

Drug related adverse pregnancy outcomes at a tertiary care hospital from the foothills of Himalayas: A Prospective observational study

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ABSTRACT

Context and Aim: Safety of drug usage during pregnancy is of utmost importance. Unrestricted usage of drugs may lead to undesirable and unpredictable pregnancy outcomes. This study was designed to detect drug-related adverse pregnancy outcomes, perform prescription audit and develop a pregnancy drug registry. **Methods and Materials:** A prospective observational study was conducted at a tertiary care hospital in northern India. Pregnant females attending antenatal clinic, irrespective of their duration of pregnancy were included in the study over a period of 1 year. The participants were followed up monthly during their pregnancy till the pregnancy outcome. Adverse pregnancy outcomes were evaluated and causality assessment was done using the WHO-UMC scale. **Statistical Analysis:** Descriptive and inferential statistical tools were used for appropriate variables. Regression model was used to establish relationship between factors proposed to be responsible for adverse pregnancy outcomes. Presence of adverse pregnancy outcome was used as an independent variable. Microsoft Excel and Strata (version 12) were used for statistical analysis. **Results:** A total 326 pregnant women were screened out of which 305 were included in the final analysis. Mean age of participants was 27.82 (± 4.51) years. Pre-existing comorbidities were present in 4.26% of participants. Average number of drugs per participant was 6.32 (± 1.94). Most drugs prescribed to participants were from FDA category B (49.23%) and category A (33.60%). Mean ADR reported per patient was 1.16 (± 1.18) with involvement of musculoskeletal (56.42%) and gastrointestinal (7.16%) being most frequent. Adverse pregnancy outcomes were reported in 25 participants among which IUGR (24%) followed by IUD (20%) and ectopic pregnancy (16%) were most frequently observed. Multivariate logistic regression showed number of comorbidities ($P = 0.037$) and number of drugs consumed during pregnancy ($P = 0.02$) to be statistically significantly associated with occurrence of adverse pregnancy outcome. **Conclusions:** Pregnancy registries have been instrumental in detection of signals for further research in drug-related adverse outcomes. Inappropriate usage of drugs has been shown to be associated with adverse pregnancy outcomes. Our study warrants need for further well-designed studies on adverse pregnancy outcomes in larger patient populations.

Keywords: Adverse pregnancy outcomes, drug, India

Introduction

Pregnancy is a highly variable physiological state where medication use can have a significant impact on the outcome.^[1] Safety of the drug usage is a key consideration in every pregnancy. Use of over-the-counter medications during pregnancy may be even higher as many women take dietary or herbal supplement other

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than multivitamins or folic acid.^[2] Identification and safety profile of use of medications in pregnancy is still incomplete.^[3] Pregnancy outcomes may vary from adverse maternal outcomes, a normal live birth, low birth weight, prematurity, stillbirth, intrauterine fetal death, early or late neonatal death and wide spectrum of congenital anomalies.^[4,5] The objective of the study was to observe the possible association between medication intake during antenatal phase and adverse pregnancy outcomes (APOs) from the first trimester to delivery or till termination of pregnancy. There is limited data on drug-induced APOs from the region. This study is the first of its kind to provide comprehensive analysis of drug-related APOs in a tertiary care hospital in Himalayan foothills.

Materials and Methods

This study was prospective and observational including pregnant women visiting antenatal clinic (ANC) of Obstetrics and Gynaecology Department at a tertiary care hospital in Uttarakhand, India. All patients attending the ANC over a period of 1 year (October 2019 to October 2020) were screened for inclusion in the study. Women with at least one documented follow-up visit or women having one of the APOs during period of study were included. Patients were briefed about the pregnancy registry and informed consent was taken from all participants before enrolment. All patients were interviewed by trained staff and health care professionals. Detailed history regarding socio-demographic details, past obstetric history, medical and surgical illness, and concomitant medication use was recorded. WHO-UMC scale was used for causality assessment of adverse drug reactions if any. After initial recruitment, patients were subsequently followed up monthly till delivery or till the time a pregnancy outcome could be determined. Prescription audit was done on each follow-up visit after initial enrolment in the study. Detailed drug history was noted down on every visit. Pregnancy outcomes were determined jointly by Obstetrician, Pediatrician, and Pharmacologist. Consensus was achieved before each decision. Other specialist opinions were taken in case of congenital anomalies. All the data was entered in a pre-designed case record form.

