

**SELECTED SPECIAL APPLICATIONS OF PHARMACOEPIDEMOLOGY: DRUG
INDUCED BIRTH DEFECTS**Sara Shreen*¹ and Syeda Noorida Muneera²^{1,2}Department of Clinical Pharmacy, Deccan School of Pharmacy, Hyderabad.***Corresponding Author: Sara Shreen**

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ABSTRACT

Birth defects are abnormalities of function, structure or metabolism that are present since birth. They often lead to mental or physical disabilities, and can sometimes be fatal. Taking certain drugs during pregnancy can cause birth defects. Around 1 in 10 birth defects are caused by using over-the-counter (OTC) or prescription drugs during pregnancy. Drugs that cause birth defects are called 'teratogens'. The teratogenic drugs interfere with the normal development of a fetus and can cause birth defects including cleft lip, cleft palate, spina bifida. There are several medications which are safe to use when a woman is expecting her baby. However, some prescription and OTC medications including aspirin, isotretinoin, vitamin A and some antibiotics pose the threat of birth defects and should not be used by pregnant women. Drugs have been categorized according to their potential to cause birth defects during pregnancy. Drugs in category 'A' are considered the safest, whereas drugs in Category 'X' cannot be used in pregnancy under any circumstances. As a rule, no medication should be taken during pregnancy without the advice of a doctor.

KEYWORDS: Birth defect, pregnancy, Teratogen, pharmacoepidemiology.

Pharmacoepidemiology is the study of the utilization and effects of drugs in large numbers of people; it provides an estimate of the probability of beneficial effects of a drug in a population and the probability of adverse effects.^[1] It can be called a bridge science spanning both clinical pharmacology and epidemiology.

ORIGIN AND HISTORY

- ADRs to drugs were as old as modern pharmacotherapy which was developed in 20th century
- Drug resistance, drug abuse, variations in rates of clinical effectiveness were the other therapeutic problems which emerged
- In 1961, the case reports of maternal use of Thalidomide with malformations in offsprings resulted in awareness of the potential for drugs to cause ADRs
- Since then a greater attention was focused on the detection, prevention and management of ADRs and the era of Pharmacoepidemiology has began^[2]
- The important ADRs detected through these systems include-
 - Grey baby syndrome due to Chloramphenicol
 - Vaginal cancer in off springs of women who took diethylstilbestrol during pregnancy
 - Isotretinoin induced birth defects
 - Triazolam induced CNS disturbances

- Suicidal ideation with Fluoxetine
- Deaths with Fenoterol
- Venous thromboembolism with Oral contraceptives
- International society of Pharmacoepidemiology (ISPE) was formed to obtain more data on risk and benefits of drugs in population and to discuss, develop and disseminate information about Pharmacoepidemiological methods
- In early 1960, the related field of drug utilization was developed along with the study of ADRs
- Previously DU studies were conducted mostly for marketing purposes and data were not available for use by health authorities
- As a result wide variations in the pattern and extent of drug prescribing, growing concern about ADRs and cost of the drugs lead to the development of Pharmacoepidemiological methods.

DRUG INDUCED BIRTH DEFECTS**Birth defects**

-Birth defects are the structure, function or metabolism that are present at birth.
-It happens while the baby is still developing inside the mother's womb
-It usually happens during the first 3 months of pregnancy i.e. the first trimester
-It can be due to genetic, environmental and unknown factors.^[4]

Drug induced birth defects-

- About 90% of women take medications during pregnancy, pregnant women may take both prescribed and OTC medicines
- Some women may suffer from chronic health conditions such as high blood pressure, diabetes, asthma and thyroid conditions
- Some women suffer from acute infections during pregnancy like respiratory infections or pneumonia
- Pregnant women need to take medicines regularly to manage the above said illnesses.

