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Adverse drug reactions monitoring in the third trimester pregnant women from rural population of central India visiting tertiary care hospital: A cross- sectional pharmacovigilance study.

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Abstract

Background: Pregnant women are often excluded from clinical trials, hence information about safety of medications during pregnancy is limited. This study aimed at assessing the prevalence of adverse drug reactions in 3rd trimester pregnancy and effect of demographic factors in reporting the ADR.

Methods: This study includes 3rd trimester pregnant women visiting outpatient and inpatient department of Obstetrics and Gynecology of tertiary care hospital situated in rural part of central India from February 2021 to December 2022 using convenience sampling method. Patients were followed up on future visits or telephonically after 15 days of medication administration date.

Results: A total of 66 (16.33%) suspected ADR events in 44(11%) women were detected in 404 enrolled patients in our study. Out of the total 66 ADRs reported in the 44 patients, nausea was the most frequent adverse reaction reported with 45.45% prevalence followed by constipation (43.18%), headache (18.18%) and loose stools (6.81%). The 46 ADR (69%) out of 66 were assigned POSSIBLE on causality assessment and remaining 20 (30%) ADRs were assigned as PROBABLE as per Naranjo's Adverse Reaction Probability Scale. The ADRs were significantly higher in multipara, urban and women with higher annual family income.

Conclusion: Adverse drug reactions are very common[1] in third trimester pregnant women and demographic factors like parity, socioeconomic status impact them significantly. Further studies with a re-challenge test will be needed for more information about ADR prevalence.

Keywords: Pregnancy; Adverse drug reactions (ADR); Third Trimester pregnancy; Pharmacovigilance; Central India

1. Introduction

The Antenatal period is the most critical and complex stage of women's life requiring special care and protection from deficiencies & diseases. Despite efforts to avoid drug use during pregnancy, pharmacotherapy is common in majority of pregnant women. The knowledge about teratogenicity was brought to light since the 1940s and highlighted by the adverse effects of Diethylstilbesterol and Thalidomide. This led to stricter Food Drug Administration [FDA] regulations and guidelines advising exclusion of women of childbearing age from early clinical trials. Thus, only 1.29% of trials mentioned pregnant patients since the 1960's.

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At least 25% of ante natal patients suffer from complications of pregnancy (like epilepsy, hypertension, diabetes) and with advancing maternal age the trend rises upwards. The worsening of co-morbidities, (especially in third trimester) makes the use of drug unavoidable with lack of sufficient data concerning safety. More studies for drug safety are need of an hour and thus, this study was conducted to monitor adverse reactions of drugs used in third trimester pregnant women visiting our tertiary care center situated in central India.

Our study was primarily aimed to estimate the prevalence of occurrence of adverse reactions of drugs used in third trimester pregnancy. We also estimated the effect of demographic factors on adverse drug reactions (ADR) as well as the severity and causality of ADRs.

2. Material and Methods

This study includes 3rd trimester pregnant women visiting outpatient and inpatient department of Obstetrics and Gynecology of tertiary care teaching hospital situated in rural part of central India from February 2021 to December 2022. We used convenience sampling method to enrol patients under the study after obtaining written informed consent. Data was collected from the outpatient department (OPD) and inpatient department (IPD) of Obstetrics and Gynecology during the duration of the study. The inclusion and exclusion criteria mentioned in appendix I.

Despite reviewing many articles none were found relevant to this study and the extensive literature search did not avail data related to prevalence of adverse drug reactions in third trimester pregnant women. Also, evidence from Hospital Information System(HIS) of Hospital was not found as there was little mentioned in the case sheets about adverse drug reactions to pregnant women. Hence, by considering 50% proportion of adverse drug reactions which gives largest sample size with 95% confidence interval at 10% allowable error. The desired sample size came out to be 96. To nullify the sampling design effect, we doubled the sampling size and to deal with the non-response rate, the overall sample size increased by 10% . Therefore, sample size came out to be around 220.

When we started our study in February 2021, CoViD-19 pandemic was widespread. We considered the possibility of less follow-up by study population and enrolled 190 more patients in our study and got the follow-up from 404 total population. Thus, we have included the results and statistical analysis of these 404 patients in our study. The ADR information was collected personally(on their follow up visit) as well as telephonically(after 15 days of starting treatment). Study protocol was approved by Institutional Ethical Committee (IEC) of our institute and prior permission was also received by Department of Obstetrics and Gynecology. (IEC approval letter no.: MGIMS/IEC/PHAR/11/2021).

