Original Article

Critical Analysis of Drug-Drug Interactions and Contraindications in Prescriptions of Pregnant Women; Findings from Lahore Pakistan

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Abstract

The careful evaluation of drug use during pregnancy is crucial due to its implications for both the mother and the unborn child's health and well-being. However, Pakistan lacks essential information regarding medication usage during pregnancy, posing significant challenges in ensuring the safety of maternal-fetal health. This study, set to take place in Lahore's tertiary care facilities, aims to analyze prescriptions for possible drug-drug interactions (DDIs) and contraindications. It's imperative to tackle the public health risks linked with prescribing medications during pregnancy to improve patient safety. The study was conducted on pregnant women visiting tertiary care government hospitals in Lahore. The data was collected through consecutive sampling from (15-08-2023 to 15-11-2023). A total of 109 prescriptions were collected. The data was analyzed using SPSS for statistical analysis. In a clinical trial involving patients aged between 26 and 30 years, 109 prescriptions revealed diverse levels of drug-drug interactions (DDIs), with 58 interactions documented. The majority of DDIs were classified as minor (21.1%) or moderate (15.6%), except for a single prescription containing severe DDIs. Benefits include comprehensive prescription evaluations and insights into potential hazards, while drawbacks may involve possible bias and challenges in FDA categorization. Overall, the study highlights the significance of assessing medications for pregnant women and enhancing prescription protocols.

Keywords: Rational use of drug, Drug-drug interaction, Contraindication, Pharmacotherapy, Pregnancy

Introduction

The rationale for the use of drugs during pregnancy requires a careful assessment, as it impacts not only the mother but also the health and life of her fetus [1, 2]. Potential drug-drug interactions (PDDIs) (can alter therapeutic efficacy, can involve adverse reactions) are one of the preventable drug-related problems having the risk of serious adverse events or therapeutic failure. In developing countries like Pakistan, this issue remains poorly addressed.

This study aimed to evaluate the patterns of drug prescriptions to pregnant women in tertiary care hospitals in Lahore, Pakistan. The drugs given to pregnant mothers for therapeutic purposes may cause serious structural and functional adverse effects in the developing child, that's why pregnant women are not included in clinical trials, resulting in limited information about the risks and safety of prescription drugs during pregnancy [3, 4]. Pharmaco-epidemiological studies (the study of interactions between drugs and human populations, investigating real conditions of life, benefits, risks, and use of drugs.) can measure the extent of prescription and teratogenic drug use in pregnant women. With this information, we intend to provide feedback and recommendations for the healthcare providers.

A woman's body undergoes major changes during pregnancy that can have an impact on many organs. Rational use of drugs has a lot of aspects and it is an important factor for developing countries that lack proper drug monitoring because improper medication puts the life at risk of both mother and the baby [5, 6].

Drug usage during pregnancy poses a significant physiological challenge for medical professionals, as it complicates the selection of appropriate medications due to

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pharmacokinetic and pharmacodynamic modifications. Additionally, some medications may harm the fetus once they cross the placenta [7].

Pregnant women often take prescription drugs, whether correctly or erroneously, to manage chronic diseases requiring continuous or intermittent treatment, such as asthma, hypertension, and epilepsy, as well as pregnancy-related disorders, potentially exposing the fetus to medications that could pose harm during gestation [8, 9].

Eight out of ten pregnant women report using drugs at least once; however, insufficient information is available to describe the fetal dangers associated with many routinely prescribed medications during pregnancy [10].

Prescription medicine use should generally be avoided during pregnancy. Avoiding all medications during pregnancy is unlikely, though, as this could put the mother and fetus at risk for complications from Untreated acute and chronic illnesses like bronchial asthma, diabetes mellitus, thyroid disorders, severe depression, and hypertension [11, 12]. Because of difficulties and chronic conditions, about 8% of pregnant women require continued medication treatment. In addition, medication treatments could be necessary for typical pregnancy-related problems such as constipation, anxiety, headaches, and respiratory infections. So, proper drug monitoring and prescription are required to avoid any kind of adverse effects that may be due to drug-drug interaction (a reaction between two (or more) drugs or between a drug and a food, beverage, or supplement) because of multiple medications. Prescription medicine during pregnancy is a difficult balance, with doctors taking the health of the mother and the fetus into account [5].

