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Review Article

MATERNAL MEDICINES AND TERATOGENICITY: A REVIEW

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A R T I C L E I N F O

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A B S T R A C T

The use of drugs in pregnancy requires great concern as it is a time of profound physiological changes. The prescribing of drugs in pregnancy requires specific caution. The changes in the physiological state in pregnancy can have an effect the pharmacokinetics of drug administered. As the total avoidance of treatment is not possible in pregnancy, one should be cautious while using a drug in pregnancy. Pregnancy may require pharmacological treatment as there are chances new medical problems like gestational diabetes or exacerbation of old ones like migraine. The Thalidomide tragedy in 1960s opened eyes to the need for caution in the drug use in pregnancy and the need for the alternatives for teratogenic drugs. This review focuses on teratogenicity and approaches to assess the risk of drug use in pregnancy and methods for the safe prescribing of drugs in pregnancy.

INTRODUCTION

Teratogenesis is a prenatal toxicity characterized by structural or functional defects in the developing embryo or fetus. It also includes intrauterine growth retardation, death of the embryo and transplacental carcinogenesis. The study of the causes and underlying mechanisms of teratogenesis is called teratology. Any agent which can cause birth defect can be called as a teratogen. Teratology is important to ensure the safety of drug use in pregnancy. The use of drugs in pregnancy is a growing concern due to the increasing risk of teratogenicity.

Some Important Teratogens from History

Thalidomide

Thalidomide was a widely used drug in the late 1950s and early 1960s for the treatment of nausea in pregnant women. It resulted in severe birth defects like phocomelia in children born to women who took thalidomide in pregnancy. Over 10,000 children were born with severe malformations. Thalidomide was subsequently withdrawn from the UK in November 1961 and by 1962 from most of the world. The Thalidomide disaster demonstrated that the fetal exposure to the drug during critical periods of development resulted in severe limb defects and other organ dysgenesis. The suffering caused by thalidomide indicated every drug has a potential to cause fetal harm.

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Benedectin, which is a combination of doxylamine and pyridoxine, was the most widely used medication in the United States to treat nausea and vomiting associated with pregnancy during 1960s.The drug was withdrawn from the market by its manufacturer in 1982,as the lawsuits claimed the drug was teratogenic. But the withdrawal of the drug did not drecrease the rate of any specific category of malformation. In Canada, the drug continues to be marketed as dialectin. It was advised by the review committee to be safe.

Isotretinoin

After the thalidomide tragedy, there were changes in the labeling of drugs, showing warnings not to be taken in pregnancy. Isotretinoin was introduced in the early 1980s for the treatment of acne. But before its clinical introduction, this drug was known to cause teratogenicity in animals. Despite explicit warning labels, scores of children with retinoid embryopathy were born in the years after the drug was introduced. Such warnings are not sufficient, because women taking isotretinoin may not plan their pregnancies, or their birth control methods may fail. In addition, some women and men are illiterate, and they may not read or understand the drug label content.

Contraceptives: An Approach in Preventing Teratogenicity

This method was first implemented in South America, were sexually active women were administered with oral medroxyprogestrone, before receiving thalidomide, reported thalidomide associated embryopathy in children of women

who continued to take the drug after the period of contraceptive efficacy(3 months).A need recognized to develop further method for effective contraception to reduce the teratogenic exposure resulted in the development of implantable hormonal compound (Levonorgestrel Implants),which documented efficacy in young women who are taking teratogen medicinally (phenytoin)or substance abuse(cocaine) in whom an oral contraception are likely to fail. But a study on "interaction between antiepileptic drugs and hormonal contraception" shows a higher incidence of breakthrough bleeding and contraceptive failure among women with epilepsy. Phenobarbitone, phenytoin, carbamazepine, oxcarbazepine, felbamate and topiramate have been shown to increase the metabolisim of ethinylestradiol and progesterone. Therefore a women is on one of the oral contraceptive pill, she will need to take a preparation containing at least 50 mcg of ethinylestradiol. In this study it was found that levonorgestrel implants are contraindicated in women receiving these AEDs because of cases of contraceptive failure.

