Prescription Analysis and Risk Category Assessment of Drugs Prescribed during Pregnancy in a Tertiary Care Center as per USFDA Classification

Kota Veena Bharathi¹, Keche Yogendra Narayanrao², Prasanta Kumar Nayak³, Gaikwad Nitin Rewaram² and Dhaneria Suryaparakash²

¹. Final Year MBBS Student, All India Institute of Medical Sciences, Tatibandh, Raipur 492099, India
². Department of Pharmacology, All India Institute of Medical Sciences, Tatibandh, Raipur 492099, India
³. Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, Tatibandh, Raipur 492099, India

Abstract: Objective: To carry out prescription analysis and assign risk category as per USFDA (United States Food and Drug Administration) to prescribed drug during pregnancy in a tertiary health care center at Raipur, Chhattisgarh. Method: This cross-sectional study was carried out over the period of 2 months in obstetric OPD (outpatient department) at tertiary health care center Raipur. Pregnant woman of any trimester was recruited from ANC (antenatal clinic) after obtaining informed written consent. Important information collected was demography, gravida, parity, trimester of pregnancy, reason for visit to clinic, history of any chronic illness, names of drugs prescribed with their doses and frequency of administration. Prescription analysis was carried out and USFDA risk category had been assigned to each of the drug. Results: Total 340 drugs were prescribed for 75 patients. And 51.43% pregnant women were from 3rd trimester of pregnancy. Most of pregnant women (92.86%) reported to OPD for regular ANC checkup. Prescription analysis shows that average number of drugs prescribed during pregnancy was 4.52 per prescription. Average FDCs (fixed dose combinations) prescribed were 1.64 per prescription. Vitamins and minerals FDCs (82.4%) were commonly prescribed FDCs. As per USFDA risk category, prescribed drugs were A (73.83%), B (18.82%), C (7.06%) and D (0.29%) respectively. Antimicrobials were prescribed in 25% pregnant women and commonly prescribed antimicrobial was nitrofurantoin (13.33%) for urinary tract infection. Conclusions: More than four drugs are prescribed in pregnancy. Drugs required to specifically treat associated health problems belong to category B which can be considered safe in pregnancy. Different class of drug though not labelled indication (off-label) needs to be prescribed as per treatment guideline to prevent the pregnancy loss and prevent post-partum complications.

Keywords: Risk category USFDA, Off label use of drug in pregnancy, Drug prescribing during pregnancy, Rational use of drug during pregnancy.

1. Introduction

Many times unnecessary drugs have been prescribed during pregnancy and that may have deleterious effect on foetus [1,2]. Chronic illnesses during the pregnancy may warrant the use of drugs during the pregnancy. Information on the use of drugs during pregnancy is scarce and rather anecdotal. Careful consideration of the benefit to the mother and the risk to the fetus is required when prescribing drugs during pregnancy [3]. USFDA (United States Food and Drug Administration) classified drugs used in pregnancy into five categories [4] A, B, C, D and X and recently on the basis of pregnancy, lactation, female and male reproductive potential called as Pregnancy and Lactation Labeling (Drugs) Rule [5].

A single intrauterine exposure to a drug can affect the fetal structures undergoing rapid development at the time of exposure. Thalidomide is an example of a drug that may profoundly affect the development of the limbs after only brief exposure [6]. In a
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In a retrospective study, it was found that the proportion of women dispensed a teratogen during pregnancy was substantially higher among women who received a teratogen in the 90 days before pregnancy compared to women who did not [7]. Sakhare and Mahale [8] and Das et al. [3] observed the use of more numbers of drugs, use of FDCs (fixed dose combinations) and prescribing drug by brand name in their study. There are no clear-cut guidelines for drug use during pregnancy in India, and guidelines are followed as per USFDA in India for risk category assignment [9].

Drug utilization studies for risk category drugs are lacking in India, and finding out indications for the use of these drugs in India is needed for prevention of adverse pregnancy outcome. It will be also helpful for adding labelling information of drugs, hence this study was planned.

2. Objectives

- To carry out prescription analysis of drugs prescribed during pregnancy.
- To assign risk category to the drugs prescribed during pregnancy.
- To find out associated disorders for which risk category drugs were prescribed during pregnancy in tertiary care center.
- To find out the compliance of prescribed drugs during pregnancy with WHO Model List of Essential Drugs [10] and National List of Essential Medicines [11].

3. Methodology

3.1 Study Design

Observational cross-sectional non-interventional study.

3.2 Study Period

Two months.

3.3 Study Site

ANC (antenatal clinic) clinic/Ward, Department of Obstetrics and Gynaecology and Department of Pharmacology, tertiary health care center, Raipur.

