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Impact of Polypharmacy on Adverse Drug Reactions in Gynaecological Patients: A Prospective Observational Study

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Abstract

Background: Adverse drug reactions (ADRs) remain a significant cause of morbidity and healthcare burden worldwide. Polypharmacy has emerged as an important and potentially modifiable risk factor for ADRs, particularly in gynaecological patients who are frequently exposed to multiple medications. ***Objective:*** To evaluate the impact of polypharmacy on the occurrence of adverse drug reactions in gynaecological patients. ***Methods:*** This prospective, observational study was conducted in the Departments of Pharmacology and Obstetrics & Gynaecology at a tertiary care teaching hospital. A total of 235 patients were monitored over 15 months. Polypharmacy was defined as the use of more than three medications per prescription. ADRs were recorded using CDSCO reporting forms and assessed for causality (WHO-UMC and Naranjo), severity (Hartwig scale), and preventability (Schumock and Thornton criteria). Data were analyzed descriptively. ***Results:*** Out of 235 patients, 163 (69.4%) experienced at least one ADR, with a total of 181 ADRs reported. A higher proportion of ADRs was observed among patients exposed to polypharmacy (58.9%) compared to non-polypharmacy (41.1%). Gastrointestinal disorders were the most frequently affected system (49.17%). Most ADRs were mild (81.77%) and non-serious. Causality assessment revealed variability between WHO-UMC and Naranjo scales, with minimal agreement ($\kappa \approx 0.26$). A considerable proportion of ADRs were found to be preventable or potentially preventable. ***Conclusion:*** Polypharmacy appears to be an important contributing factor to ADR occurrence in gynaecological patients. Rational prescribing and regular medication review may help reduce ADR burden and improve patient safety.

Keywords: Polypharmacy; Adverse Drug Reactions; Pharmacovigilance; Gynaecology; Drug Safety; Medication Burden

INTRODUCTION

Pharmacovigilance plays a pivotal role in modern healthcare by ensuring the detection, assessment, and prevention of adverse drug reactions (ADRs) during routine clinical use. Despite rigorous pre-marketing evaluation, many adverse effects remain undetected until drugs are widely used in real-world settings, highlighting the need for continuous post-marketing surveillance. Effective pharmacovigilance systems are therefore essential to improve medication safety and optimize therapeutic outcomes.1 Adverse drug reactions (ADRs) not only compromise patients' quality of life but also place a substantial burden on healthcare systems. They contribute significantly to increased morbidity and mortality and represent an important public health concern.2

Among these risk factors, polypharmacy—commonly defined as the concurrent use of multiple medications—has gained increasing attention. Contemporary studies have consistently demonstrated that polypharmacy is strongly associated with an increased risk of ADRs, largely due to drug–drug interactions, altered pharmacokinetics, and cumulative toxicity.3,4 In recent observational analyses, polypharmacy has been shown to independently increase the odds of ADR occurrence, with some studies reporting more than a twofold rise in risk among patients receiving multiple medications.3 Furthermore, the likelihood of adverse outcomes has been shown to increase progressively with the number of drugs prescribed.5

Polypharmacy also contributes to a spectrum of adverse clinical consequences, including medication errors, reduced adherence, hospitalization, and increased mortality.6 These risks are further amplified in real-world clinical settings where patients often receive complex therapeutic regimens. The growing burden of multimorbidity and the expanding availability of pharmacological therapies have made polypharmacy an increasingly common and clinically significant issue across healthcare systems.6,7

Women, particularly those seeking gynaecological care, represent a population that may be especially vulnerable

to ADRs. Biological differences such as variations in body composition, hormonal influences, and drug metabolism can alter pharmacokinetic and pharmacodynamic responses. Additionally, gynaecological patients are frequently exposed to multiple classes of drugs—including antibiotics, analgesics, hormonal therapies, and antifibrinolytics—often in combination, thereby increasing the likelihood of polypharmacy.8

In gynaecological practice, the need to manage diverse clinical conditions often necessitates the use of multiple medications simultaneously. While such approaches may be clinically justified, they also increase the risk of adverse drug reactions, particularly in the absence of targeted pharmacovigilance data. Despite growing global evidence on polypharmacy-related risks, there remains a relative paucity of studies specifically evaluating its impact on ADRs in gynaecological patients, especially in the Indian context.3,5

Given the clinical importance of safe prescribing, it is essential to understand the relationship between polypharmacy and ADR occurrence in this population. Therefore, the present study was undertaken to evaluate the impact of polypharmacy on adverse drug reactions in gynaecological patients through prospective observational monitoring. The findings are expected to provide insights that may help in optimizing prescribing practices and reducing preventable drug-related harm.