Assessing Risk VS Safety of Drugs in Pregnancy

For a drug to get it approved and marketed, it has to go through different stages of clinical trial to asses its safety and efficacy. But if the sole purpose of the study was to ascertain the possible teratogenic effect of drug, it would be unethical to enrol pregnant or soon to be pregnant women, so the data from studies in animals provide the initial guidelines. But the thalidomide associated embryopathy itself proves that human teratogenicity could not be predicted on the basis of studies in animals, were in case of isotretinoin the studies in animals prevented a disaster similar to thalidomide tragedy. Dose of drug is also an influential factor in considering the teratogenicity. A classic example is high dose of gluccocorticoids caused oral cleft in animals, but clinically relevant dose in humans have no such effect, conclude that studies in animals may identify teratogenic effects, it can be difficult to extrapolate these effects to humans.

Epidemiological Studies

Due to the ethical reasons, experimental teratology studies or randomized cotrolled trials are rarely conducted in pregnant women. Other methods which are used to identify possible drug teratogens include case reports, case studies and observational studies. The adverse fetal effects are usually published in the form of case reports. If the drug is taken by practically small numbers of women, like isotretinoin or if the drug causes a rare malformation, then a strong association can be established between the drug and teratogenicity. It was from the case reports that the drugs like Warfarin, diethylstilbesterol, isotretionoin were identified as teratogens initially. But if the drug is taken by relatively higher number of pregnant women, a small number of case reports of abnormalities may simply reflect the spontaneous occurance of malformations in the general population in the general population, ranging from 1 to 5 percent, unless there is a characteristic pattern of malformations.

Epidemiological studies are intended to determine whether mothers who took a specific drug during pregnancy have a larger number of malformed children than mothers who did not(cohort studies) or whether mothers of children with a specific malformation took the drug more often than mothers of the children without the malformation(case control studies).The development of teratology information services has helped in the development of source data for prospective observational research. Pregnant women taking prescription or over the counter drugs, call these centres for the risk assessment counseling. Collaboration among these services can yield the large samples needed to study the rare events more effectively. Postmarketing cohort studies of prospectively reported exposures may be performed by the drug manufacturers. All these epidemiological studies can help to gather data and find out association between the drug and teratogenic effect.

Factors Affecting In Establishing Risk Vs Benefict of Drugs in Pregnancy

There are many factors which affect in defining the safety or risk of drugs in pregnancy. One among them is sample size. Sample size has a large effect on the reproducibility of results. Many of the congenital malformation occurs rarely, and there are some teratogens which are known to be associated with some defined malformation, sometimes do not affect the great majority of exposed fetuses. In point of fact, very few (isotretinoin, thalidomide) drugs increase the total malformation rate by a factor of more than two. For instance, if 3 percent is the risk of major malformation in a given population, then at least 220 pregnancies with specific exposure and similar number of controlled pregnancies will be required to show a risk that is increased by a factor of 2.5, with a power of 80%.

Presence of maternal disease is the other factor which affects the study. Infants with intrauterine growth retardation is likely to happen in pregnant women with hypertension or cancer. Defined malformations are known to happen in pregnancy with epilepsy or diabetes mellitus. For that reason, presence of maternal disesease must be considered in any attempt to establish the role of fetal exposure to drugs and malformations.

In a population based cohort study in 1537860 singletons born in Denmark (1978-2004) on "Association between preeclampsia and risk for epilepsy in offsprings", it was found that prenatal exposure to preeclampsia was associated with an increased risk for epilepsy among children with a gestational age at birth of at least 37 weeks.

Other component that influences the study is the recall bias or reporting bias in retrospective studies. Those women who gave birth to malformed children may be more likely to rememeber the course of their pregnancies, with the purpose to understand what went wrong, than women with normal children, thus causing false positive association. A classic example is diazepam, which was initially thought to be a teratogenic drug causing oral clefts, but subsequently refuted that no risk associated through large cohort and case control studies.

In non randomized observational studies, the confounding factors are not randomly distributed between the exposed and non exposed groups. As an example, in comparing the outcome of pregnancy in women who were treated with carbamazepine and other group who received phenytoin, one must consider that the two groups of women had the same type and severity of seizure disorder, if not then the study is likely to be pointless.

The quality of information received by the drug manufacture is usually poor and the outcome data are scanty because of loss of follow up, importantly, women and health professionals

contacting the manufacturer as likely to report adverse fetal outcomes, not uneventful ones.

And there are several drawbacks in considering meta analysis in establishing the risk and benefict of drugs in pregnancy, because the data obtained might be inequivalent in terms of its quality and method.