Statistical analysis

Descriptive and inferential statistical tools were for appropriate variables. T-test was used to analyze the difference in quantitative variables among the three trimesters. Qualitative variables were compared by Chi-square test and Fisher's exact test. Bivariate logistic Regression was used to establish relationship between factors proposed to be responsible for APOs. Presence of APO was used as an independent variable. Microsoft Excel and Strata software was used for statistical analysis. Institute Ethics Committee (IEC), AIIMS Rishikesh approval was taken before initiation of the study (AIIMS/IEC/19/737 dated 12/04/2019).

Results

Participant's characteristics

A total of 326 patients were screened over the study period. 21 patients were lost to follow up hence excluded from the final

analysis. Among them 19 patients moved to other hospitals for their delivery and two refused to participate in the study. Final analysis included 305 participants. Mean age of participants recruited in the study 27.82 (± 4.51) years with range of 20 to 47. Majority (95.74%) of the participants did not have any significant past medical history whereas 4.26% of total had pre-existing diseases like diabetes mellitus (1.64%), seizure (1.31%), and tuberculosis (0.98). Among the participants, 241 (79.02%) had no history of any obstetric complications while 53 (17.38%) had undergone caesarean section due to previous pregnancy. 8 (2.62%) had recurrent abortion due to unknown cause and 2 (0.66%) had intrauterine death of fetus. None of participants were smokers or alcoholic. In total, 186 (60.98%) participants in the study did not have any comorbid condition during the course of pregnancy while 104 (34.01%) had at least one comorbid condition in antenatal period and 15 (4.92%) suffered from more than one comorbidity [Table 1].

Mean weight of the participants in first trimester was 55.72 (± 6.95) kg, second trimester was 57.63 (± 10.75) kg, and third trimester was 60.26 (± 13.39) kg. Mean height of the participants was 158.6 (± 5.05) cm.

Mean hemoglobin level in first trimester was 10.36 (± 1.6) g/dL, second trimester was 10.72 (± 1.8) g/dL, and in third trimester was

Table 1: Maternal and neonatal characteristics in the study participants

Sociodemographic and Obstetric parameters	n	(%)
Maternal Age (years)	n=305	
<20	5	1.64
21-30	228	74.75
31-40	69	22.62
>40	3	0.98
Past Medical History	n=305	
None	292	95.73
Present	13	4.27
Gravidity	n=305	
Primigravida	132	43.27
Multigravida	173	56.72
Past history of obstetric complications	n=305	
None	241	79.01
Present	64	20.98
Comorbidities	n=305	
None	186	60.98
With one comorbidity	104	34.10
More than one comorbidity	15	4.92
Neonatal Sex	n=291	
Female	153	52.57
Male	138	47.42
Birth Weight	n=291	
<2500g	88	28.85
2500-4000 g	196	64.26
>4000 g	7	2.30
Delivery method	n=297	
Normal vaginal delivery	183	61.61
LSCS (Lower segment caesarean section)	100	33.67
Instrumental delivery	14	4.71

11.12 (± 2.64) g/dL. There was a statistically significant difference between mean hemoglobin levels among first and second trimester ($P = 0.0004$), second and third trimester ($P = 0.0001$). None of the participants showed severe hemoglobin deficiency status [Figure 1].

Present medical condition

A total of 134 medical conditions were present in this study participants. Hypothyroidism was the most common comorbid condition present in 33 (0.1%) of the study population followed by hypertension in 14 (0.04%), fever in 8 (0.02%), asthma and UTI in 7 (0.03%) each [Table 1].

Obstetric complications

A total of 31 obstetrics and gynecological complications were associated with pregnancy. Pre-eclampsia, 5 (16.12%), followed by pregnancy-induced hypertension, twin pregnancy and uterine fibroids, in 4 (12.9%) participants were reported. Three participants had oligohydramnios whereas two participants each had marginal placenta and cephalopelvic disproportion (CPD).

Drugs used in study population during pregnancy

Average number of drugs consumed by each participant during the course of pregnancy was 6.32 (± 1.94). Depending on the medical condition of participant, intake of medication ranged between 0 to a maximum of 11 drugs per patient.

Most of the drugs prescribed during pregnancy to participants were from category B (49.23%) and category A (33.60%) followed by category C (13.76%), category D (0.37%), and category X (0.06%). Drugs with no information available on database were categorized under unknown (2.98%).

Categorization of drugs was done according to ATC classification given by World Health Organization (WHO). Drug from Alimentary tract and metabolism (Class A) were most frequently used group (74.57%) followed by Respiratory system (Class R-12.66%), Anti-infective for systemic

use (Class J-3.88%), Hormonal preparations (Group H- 3.51%) and Cardiovascular (Class C-2.77%). Least commonly used group was Antiparasitic (Class P- 0.11%) and Blood and blood-forming products (Class B-0.05%).