MATERIALS AND METHODS

Study Design and Setting

This prospective, observational, non-interventional study was conducted to evaluate the impact of polypharmacy on adverse drug reactions (ADRs) in gynaecological patients. The study was carried out in the Department of Pharmacology in collaboration with the Department of Obstetrics and Gynaecology at Pt. B.D. Sharma Post Graduate Institute of Medical Sciences (PGIMS), Rohtak, Haryana. The Department of Pharmacology functions as an Adverse Drug Reaction Monitoring Centre (AMC) under the Pharmacovigilance Programme of India (PvPI), Ministry of Health and Family Welfare, Government of India.

The study was conducted in accordance with the principles of Good Clinical Practice (GCP) and the Declaration of Helsinki and its subsequent amendments. Institutional Ethics Committee approval was obtained prior to the initiation of the study.

Study Population

Patients attending the gynaecology outpatient department as well as those admitted to the gynaecology wards and receiving treatment for various gynaecological disorders were included in the study. Patients who were prescribed medications and were likely to report adverse events were eligible for inclusion. Pregnant women, patients with a history of drug abuse, and those with drug overdose were excluded from the study. A total of 235 patients were screened over a period of 15 months (March 2015 to July 2016), of whom 163 patients experienced at least one ADR, accounting for a total of 181 ADRs.

Definition of Polypharmacy

For the purpose of this study, polypharmacy was defined as the concurrent use of more than three medications per prescription, while patients receiving three or fewer drugs were categorized as non-polypharmacy group.

Data Collection and Adverse Event Monitoring

Adverse event monitoring was performed using both spontaneous and solicited reporting methods. Patient data including demographic details, diagnosis, laboratory findings, prescribed medications, and details of ADRs were recorded in a structured Case Record Form (CRF). All suspected ADRs were documented using the Central Drugs Standard Control Organization (CDSCO) ADR reporting proforma. Each report included patient information, details of the suspected reaction, suspected medications, and reporter information. The reports were subsequently uploaded into the Vigiflow database, which is part of the WHO Programme for International Drug Monitoring.

Drug Classification

All prescribed drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system, which categorizes drugs based on their therapeutic use and pharmacological properties.

Assessment of Adverse Drug Reactions

ADR Coding

All ADRs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and categorized according to System Organ Class (SOC).

Causality Assessment

Causality between the suspected drug and ADR was assessed using the WHO-UMC scale and the Modified Naranjo scale.

Severity Assessment

The severity of ADRs was assessed using the modified Hartwig scale and categorized as mild, moderate, or severe.

Seriousness Assessment

Seriousness of ADRs was determined based on CDSCO criteria, including outcomes such as death, life-threatening events, hospitalization, disability, or congenital anomaly.

Preventability Assessment

Preventability was assessed using the modified Schumock and Thornton criteria and categorized as definitely preventable, probably preventable, or not preventable.

Outcome Measures

The primary outcome of the study was the occurrence of ADRs in patients with and without polypharmacy. Secondary outcomes included comparison of severity, causality, and preventability of ADRs between the two groups.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using IBM SPSS Statistics version 20.0. Descriptive statistics were used to summarize demographic and clinical variables.

Patients were categorized into polypharmacy and non-polypharmacy groups, and the association between polypharmacy and ADR occurrence was analyzed using the Chi-square test. Odds ratio (OR) with 95% confidence intervals (CI) was calculated to determine the strength of association. A p-value of <0.05 was considered statistically significant.

RESULT

Study Population and Overall ADR Burden

During the study period, 235 patients receiving treatment for gynaecological conditions were evaluated. Of these, 163 patients developed at least one adverse drug reaction (ADR), yielding a substantial ADR burden within the study cohort. A total of 181 ADRs were documented, with a small subset of patients (n = 18) experiencing more than one reaction, indicating clustering of events in certain individuals. This is shown in Table 1.