This purely being an Observational study, we did not intervene in the on-going treatment on our own. When patients who were followed up telephonically reported any adverse effect, they were suggested to visit the OPD of Obstetrics and Gynecology department and report the adverse drug reaction to the Obstetrician. Most of these patients and IPD admitted patients who reported adverse drug reactions were given alternative combinations or brands available or very few patients were suggested to stop the medication causing adverse reactions, as we found out on the follow-up.The statistical analysis was done by using descriptive and inferential statistics using Chi-square test and software used for the analysis was SPSS 27.0 version and $p<0.05$ is considered as level of significance. Causality assessment of ADRs was done by using Naranjo's Probability scale[2] Severity assessment of ADRs was done using Hartwig and Siegel scale.

3. Results and Discussion

Out of the 404 patients, 44 (11%) reported one or more ADRs. A total of 66 (16.33%) suspected ADRs were detected in 404 patients in our study. This data analysis pertains to 66 number of ADRs of 404 patients, who were on various medications for different conditions.

According to the Wills and Brown classification of ADRs, all were Type A (Augmented) adverse reactions in our study; that is, they were relatively common, pharmacologically predictable, dose related and improved when the medicine was withdrawn. No new ADRs were reported in our study.

Out of the total 66 ADRs reported in the 44 patients, nausea was the most frequent adverse reaction reported with 45.45% prevalence followed by constipation (43.18%), headache (18.18%) and loose stools (6.81%). The details mentioned in Table no. 1

Table 1 Distribution of patients based on adverse drug reactions reported

Adverse drug reaction	No of patients	Percentage (out of total 66 ADRs reported)
Abdominal Pain	2	4.54
Nausea	20	45.45
Constipation	19	43.18
Disturbed Sleep	2	4.54
Dizziness	2	4.54
Drowsiness	3	6.81
Flushing	2	4.54
Headache	8	18.18
Pain in breasts	3	6.81
Loose Stools	3	6.81
Vomiting	2	4.54
Total	66 (ADR events)	100%

The causality assessment was carried out by Naranjo's Adverse Reaction Probability Scale as mentioned previously. The 46 ADR (69%) out of 66 were assigned POSSIBLE on causality assessment and the remaining 20 (30%) ADRs were assigned as PROBABLE. None of the ADR event was assigned in "DEFINITE" category, as re-challenge was not done in the study.

As per Hartwig and Siegel scale, 56 (84.84%) ADRs out of 66 ADRs were mild(Level 1 & 2) in severity. Majority of mild ADRs were related to GIT - 40(60.60%) and CNS- 11(16.66%), Endocrine- 3(4.54%), and Miscellaneous -2 (3.03%). The 10(15.15%) ADRs were of MODERATE(Level 3 & 4) severity. Majority of moderate ADRs were related to GIT- 6(9.09%). Other system with ADRs of MODERATE severity was CNS- 4 (6.06%). None of the ADR were severe(Level 5, 6 & 7) on assessment scale.