Supplements followed by antihistaminic and NSAID were most commonly prescribed drugs in study population [Figure 2]. Sofosbuvir/Velpatasvir was the only category X drug used in study for Hepatitis C. Potentially teratogenic drugs prescribed to the participants in study were sofosbuvir/velpatasvir (Category X drug) for HCV ($n = 1$), efavirenz (Category D drug) was given for HIV ($n = 1$), naproxen (Category D drug) was prescribed for chronic pain ($n = 2$), and telmisartan (Category D drug) was prescribed for hypertension ($n = 4$).

Associated adverse drug reaction/adverse reaction during pregnancy

Adverse drug reactions were monitored in the study participants. Mean ADR reported per patient was 1.16 (± 1.18) among study participants. Presentation of ADR ranged from 0 to maximum 4 ADR per patient. Characterization of ADR was done systemically among participants.

Total 337 adverse events were recorded among study population. Most common ADE reported in study population was back pain 44 (13.06%) followed by constipation 28 (8.31%), vomiting 27 (8.01%), nausea 22 (6.54%), allergic reaction 21 (6.23%), drowsiness 21 (6.23%). 18 (5.34%) ADR were headache and fatigue. Severity assessment was done for presenting ADRs. Serious and nonserious adverse events occurring during the study were 10.3% and 89.6%, respectively. Among 34 serious adverse events, 24 of them were nausea and vomiting [Table 2].

Outcome of pregnancy

Among 305 participants, 285 (93.44%) neonates were viable, 6 (1.97%) were non-viable and 6 (1.97%) presented with birth defect.

Among the participants 280 (91.80%) had normal live birth. 5 (1.64%) presented with intrauterine growth retardation, 6 (2.30%) ended with intrauterine death, 4 (1.31%) had congenital anomalies, and 9 (2.95%) experienced spontaneous abortion, ectopic pregnancy or fetal loss due some other cause.

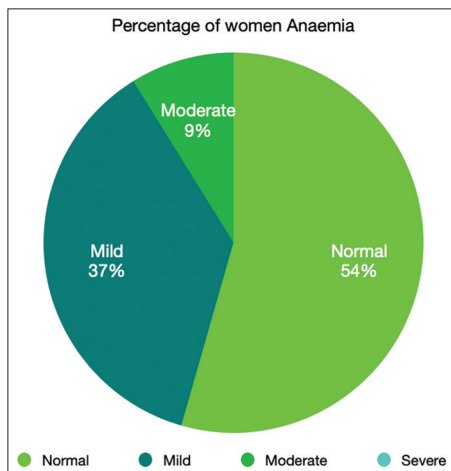


Figure 1: Frequency of anemia in study participants as per WHO

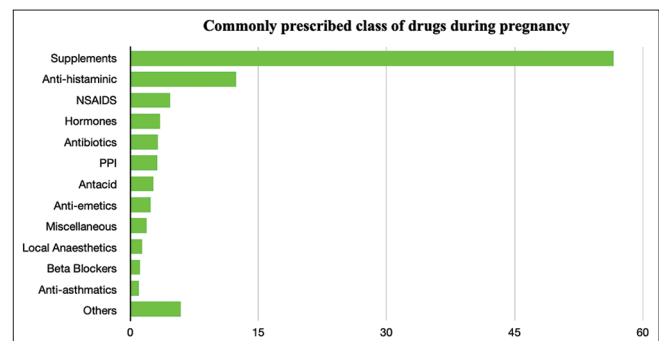


Figure 2: Commonly classified class of drugs in pregnancy

Table 2: System wise classification of adverse events that occurred in study population

System	n (%)
Gastrointestinal	24 (7.12)
Genitourinary	10 (2.97)
Musculoskeletal	197 (58.46)
Cardiovascular	1 (0.30)
Neurological	57 (16.91)
Dermatological	23 (6.82)
Respiratory	4 (1.19)
Reproductive	21 (6.23)

Among 305 participants, 25 major APOs were noted. IUD (6), IUGR (5) followed by ectopic pregnancy (4), spontaneous abortion (3), valvular heart defects (3), orofacial malformation (cleft lip/palate) in 2 cases were seen. 1 case each was reported with trisomy 21, and preterm delivery [Figure 3].