Effects of drugs on fetus-

- Certain drugs act directly on fetus and cause birth defects
- These drugs reduce the supply of nutrients and oxygen supply to fetus which leads to underweight or under development of fetus
- Some drugs because the muscles in uterus to contract forcefully which injures the fetus by reducing the blood supply to fetus or preterm labor and delivery^[5]
- Such drugs are known as teratogenic drugs

TERATOGENESIS

It is a uniquely affects an organism (the fetus) other than the one for whom a medication was intended (the mother). Premarketing studies typically avoid pregnant women and thus rarely provide useful information on fetal risks and safety, and a medication's class and pharmacologic characteristics do not predict its potential teratogenicity^[6] Thus, post marketing studies are required to identify the risks and safety of every medication to which a fetus may be exposed in uterus, including not only prescription but also over the counter medications, the latter being more widely used in pregnancy. Gestational timing of exposure is critical because fetal organs vary in developmental timing. Teratogens increase risks of specific birth defects rather than birth defects overall, and specific defects occur rarely (1 or fewer per 1000 births). Cohort and case-control approaches offer complementary approaches to the study of drug risks and safety, each design having its own strengths and limitations.

CLASSIFICATION OF DRUGS BASED ON TERATOGENIC RISKS

- A- Drugs taken by large number which has no any proven increase risks.
- B- Drugs only taken by limited number of pregnant women. Human data is lacking.
 - B1- Animal studies have not shown any increased risk.
 - B2- There is no increased risk.
 - B3- Animal studies show an increased risk, but it is not clear if this risk applies to humans.
- C- Drugs may cause harm to the fetus without causing birth defects. These effects maybe reversible.
- D- Drugs that have caused or may not cause birth defect, the health benefit may outweigh the risks.

X- Drugs that have a high risk of birth defects and should not be used during pregnancy

CLASSIFICATION OF TERATOGENIC DRUGS BASED ON SEVERITY

- High risk teratogens-
Drugs that produce major defects in a high proportion(roughly 25%) of exposed pregnancies.
Eg- Thalidomide, Isotretinoin
- Moderate risk teratogens
Drugs which increase the rate of specific birth defects by perhaps 5-20 fold
Eg- Carbamazepine

DRUGS FOR WHICH TERATOGENIC RISK IS UNKNOWN

Most prescription and non prescription(OTC) drugs fall into a much bigger category of drugs with unknown teratogenic risks. This is because pregnant women are excluded from clinical trials. As a result in drugs where the true teratogenic risk is nil, these warnings deny potentially useful therapy.

DRUGS FOR WHICH TERATOGENESIS IS ALLEGED AND CLINICAL CONSEQUENCES-

At one time or another many drugs have been alleged to be teratogenic, with profound clinical consequences. For example 30 years ago the widely used anti nausea drug Bendectin was alleged to cause various birth defects. Despite the lack of support for these allegations, legal concerns led to manufacturer to withdraw the drug from the market.

Ironically the aggregate data for Bendectin have provided the strongest evidence for safety for any drug used in pregnancy.

Thus before reporting a birth defect caused due to a drug, all other factors must be considered and it must be made sure that the defect is due to the said drug.

SAMPLE SIZE CONSIDERATIONS TO STUDY TERATOGENIC DRUGS

- Birth defects is not a single, homogenous outcome and teratogens do not uniformly increase the rates of all birth defects but rather increase rates of selected defects. Defects may vary widely in terms of gestational timing, embryological tissue of origin and mechanism of development.
- Thus it is necessary to consider a large sample size to get significant results and data about different types of birth defects.

STUDIES USED FOR DRUG INDUCED BIRTH DEFECTS

- Cohort studies are mainly used to study teratogenic drugs as it helps in comparing the exposed group vs unexposed group i.e women taking drugs suspected to be cause of defect vs women taking no drugs.

- Three types of cohorts relevant to the pharmacoepidemiologic study of birth defects is designed to include studies designed to follow large populations exposed to various agents, use of data sets created for other purposes, and follow up studies of selected exposures. Though many cohorts are sufficiently large to assess risk of birth defects overall, few cohorts have sufficient numbers of exposed subjects with specific defects, most of which have background rates ranging from 1 per 1000 to 1 per 10,000.