The discovery of diethylstilbestrol's teratogenic effects in 1971 and the thalidomide incidence in the 1960s highlighted the serious problem of medication usage during pregnancy. Subsequently, healthcare professionals have implemented proper guidelines to identify potential risks and contraindications, aiming to avoid the use of these medications in pregnant women. The FDA classifies drugs into five main categories (A, B, C, D, X), indicating their effect on the fetus based on data from both humans and animals and suggesting the level of precaution to be taken. Concerns regarding drug use during pregnancy have been raised globally since the discovery of birth abnormalities linked to thalidomide usage in early pregnancy.

The prevalence of drug-drug interactions (DDIs) was investigated through a comprehensive review of various articles, revealing distinct percentages across different countries. In Pakistan, research indicated that over one-third (37%) of women aged 15-49 encountered at least one maternal complication or morbidity before conception [13]. In the UK, approximately 2-3% of live births were associated with congenital anomalies. While exogenous factors, including drugs, contributed to only 1-5% of these cases (affecting <0.2% of all live births) [14, 15], it was emphasized that drug-associated malformations were largely preventable [1].

The current study set out to investigate the usage of prescription medications in pregnant women attending the outpatient departments (OPDs) of tertiary care hospitals, in Lahore, Pakistan for routine check-ups or due to specific medical conditions. The purpose of this study was to look into the drug use patterns and by analyzing the drug profile, determine potential drug interactions and contraindications, to ensure optimal mother and fetal health. The findings of our study can not only reduce the chances of irrational drug use during pregnancy but also guarantee enhanced knowledge about safe medication usage during pregnancy.

Materials and Methods

Study Design

This study is an observational cross-sectional descriptive approach coupled with analytical components. A Consecutive Sampling Technique was utilized. The sample size for this study was calculated using Rao Soft Formula [16] resulting in the approximate selection of 97 Prescriptions of Pregnant Ladies. A total of 143 samples were collected, and 34 samples were excluded based on exclusion criteria.

Study Setting

The study was conducted across various tertiary care hospitals including tertiary care hospitals located in Lahore, Punjab, Pakistan. The duration of our study was three months (15-08-2023 to 15-11-2023) during which the prescriptions were collected through the outpatient departments (OPD) of mentioned hospitals. Pregnant women from age 18 to 40 years, patients visiting the OPDs, and pregnant women in any trimester with or without any comorbidity were included. For pregnant women less than 18 and more than 40 years, single drug-containing prescriptions are excluded. Pregnant women who had incomplete medical records were also excluded.

Data Collection

Our study tool was the prescriptions of the pregnant ladies attending outpatient departments of hospitals. Our study focused on currently pregnant women attending the outpatient departments (OPDs) of a tertiary care hospital for routine check-ups or due to specific medical conditions. To collect information, the hard copies were used. These forms included a range of variables, like the women's age, gestational age, and the number and names of prescribed medications [17].

A detailed Excel spreadsheet was designed to organize the data that was collected in the forms, utilizing separate columns for each variable. Additionally, a dedicated column was created to document and classify drug-drug interactions (DDIs) based on their severity (Minor, Moderate, and Severe). To ensure accuracy and reliability, we used reputable online databases such as drugbank.com, drugs.com,

and Medscape for DDI identificatiom [18]. Drugs categorized as Class A and B, considered safe during pregnancy, were omitted from the spreadsheet, while Classes C, D, and X were highlighted. This comprehensive Excel sheet served as a secure repository and backup during subsequent data analysis. We analyzed trimesters, weight, age, and vitals including Heart Rate, Respiratory Rates, and Blood Pressure. We also analyzed their Blood Sugar, Hemoglobin, WBCs, and Platelets.

Statistical Analysis

Following the essential data refinement, an in-depth analysis was conducted employing the Statistical Package for Social Sciences (SPSS). Descriptive statistical methods were also used to compute the prevalence of drug-drug interactions. The outcomes were portrayed through graphical representations and tabulated formats, ensuring accessibility and clarity for enhanced comprehension.

Results and Discussion

Age-Based Analysis for Drug-Drug Interactions

In this study, a comprehensive analysis of 109 prescriptions collected from three diverse hospital settings was conducted. Patients were categorized based on age groups to discern any age-related patterns in prescription trends.