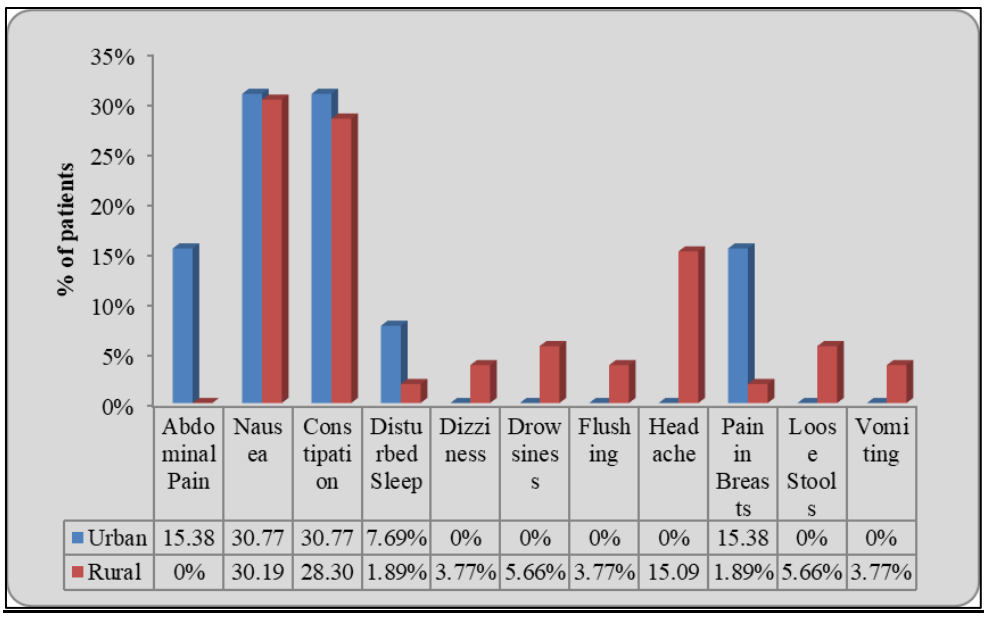

Figure 1 Correlation of Residence and Adverse Drug Reactions

The statistically significant difference was found between the percentage of ADRs reported in the urban and the rural population (*p* value = 0.048), with more adverse reactions reported by urban population (details mentioned in Fig. 1).

Similarly, the ADR were significantly more in the multipara compared to primipara(p=0.017) and patient with higher annual family income (>= 4 lakh) compared to lesser annual family income (p=0.033)(Fig. 2 & 3). There was no correlation found for age, education, and occupation of the patient.