OUTCOME

- Though birth defects are often classified by organ system (Eg- musculoskeletal) whenever possible they should be classified on the basis of the embryologic origin for a given defect.
- For Eg- neural crest cells form various structures of the ear, heart and neural tube, and it is of note that the retinoid Isotretinoin, which interferes with neural crest cell migration/development, produces malformations of the ear, heart and neural tube.

CONFOUNDING

- Potential confounders that are routinely considered in teratologic studies include maternal age, race, geography and socio economic status.
- However additional potential confounders must be identified based on understanding the epidemiology of specific defects.
- Prominent among these is exposure to periconceptional folic acid, which is known to reduce the risk of number of defects such as exposure typically in the form of multivitamins, should not be confused with exposure to prescribed prenatal folate containing multi vitamins which are typically taken after the critical period for the development of a number of folate preventable defects. In addition to this various health behaviors like smoking and alcohol should also be considered.

FUTURE RECOMMENDATIONS

Integration Of Epidemiology And Biology

- Advances in molecular biology and genetics will markedly enhance our ability to classify defects in biologically meaningful categories and facilitate development of biologically plausible hypothesis.
- Even the most notorious human teratogens do not produce malformations in all exposed fetuses and this incomplete penetrance is likely due to differences in host susceptibilities such as host's handling of drugs.

THE LEGAL AND REGULATORY CLIMATE

- Pharmacoepidemiologic studies of teratogenesis require access to information that identify women who have become pregnant, their medication exposure and details of the pregnancy outcomes of those pregnancies.

- It is critical that the researchers engage their communities about the public health value of epidemiologic research and the need for balancing privacy concerns with the need to provide critical information on the risks and safety of medications taken in pregnancy.

HOPE FOR AN INTEGRATED APPROACH-

- Future studies of birth defects should consider secular changes in use not only related to prescription drugs (including vaccines) but also OTC and herbal products and they will undoubtedly focus increased attention on issues of validity and statistical power.
- Although thalidomide debacle did much to stimulate research and regulatory attention on the adverse effects of medications, it is ironic that in the 50 years since that teratogenic disaster, drugs have yet to come under systematic study for their potential teratogenic risks.

KEY POINTS FOR STUDIES OF DRUG INDUCED BIRTH DEFECTS

- Because teratogenesis involves maternal exposure that adversely effect another organisms development, it creates unique issues for pharmacoepidemiologic studies.
- Known teratogens do not increase risk of all birth defects, but rather one or several specific defects, with baseline birth prevalence of about 1 per 1000 to 1 per 10,000, specific defects are outcomes.
- Pregnancy registries (small cohorts) are useful to identify high risk teratogens (Eg- isotretinoin) but are underpowered to identify lesser risks.
- Larger databases (Large cohorts) can sometimes provide adequate power but are usually constrained by serious limitations in information available on exposures, outcomes and covariates.
- Case control studies and particularly case control surveillance are well suited to assess risks of birth defect in relation to various antenatal exposures.
- In the absence of knowledge regarding biologic mechanisms for the development of birth defects, a presumably valid and consistently observed association between an exposure and particular birth defect should not be dismissed because biologic plausibility cannot be demonstrated

EXAMPLES OF TERATOGENIC DRUGS AND THEIR EFFECTS

- Thalidomide- Causes extreme under development of arms and legs and causes defects of the intestine, heart and blood vessels in infants.
- Oral hypoglycemic- It caused high blood sugar levels in infants. However insulin injections will not cause any harm.
- Etretinate- Used to treat skin disorders but also a teratogenic drug

- Anti hypertensives-Used to treat high blood pressure, reduces blood flow to placenta causing damage to fetus
- Digoxin – Used to treat heart failure,has a teratogenic effect either before or after the birth of the infant^[3]

-Other effects included deformed eyes, deformed heart, deformed alimentary, deformed urinary tract, blindness and deafness.

