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ASSESSMENT OF DRUG UTILIZATION PATTERN AND TERATOGENICITY RISK AMONG PREGNANT WOMEN ATTENDING A TERTIARY CARE HOSPITAL, ANDHRA PRADESH

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ABSTRACT: Objectives: The aim of this study was to assess the drug utilization pattern and teratogenicity risk among pregnant women attending a tertiary care hospital, Andhra Pradesh. **Materials and Methods:** A cross-sectional observational study was carried out on antenatal women (total=1163) more than 18 years of age attending the antenatal clinic of Obstetrics and Gynaecology (OBG) Department. Demographic and pregnancy-related details were collected in case-record forms. Each prescription prescribed was assessed as per USFDA (United States Food and Drug Administration) categorization of drugs for use in pregnancy and WHO (World Health Organisation) core prescribing indicators. The resultant data was analyzed using MS Excel 2007 and the Statistical Package for Social Sciences (SPSS) statistical software, version 21. Qualitative variables were expressed as percentages and Inter-group comparison was done using Chi-square test. For all statistical analysis, $p<0.05$ was considered statistically significant. **Results:** Of the total number of drugs used, Category A drugs were the most common (75.5 %) followed by Category B (17.5 %), Category C (5.28 %), Category D (1.55 %) and Category X (0.17 %) respectively. Category B and Category C drugs were given more commonly in IPD (Inpatient Department) patients than OPD (Outpatient Department) patients respectively. **Conclusion:** The present study revealed that as there has been usage (though less) of Category D and X drugs in pregnant women, chances of teratogenicity cannot be ruled out in the offsprings. Also, medications should be prescribed in accordance with WHO indicators to ensure rational drug therapy.

INTRODUCTION: Prescribing medications in pregnancy requires utmost diligence. Certain medications may cause harm to the foetus due to their (of the drugs') potential teratogenic effects and the physiological adjustments occurring in the mother during pregnancy.[1]

Events such as the Thalidomide crisis in the 1960s and teratogenic effects related to the use of Diethylstilboestrol in 1971 have invoked the concern on the use of medications in pregnancy. Such events led the United States Food and Drug Administration (USFDA) to form strict regulations pertaining to the usage of medications in pregnancy.[2] Drugs taken during pregnancy to treat a disorder or symptom accounts for approximately 2-3% of all birth defects.[3] As per USFDA categorisation of drugs for use in pregnancy, Category D or Category X drugs cause harmful and/or teratogenic effects in foetus.[4]

A study [5] conducted in USA showed that 5.8% of pregnant women received USFDA category D or Category X drugs. A study by Sharma R *et al.,*[1] conducted in North India showed that 6% and 5.71% of the drugs used in the first trimester of pregnancy belonged to category D and category X group of drugs respectively. Irrational use of drugs is an important issue in modern medical practice; it can lead to consequences such as improper treatment, adverse and/or teratogenic effects, increased economic burden on the pregnant women, etc.

Hence, pharmacoepidemiological studies are conducted, which provide valuable information on the existing medication usage pattern and also help in planning appropriate options for medications in pregnancy. [6]

The present study has been undertaken to assess the pattern of usage of medications in pregnancy to observe possible teratogenicity risk, which will assist in ensuring rational drug therapy and hence reducing the occurrence of adverse or harmful effects of drugs.

MATERIALS AND METHODS: This was a cross-sectional observational study conducted at a tertiary care hospital in Rajahmundry, Andhra Pradesh, India, from January to March, 2017, after obtaining approval from the Institutional Ethics Committee.

The study participants consisted of antenatal women more than 18 yrs of age, attending the antenatal clinic of Obstetrics & Gynaecology (OBG) Department of the said hospital; the participants were selected using Stratified Random Sampling method. Antenatal women who attended the Outpatient Department (OPD) for antenatal checkups and those who were admitted during their antenatal period (IPD) were included in the study; those who were less than 18 yrs of age and those not willing to participate were excluded from the study.

After detailed explanation of the nature and purpose of the study (in local language), a total of 1163 pregnant women were included; written, informed consents were taken from the study participants before enrolling them in the study.

Demographic details (age, occupation, educational status) and pregnancy-related details (term of pregnancy, gravida, time of first Antenatal checkup or ANC, total number of ANCs) along with existing medical illness, if any, were noted in case record forms.