Table 1: Study Population and ADR Distribution

Parameter	Number	Percentage (%)
Total patients	235	100
Patients with ADRs	163	69.4
Patients without ADRs	72	30.6
Single ADR	145	89.0*
Multiple ADRs	18	11.0*

*Among ADR patients

Polypharmacy Exposure Among ADR Patients

Among patients who developed ADRs, a greater proportion were exposed to polypharmacy (>3 drugs per prescription) compared to those receiving fewer medications. Specifically, 58.9% of ADR cases occurred in patients receiving multiple drugs, reflecting a higher representation of ADRs in the polypharmacy group. This distribution suggests that increased medication burden may contribute to heightened susceptibility to adverse events. This is shown in Figure 1.

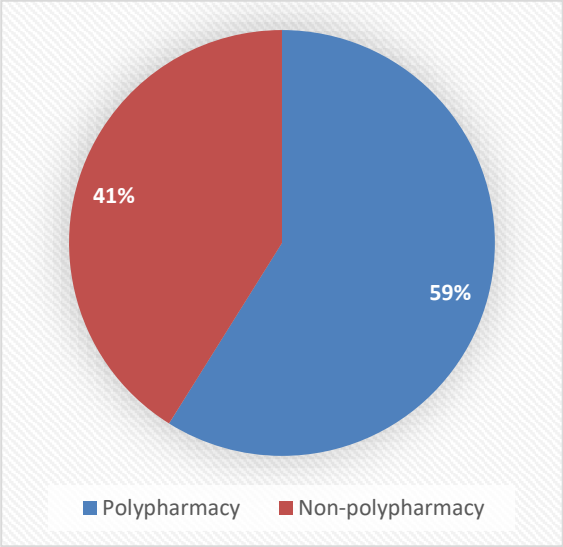

Figure 1: Proportion of ADRs by Polypharmacy Exposur

Clinical Characteristics of ADR Cases

The mean age of patients experiencing ADRs was 37.28 ± 12.71 years, with a concentration in the middle reproductive age group. A predominance of patients were from rural backgrounds, and comorbid conditions were relatively uncommon. A larger share of ADRs was observed in patients treated for non-infective gynaecological conditions, suggesting that chronic or symptomatic conditions requiring sustained pharmacotherapy may contribute to cumulative drug exposure.

Medication Burden and Prescription Profile

A total of 660 drugs were prescribed to 163 patients, indicating a high average drug exposure per patient. Antibacterials constituted the largest share of prescribed medications, followed by anti-inflammatory agents and drugs targeting acid-related disorders. The predominance of these drug classes reflects routine prescribing practices in gynaecology but also indicates potential contributors to adverse reactions due to their known pharmacological profiles. This is shown in Table 2.

Table 2: Distribution of Prescribed Drugs (ATC Classification)

Drug Category	Number	Percentage (%)
Antibacterials	207	31.36
Anti-inflammatory drugs	116	17.58
Acid-related drugs	92	13.94
Antianaemics	80	12.12
Antifibrinolytics	45	6.81

Drug Classes Associated with ADRs

Out of the total drugs implicated in ADRs (n = 387), antibacterial agents accounted for the largest contribution. This was followed by drugs used for acid-related disorders and anti-inflammatory agents. Rather than reflecting isolated drug effects, this pattern likely represents cumulative exposure to commonly co-prescribed medications in clinical practice. This is shown in Figure 2.