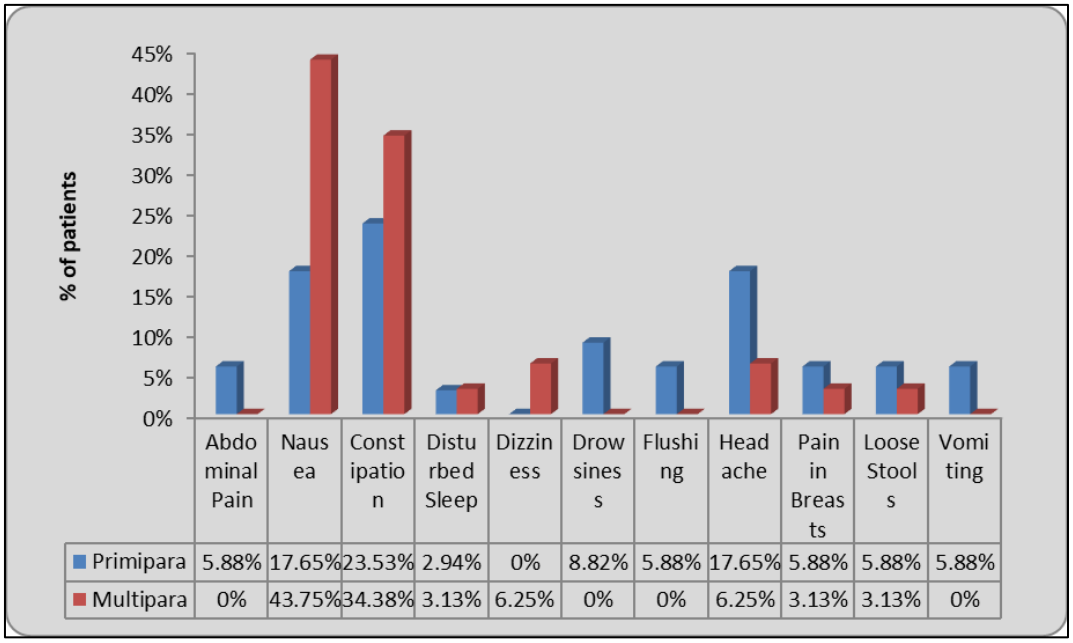

Figure 2 Correlation of Parity and adverse drug Reaction

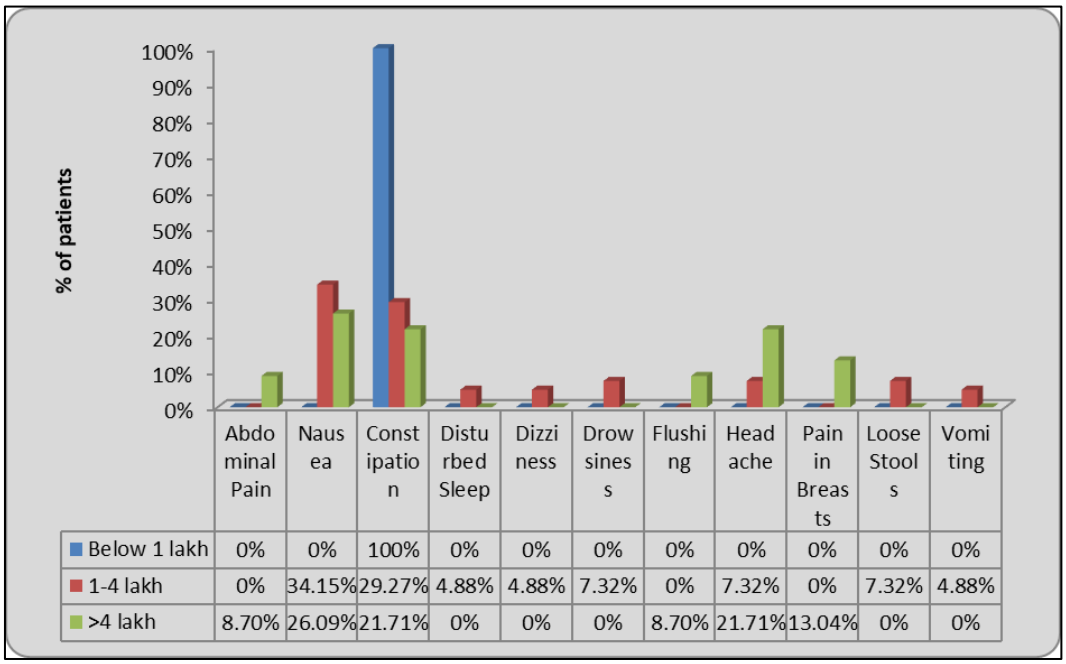

Figure 3 Correlation of annual family income and adverse drug reaction

A total of 404 third trimester pregnant women in this study population were followed up on subsequent visits or telephonically after 15 days and enquired about any adverse reactions they were experiencing. As we did not follow the study population for longer period, we only have the data related to acute adverse drug reactions. The magnitude of adverse drug reactions reported in the study population was analysed and classified depending on the various body systems involved; furthermore, their correlation with different demographic factors was evaluated.

The mean age of our study population was 24.98±3.71 (19-35 years) with majority belonging to age group of 23-26 years(38.61%). This study's age group was comparable to a study by Jain D. et al.[3]; they had maximum number of their patients in the age group of 20-25 years of age and 23.9 years was the mean age of study population of Prabahar K. et al.[4] In our study, 295 patients, that is 72.77% of the total patients belonged to the rural area while rest of the 27.23% to the urban area in accordance with location of our institute.

The Primipara (~55%) out-numbering Multipara (~45%), similar to the findings of a cross sectional observational study by Adhikari et al.[5] where 51.4% of the total patients were primipara. This prevalence is probably because they were given more attention by the family members and are taken to higher centres right from the confirmation of pregnancy in the primipara subset. The multipara patients in their interviews mentioned visiting nearby dispensaries, subcentres for minor ailments. Also, obstetric complications are more commonly seen in primiparae[6][7]. In a study by Sneha K. et al. in tertiary care centre of Maharashtra, majority of the patients in preterm labor were primipara 26.21% in contrast to 17.32 % multipara; same contrast was observed with the prevalence of Heart disease and Gestational Diabetes Mellitus[6] in the same study. In another tertiary care centre-based study by Kaur J. et al.[7] revealed that 51.92% primipara landed up in pre-term labor while 35.41% were multipara; similar contrast of more prevalence in primipara was observed with PIH, IUGR, Foetal distress and oligohydramnios in the same study.

None of the patients in our study population were uneducated, around 4% were post-graduates while 18% were graduates. Half (50%) of the patients who were included in the study had completed their primary schooling while the rest of 30% had been to secondary school. Comparable characteristics of study population were observed in a study by Jain D. et al.[3]: Despite high demand for schools, supply-side factors related to teacher availability and infrastructure leave much room for improvement in rural areas of India[1]. Also the average age of marriage in Indian females according to latest census is 19.3 years[8]. This might explain most women not pursuing further education after getting married, as we got know in our interviews with the study population.