Medication details such as name of the medications, their dosage, route of administration, frequency of drug administration, duration of usage, number of drugs used per subject, etc. were also recorded. Each prescription given to the participant was analysed according to USFDA categorisation of drugs for use in pregnancy [4] and World Health Organization (WHO) core prescribing indicators [7].

In order to preclude any potential bias, the disclosure of name of the responder was made optional. The obtained data was analyzed by using MS excel 2007 and SPSS software version 21. Qualitative variables were expressed as percentages and Inter-group comparison was done using Chi-Square test. For all statistical analysis, $p<0.05$ was considered statistically significant.

RESULTS: Out of 1163 pregnant women, 1008 (86.67%) were from OPD (OPD participants) and 155 (13.33%) were from IPD (IPD participants).

Table 1 shows the demographic and pregnancy-related details of the study participants. The mean age of OPD subjects was 21.78 ± 2.56 years while that of IPD participants was 22.15 ± 2.91 years. 69.22 % of total (OPD and IPD) study subjects were between 21 to 25 years of age. As far as occupation was concerned, only 6.45 % of all the participants were working women. Regarding the educational status of the antenatal women (total) concerned, most of them (41.7%) had completed secondary level of education. 42.56% of the total number of participants presented during the third trimester of pregnancy.

Of all the study subjects, 62.25% of antenatal women presented as primigravidae. 49.96% of the total number of study participants attended for first ANC during their first trimester. Most of the pregnant women (57.18%) had completed more than 5 ANCs.

TABLE 1: DEMOGRAPHIC AND PREGNANCY-RELATED DETAILS OF THE STUDY PARTICIPANTS

Variable	Number of OPD subjects n (%)	Number of IPD subjects n (%)
Age (in years)		
< 20	191 (18.95)	23 (14.84)
21-25	703 (69.74)	102 (65.81)
26-30	102 (10.12)	26 (16.77)
>30	12 (1.19)	4 (2.58)
Occupation		
Housewife:	947 (93.95)	141 (90.97)
Working women:	61 (6.05)	14 (9.03)
Educational status		
Primary	193 (19.15)	30 (19.35)
Secondary	423 (41.96)	62 (40)
Higher secondary	342 (33.93)	54 (34.84)
Degree and above	50 (4.96)	9 (5.81)
Term of pregnancy		
First Trimester	302 (29.96)	49 (31.61)
Second Trimester	276 (27.38)	41 (26.45)
Third trimester	430 (42.66)	65 (41.94)
Gravida		
Primigravidae	626 (62.1)	98 (63.23)
Multigravidae	382 (37.9)	57 (36.77)
Time of first ANC		
First Trimester:	504 (50)	77 (49.68)
Second Trimester:	434 (43.06)	65 (41.93)
Third trimester:	70 (6.94)	13 (8.39)
Total number of ANCs		
<3	141 (13.99)	24 (15.48)
3 to 5	292 (28.97)	41 (26.45)
>5	575 (57.04)	90 (58.07)

n- Number of subjects, OPD – Outpatient Department, IPD – Inpatient Department, ANC – Antenatal checkup

Table 2 shows the commonly associated medical illness present among the study subjects; gastritis (6.75%) and urinary tract infection (12.26%) were the most commonly found associated illness among the OPD and IPD subjects respectively.

TABLE 2: COMMONLY ASSOCIATED MEDICAL ILLNESS PRESENT IN THE STUDY POPULATION

Commonly associated medical illness in study participants			
In IPD		**In OPD**	
	n (%)		n (%)
Urinary Tract Infection	19 (12.26)	Gastritis	68 (6.75)
PregnancyInduced Hypertension	17 (10.97)	Hypothyroidism	33 (3.27)
Gastritis	16 (10.32)	Hypertension	30 (2.98)
Gestational diabetes	12 (7.74)	Bronchial asthma	11 (1.09)
Diarrhoea	10 (6.45)	Diabetes Mellitus	8 (0.79)
Malaria	9 (5.81)	Epilepsy	7 (0.69)
Upper Respiratory tract Infection	8 (5.16)	---	---
Hyperemesis graviduram	8 (5.16)	---	---
Severe anaemia	8 (5.16)	---	---

OPD-Outpatient Department; IPD-Inpatient Department; n-Number of cases

Table 3 shows the USFDA categorization of the various types of drugs used by these antenatal women. Category A drug was the most commonly used drug and it consisted of 76.18 % and 71.25 % of the total number of drugs used in OPD and IPD subjects respectively. On the other hand, Category B, Category C drugs Category D and Category X drugs belonged to 17.5 %, 5.28 %, 1.55% and 0.17 % of the total number of drugs used (including OPD and IPD) during pregnancy respectively.