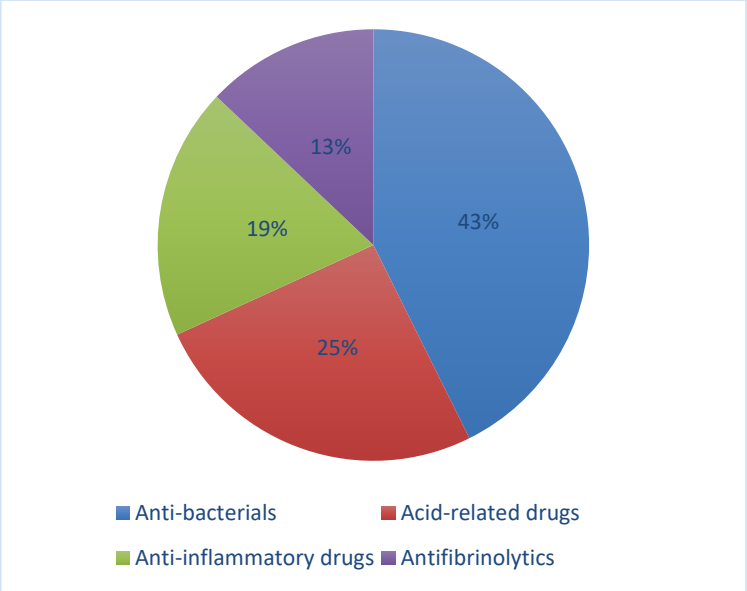

Figure 2: Distribution of Drug Classes Implicated in ADRs

Spectrum of Adverse Drug Reactions

When categorized by System Organ Class (SOC), ADRs involving the gastrointestinal system constituted the largest proportion, followed by nervous system manifestations and dermatological reactions. This distribution may reflect the route of administration and pharmacodynamic effects of commonly prescribed drugs, particularly those affecting gastric mucosa and central pathways. This is shown in Table 3.

Table 3: Distribution of ADRs by System Organ Class

System Organ Class	Number	Percentage (%)
Gastrointestinal	89	49.17
Nervous system	52	28.73
Dermatologic	20	11.05

Severity and Clinical Impact

Most ADRs were categorized as mild, while a smaller proportion were moderate in intensity. No severe reactions were documented. This suggests that although ADRs were frequent, they were generally manageable and did not result in serious clinical consequences. This is shown in Figure 3.

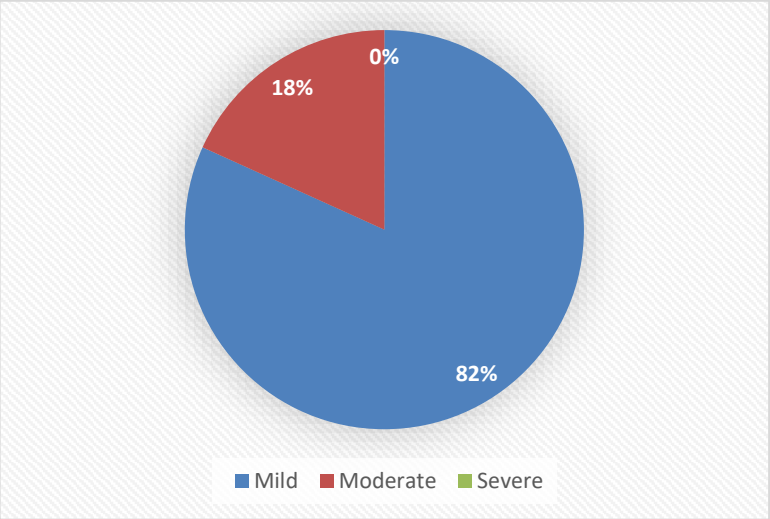

Figure 3: Severity Distribution of ADRs

Causality Assessment

Evaluation using WHO-UMC criteria indicated that most ADRs fell within the "probable" category, with the remaining classified as "possible."Assessment using the Modified Naranjo scale showed a shift toward "possible" categorization, reflecting variability in causality interpretation between assessment tools. The observed discordance between scales ($\kappa \approx 0.26$) suggests limited agreement and highlights the subjective component of causality assessment. This is shown in Table 4.

Table 4: Causality Assessment of ADRs

Scale	Category	Number	Percentage (%)
WHO-UMC	Probable	132	72.93
WHO-UMC	Possible	49	27.07
Naranjo	Possible	129	71.27
Naranjo	Probable	52	28.73

Preventability Profile

A considerable proportion of ADRs were identified as preventable or potentially preventable, indicating opportunities for improving prescribing practices and monitoring strategies.

DISCUSSION

World Health Organization (WHO) defines ADR as "a response to a medication that is noxious and unintended and occurs at doses normally used in man.9 The present study highlights the substantial burden of adverse drug reactions (ADRs) in gynaecological patients and explores the contribution of polypharmacy as a potential determinant. The high proportion of patients experiencing ADRs underscores the importance of continuous pharmacovigilance in routine clinical practice, particularly in specialties where combination therapy is frequently employed.10 A key finding of this study is the greater representation of ADRs among patients exposed to polypharmacy. The concurrent use of multiple medications has been consistently identified as a major risk factor for ADRs due to increased potential for drug–drug interactions, altered pharmacokinetics, and cumulative toxicity.11,12 Several recent studies have demonstrated that the likelihood of ADRs increases progressively with the number of medications prescribed, supporting the observations of the present study.12 This emphasizes the need for rational prescribing and periodic medication review to minimize unnecessary drug exposure.