3.1. Adverse drug reaction analysis

Overall, 66(16.33%) suspected ADRs were detected in 404 patients in our study. Our results are comparable to 10.7% ADRs reported in similar studies conducted by Silva K. et al.[9] and 9.41% ADRs reported by Oliveira A. et al.[1] Higher number of ADRs- 27.18% were reported in a study by Costa T. et al.[5] in high-risk pregnant women, possibly because it was a study conducted in patients admitted in intensive care units, where the conditions may have warranted use of potentially ADR causing drugs. Also, patients were under continuous monitoring and ADRs were mostly, actively noted by the health care professionals. Also, lesser magnitude of ADRs reported in our study could be due to more patient load and lesser doctor-patient ratio[10] in our country leading to ignorance on the part of the doctors towards minor ADRs. We looked for the ADRs reported by the patients who were not receiving medications other than nutritional supplements. Eight(12.12%) out of 66 patients who were only taking nutritional supplements reported adverse reactions while rest of the adverse drug reactions reported were in the patients who were taking medications other than nutritional supplements. These results imply that nutritional supplements do not cause additional risk of increased ADRs and there is no need of calculative administration or reduction in prescription of nutritional supplements.

Table 2 Magnitude of Adverse drug reactions in our study compared to other similar studies**-**

Study Population	**Author**	**Magnitude of ADR**
Present study- third trimester pregnant women	Shinde et al	16.33%
High risk pregnant women	Costa T. et al.[11]	27.18%
High risk pregnant women	Silva K. et al.[9]	10.70%
High risk pregnant women	Oliveira A. et al.[12]	9.41%
Patients consuming Ferric carboxy maltose	Jain D. et al.[3]	12%
Patients receiving antihypertensive drugs used in gestational hypertension	Prabahar K. et al.[4]	2%
Pre-term labor patients receiving tocolytic treatment	Heus R. et al.[13]	1.28%

3.2. Distribution of patients based on adverse drug reactions reported

Out of 66 ADRs, nausea was the most frequent adverse reaction reported with 45.45% frequency followed by constipation (43.18%)(details mentioned in the Table no. 1). To summarise, system wise, 69.6% ADRs were GIT related, 22% ADRs were CNS related, 4.54% were Endocrine system related, and the rest were 3%. Comparable results were found in an observational study conducted by Jayanthi C R et al. to analyse the ADRs reported spontaneously from the department of OBGY at a tertiary care hospital to the ADR monitoring Centre of Bangalore Medical College and Research Institute. GIT ADRs were 51%, Central nervous system 1%, and others were 48% in this study. As our study was observational, the re-challenge was not done after the de-challenge for establishing the association of reported ADR with the specific medication amongst the many, received by each study subject.

Table 3 System wise Severity assessment of ADR

System	Mild	Moderate	Severe	Total
CNS	11	4	0	15
GIT	40	6	0	46
Endocrine	3	0	0	3
Others	2	0	0	2

The reason for maximum GIT related side-effects could be that the spectrum of drugs used in our study had most common side effects affecting gastrointestinal system as mentioned in the table no. 4. Majority of ADRs like nausea, constipation, and loose stools as we suspect were due to oral ferrous fumarate. Nausea as is also a known side-effect of Amoxicillin-Clavulanic acid, Norfloxacin, L-arginine, Isoxsuprine, Aspirin, Metronidazole, Hydrocortisone, Nifedipin, Paracetamol. These drugs might have caused the reported adverse effect. Loose stools can be associated with antibiotics administered. As its association is established in literature as a side effect with Cefixime, Metronidazole, Ceftriaxone and sulbactam and also with Arginine, Amino acids. Abdominal pain was seen in patients receiving Ferrous Fumarate, Metronidazole, Erythromycin, Ondansetron, Dexamethasone, Arginine, Aspirin; it is justifiable as these drugs are known for causing abdominal discomfort and pain.

3.3. Central Nervous System related adverse drug effects reported in our study

Drowsiness and dizziness, as we noted the pattern was mostly reported in the patients receiving the drugs-Ondansetron, Isoxsuprine, Labetalol, Metronidazole and Nifedipin. Headache was reported as an adverse reaction in patients who were prescribed arginine, Levothyroxine, Ondansetron, Metronidazole, Nifedipin, Pantoprazole. Disturbed sleep was complained by patients receiving Dexamethasone, Levothyroxine.