3.4 Inclusion Criteria

1. Pregnant woman who will be attending the tertiary health care center, Raipur;
2. Pregnant woman of any trimester (1st/2nd/3rd).

3.5 Exclusion Criteria

1. High risk pregnancy
2. Elderly primigravida (1st time pregnant woman at the age of 35 years or more)
3. Pregnant woman requiring special care

It was a non-interventional cross-sectional study. Data from the prescriptions of pregnant women visiting ANC OPD (outpatient department) were collected with the help of semi-structured questionnaire. Written informed consent was obtained from each of the study participants. After explaining about the study procedure with patient information sheet, information was collected in the Case Record Form cum Questionnaire.

3.6 Information Collection in the Case Record Form cum Questionnaire

Age, weight, education level, occupation, monthly income, gravida, parity, trimester of pregnancy, number of visits to ANC clinic, reason for visit to clinic, history of any chronic illness, names of drugs prescribed during visit with their doses and frequency of drug administration, diagnosis for the drug prescription and information of ADRs to risk category drug if any were noted during the therapy.

Risk category was assigned to prescribed drug with the help of different drug indices of marketed drugs and with the help of USFDA guidelines as well as USFDA and Central Drug Standard Control Organisation CDSCO website and National Formulary of India 2016 [9].

Risk category of the drug will be based on the USFDA classification [4] (Table 1) and Pregnancy and Lactation Labeling (Drugs) Rule [5] (Table 2).
Compliance of the prescribed drugs in ANC OPD with National List of Essential Medicines of India (2015) [11] and WHO Model List of Essential Medicines 21st list (2019) [10] was studied.

3.7 Sample Size and Statistical Analysis

Data collected in 2 months for the 75 patients, hence were final sample size for this study. Statistical analysis was carried by using Microsoft excel and OpenEpi software.

4. Results

Total 340 drugs were prescribed for 75 patients. And 51.43% pregnant women were from 3rd trimester of pregnancy. Most of pregnant women(92.86%) reported to OPD for regular ANC checkup. Prescription analysis shows that the average number of drugs prescribed during pregnancy was 4.52 per prescription; 70% single drugs and 39% FDCs prescribed during pregnancy were in compliance with both WHO 2019 and India 2015 National List of Essential Medicines (Table 3). Cholecalciferol and inj hCG are the two drugs included in National Essential List of Medicines, India 2015 [11] but not in WHO Model List of Essential Medicines 2019.

Average FDCs prescribed were 1.64 per prescription (Table 3). Vitamins and minerals FDCs(82.4%) were commonly prescribed FDCs. As per USFDA risk category, prescribed drugs were A(73.83%), B(18.82%), C(7.06%) and D(0.29%) respectively (Table 4). Hypothyroidism (20 patients) and Hyperemesis gravidarum (18 patients) and urinary tract infection (10 patients) were the common clinical conditions for which these patients were visited ANC OPD (Table 5). Low dose aspirin and enoxaparin in 2 patients, ursodeoxycholic acid in 1 patient, tranexamic acid in 1 patient and arginine in 3 patients was prescribed (Table 6).

Antimicrobials were prescribed in 25% pregnant women and commonly prescribed antimicrobial was nitrofurantoin(13.33%) for urinary tract infection.

5. Discussion

Seventy percent (70%) single drugs and 39% FDCs prescribed during pregnancy were in compliance with both WHO 2019 [10] and India 2015 [11] National List of Essential Medicines.

Cholecalciferol and inj hCG are the two drugs included in National List of Essential Medicines, India 2015 [11] but not in WHO Model List of Essential Medicines 2019 [10].

Low dose aspirin and enoxaparin was prescribed in 2 patients to avoid pregnancy loss due to antiphospholipid syndrome. Combination treatment of aspirin and LMWH leads to a high live birth rate among women.
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Table 2  Revised Food and Drug Administration risk categories of drugs during pregnancy [5]

| S.No. | Risk categories | No. (%) of patients |
|-------|-----------------|---------------------|
| 1     | A              | 251 (73.83)         |
| 2     | B              | 64 (18.82)          |
| 3     | C              | 24 (7.06)           |
| 4     | D              | 1 (0.29)            |
| 5     | X              | 0 (0)               |

8.1 Pregnancy category includes labour and delivery will deal with information pertaining to the use of drugs in pregnant women, like dosing and probable risks to the developing fetus, and also information about whether there is a registry that collects and maintains data on the effects of the drug or biological product on pregnant women.

