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Original Research Article

# To Study Suspected Adverse Reactions Including Birth Defects in Tertiary Care Centre Almora (Uttarakhand) India

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**Abstract:**

According to the World Health Organization definition, this is any noxious, unintended, and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy. This definition excludes therapeutic failures, intentional and accidental poisoning (ie, overdose), and drug abuse. Also, this does not include adverse events due to errors in drug administration or noncompliance (taking more or less of a drug than the prescribed amount). Using this conservative definition avoids overestimating the ADR incidence. A WHO report in 1972 held that a term congenital malformations should be confimed to structural defect at birth, and the term congenital anomaly being used to include all biochemical, structural and functional disorders present at birth. In the study three hundred seventeen pregnant women were monitored for various birth defects and found that 82 birth defects where associated with various drugs taken by women during pregnancy. largest number of birth defects mothers were in 21-25 years of age group and majority of mothers were age group of 20-35 yrs. The babies with birth defects were categorized into premature without congenital anomalies 154 (48.58%), premature with congenital anomalies 7(2.20%), Intrauterine death IUD without congenital anomalies 126 (39.74%), IUD with congenital anomalies 15(4.73%) and abortions 15(4.73%). In this study the number of drug induced birth defect cases were reported in various drug and following percentage -paracetamol 31 case (37.80%), chloroquine phosphate 23 cases (28.04%), metoc1opramide 21 cases (25.60%), ciprofioxacin 18 case (21.95%), metronidazole 17 cases (20.17%) diazepam 16 cases (19.51 %), dicyclomine Hc112 cases (14.63%), ibuprofen 11 cases (13.41) isoxsuprin 9 cases (10.97%), ergot preparata 8 cases(9.75%). Increased awareness of possible damage to the fetus by drugs during pregnancy had led to be a few well controlled scientific studies as well as a vast array of anecdotal reports suggesting the teratogenic effect of various environmental agents.

**Keywords:** World Health Organization, Adverse drug reactions, Pregnancy, IUD.
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## Introduction

An adverse drug reaction is an expression that describes harm associated with the use of given medications at a normal dosage during normal use. ADRs may occur following a single dose or prolonged administration of a drug or result from the combination of two or more drugs. The meaning of this expression differs from the meaning of "side effect", as this last expression might also imply that the effects can be beneficial [1]. Adverse drug reactions are important. They should be considered in differential diagnosis of a wide range of conditions, as any bodily system can be affected and any disease process mimicked. The safe use of medicines is a critical issue for doctors, Pharmacists, nurses, regulatory authorities, pharmaceutical industries and public. Although prescribers aim to use medicines that help patients and do no harm, no drug is administered without risk [2]. Healthcare professionals have a responsibility to their patients, who themselves are becoming more aware of problems associated with drug therapy. It is essential that all involved have some knowledge of the potential adverse effects of medicines [3]. The main challenge is to prevent the occurrence of ADRs; to do this effectively requires an assessment of the balance between benefits and Harms [4]. According to-

"If the whole materia medica as it now used, could be sunk to the bottom of the sea, it would be all the better for mankind and all the worse for the fishes".

**- O. W. Holmes**

"No physicians can honestly guarantee that he will cure disease or that his treatment will not cause undesirable symptoms or temparany discomfort"

**- A.C. Ivy, 1948**

**WHO Technical report No. 498 (1972):**

"A response to a drug which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function".

Several definitions have been provided for Adverse Drug Reactions (ADR).The simplest and quite exhaustive would be to label any undesired or unintended effect of drug treatment as ADR[5]. The definition has been kept broad intentionally and covers from pre-natal to next generation effects, predictable or unpredictable responses as well as withdrawal symptoms or rebound responses after discontinuation of treatment. ADR divided into such types i.e. A, B, C, D, E, F,G and I.

**Type A Adverse Effects:** Augmented pharmacologic effects - dose dependent and predictable Type A reactions, which constitute approximately 80% of adverse drug reactions, are usually a consequence of the drug's primary pharmacological effect (e.g. bleeding from warfarin)or a low therapeutic index (e.g. nausea from digoxin), and they are therefore predictable[6]. They are dose-related and usually mild, although they may be serious or even fatal (e.g. intracranial bleeding from warfarin). Such reactions are usually due to inappropriate dosage, especially when drug elimination is impaired. The term 'side effects' is often applied to minor type A reactions [7].