The distribution among distinct age groups showed these demographics: 10 patients (9.2%) fell below the age of 20, while 35 individuals (32.1%) were within the 20 to 25 age **(Table 1)**. A substantial portion, comprising 45 patients (41.3%), belonged to the 26 to 30 years demographic, while 14 individuals (12.8%) were aged between 31 to 35. Notably, a smaller subset of 5 patients (4.6%) were categorized in the 36 to 40 years range, rounding out the age distribution.

Table 1. Patient Demographics and DDI's Found

Age-Groups (Years)	No of Patients	Percentage (%)	Number of DDI's Found	Percentage of DDI's
<20	10	9.2	4	6.89
20-25	35	32.1	13	22.4
26-30	45	41.3	25	43.1
31-35	14	12.8	9	15.5
36-40	5	4.6	7	12
Total	109	100.0	58	100.0

A thorough analysis of prescriptions for pregnant women was conducted to identify potential drug-drug interactions (DDIs). The examination revealed the prevalence of these interactions across different age groups.

Among individuals aged less than 20 years, just 4 instances of DDIs were observed, constituting approximately 6.89% of the studied cases. In the age bracket of 20-25 years, the count to 13 cases, comprising around 22.4%. Furthermore, in the age ranges of 26-30, 31-35, and 36-40 years, the instances were recorded at 25 (43.1%), 9 (15.5%), and 7 (12%) respectively **(Table 1)**.

From **Figure 1**, Relation between Pregnant Patients and Their Age Groups, It is clear that most of the pregnant women were falling under the 26-30 years age group.

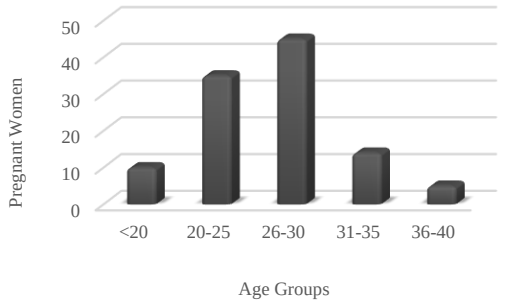

Figure 1. Relation between Pregnant Patients and Their Age Groups

Quantifying Prescribed Medications

The prescribed medications varied in quantity, ranging from a minimum of 2 to a maximum of 9 within the evaluated prescriptions. The study aimed to assess the frequency distribution of medications per prescription. Among the 109 patients evaluated, the analysis revealed that 17 individuals (15.6%) were prescribed only 2 medications, while 37 patients (33.0%) received 3 medicines. Furthermore, 30 women (27.5%) were prescribed 4 drugs, 11 patients (10.1%) received 5 medications, and 8 patients (7.3%) were prescribed 6 drugs **(Table 2)**. Additionally, 4 individuals received 7 prescribed medications, and a minimal 2 patients were found to be prescribed 9 medications, showing the diverse range in medication counts across the evaluated prescriptions.

Table 2. Quantifying Prescribed Medications

Number of Prescribed Medications	Number of Patients	Percentage (%)
2	17	15.6
3	37	33.9
4	30	27.5
5	11	10.1
6	8	7.3
7	4	3.7
9	2	1.8
Total	109	100.0

Assessment of Prescriptions for Drug-Drug Interactions Based on Severity Levels_ Minor, Major, and Severe

As shown in **Table 3**, 21.1 % of the prescriptions had minor DDI's, the percentage of moderate DDI's is 15.59% and severe DDI's were only present in 1% of prescriptions.

Table 3. Prescriptions Found with DDI's

Minor DDI's		Moderate DDI's		Severe DDI's	
Prescriptions	**Percentage (%)**	**Prescriptions**	**Percentage (%)**	**Prescriptions**	**Percentage (%)**
23	21.1	17	15.6	1	0.9%
Total Minor DDI's = 36		Total Moderate DDI's = 20		Total Severe DDI's = 2	

Upon thorough assessment, it was discovered that out of the 109 prescriptions, a noteworthy count of 36 minor drug-drug interactions (DDIs) was identified across 26 prescriptions While moderate DDIs were observed in 17 prescriptions, accounting for 20 distinct moderate interactions. Remarkably, only a solitary prescription exhibited a severe DDI, having 2 such interactions.