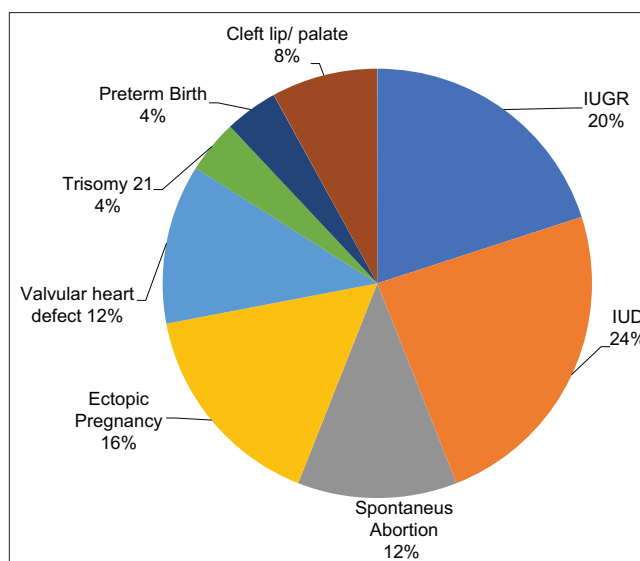
Causality assessment of the outcomes was done for the participants with APO according to the WHO-UMC scale. Among the 25 participants, majority (66.4%) of the adverse drug reactions were unlikely associated with the drug use. The side effects were probably due to associated comorbidities or physiological state of pregnancy. Possible association was seen 28.8% of events. Probable association was in 4.8% of events. Anti-inflammatory drugs like Naproxen, Acetaminophen, Diclofenac followed by antiemetics like Ondansetron, Propranolol, Flunarizine, Levetiracetam were found to be drugs with probable association with APO.

Presence of comorbid conditions in women led to increase in occurrence of APOs ($P = 0.02$).

Bivariate logistic regression was used to analyze the association with various variables with occurrence of APOs. Values with $P < 0.2$ were included in multivariate logistic regression model. It was found that total number of comorbidities ($P = 0.037$) and total number of drugs consumed during pregnancy ($P = 0.02$) were statistically significantly associated with the occurrence of APO among the study participants [Table 3].

Discussion

This study highlighted the pregnancy registry-based analysis of drug usage at tertiary care center. Prevalence of APO at AIIMS, Rishikesh a tertiary care hospital in Northern India catering to the population of mainly two states of Uttar Pradesh and Uttarakhand was 8.1%. Incidence in our study was similar to the previously conducted studies.^[6-9] Our study showed IUGR in 1.64% participants, whereas national data showed incidence of 9.65%.^[10] Lesser incidence of IUGR cases in our study is probably due to limited sample size. The prevalence of APO in African countries is probably higher due to poor socioeconomic conditions, low antenatal check-ups and lack of basic medical facilities. Antenatal screening for anemia, pre-eclampsia, GDM, previous pregnancy loss, and regular antenatal visits are

**Figure 3: List of adverse pregnancy outcomes in study**

contributing factors that may reduce occurrence of APO.

IUD has been reported in 2% of pregnancies worldwide where most common causes include placental abnormalities followed by congenital anomalies.^[11] Incidence of IUD was 2.3% in our study which was slightly higher than previous reports. This was probably due to associated comorbidities like SLE, retroplacental hemorrhage, PIH and fibroid uterus. Prevalence of congenital anomalies in our study was 1.31% which is lower to that of 3.0% global prevalence as estimated by WHO.^[12]

Average number of drugs consumed by each participant during the course of pregnancy were 6.32 (± 1.94). Sevene *et al.*^[13] reported an average drug used of 3.9 (SD = 2.1) whereas Mosha *et al.*^[14] reported that 98% of participants had taken minimum three groups of drugs during pregnancy. Our study has shown higher usage of drugs per patient. This may be due to higher associated comorbidities in the study population. Mean weight of neonate was 2620 g (SD = 750) and incidence of low birth weight in the study was 28.85%. And a meta-analysis conducted by Bhilwar M, *et al.*^[15] stated that prevalence of low birth weight was 27% and the pool prevalence was 31%. This is almost similar to our study.

Commonly prescribed class of drugs during pregnancy were supplements and anti-histamines followed by NSAIDs, hormonal preparation and antibiotics. Sevene *et al.*^[13] in Mozambique reported that antibiotics (41.2%) followed by antimalarials (23.8%) were most commonly used.