**Type B Adverse effects**: Bizarre effects (or idiosyncratic) - dose independent and unpredictable

**Type C Adverse effects:** Chronic effects

**Type D Adverse effects:** Delayed effects

**Type E Adverse effects:** End-of-treatment effects

**Type F Adverse effects:** Failure of therapy

**Type G Adverse effects:** Genetic reactions

**Type I Adverse effects:** Idiosyncratic

Types A and B were proposed in the 1970s,[8] and the other types were proposed subsequently when the first two proved insufficient to classify ADRs[9].

Severity of adverse drug reaction has been graded by Seidl et al., 1965 as-

**Minor:** No therapy, antidote or prolongation of hospitalization required.

**Moderate:** Requires change in drug therapy, specific treatment or prolong hospital stay by at least one day.

**Severe:** Potentially life-threatening causes permanent damage or requires intensive medical treatment [10].

**Lethal:** Directly or indirectly contributes to the death of the patient.

**Birth Defects:** A WHO report in 1972 held that a term congenital malformation should be confirmed to structural defect at birth, and the term congenital anomaly being used to include all biochemical, structural and functional disorders present at birth [11].

Approximately 3% of all known newborn have a congenital anomaly requiring medical attention and approximately one third of these conditions can be regarded as life threatening. The concept that placenta protects the foetus from noxious agents has been shattered [12]. The first teratogenic linkage observed was with rubella virus in 1941 and later with thalidomide in 1962.Teratogenic is a unique kind of adverse reaction that it affects the organism (the foetus) other than the one for whom the drug was intended (mother)[13,14].

**Adverse Drug Reaction status in India:**

Data on adverse drug reaction (ADR) is woefully lacking in India. Few cases see the light of the day through different journal, but these are few and far in between, and lack a proper data record[15]. In India a number of alternative schools of medicine (e.g., Unani, Homeopathy, Ayurveda etc.,) with doctors passing out of these schools often start to prescribe allopathic drugs without adequate knowledge about them[16,17]. This adds to the unwarranted increase in the number of adverse effects. To add to these is often the role of quacks in Indian medicine. These people are not doctors but people with very little knowledge of medicine usually gained while working with qualified practitioner as a dispenser of drugs [18]. They too contribute to ADRs with occasionally a fatal consequence [19, 20].

**Material and Methods**

The present study was done on 317 women who were monitored for foetal anomalies in Department of Obstetrics & Gynecology, Soban Singh Jeena Government Institute of Medical Sciences and Research, Almora (Uttarakhand).

The exclusion criteria were as below:

**A. Infections:**

1. Viral Infections: Rubella, Cytomegalic inclusion, Viral hepatitis, Influenza, Mumps, Measles, Herpes simplex virus, HIV virus etc.

2. Bacterial Infection: Leprosy

3. Fungal Infection: Monilial vaginitis

4. Parasitic Infection: Malaria

5. Protozoal Infection: Toxoplasmosis

6. Spirochaet : Syphilis

7. Chlamydial Infection: Chalamydial trochomatis

**B. Maternal hypoxia and shock:** Acute and chronic respiratory diseases, heart failure, severe anemia, hyperpyrexia.

**C. Chronic illness**: Hypertension, chronic nephritis, chronic wasting diseases.

**D. Endocrine Factors:** Hypothyroidism, Hyperthyroidism, Diabetes mellitus.

**E. Cervico** - Uterine Factors: Cervical incompetence, cervial polyp, congenital malformation of uterus vagina, carcinoma of cervix, fibroid, ovarian, tumour, retroverted uterus.

The birth defect suspected to have been caused by drugs used during antienatal period will be classified according to the criterion laid down by World Health Organization. The criterion are as certain, Probable/ Likely, Possible, Unlikely, Conditioned/Unclassified, Unassessible / Unclassifiable, Causality assessments.

Whilst "conditional/unclassified" and unassessible / unclassifiable" are not causality terms, they describe the status of adverse reaction reports and therefore allow for practical communication about ADR issues.

**Results and Discussion**

There were 317 women, who were monitored for foetal anomalies in the department of Obstetrics and Gynecology, Soban Singh Jeena Government Institute of Medical Sciences and Research, Almora India. These includes 161 premature baby,141 intrauterine death (IUDs) and 15 abortions. Babies delivered these women has birth defects which include premature, IUDs abortions, Low birth baby(LBW)and other congenital anomalies(CA).

