www.jmscr.igmpublication.org
Impact Factor (SJIF): 6.379
Index Copernicus Value: 71.58
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossrefDOI: https://dx.doi.org/10.18535/jmscr/v6i7.91

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Drug safety in pregnancy: Assessment by FDA Safety Rating system and WHO prescribing Indicators

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Abstract
Objectives: *To determine the safety, extent of drug use, management of diseases in pregnancy with regard to the WHO prescribing indicators and US FDA safety rating system.*
Methodology: *A prospective observational study was conducted in St James Hospital, Chalakudy, Thrissur by collecting inpatient's medical data in the obstetrics and gynaecology departmentover 100 patients for a period of 6 months. Datas were collected by using "Patient data collection proforma" and results were statistically analysed by Pearson chi square test and simple graphical methods.*
Results: *Majority of the drugs are Category B(50.9%) and C (33.4%).The average number of drugs per prescription was 5.74 (polypharmacy) and percentage of encounters with injections and antibiotics were 76% and 44% respectively.*
Conclusion: *Drug use was safe and rational as per FDA safety rating and WHO prescribing indicators except for high incidence of Category C drugs, polypharmacy, and increased number of antibiotics and injection per prescription.*
Keywords: *Pregnancy, US FDA safety rating system, PIH ,GDM, Pregnancy trimesters, WHO indicators.*

Introduction

Pregnancy is a special physiological condition where drug treatment presents a special concern. Careful consideration of the benefit to the mother and the risk to the foetus is required while prescribing drugs during pregnancy[1]. During pregnancy; your body goes through many emotional and physiological changes. Fertilization and early embryo formation cause significant changes in all of your body's systems. This is how your body prepares and helps the pregnancy develop into successful childbirth.

Common conditions encountered in pregnancy involves anaemia, gestational diabetes (GDM), hyper emesis gravidarum (HEG), urinary tract infections (UTI), preeclampsia, pregnancy induced hypertension(PIH), thyroid disorders etc. It requires the initiation of the therapy, based on the drug characteristics such as molecular weight ionization, lipophilicity, degree of protein binding[2].

In 1979, the United States Food and Drug Administration (FDA) introduced a system of rating pregnancy-risk associated with pharmacological agents, which categorized all drugs approved after 1983 into one of five pregnancy risk categories (A, B, C, D, and X)[3.] Category A includes drugs having no risk to the foetus in the first trimester whereas Category B showing no risk in animal studies and lack human studies. Category C &D produce adverse effect on animal and humans respectively, but can be used when potential benefit outweigh the risk. In 2015 the FDA replaced the former pregnancy risk letter into Thee Pregnancy and Lactation Labeling Final Rule (PLLR) which is being implemented.

Materials and Methods

A prospective observational study was conducted in the department of obstetrics and gynaecology at a tertiary care hospital (St. James Hospital, Chalakudy, Thrissur) by collecting data from the medical records of inpatients in the obstetrics and gynaecology department for a period of 6 months over 100 pregnant patients.

Inclusion Criteria

- Pregnant women admitted in the department of the obstetrics and gynecology was included in the study.

Exclusion Criteria

- Abortion
- Pregnant women who visited OP department of Obstetrics and gynecology

All the necessary and relevant baseline information for the study was collected using a self-designed "Patient data collection proforma", which includes patient demographics, disease status and the drugs prescribed during pregnancy.

Statistical Analysis

The results in the study are expressed by Mean ± SD and the statistical analysis were done by using Pearson Chi Square test and graphical methods.

Results

In our study a total of 100 patients were selected and categorised on the basis of their age, pregnancy trimesters, comorbid conditions.

Table: 1: Distribution of Cases According to age group.

Age	No. of Patients	Percentage
18-24	30	30 %
25-30	42	42%
31-36	20	20%
37-42	8	8%
Total	N =100	100%

According to the table, out of 100 patients majority of them were in the age group of 25-30 and the minority were in 37-42 group.The mean age was represented as 30.375± 5.62.