TABLE 3: USFDA CATEGORIZATION OF DRUGS USED IN ANTENATAL WOMEN

Category of Drugs		1st Trimester n (%)	2nd Trimester n (%)	3rd Trimester n (%)	p-value
A	OPD	536 (80.84)	674 (76.16)	1074 (74.07)	
	IPD	85 (75.22)	98 (70)	164 (70.1)	p=0.86
B	OPD	97 (14.63)	159 (17.97)	266 (18.34)	
	IPD	18 (15.93)	25 (17.86)	45 (19.23)	p=0.88
C	OPD	20 (3.02)	35 (3.95)	92 (6.35)	
	IPD	5 (4.42)	11 (7.86)	21 (8.97)	p=0.75
D	OPD	9 (1.36)	16 (1.81)	18 (1.24)	
	IPD	3 (2.66)	4 (2.85)	4 (1.7)	p=0.89
X	OPD	1 (0.15)	1 (0.11)	0 (0)	
	IPD	2 (1.77)	2 (1.43)	0 (0)	---

OPD-Outpatient Department; IPD-Inpatient Department; n- number of drugs; p<0.05 is considered statistically significant

Table 4 shows the categorization of drugs prescribed according to various WHO core prescribing indicators. Percentage of drugs prescribed as per the generic name during the total antenatal period of pregnancy were 95.1% and 94.46% among OPD and IPD participants respectively. Percentage of encounters with antibiotics and injections during pregnancy were higher in IPD subjects (23.61% and 19.92% respectively). Average number of drugs per prescription was 3.14 in IPD subjects and 2.97 in OPD subjects.

TABLE 4: WHO CORE PRESCRIBING INDICATORS AS ASSESSED FROM THE PRESCRIPTIONS

Indicators	OPD/IPD	1ST Trimester Value n (%)	2ND Trimester Value n (%)	3RD Trimester Value n (%)	Total Value n (%)	Reference Value (as per WHO)
Percentage of drugs prescribed by generic name	OPD	636/663 (95.93%)	834/885 (94.24%)	1381/1450 (95.24%)	2851/2998 (95.1%)	100
	IPD	106/113 (93.81%)	132/140 (94.29%)	222/234 (94.87%)	460/487 (94.46%)	
Percentage of encounters with antibiotic prescribed	OPD	127/663 (19.16%)	186/885 (21.02%)	335/1450 (23.1%)	648/2998 (21.61%)	20-26.8
	IPD	24/113 (21.24%)	32/140 (22.86%)	59/234 (25.21%)	115/487 (23.61%)	
Percentage of encounters with an injection prescribed	OPD	100/663 (15.08%)	152/885 (17.18%)	277/1450 (19.1%)	529/2998 (17.65%)	13.4-24.1
	IPD	19/113 (16.81%)	27/140 (19.29%)	51/234 (21.79%)	97/487 (19.92%)	
Average number of drugs per prescription	OPD	663/302 (2.2)	885/276 (3.21)	1450/430 (3.37)	2998/1008 (2.97)	1.6-1.8
	IPD	113/49 (2.31)	140/41 (3.41)	234/65 (3.6)	487/155 (3.14)	

OPD-Outpatient Department; IPD-Inpatient Department; WHO-World Health Organization

DISCUSSION: The present study revealed that among all the drug categories as per USFDA, Category A drugs which consists of drugs like Iron and Folic acid (also Calcium supplements), were the most commonly used one. This was followed by Category B drugs which include drugs like Ranitidine, Omeprazole, antimicrobials (like Ampicillin, Cephalosporins), antacids, analgesics (like Paracetamol), etc. This is in concordance with the study conducted by Kureshee *et al.,* [8] which showed that Category A followed by Category B drugs were mostly prescribed during pregnancy.