Assessment of Drug-Drug Interactions in Prescriptions for Pregnant Women

Upon evaluation, our study revealed that a significant majority, precisely 86 out of 109 prescriptions, exhibited no detectable minor drug-drug interactions(DDIs). However, among the remaining prescriptions, 14 cases (12.8%) revealed the presence of a single minor DDI, while 6 prescriptions (5.5%) showed the involvement of 2 minor DDIs. Furthermore, 2 prescriptions (1.8%) evidenced 3 minor DDIs, and remarkably, a solitary prescription (0.9%) displayed the occurrence of 4 distinct DDIs **(Table 4)**. This detailed analysis underscores the varying prevalence and scope of DDIs within the prescriptions reviewed.

As shown in **Table 4**, 86 of 109 prescriptions were found with no minor DDI (78.9%). 14 prescriptions were found with 1 minor interaction (12.8%). While 6 prescriptions were found with 2DDI's (5.5%), 2 with DDIs (1.8%), and 1 with 4 DDIs (0.9%). In the assessment of 109 prescriptions of pregnant women, a majority, constituting 84.4% (92 out of 109), were found to exhibit no moderate drug-drug interactions (DDIs). A smaller proportion, comprising 13.8% (15 prescriptions), displayed a singular moderate interaction. Intriguingly, minimal occurrences of multiple interactions were noted, with just 0.9% of each represented by a prescription containing two distinct DDIs and another featuring three separate DDIs **(Table 4)**.

A total of 92 prescriptions were found with no moderate DDI (84.4%). 15 prescriptions were found with 1 moderate interaction (13.8%). While just 1 prescription was found with 2 DDIs (0.9%) and 1 with 3 DDIs (0.9%).

As shown in **Table 4**, only 2 severe drug-drug interactions were found in 1 prescription (0.9%).

Table 4. Categorization of DDI's

Minor DDI's		Moderate DDI's		Major DDI's	
Number of Minor DDI's	**Number of Prescriptions Having Minor DDI's**	**Number of Moderate DDI's**	**Number of Prescriptions Having Moderate DDI's**	**Number of Major DDI's**	**Number of Prescriptions Having Major DDI's**
0	86	0	92	0	108
1	14	1	15	2	1
2	6	2	1		
3	2	3	1		
4	1				
Total	109		109		109

Contraindicated Drugs

The Overall ratio of potential risk of drugs used was low. As shown in **Figure 2**, Drug category groups are made and encoded. The "0" denotes prescriptions having no potential risk, the "1" denotes prescriptions containing category C drugs, and the "2" denotes prescriptions containing category D drugs. No category X drugs were found.

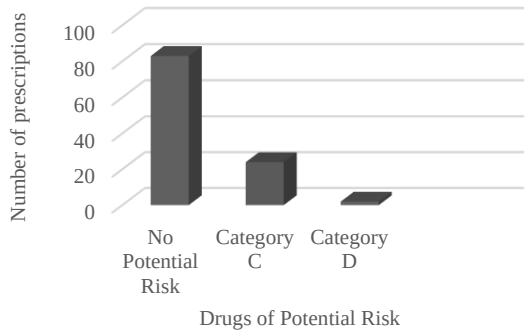

Figure 2. Drugs of Potential Risk

To check the rational use of drugs (RUD) and the safety of drugs in pregnancy is of prime importance as any wrong practice during prescribing or usage can cause potential harm to pregnant women and child. This study provides a good comprehension of drug-drug interactions and contraindications in pregnant women attending the OPDs of various tertiary care hospitals in Lahore, Punjab, Pakistan.

Many such studies have been conducted in Western countries [19, 20] but there is not enough data available in Pakistan, so this study has a contribution to fill that research gap. Moreover, usually, pregnant women are not included in clinical trials due to ethical or legal concerns [21] which has significantly hindered the accumulation of adequate data essential for ensuring the availability of safe and effective drugs during pregnancy, so drugs based on animal trials are used in pregnancy. This study evaluates the physical prescriptions of pregnant women rather than asking the patients about the drugs they have been using in the past months of pregnancy [22] which can lead to misunderstanding and biases. The results of this study show similarity with the prior literature [13].

We comprehensively analyzed the prescriptions for potential drug-drug interactions and contraindications to analyze them quantitatively based on their age. Almost half of DDIs 43% were found in the age group of 26 to 30 years then 22.4% of DDIs were seen in the age group of 20-25 years that may be due to the reason that the major number of patients visiting the OPDs lie in this age group and resultantly major number of prescriptions were collected from them. An assessment of several medications prescribed to the patients was analyzed which gave us the information that almost 34% of patients were prescribed 3 drugs that may be vitamin, iron mineral supplements, or any drug that was for treatment of any particular disease. Our analysis showed that most of the women were prescribed folic acid supplements. It is very important to differentiate drugs from supplements [23] that are often necessary during pregnancy to prevent complications and unsuccessful pregnancy outcomes. Iron deficiency anemia is the leading problem in pregnant women. World Health Organization, WHO estimates that 52% of pregnant women in developing countries like Pakistan are anemic. The iron stores are not being replenished due to poor iron intake, multiple pregnancies, or high requirement of iron during pregnancy [24, 25].

