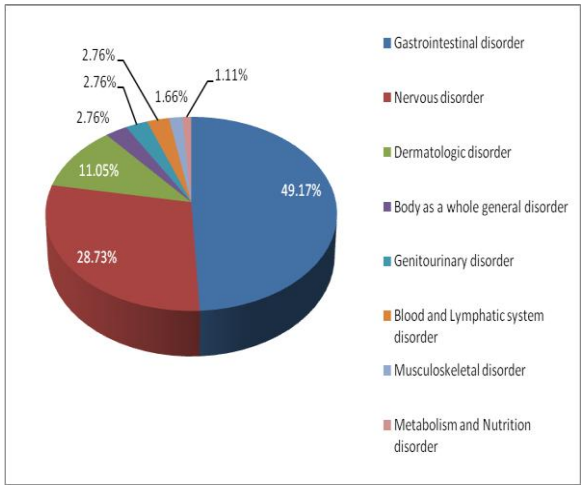


Figure 1: Distribution pattern of ADRs as per SOC in percentage

Causality assessment of the ADRs, revealed that 72.93% of the ADRs were 'probable' and 27.07% ADRs were 'possible' according to WHO-UMC scale. None of the ADRs were classified as certainor unlikely. (Figure 2)

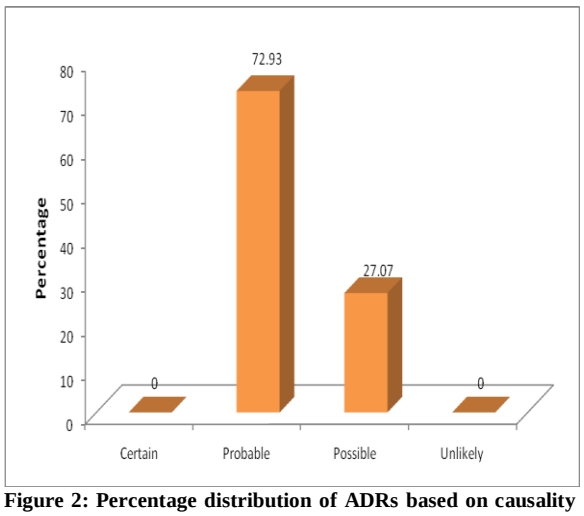


Figure 2: Percentage distribution of ADRs based on causality assessment done by WHO-UMC scale

Seriousness of ADRs was evaluated as per criteria in CDSCO ADR proforma. All the 181 ADRs observed with various gynaecological drugs, were classified as non-serious. Severity assessment according to modified Hartwig scales showed that81.77% ADRs were mild, 18.23%were moderate and none of the ADR was severe (Table 1).

Table 1: Severity assessment of ADRs according to modified Hartwig scale

Severity	Number of ADRs (n=181)	Percentage of ADRs (%)
Mild	148	81.77
Moderate	33	18.23
Severe	0	0

Preventability assessment of ADRs was done according to modified Schumock and Thornton criteria. Out of 181 ADRs reported, 7.74% ADRs were categorized as 'definitely preventable', 44.75% were 'probably preventable' and 44.51% ADRs were 'not preventable'. (Figure 3)

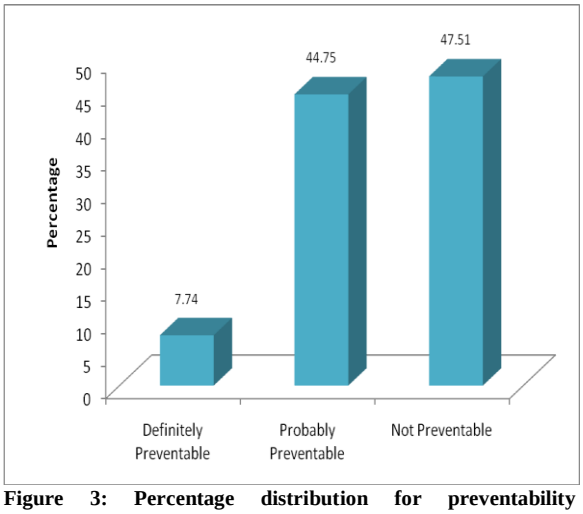


Figure 3: Percentage distribution for preventability assessment of ADRs according to modified Schumock and Thornton criteria

Table 2 shows how the observed ADRs were managed. 59.6% of the ADRs were managed by withdrawing the suspected drugs, 3.86% ADRs were managed by decreasing the dose of the suspected drug. In 18.23% of ADRs treatment was continued as such and no change was made while 18.23% ADRs required some drug intervention for their management.

Table 2: Management of ADRs

Management of ADRs	Number of ADRs (n=181)	Percentage of ADRs (%)
Suspected Drug Withdrawn	108	59.68
No Change in Therapy	33	18.23
Required Drug Intervention	33	18.23
Decreasing the Dose of the Suspected Drug	7	3.86

DISCUSSION

As the flow of patients in gynaecology department has increased, more drugs are being prescribed for various gynaecological disorders; hence the need for heightened vigilance is growing more than ever before. A total of 235 patients were observed over a period of 15 months. Demographic characteristics of the patients who reported ADRs showed that the most of the patients presenting with the ADRs belonged to middle and peri-menopausal age group (30-50 years). This might be due to the fact that most of the patients presented in the gynaecological OPD during study period belonged to this age group.