3.4. Endocrine System related and other side effects

Flushing was reported by the patients on Isoxsuprine, Norfloxacin, Pantoprazole. We had Pantoprazole and Nifedipine given to our study population known to cause pain in breasts, rarely. 4.54% (that is 3 out of 66 patients who reported it, when asked, if they experienced any side-effects), patients who complained of the same might also be due to its known prevalence in pregnancy.[14][15]

3.5. Correlation of ADRs with the demographic factors

3.5.1. Correlation of Parity and Adverse Drug Reactions

Significant statistical difference was found between the percentage of Adverse drug reactions reported in Primipara and Multipara with the p value of 0.017. Multiparous women were the ones who reported majority of the adverse effects as compared to primiparas. The reason for this difference as we observed while interviewing patients was the lack of knowledge and experience amongst the primiparas about the normal physiological changes in pregnancy and the adverse effects of the medications that need to be addressed and reported to the physician to get the treatment changed.

3.5.2. Correlation of residence and Adverse Drug Reactions

With the p value of 0.048, percentage of ADRs reported by urban population were significantly higher than those reported by rural population. This is because urban population tend to utilise healthcare facilities more and are more aware about their health care needs[16].

3.5.3. Correlation of Annual Family Income and Adverse Drug Reaction

With the p value of 0.033, statistically significant difference was found between the percentage of adverse reactions reported in patients with the annual family income more than 4 lakhs than in the patients with family income between 1-4 lakhs and the rest having below 4 lakhs of income. Patients belonging to better socio-economic status are apparently more concerned about their health and have resources (transport facilities, time, and money) and awareness (education) to address and report the slightest discomforts they experience.

3.6. Causality and severity assessment of ADRs reported

A total of 46 ADR (69%) out of 66 were assigned POSSIBLE and 20 ADRs (30%) out of 66 were assigned PROBABLE on causality assessment. In a study by Jayanthi C R et al.[17], 61% ADRs were Probably associated with the medications received and 39% ADRs were possibly related. No ADR was assigned in "DEFINITE" category, as re-challenge was not done in the study.

3.7. Severity assessment of ADRs using Hartwig and Siegal Severity assessment scale

A total of 56 (84.84%) out of 66 ADRs reported in our study were mild in severity which were comparable to results of a study done by Oliveira A. et al.[12] and Jayanthi C R et al[17]. In our study, 10(15.15%) out of 66 total reported ADRs were MODERATE in severity comparable with Oliveira A. et al[12]. No ADR was found to be SEVERE on assessment scale.

3.7.1. Under-reporting

There were chances of missing certain ADRs during the study period since some of them may have been transient or not severe enough to significantly trouble the patient. The other factors contributing to under reporting were financial burden on family, lack of attention towards female health, overburdened public health infrastructure and resources to report ADR in India.

3.7.2. Impact of our study

Due to regular counselling, the patients became more vigilant about noticing and reporting ADRs. They even contacted us telephonically and reported the ADRs. The physicians whom we contacted for our study started actively noticing and reporting even the milder ADRs which they initially thought to be non-significant. Our study on Pharmacovigilance will contribute to generating the hospital ADR database and health programs can be modified as regional epidemiology.

3.7.3. Limitations of our study

The main limitation of this cross-sectional study is 15 days recall history, hence long-term consequences of ADRs could not be reported. To assign ADRs to "Certain" category in causality assessment, rechallenge tests are required but due to ethical constraints re-challenge tests were not performed. Our study lacks objective laboratory investigation to emphasize causality correlation. Further studies are needed to ascertain the specific ADR caused by specific drugs.

4. Conclusion

Adverse drug reactions are very common[1] in third trimester pregnant women and demographic factors like parity, socioeconomic status impact them significantly. Severity assessment revealed that majority of ADRs were only mild to moderate. A prospective study with long term follow up and re-challenge test will be needed for more information about ADR prevalence.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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Appendix I

Inclusion Criteria

Third trimester pregnant women visiting Department of Obstetrics and Gynecology.

Exclusion Criteria

- Patients not willing to take part and not giving written informed consent.

- Those unable to understand for other reasons.
- Mentally unstable patients admitted in Obstetrics and Gynecology ward.
    - ADR data was collected using suspected ADRs monitoring form from CDSCO (Central Drug Standard Control Organization)[13] and forwarded to higher pharmacovigilance center through Department of Pharmacology of our Institute.