In our data, the number of medications ranged from 2 to 9. Although the percentage of patients receiving 9 medications was too low that was just 1.8%. Many women in the third trimester found visiting the hospital for the first time in the current pregnancy saying, “We did not feel the need”. It clearly shows a lack of awareness that can ultimately lead to complications, and to overcome that issue, doctors may prescribe multiple medications, and as previous literature shows a strong relationship between the number of drugs prescribed and potential drug-drug interactions [26].

The study examined the rationality of drug utilization, for diverse drug-drug interactions categorized by their severity—ranging from minor to severe interactions or contraindications. Our findings showed a total of 58 drug-drug interactions, encompassing minor, moderate, and major categories. Specifically, 23 prescriptions were identified with 36 minor interactions, while 17 prescriptions exhibited 20 moderate interactions. Alarming was the discovery of a single prescription entailing 2 severe drug-drug interactions (category D), bearing significant risks to both the mother and the developing fetus. These findings are nearly similar to a study conducted at a tertiary care hospital for the Prevalence of Potential Drug-Drug Interactions Among Hypertensive Pregnant Women Admitted to a Tertiary Care Hospital [27].

In 1979, the Food and Drug Administration categorized the drugs to check their safety in pregnancy. Category A and B drugs are considered safe in pregnancy and have failed to show any damage to the fetus. Animal studies did not show any risk for Category C drugs but due to lack of human studies, they can be used with benefit to risk ratio. Category D drugs have positive evidence of risk but may be used when the benefit outweighs the risk. While Category X drugs are contraindicated in pregnancy for teratogenic effects [28]. During analysis, FDA categories for all drugs were checked, no drugs of Category X were observed, 24 out of 109 prescriptions featured Category C drugs, 2 prescriptions contained drugs falling under Category D.

Some drugs are not contraindicated in the whole period of pregnancy but are not recommended in the first trimester especially 2nd and 3rd months, and are considered teratogenic because that time is considered very critical because cell differentiation and organ development start from 29th day of gestation. The main organ forming period lasts from 29th to 70th gestational day [12]. During analysis, we found some such drugs in the data that were prescribed to pregnant ladies including Spasfon (an antispasmodic medication) and tetracycline (an antibiotic) that may cause specific birth defects when used in first trimester [29]. We also found some drugs with serious potential risks with category D in 3rd trimester including Ibuprofen and Diclofenac Na, both are NSAIDs and can cause fetal

cardiovascular damage [30], but these drugs can be used with benefit to risk ratio [31].

Strengths and Limitations

Strength of this study is that it tries to fill the research gap of evaluation for DDIs and contraindications in pregnant women and highlights the ultimate need that there must be alternate to Category C and D medications available in pharmacies of tertiary care hospitals. The findings of this study will assist in the Rational Use of Drugs in pregnancy and will help the physicians to prescribe safer drugs. The limitation is that, as this study conducted across three tertiary care hospitals in Lahore, hence the results may not applicable to the prescription practices across other regions of Pakistan and biasness can also be there. Also, it is a cross-sectional study and data is collected at a single point time, hence, it cannot determine causes and effects of mentioned issues.

Conclusion

In conclusion, our study on pregnant women's prescriptions in Lahore's tertiary care hospitals revealed insights into drug-drug interactions (DDIs) and potential risks. Pregnant women, particularly those aged 26- 30, often received three medications. We observed varying DDI severities, with a notable but limited number of severe interactions. FDA category C drugs were prevalent, indicating potential risks. The study emphasizes the need for cautious prescribing during pregnancy. Despite limitations like hospital-specific data and brief duration, the findings underscore the importance of improving prescription practices for maternal healthcare and fostering awareness about safe drug use in pregnant.

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ETHICS STATEMENT: The research protocol was approved by the research and human ethics committee of UVAS Lahore. In addition, ethical permission from the concerned health care facility was also taken before proceeding with the data collection.

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