Table 2: Distribution based on comorbid conditions in pregnancy

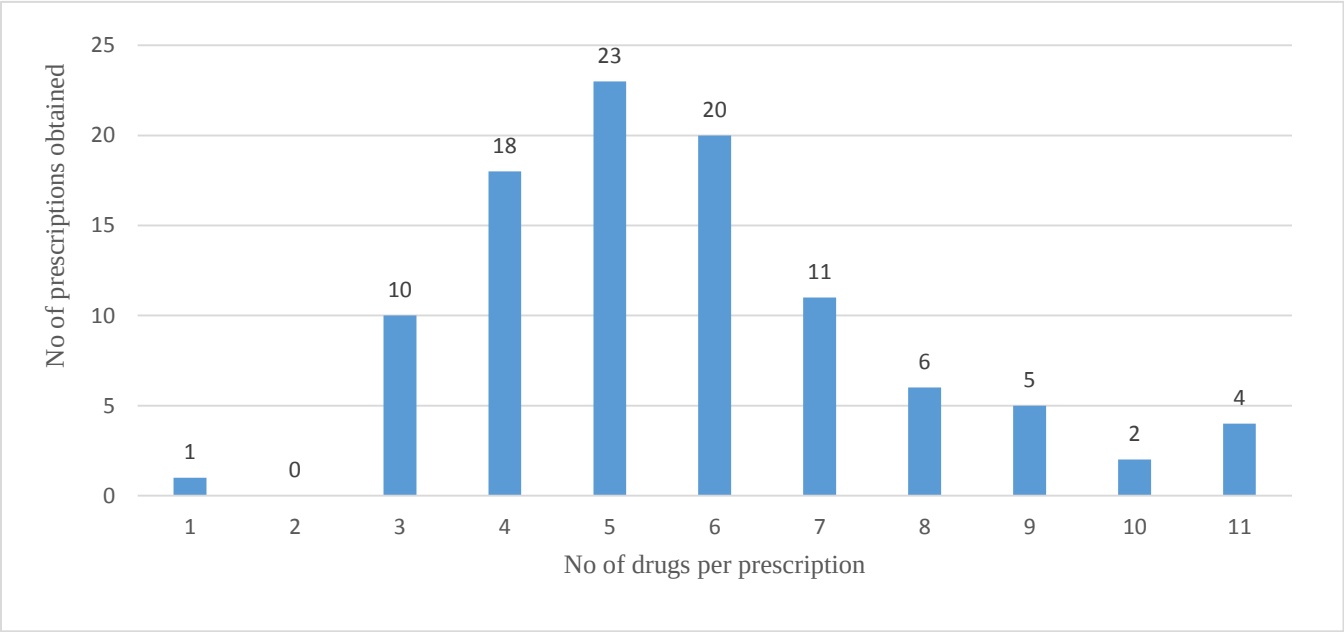
Sl.No	Comorbid conditions	No of cases
1	Gestational diabetes mellitus	22
2	Pregnancy induced hypertension	12
3	Urinary tract infection	14
4	Others	52

Gestational diabetes mellitus was the most commonly occurring (22) followed by pregnancy induced hypertension (12), hyperemesis gravidarum (15), Urinary tract infections (14) and others(52).

Table 3: Distribution based on the number of drugs appearing in a prescription

No of drugs per prescription	No of prescriptions obtained
1	1
2	0
3	10
4	18
5	23
6	20
7	11
8	6
9	5
10	2
11	4

Figure 1: Distribution based on the number of drugs appearing in a prescription



The prescriptions were having drugs ranging from a single to 11in numbers. Those having 5 number of drugs were found maximum, followed bythe numbers 6 and 4, while the one having 2 drugs were minimum.The average number of drugs per prescription was found to be 5.72 ± 2.045. The datas are expressed in the Table (3), and Figure (1).

Table 4 : Distribution based on the categorisation of drugs

Category	Name of drugs
A	Folic acid, Iron, Levothyroxine Sodium, Omega -3-fatty acids, Pyridoxine
B	Methyldopa,Cefotaxime,Metronidazole,Paracetamol,Cefuroxime, ondansetron,Loratidine,Ranitidine,pantorazole,Metoclopramide,Dicyclomine, Monteleukast+Levocetrizine,Amoxicillin,Ampicillin,Cefixime,Progesterone,Metformin,Insulin,Phenazopyridine,Disodiumhydrogencitrate,Cinnarizine,Cefalexin,Nitrofurantoin,Pethidine,Rabeprazole,Ceftriaxone,Lactulose,Cetrizine Flavoxatehydrochloride,Esomeprazole,Bisacodyl,Cefpodoxime,Tranexamic acid, Cefoperazone+Sulbactum, Dydrogesterone, Azithromycin
C	Labtetolol,Calcium,MVT,Aspirin,TT,DNS,Promethazine, CPM+Phenylephrine, Theophylline+Etophylline, Hyoscine butyl bromide, Tramodol, Pentazocine, Trisodium citrate dihydrate, Fuscidicacid, Levofloxacin, Isoxsuprine, Clotrimazole, RL,Dexamethasone,Terbutaline,Levosalbutamol+Ipratropiumbromide,Codeine, Dextromethorphan, Heparin, Mefenamic acid, Aminoacids, NS, Betamethasone, Oseltamivir, Xylometazoline ,Simethicone, ambroxol, Omepraole, Levosulpiride, Nifedipine, Fluconazole, Norfloxacin, Ketorolac, Mebendazole, Budesonide, Salbutamol, Glimipiride
D	Diazepam, Alprazolam, Neomycin, Diclofenac, Propylthiouracil, Sodium valproate
X	Diethyl carbamazepine
Not Specified	Lactobacillus

Table 5: Categorisation of drugs on FDA pregnancy risk category and trimesters

Pregnancy Category	First trimester	Second trimester	Third trimester	P value
A	26	14	19	0.1565
B	92	83	117	0.0412
C	48	61	83	0.0075
D	7	5	12	0.1969
X		1		-
Not specified			6	-

As per the table, pregnancy category of drugs were compared for their distribution across various trimesters. It showed the category B & C to be significant that B drugs are commonly prescribed in the first and third trimester and C drugs on second and third respectively.