**Table 1: Correlation of mother's age with birth defects**

| Mother age (years) | Total numbers | Premature n= 161 | | IUD n=141 | | Abortion n=15 | |
|---|---|---|---|---|---|---|---|
| | | No. | % | No. | % | No. | % |
| **15-20** | 35 | 17 | 10.55 | 17 | 12.05 | 1 | 6.66 |
| **21-25** | 122 | 68 | 42.23 | 52 | 36.87 | 2 | 13.33 |
| **26-30** | 107 | 48 | 29.81 | 52 | 36.87 | 7 | 46.66 |
| **31-35** | 42 | 24 | 14.90 | 13 | 9.21 | 5 | 33.33 |
| **36-40** | 11 | 4 | 2.48 | 7 | 4.96 | 0 | 0 |

**Table 2: Numbers and percentage of birth defects monitored**

| Birth defects n = 317 | | | |
|---|---|---|---|
| | | Number | Percentage |
| Premature without congenital anomalies | Premature n= 161 | 154 | 48.58 |
| Premature with congenital anomalies | | 7 | 2.20 |
| Intrauterine death(IUD) without congenital anomalies | IUDs n= 141 | 126 | 39.74 |
| IUD with congenital anomalies | | 15 | 4.73 |
| Abortion | Abortion 15 | 15 | 4.73 |

**Table 3: Birth defects observed in babies born of mother who had taken following drugs during pregnancy.**

| S. No. | Drug name | Total number of cases n=82 | Prematiurs (%) | | IUD's (%) | | Abortions (%) | |
|---|---|---|---|---|---|---|---|---|
| 1. | Paracetamol | 31 | 13 | 15.85 | 17 | 20.17 | 1 | 1.21 |
| 2. | Cholorquine phosphate | 23 | 8 | 9.75 | 14 | 17.07 | 1 | 1.21 |
| 3. | Metoclo-pramide | 21 | 4 | 4.87 | 16 | 19.51 | 1 | 1.21 |
| 4. | Ciprofloxacin | 18 | 6 | 7.31 | 11 | 13.41 | 1 | 1.21 |
| 5. | Metronidazole | 17 | 6 | 7.31 | 10 | 12.91 | 1 | 1.21 |
| 6. | Diazepam | 16 | 11 | 13.41 | 5 | 6.09 | 0 | 0 |
| 7. | Dicyclomine HCl | 12 | 2 | 2.43 | 9 | 10.97 | 1 | 1.21 |
| 8. | Ibuprofen | 11 | 4 | 4.87 | 7 | 8.53 | 0 | 0 |
| 9. | Isoxsuprine | 9 | 3 | 3.65 | 6 | 7.31 | 0 | 0 |
| 10. | Ergot preparation | 8 | 2 | 2.43 | 5 | 6.09 | 1 | 1.21 |

**Table 4: Drugs which were suspected to be associated into foetal malformation less than five cases each**

| S. No . | Drug name | Total no of case ( n=82) | Prematines | IUD's | Abortions |
|---|---|---|---|---|---|
| 1. | Chlorpheniramine | 5 | 1 | 4 | 0 |
| 2. | Alprazolam | 4 | 4 | 0 | 0 |
| 3. | Trimethoprim+ sulfamethoxazole | 4 | 2 | 1 | 1 |
| 4. | Doxycycline | 2 | 0 | 2 | 0 |
| 5. | Lorazepam | 2 | 2 | 0 | 0 |
| 6. | Ampicillin | 2 | 2 | 0 | 0 |
| 7. | Cloxacillin | 2 | 2 | 0 | 0 |
| 8. | Loperamide | 2 | 2 | 0 | 0 |
| 9. | Phenytoin Sodium | 2 | 2 | 0 | 0 |
| 10. | Nefidipine | 2 | 2 | 1 | 0 |
| 11. | Codeine phosphate | 2 | 1 | 1 | 0 |
| 12. | Diclofenec sodium | 2 | 1 | 1 | 0 |
| 13. | INH | 2 | 1 | 1 | 0 |
| 14. | Rifampin | 2 | 1 | 1 | 0 |
| 15. | Ranitidine | 1 | 1 | 0 | 0 |
| 16. | Furazolidine | 1 | 1 | 0 | 0 |
| 17. | Etophylin + theophyllin | 1 | 1 | 0 | 0 |
| 18. | Furosemide | 1 | 1 | 0 | 0 |
| 19. | Semithicone | 1 | 0 | 1 | 0 |
| 20. | Megaldrate | 1 | 0 | 1 | 0 |
| 21. | Entroquinol | 1 | 0 | 1 | 0 |
| 22. | Atenolol | 1 | 1 | 0 | 0 |
| 23. | Clotrimazole | 1 | 1 | 0 | 00 |