8.2 Lactation category includes nursing mothers will consist of information about using medications during breastfeeding, such as the amount of drug secreted in breast milk and possible effects on the breastfed child.

8.3 Females and males of the reproductive potential category will provide data about pregnancy testing, contraception, and about infertility as it relates to the drug.

Table 3  Demographic characteristics of the study participants

| S.No. | Parameter                   | No. (%)          |
|-------|-----------------------------|------------------|
| 1     | Average age (years)         | 26.74            |
| 2     | Primigravida                | 43 (57.33)       |
| 3     | Multigravida                | 32 (42.67)       |
| 2     | Total number of drugs prescribed | 340 (100)     |
| 3     | Single drug prescribed      | 218 (64.12)      |
| 4     | Single drugs from WHO EML (2019) | 151 (49.27)  |
| 5     | Single drugs from NELM 2015 India | 154 (70.64)  |
| 6     | FDCs prescribed             | 122 (35.88)      |
| 7     | FDCs from WHO EML (2019)    | 47 (38.52)       |
| 8     | FDCs from NELM 2015 India   | 47 (38.52)       |
| 9     | Average number of drugs per prescription | 4.52     |
| 10    | Average number of FDCs per prescription | 1.64     |

Table 4  Risk categories of drugs prescribed during the pregnancy

| S.No. | Risk categories | No. (%) of patients |
|-------|-----------------|---------------------|
| 1     | A               | 251 (73.83)         |
| 2     | B               | 64 (18.82)          |
| 3     | C               | 24 (7.06)           |
| 4     | D               | 1 (0.29)            |
| 5     | X               | 0 (0)               |

Table 5  Common health problems for which drugs were prescribed during the pregnancy

| S. No. | Health problem                        | Number of patients |
|--------|---------------------------------------|--------------------|
| 1      | Urinary tract infection               | 13                 |
| 2      | Hyperemesis gravidarum                | 18                 |
| 3      | Hypothyroidism                        | 20                 |
| 4      | Diarrhoea                             | 2                  |
| 5      | Gastritis                             | 9                  |
| 7      | Vaginal local infection               | 5                  |
| 8      | Upper respiratory tract infection     | 10                 |

Table 6  Off label use of drug during the pregnancy

| S.No | Name of the drug                  | No. of patients | Off Label Indication for the use of drug during pregnancy |
|------|-----------------------------------|----------------|----------------------------------------------------------|
| 1    | Low dose aspirin & enoxaparin     | 2              | Antiphospholipid antibody syndrome                        |
| 3    | Urodeoxycholic acid               | 1              | Pruritus                                                  |
| 4    | Tranexamic acid                   | 1              | Post-delivery blood loss                                  |
| 5    | Arginine                          | 3              | Oligohydramnios                                          |
with recurrent miscarriage and antiphospholipid antibodies. This combination promotes successful embryonic implantation in early stages of pregnancy & protects against thrombosis of uteroplacental vasculature after successful placentation[12].

Arginine was prescribed to 3 patients for oligohydramnios. L-arginine supplementation is promising in improving volume of amniotic fluid in cases of oligohydramnios and prolonging pregnancy by a mean of 2.4 weeks, allowing fetal lung maturation thus benefiting the neonatal outcome [13].

Urodoxycholic acid was prescribed in 1 patient for pruritus caused by cholestasis. Urodoxycholic acid is effective and safe in patients with intrahepatic cholestasis of pregnancy of early onset, attenuating pruritus and correcting some biochemical abnormalities in the mothers. Relevant aspects of fetal outcome were also improved in patients receiving urodoxycholic acid [14].

Tranexamic acid was prescribed to 1 patient to reduce amount of post-delivery blood loss. Clinical studies suggest that tranexamic acid reduces the amount of blood loss after delivery during cesarean sections and vaginal deliveries, and reduces the requirement for blood transfusion. Tranexamic acid seems to be safe and effective in the prevention and management of bleeding during pregnancy[15].

6. Limitations of Study

Sample size was too small, hence further research is needed in this area. We did not get data of new USFDA risk classification based on pregnancy, lactation, female and male reproductive potential called as Pregnancy and Lactation Labeling (Drugs) Rule [5]. Hence we could not categorize as per new rule.

7. Conclusions

More than four drugs are prescribed in pregnancy and 70% of prescribed drugs were in compliance with WHO and National Essential Medicines List of India. FDCs prescribed mostly of vitamins and minerals. Drugs required to specifically treat associated health problems belong to category B which can be considered safe in pregnancy. Different class of drug though not labelled indication (off-label) needs to be prescribed as per treatment guideline to prevent the pregnancy loss and prevent post partum complications.

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