Drug distribution based on management of diseases

Table 6: Urinary tract infection

Drugs	Category	No. of prescriptions	Percentage (%)
Cefotaxime	B	20	39.2
Metronidazole	B	15	29.3
Flavoxate Hydrochloride	B	6	11.8
DHC	B	6	11.8
Levofloxacin	C	1	2.0
Nitrofurantoin	B	2	3.9
Norfloxacin	C	1	2.0

Cefotaxime (39.2%) was the mostly prescribed drug for urinary tract infections followed by Metronidazole (29.3%), Flavoxate. Hcl (11.8%), DHC (11.8 %), Nitrofurantoin (39%),and Norfloxacin(2%).

Distribution based on WHO prescribing pattern

As per the Table9, average number of drugs per prescription was found to be 5.74 and percentage of antibiotics and injections were 44% and 76% respectively, elevated from the normal suggested by WHO. The common prescribed antibiotics includes Cefotaxime (29.9%), Amoxicillin(17.9%), Ampicillin (10.3%),Ceftriaxone (11.9%) etc.and the least prescribed was oral cephalexin(1.5%).The percentage of drugs prescribed by generic name was (13.8%) and percentage of drug from hospital formulary were (99.5%),which were found to be rational as advised by the WHO.

Table No 7: WHO prescribing indicators for the assessment of drug use pattern

Prescribing Indicators	Total drugs	Value
Average number of drugs per encounter	574	5.74
Percentage of encounter with antibiotics	67	44%
Percentage of encounter with injections	196	76%
Percentage of drugs prescribed by generic name	79	13.8%
Percentage of drug from hospital formulary	571	99.5%

Discussion

In our study, a total of 100 pregnant patients were selected, to assess the medical management of comorbid conditions in pregnancy and to evaluate the prescribing pattern with respect to the WHO prescribing indicators.

A total of 574 drugs were prescribed among 100 pregnant women. The age of patients ranged from 18-42 years. Majority of the patients in the study were in the age group 25-30 years (42%), which represents the normal reproductive age group followed by 18-24 years (30%), 31-36 years (20%) and 37-42 years (8%). The mean age was represented as 30.375± 5.62.It is represented in (Table 1). In the study most of the women were in the third trimester (37%), while 27% were in the first trimester, and 26% were in the second trimester, who visited the antenatal care department which is likewise to the study by Prasanand Sasidharan et al[4] in which most of the women (41.67%) were in the third trimester, while 31.94% were in the first trimester, and 26.39% were in the second trimester who visited the antenatal care department.

The pattern of medical conditions obtained in this study (GDM, PIH, UTI, Others (HEG, anemia, thyroid disorders etc.) varied with those reported in a study performed by Das B et al[5]where problem oriented drug use was mainly due to gastrointestinal tract problems (nausea and vomiting, dyspepsia), and vaginal spotting/ bleeding represented in (Table 2)

Among 100 prescriptions, majority of prescriptions contained 5 drugs (23) followed by 6 drugs in 20

prescriptions. The average number of drugs per prescription was found to be 5.72± 2.045.(Table-3) (Figure-1).

The antibiotics accounting for n=67, wherein the most commonly prescribed drugs were cefotaxime (29.9%), followed by amoxicillin (17.9%) and the least prescribed was oral cephalexin(1.5%).

In our study majority of drugs were prescribed from category B (50.9%) followed by category C(33.4%), category A (10.3%), category D (4.2%) ,category X(0.2%) and 1.0% of drugs with category not specified which is similar to the study conducted by Shailesh Yadav et al[6]. Category B drugs to be safe differ from C, that C drugs are advised only when benefit outweigh the risk. The distribution pattern across various trimesters were analysed by Pearson Chi square test and was arrived with a "P value" of 0.0412 and 0.0075- significant with a level of significance (α - 0.05).It implies that B drugs are commonly prescribed in the first and third trimester and C drugs on second and third respectively.The distribution of individual drug based on FDA risk category is listed in Table (4).

Majority of the patients admitted for UTI was treated with Cefotaxime (20) and Metronidazole (15) and the least prescribed drugs were Levofloxacin (1) and Norfloxacin (1). were cephalosporins are the first line choice.

The average number of drugs per prescription in this study (5.74) was higher than the range of the standard set by WHO (1.6-1.8) The prescribing indicators had shown that percentage of prescribed injections and antibiotics were 76 % and 44% which were greater when compared to the standard set by WHO (13.4-24.1) and (20.0-26.8) respectively. 13.8% of drugs were prescribed by generic name and the standard reference value was 100%. Percentage of drugs prescribed from hospital formulary was 99.5% showing adequate drug dispensing from the hospital pharmacy.

Conclusion

The drug utilization pattern was almost rationaland safe except for prescribing injections, antibiotics and the case of polypharmacy Pregnant women with diseases like UTI were continued with appropriate drugs with a wide range of category B drugs in I, III and C drugs in II,III trimesters, considering the risk benefit ratio.Special attention should be given to the opportunities of prescribing generic medicines. Usage of category B drugs must be reduced, and complete avoidance of category D and X drugs is advised.

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