-Other malformations occurred affecting the cardiovascular system, gastrointestinal tract, kidney and the special sense organs.

THE THALIDOMIDE DISASTER

-It was prescribed as a sedative and claimed to cure anxiety, insomnia, gastritis and tension.

-It was used against nausea and to alleviate morning sickness in pregnant women.

-Those subjected to Thalidomide while in the womb experienced limb deficiencies.

Thalidomide history

-It was first marketed in West Germany in the year 1957

-It was given to pregnant women to alleviate morning sickness. After the drug was sold about 5000-7000 infants were born with phocomelia. Only 40% of them survived.

-Throughout the world 10,000 cases were reported out of which only 50% of the 10,000 survived

-Now it is being marketed by Celgene as a treatment for Cancers, leprosy, HIV/AIDS.

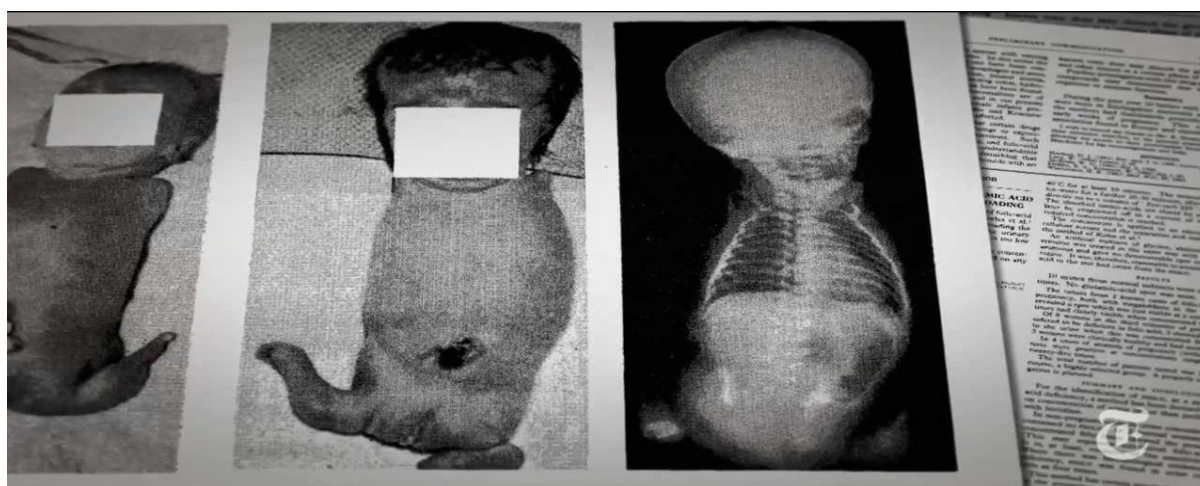


Fig.1: Thalidomide history.

EMBRYO FETAL TOXICITY

-When taken during pregnancy causes severe birth defects or embryo fetal death.

-Even single dose taken by a pregnant women during her pregnancy can cause severe birth defects

-It was suspected due to the antivitaminic effect of thalidomide as derivatives of glutamic acid.

-The antiangiogenic action of drug that causes limb defects through preventing blood vessels migration into developing limb bud.^[2]

SIDE EFFECTS OF THALIDOMIDE

- | | |
|-----------------------|------------------------|
| -Sleeplessness | - Nausea |
| -Constipation | -Pain in arms and feet |
| -Skin rashes | -Shivering |
| -Severe headaches | -Giddiness |
| -Stomach aches | -Depression |
| -Numbness | -Mood swings |
| -Dizziness | -Buzzing in the ears |
| -Severe birth defects | |

APPLICATION OF PHARMACOEPIDEMIOLOGY TO PREVENT DRUG INDUCED BIRTH DEFECTS

Pharmacoepidemiology is the application of the principles of epidemiology to drug effects and drug use

and thus used to study the effects of drugs in larger population.