Category C drugs like Nifedipine, Quinine, antifungal drugs like Ketoconazole and Category D drugs which include anticonvulsants (Phenobarbitone, Phenytoin), Doxycycline, etc., belonged to 5.28% and 1.55% of the total number of drugs used in antenatal women respectively. These values are in contrast to the study conducted by Fikadu *et al.,* [9] where Category C and D drugs were used in 24.34% and 9.43% of pregnant women respectively. Category X drugs like Misoprostol consisted of 0.17% of the total number of drugs used. Such finding is in contrast to a study conducted in

Ethiopia [9], where, 1.09% of the total drugs prescribed belonged to Category X. In the present study, Category B and Category C drugs have been used more in IPD patients (18.07% and 7.6% of the total number of drugs used in IPD respectively) than in OPD patients (17.41% and 4.9% of the total number of drugs used in OPD respectively) due to more number of pregnant women suffering from medical conditions or illnesses like Acute Gastritis, Upper respiratory tract Infection, Malaria, etc. (in IPD). A study conducted by Savitha A *et al.,* [10] showed that Category B and Category C drugs consisted of 50.35% and 1.3% of the total number of drugs prescribed respectively.

In spite of the fact that drugs should be avoided as much as possible during pregnancy, such women are exposed to one or more number of drugs. [11] Medications prescribed to pregnant women can affect the foetus in different ways. They may cause foetal damage, birth defects or death. They might hamper placental function, thereby diminishing supply of oxygen and nutrients to the foetus resulting in delivery of an underweight and/ or underdeveloped baby. [3] In 1979, USFDA, devised a system to determine the teratogenic risk of drugs based on the quality of data obtained from animal and human studies which would provide therapeutic guidance to the clinicians. [2]

Category A includes those drugs that have shown no risk to the foetus after adequate, well-controlled studies in pregnant women; Category B drugs include those drugs for whom animal studies have revealed no evidence of harm to the foetus or any adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the foetus. Category C drugs are those that have shown an adverse effect in animal studies and there are no adequate and well-controlled studies in pregnant women. Category D drugs have demonstrated positive evidence of risk to the human foetus (but the potential benefits from their use might be acceptable in spite of such risk). Category X drugs have demonstrated abnormalities in foetus in animal or human studies and hence are absolutely contraindicated (since potential risk outweighs benefit). [4, 12]

In the present study, we found that though less number of Category D and Category X drugs

(1.55% and 0.17% out of the total number of drugs used respectively) have been utilized by these antenatal women, but still there are chances of teratogenicity in their foetus. Hence, minimal and/or cessation of usage of drugs belonging to Category D and Category X respectively, should be done.

As far as prescribing of medications in accordance with WHO Core prescribing indicators were concerned, percentage of drugs prescribed by generic name in the present study was less (95.1% in OPD and 94.46% in IPD) than the WHO reference value. Such findings are in line with the findings of Gawde SR *et al*., [13] where 96% of the drugs were prescribed by generic name. The reason for such finding in our study might be due to prescription of some drugs as per their brand names. Percentage of encounters with injectables was slightly higher in the IPD patients (19.92%) as compared to the OPD patients (17.65%). The reason is due to cases like Malaria, Diarrhea, Hyperemesis graviduram, etc. in IPD which needed fluid and electrolyte maintenance. Such findings are in contrast to a formerly conducted study [14] where percentage of encounters with injectables was 2.17%.

In this study, percentage of encounters with antibiotics (21.61% in OPD and 23.61 % in IPD) among patients were within the range of WHO reference values. The reason might be due to judicious use of antibiotics in pregnant women, which is praiseworthy. In a study [10] conducted in Karnataka, percentage of encounters with antibiotics prescribed was 26 %. Average number of drugs per prescription prescribed during the entire antenatal period was 2.97 and 3.14 among OPD participants and IPD participants respectively; both of these findings are in line with the study finding of Eze UI *et al.,* [15] where average number of medicines per encounter was 3. Both these values found in this study were higher than the WHO reference range. Such findings might be due to the prescription of routine drugs along with other medicines.

WHO core prescribing indicators are useful parameters to assess the rationality of prescribing of medications. They are helpful in preventing polypharmacy, overuse of antibiotics, usage of

costly forms of therapy, etc.[7] As the present study suggests that more number of drugs (as compared to WHO reference value) were prescribed per prescription, so this might increase the chances of adverse reactions and/or drug-drug interactions in these women, which might be harmful for them as well as the baby. Also the clinicians should prescribe optimum number of generic drugs (as per the WHO reference range). Finally based on these study findings, the following suggestions might be considered by the clinicians while prescribing medications to antenatal women:

1. Clinicians should prescribe medications in optimum correlation with the WHO core prescribing indicators.
2. While prescribing medications, clinicians should adhere firmly to the rule of RIGHT (right drug, right patient, right dosage, and right cost) [6] and SANE criteria (safety, affordability, need, efficacy).[16]
3. Every hospital should form a medical body of their own so as to monitor and promote rational drug therapy.
4. Attempts should be made by the healthcare system authorities for continuous development and revision of standard treatment guidelines or prescribing policies.
5. Healthcare professionals should be sensitized regularly through continuous medical educational programs regarding the recent updates on medications and treatment guidelines.