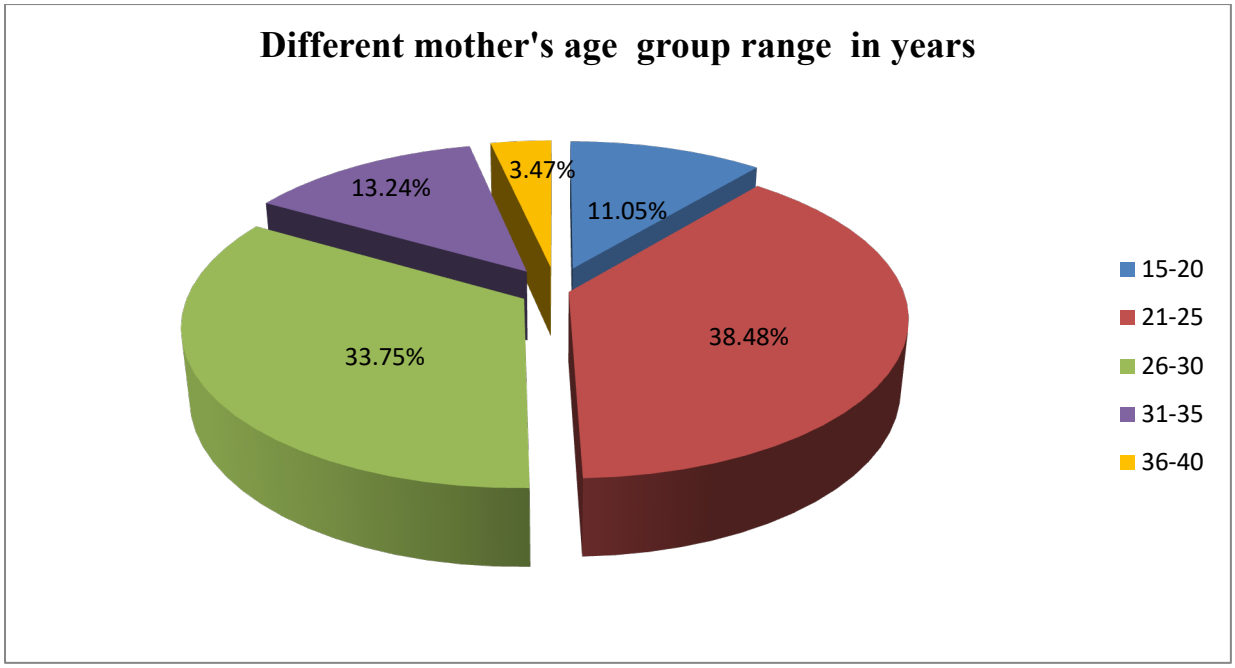


**Figure (1) Percentage of Pregnancy in different mother's age group**

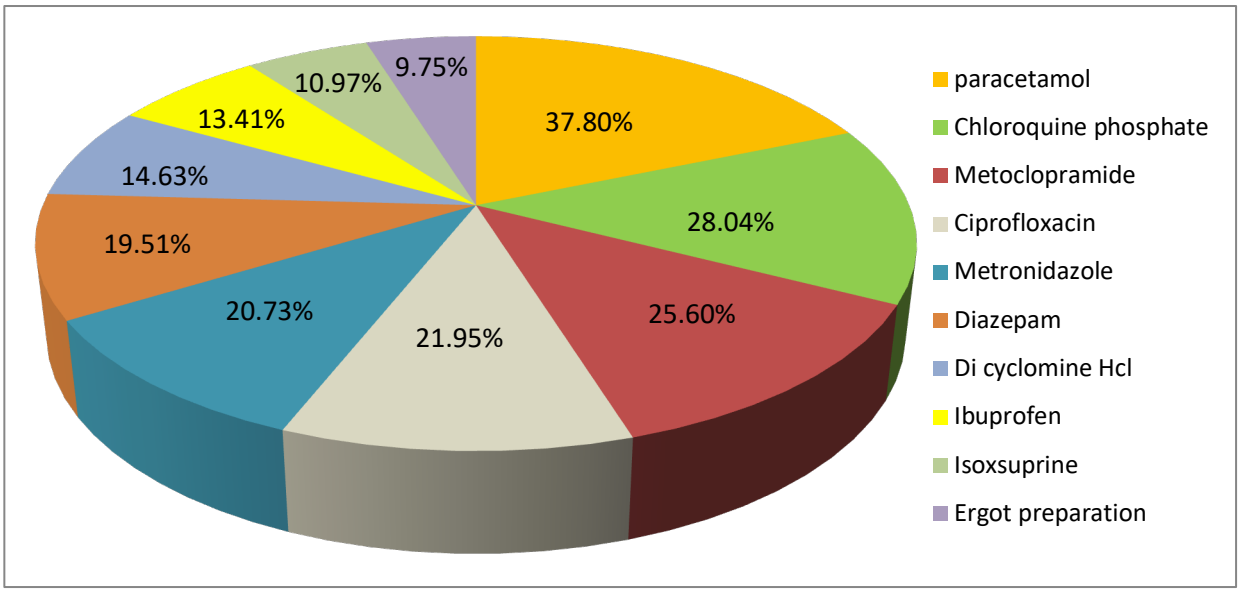


**Figure (2). Percentage birth defects observed in babies born of mother who had taken following drugs during pregnancy**

In the study three hundred seventeen pregnant women were monitored for various birth defects and found that 82 birth defects where associated with various drugs taken by women during pregnancy. As shown in table (1) largest number of birth defects mothers were in 21-25 years of age group and majority of mothers were age group of 20-35 yrs. The percentage of mothers age group were highest in 21-25 years and lowest in age group 36-40 years as shown in figure (1).

The babies with birth defects were categorized into premature without congenital anomalies 154 (48.58%), premature with congenital anomalies 7(2.20%), Intrauterine death IUD without congenital anomalies 126 (39.74%), IUD with congenital anomalies 15(4.73%) and abortions 15(4.73%) are listed in table (2).

In this study the number of drug induced birth defect cases were reported in various drug and following percentage -paracetamol 31 case (37.80%), chloroquine phosphate 23 cases (28.04%), metoc1opramide 21 cases (25.60%), ciprofioxacin 18 case (21.95%), metronidazole 17 cases (20.17%) diazepam 16 cases (19.51 %), dicyclomine Hc112 cases (14.63%), ibuprofen 11 cases (13.41) isoxsuprin 9 cases (10.97%), ergot preparata 8 cases(9.75%) (Table 3) & (Fig 2). The number of cases where association of drug into birth defect

could be established was much less when compared to with other causes leading to birth defect. (Table-4).

Prior to 1960, most birth defects were regarded as genetic in origin. The fetus was believed to occupy a privilaged site within the uterus protected from the effects of environmental agents to which the mother .might be exposed, but now it is believed that 4 to 5 percent birth defects are associated with various drugs taken during pregnancy. A vast majority of Mpopulation of North India still prefer consanguineous marriage (Individuals who are related through one or more common biological ancesters are called consanguineous relatives) (Badaurddoza, 1992; Badaruddoza et al., 1998). The present study also revealed that Muslim women are more involved in birth defect as compared to Hindus.

**Conclusion:** The teratogenic potential of most drugs is unknown, whereas only a few drugs have been shown to be teratogenic in humans, the majority have not been adequately tested for their teratogenic effects this creates an obvious dilemma for the physician attempting to provide optimum care of pregnant women. Increased awareness of possible damage to the fetus by drugs during pregnancy had led to be a few well controlled scientific studies as well as a vast array of anecdotal reports suggesting the teratogenic effect of various environmental agents.

The pendulum has now swing in the opposite direction, virtually every drug is suspected of being a teratogen and total pharmacologic prohibition throughout pregnancy has been proposed by many researchers.

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