Sofosbuvir (category-X) was used in a patient for chronic Hepatitis C infection. The neonate presented with extremely low birth weight. ADR was categorized as probably associated with the drug. Prenatal and postnatal developmental anomalies are often associated with Sofosbuvir; hence, it is absolutely contraindicated in pregnant females.^[16] Efavirenz (category

Table 3: Bivariate and multivariate logistic regression of adverse pregnancy outcome with various study variables

Variable	Unadjusted odd ratio (95% CI), P	Adjusted odd ratio (95% CI), P
Age	1.0 (0.92-1.1), 0.83	-
Obstetric history (Gravida)	1.34 (0.97-1.84), 0.071	1.19 (0.76-1.87), 0.438
Obstetric history (Abortion)	1.88 (1.17-3.01), 0.008	1.4 (0.71-2.79), 0.326
Obstetric history (previous live birth)	1.11 (0.71-1.74), 0.628	-
Presence of anaemia	1.04 (0.55-1.93), 0.9	-
Presence of comorbidities	1.86 (1.02-3.41), 0.043	1.94 (1.04-3.63), 0.037
Total number drugs	0.76 (0.62-0.93), 0.008	0.78 (0.63-0.96), 0.020
Total number of adverse events	1.18 (0.85-1.65), 0.303	-
Blood group	0.96 (0.73-1.27), 0.814	-
Neonate sex	1.09 (0.47-2.48), 0.835	-

D) was used in a HIV-positive patient. Although no APO was detected, CNS malformations have been observed in primates at doses comparable to systemic human exposure. A recent meta-analysis described incidence of neural tube defects in babies of mothers receiving EFV was not higher than ARV regimens not containing EFV.^[17,18]

Naproxen (Category-D) was used in another participant for chronic pain. Although the patient did not present with APO, a study by Nielson *et al.*^[19] on 1462 pregnant women was associated with increased risk of miscarriage.

A participant on Telmisartan delivered with low birth weight. Alwan S, *et al.*^[20] showed telmisartan resulted in increased incidence of still birth, renal damage, fetal growth retardation, pulmonary hypoplasia. Therefore, it is preferable to avoid during pregnancy.

Acetaminophen was consumed by many pregnant women among whom one fetus developed IUGR. Avella-Garcia B, *et al.*^[21] reported that prenatal exposure to drug was associated with attention function and autism in children. Diclofenac usage in pregnancy is associated with low birth weight and maternal vaginal bleeding as reported by Nezvalova-Henriksen K, *et al.*^[22] Our patient reported retroplacental hemorrhage which led to IUD with same drug. Padberg S, *et al.*^[23] had also reported major birth defects and spontaneous abortion. Hence it is very likely that diclofenac had caused IUD in our patient. Ranitidine was commonly prescribed in females. A study by Ruigómez, *et al.*^[24] showed that the use of cimetidine, omeprazole, and ranitidine increased the relative risk of non-genetic malformation by 1.2%.

Anti-asthmatic drugs (montelukast and salmeterol) were administered to the asthmatic female who had IUGR. A study by Sarkar M, *et al.*^[25] had reported that 25% of women who consumed montelukast during pregnancy had presented with fetal distress in newborn. Lavecchia M, *et al.*^[26] stated that prenatal exposure to ondansetron led to increased risk of cleft palate. Carstairs *et al.*^[27] reported cardiac abnormalities in neonates with a mother who had ondansetron during pregnancy. Participants in our study also presented with a heart defect had also taken the same drugs. Hence a probable association could be related.

Registry-based pregnancy studies on various comorbidities and associated drug-induced risk factors have indicated a strong need for rational drug usage during pregnancy and proper monitoring of adverse events.^[28-30]

Overall, high usage of drugs (6.32) was seen among the participants with APO in 7.6% of participants. IUGR followed by IUDs were the most common APO reported. Sofosbuvir (category-X) followed by Naproxen, Telmisartan, and Efavirenz (Category-D) suspected drugs used in the study population.

Strength of this study

This study is the first of its kind to analyze the pregnancy-drug registry and drug prescribing pattern among pregnant females from the foothills of the Himalayas of Uttarakhand in the northern part of India. The understanding of drug-related APOs will immensely help in rationalizing therapeutics in pregnant females and limiting unwanted toxicities. This study depicts the trend in drug usage, demographic characteristics, and obstetric history from the institutional pregnancy registry. Rationalizing pharmacotherapeutics will help to guide primary healthcare physicians to optimize treatment modalities in resource-limited settings.

Limitations of the study

Owing to the limited amount of time of study period, sample size of this study can be considered as a limitation. Also, short duration of follow-up, and study being done at the tertiary care center. The outbreak of COVID-19 rapidly spreading throughout the world, led to nationwide lockdown which resulted in a substantial decrease in attendance of women visiting ANC. Many patients were lost to follow-up and their pregnancy outcome could not be recorded.

Conclusion

APO has been associated with significant morbidity and mortality. Pregnancy registries have been associated with detection of signals for further research in drug-related adverse outcomes. Inappropriate usage of drugs has been shown to be associated with APOs. Our study warrants a need for further well-designed studies on APOs on larger patient populations.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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