The demographic profile observed in this study, with a predominance of ADRs in women of reproductive and peri-menopausal age, may be explained by increased healthcare utilization and pharmacological exposure during this period. Additionally, sex-related physiological differences, including variations in drug metabolism and hormonal influences, have been shown to affect drug response and susceptibility to ADRs.13 The predominance of ADRs in patients with non-infective gynaecological conditions suggests that prolonged or repeated pharmacotherapy may contribute to adverse outcomes. Chronic conditions often necessitate long-term medication use, increasing the likelihood of cumulative drug exposure and polypharmacy. This aligns with evidence indicating that long-term pharmacotherapy is associated with increased risk of medication-related harm.14

The prescribing pattern observed in this study reflects common clinical practice, with antibacterials, anti-inflammatory agents, and drugs for acid-related disorders forming the major therapeutic groups. These classes are known to be frequently implicated in ADRs, particularly gastrointestinal and neurological adverse effects.15 The predominance of these drug groups in both prescription and ADR profiles suggests that commonly used medications contribute significantly to the overall burden of ADRs, especially when used in combination. The pattern of ADRs observed, with gastrointestinal and nervous system manifestations being most frequent, is consistent with the known pharmacological effects of commonly prescribed drugs. Gastrointestinal disturbances are frequently associated with antibiotics and non-steroidal anti-inflammatory drugs, while central nervous system effects such as headache and dizziness are commonly reported with multiple drug classes.15,16 These findings indicate that ADR patterns may be predictable based on drug exposure profiles, particularly in settings with high medication use.

Most ADRs in the present study were mild to moderate in severity and did not result in serious clinical outcomes. Similar observations have been reported in pharmacovigilance studies, where the majority of ADRs are non-serious but still clinically relevant due to their impact on patient adherence and quality of life.17 Even mild ADRs can lead to treatment discontinuation or poor compliance, thereby affecting therapeutic outcomes. Causality assessment demonstrated variability between WHO-UMC and Naranjo scales, with limited agreement between the two methods. This finding reflects the inherent subjectivity in causality assessment and is consistent with previous studies reporting discrepancies between different assessment tools.18 Such variability highlights the need for cautious interpretation of causality results and suggests that a combination of clinical judgment and standardized tools may provide a more comprehensive assessment.

An important observation from this study is that a considerable proportion of ADRs were preventable or potentially preventable. This finding is clinically significant, as it indicates that many ADRs could be avoided through appropriate prescribing practices, patient counseling, and monitoring strategies. Previous studies have similarly emphasized that a substantial proportion of ADRs are preventable, particularly those associated with polypharmacy and inappropriate prescribing.19

Limitations

This study has certain limitations. First, the observational design limits the ability to establish a causal relationship between polypharmacy and ADR occurrence. Second, the absence of polypharmacy stratification among patients without ADRs restricted the use of inferential statistical measures such as odds ratio. Third, the study was conducted in a single tertiary care center, which may limit the generalizability of findings. Additionally, underreporting of ADRs cannot be excluded despite active surveillance methods.

Future Directions

Future studies should focus on multicentric designs with larger sample sizes to improve generalizability. Analytical studies incorporating control groups and regression models are needed to quantify the independent effect of polypharmacy on ADR risk. Interventional studies evaluating deprescribing strategies and medication review protocols in gynaecological practice may further help in reducing ADR burden. Integration of digital pharmacovigilance tools and real-time monitoring systems may also enhance ADR detection and prevention.

CONCLUSION

The present study highlights a substantial burden of adverse drug reactions among gynaecological patients and underscores the potential role of polypharmacy as a contributing factor. Although most ADRs were mild and non-serious, a significant proportion were preventable, indicating scope for improvement in prescribing practices. Rational drug use, periodic medication review, and strengthened pharmacovigilance systems are essential to minimize ADR risk and enhance patient safety in gynaecological care.

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