ADRs were categorized into different System Organ Class (SOC) based on MedDRA, which is an adverse event classification dictionary. This was done to harmonize medical terms which aid authorities to exchange and analyze data, related to safe use of medicines more efficiently. The most commonly affected organ class was the gastrointestinal system followed by nervous system, dermatologic system, genitourinary system, body as a whole general disorders and blood lymphatic disorders followed by musculoskeletal system and metabolism and nutrition disorders. Since most of the drugs in present study were prescribed by oral route, gastrointestinal system was a common site for development of adverse reactions. [17] High incidence of gastrointestinal system involvement observed in this study can also be attributed to the use of various antibiotics for systemic use and anti-inflammatory drugs for various gynaecologic conditions for extended periods which can cause increased gastric acidity. This pattern of affected organ class was similar with a study done by Dhar et al, [18] who reported that gastrointestinal and dermatologic system were the most commonly affected organ class after genitourinary system disorders.

Most of the ADRs belonged to probable and possible category and none of the ADRs were in certain or unlikely category. In 72.93% cases, dechallenge criteria came out to be positive and they were labelled as probable. 27.07% cases were labelled as possible as positive dechallenge criteria was not met for the following reasons: dechallenge was not performed or information regarding dechallenge was lacking or a negative dechallenge, i.e. adverse drug reaction did not subside on drug withdrawal. Hence, according to the WHO, causality was labelled as possible in these cases. Similar to present study data, in a study done by Dhar et al, [18] causality assessment by WHO scale revealed that majority of ADRs (80.95%) were probable followed by possible (19.04%) and none were categorized into certain or unlikely.

None of the reported ADRs reported was serious or required any hospital admission due to ADR development and all the patients recovered from ADRs without any sequelae or disability. Above findings are in agreement with a study done by Zaidenstein et al, [19] where majority (96%) of ADRs were non-serious and only 4% of ADRs were serious and all the patients recovered. In the present study, majority of the suspected ADRs were mild followed by moderate and none of the observed ADR was severe. These findings are similar with a study done by Halkai et al [20] in which majority of the ADRs were of mild category (87%) followed by moderate (8%) and least number of ADRs reported were of severe category (5%). This can be explained by the fact that majority of the ADRs were transient and did not require any intervention for the ADR management. In the present study most of the ADRs were

managed by withdrawing the suspected drug or no change in drug therapy was made in other ADRs while in some of the ADRs drug intervention was done to manage the ADRs and few were managed by altering the dose of the suspected drug. Since majority of the ADRs were mild no active intervention was required to control them. Present study findings are comparable with a study done by Dhar et al, [18] where majority of (50.79%) ADRs were managed by withdrawing the drug, while in 23.80% ADRs no change in the drug therapy was made and 17.46% ADRs were managed by altering the dose of drug and there was no ADR for which drug intervention was required. In the present study, majority of ADRs were not preventable and few of ADRs were definitely preventable. Similarly, in a study done on Indian population, preventability of suspected ADRs showed that majority (77.11%) of ADRs were not preventable, while 22.5% of ADRs were probably preventable and only 0.062% of ADRs were definitely preventable. [21]

Above findings suggest that drug prescribed for gynaecological disorders are generally safe. Drugs with potential to cause serious ADRs were either avoided or prescribed cautiously. Present study gives baseline information about ADRs in women with gynaecological disorders. The data presented here will be useful in future, long term and more extensive ADR monitoring in the hospital and will be useful in framing policies towards rational use of drugs.

Monitoring of adverse drug reactions is an ongoing, ceaseless and continuing process. Since newer and newer drugs hit the market, the need for monitoring of ADRs is growing. The health system should promote the spontaneous reporting of adverse drug reactions to drugs, proper documentation and periodic reporting to authorities, to ensure drug safety. The active involvement of health care professionals for detecting the adverse drug reactions and delivering the awareness classes for the health care professionals regarding the need of reporting the incident could improve the ADR reporting scenario in India. There were some limitations in present study. This study involved few number of patients and also it was a single centre study.

CONCLUSION

Overall, drugs for gynaecological disorders appear to be a safe option for patients but they still have potential to cause ADRs. Relatively, high incidence of gastrointestinal and central nervous system ADRs warrants that the patients should be made aware for these ADRs and the need to seek treatment if required. As the flow of patients in gynaecology department has increased, more drugs are being prescribed for various gynaecological disorders; hence the need for heightened vigilance in monitoring the ADRs is growing more than ever before. Such more studies are required to promote the safe use of medicines in specific settings and to create awareness among prescribers and patients about safe and rational use of drugs.

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