Such practice will enhance rational prescribing of drugs to the pregnant women and hence will help in preventing adverse and/or teratogenic effects in offsprings.

CONCLUSION: Though the present study showed that Category D and Category X drugs have been less prescribed to the antenatal women, still use of these drugs should be minimized or stopped. Average number of drugs prescribed per prescription was higher than the WHO reference value which calls for caution. Further improvement in adherence to the prescribing of drugs as per their generic name should be practiced. Such rational practice will ultimately help in further improvement of the health status of the mother and her offspring.

REFERENCES:

1. Sharma R, Kapoor B, Verma U. Drug utilization pattern during pregnancy in North India. Ind J Med Sci. 2006; 60(7): 277–87.
2. Sachdeva P, Patel BG, Patel BK. Drug use in pregnancy; a point to ponder. Indian J Pharm. Sci. 2009; 71: 1–7.
3. http://www.msdmanuals.com/home/women - s - health-issues/drug-use-during-pregnancy/ drug - use - during-pregnancy (accessed 4th April 2017)
4. Tripathi KD: Essentials of Medical Pharmacology. Jaypee Brothers Medical Publishers (P) Ltd., New Delhi, Edition 7, 2013:82-91.
5. Andrade SE, Raebel MA, Morse AN, Davis RL, Chan KA, Finkelstein JA *et al.* Use of prescription medications with a potential for fetal harm among pregnant women. Pharmacoepidemiol Drug Saf. 2006; 15: 546-54.
6. Sasidharan P, Kolasani BP, Divyashanthi CM. An observational prospective study on prescribing pattern of drugs among pregnant women admitted in antenatal ward of a tertiary care teaching hospital in coastal town of South India. Natl J Physiol Pharm Pharmacol 2017; 7 (1): 25-31.
7. World Health Organization. How to Investigate Drug Use in Health Facilities, Selected Drug use Indicators, WHO/ DAP/93.1. Geneva: World Health Organization; 1993. Available from: http://apps.who.int/medicinedocs/ pdf/s 2289e/s2289e.pdf (accessed 4th April 2017).
8. Kureshee NI, Dhande PP. Awareness of mothers and doctors about drug utilization pattern for illnesses encountered during pregnancy. JCDR. 2013; 7(11): 2470-4.
9. Fidaku M, Kebebe D, Amelo W, Gashe F. Drug utilization pattern and potential teratogenicity risk among pregnant women visiting Antenatal clinic: The case of a primary hospital. Indian Journal of Pharmacy Practice 2015; 8(1): 27-33.
10. Savitha A, Sarita H, Gumma K. Drug pattern use during pregnancy: A prospective study at tertiary care teaching hospital. Int J Basic Clin Pharmacol 2016; 5(1):192-5.
11. Varghese BM, Vanaja K, Banu R. Assessment of Drug Usage Pattern during Pregnancy at a Tertiary Care Teaching Hospital. Int J. Med. Public Health, 2016; 6(3):130-5.
12. Inamdar IF, Aswar NR, Sonkar VK, Doibale MK. Drug utilization during pregnancy. Indian Medical Gazette 2012 Aug: 305-11.
13. Gawde SR, Bhide SS, Patel TC, Chauhan AR, Mayadeo NM, Sawardekar SB. Drug prescription pattern in pregnant women attending antenatal outpatient department of a tertiary care hospital. Br J Pharm Res. 2013; 3(1):1-12.

14. Joshi H, Patel S, Patel K, Patel V. Drug use pattern during pregnancy: A prospective study at tertiary care teaching hospital. NHL J Med Sci. 2012; 1(1):14-7.
15. Eze UI, Eferakeya AE, Oparah AC, Enato EF. Assessment of prescription profile of pregnant women visiting antenatal clinics. Pharm Pract. 2007; 5(3): 135-9.
16. Tahniyath F, Hafeez F, Sultana H, Hussain MA, Rozati R. Prescription pattern of drugs in pregnancy: A review. Int Res J Pharm 2015; 6 (7): 403-6.