Drug resistance, drug abuse and variations in rates of clinical effectiveness, thalidomide disaster occurred in 1960s which resulted in awareness regarding the severity of ADRs and the need to monitor them. This led to the development of pharmacoepidemiology and pharmacovigilance^[10]

ADR REPORTING SYSTEM IN DIFFERENT COUNTRIES-

➤ UK- Yellow Card System^[8]

The Yellow Card Scheme is the UK system for collecting information on suspected adverse drug reactions (ADRs) to medicines. The scheme allows the safety of the medicines and vaccines that are on the market to be monitored.

➤ USA- MEDWATCH

MedWatch is the Food and Drug Administration's "Safety Information and Adverse Event Reporting Program." It interacts with the FDA Adverse Event Reporting System (FAERS or AERS). MedWatch is used for reporting an adverse event or sentinel event.

➤ AUSTRALIA- BLUE CARD SYSTEM^[7]

The blue card system is used in Queensland as a prevention and monitoring system for people working with children and young people. Other states have similar systems, but their cards are not called "blue cards". The government of India has launched the Pharmacovigilance Programme for India (PVPI) in July 2010 through CDSCO to monitor such developments. It is to be launched in five phases. The first phase was introduced in mid-2010 with an objective of inducting ADR Monitoring Center (AMC) in 40 Medical colleges in one year; 60 more AMC centers are to be added by early 2012 and 100 by 2013. Various hospitals, Medical Colleges and private nursing homes will be covered till 2014. CDSCO will provide the operational and logistic support such as Internet connection, computer, telephone line and WHO will provide free softwares for ADR monitoring such as VigiBase and PaniFlow for ADRs due to vaccines. The National Coordinating Center (NCC) of PVPI is located at 'Indian Pharmacopoeia Commission (IPC), Ghaziabad' and provides all the technical supports to the CDSCO office. ADR reports generated at AMCs are sent to coordinating center which collate, assess and incorporate them into Pharmacovigilance database. The reports finally conveyed to WHO-Uppsala Monitoring Center ADR database.

➤ India- Adverse Event Reporting System (AERS) generated by CDSCO

With the increasing pressure to manage research and development (R and D) in pharmaceutical industry, the government is taking many more initiatives to regulate it.

REPORT CHARACTERISTICS-

The quality of report must be compatible with ICH guidelines. The report should consist of –

- 1) Product information-
 - a) Identification of active ingredient /product
 - b) Formulation of product
 - c) Pharmacokinetics
 - d) Product quality defect
 - e) Information on manufacture & batch number
- 2) Report must be desirable- It must describe-
 - a) Medication error
 - b) Potential for medication error
 - c) Information on the product
 - d) Work environment in which error occurred
 - e) Type of error occurred
- 3) Characteristics of good quality case report-
 - a) Adequate information on product use
 - b) Patient characteristics
 - c) Medical history
 - d) Concomitant treatment
 - e) Description of ADRs/ADEs including response to treatment and clinical outcomes^[11]

Prescription of medications to pregnant women is usually a challenge as the drug benefit has to be considered

regarding its potential adverse effects. As medication use is common in pregnant women, by chance or necessity, it gives the opportunity to evaluate the consequences of prenatal drug exposure in real life through pharmacoepidemiologic studies. An efficient system could follow up each pregnant woman, who had taken a medication, and consider her as a precious information for the knowledge of drug potential adverse actions against the child, who must be followed up to identify long term-effects. The diversity of data sources and approaches of pharmacoepidemiological studies, the implementation of international networks as well as the improvement of adverse signal detection are the keystones of such an evaluation.^[12]

CONCLUSION

• There is a need to study drug induced birth defects as the new drugs are being marketed and preclinical trails provide limited data as it includes limited number of population and avoid special groups are excluded, hence it is difficult to study rare events in preclinical studies. Hence by encouraging the use of pharmacoepidemiological studies to study drug induced birth defects by reporting systems. Newly identified drugs which cause birth defects can be brought to the notice, which can be helpful in preventing birth defects.

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