Care and Counselling on Fetal Health Effects of Preconceptional Period Maternal Drug Use

Preconceptional care provides the opportunity to optimize the use of medications in the period when the woman is preparing for pregnancy. Preconceptional care involves determining the condition that need to be used in the pre-pregnancy period, and avoiding the use of unnecessary medications, management of the necessary treatments to optimize maternal health with the protection of embryo and fetus at every stages of pregnancy.

Women who are pregnant or planning a pregnancy should be properly counselled about the nature and magnitude of risk associated with the use of a drug in pregnancy. For example, a women with manic depression treated with lithium in the first trimester will need to understand not only the slightly increased risk of fetal cardiac anomalies associated with the drug(<1%) but also the increased genetic risk of manic depression in her child.

A survey in Midi-Pyrenees area on perception of teratogenic and fetotoxic risk by health care professionals aimed to assess the teratogenic and fetotoxic risk perception of common medications by general practicioner and community pharmacist. In this study 103 GPs and 104 CPs were interviewed. And for each given drug the mean value of perceived teratogenic risk by health professionals was higher than the values that can be found in scientific references, which concluded that potential teratogenic and fetotoxic risk of several commonly used rugs is unknown by health professionals. This misperception can lead to inappropriate decision for pregnancy outcomes.

It shows that more efforts are needed to sensitize general practicioner and community pharmacist during initial and continuous training and to better communicate on teratogenic risk to inform pregnant patients.

Risk Classification Systems for Drug Use during Pregnancy

FDA has established a system that classifies drugs on the basis of data from human and animal studies, ranging from class A, which are designated as safe for use in pregnancy to class X drugs which are contraindicated in pregnancy for the better interpretation of teratogenic risk associated with prescription drugs for physician.

FDA Pregnancy Categories

Category A: Controlled studies shows no risk:adequate, well controlled studies in pregnant women have failed to demonstrate risk to the fetus.

Category B: No evidence of risk in humans: either animal findings show risk, but human findings do not: or, if no adequate human studies have been done, animal findings are negative.

Category C: Risk cannot be ruled out: human studies are lacking and animal studies are either positive for fetal risk or lacking as well. However, potential benefit may justify potential risk.

Category D: Positive evidence of risk: investigational or post marketing data shows risk to the fetus. Nevertheless potential benefit may outweigh the risk.

Category X: Contraindicated in pregnancy. studies in animals or humans, or investigational or post-marketting reports have shown fetal risk that clearly outweighs any possible benefit to the patient.

But this system of classification resulted in doubtful statements that may be difficult to interpret and use for counselling and can cause anxiety among women. As a result, the Teratology society has proposed that the FDA has abandoned the current classification system in favor of more meaningful, evidence based narrative statements, and the proposal received public support, resulted in the development of different classification systems for different countries.

In a study conducted by Antonio Addis on "Risk classification systems for drug use during pregnancy" to compare and analyse the consistency between and the criteria for risk classification for medication used during pregnancy included in 3 widely used international risk classification system (FDA,ADEC,FASS). It was found that only 61(26%) of the 236 drugs common to all 3 systems were placed in the same risk factor category. Differences in the category allocation for the same drug can be a source of great confusion among users of the classification system as well as those who require informations regarding risk for drug use during pregnancy, and may limit the usefulness and reliability of risk classification systems.

Prescription of Drugs during Pregnancy

Owing to the paucity of evidence available on the risk and benefits of drug use in pregnancy, use of medicines in pregnancy is a concern for both the pregnant women and their healthcare providers. Most of the pregnant women require drug therapy because of pregnancy induced medical conditions like nausea and vomiting, diagnosed with chronic or acute conditions.

A common concern about the care of pregnant women involves the use of OTC medications. Pregnant women should be discouraged from taking OTC medications. Although most OTC medications have an excellent safety profile, some have unproven safety or known to adversely affect the fetus. The safety profile of some medications may change according to the gestational age of the fetus. For eg; NSAIDs may be taken safely during the first trimester of pregnancy, but there is increasing evidence that some NSAIDs constrict or even close the fetal ductus arteriosus during the late pregnancy.

Fetal safety must be considered while selecting a drug during pregnancy and to minimize the fetal risk, drug dose at lower end of therapeutic range should be prescribed during pregnancy. However because of increased body weight and more rapid clearance of many drugs (lithium, digoxin), during late pregnancy some women may need higher than normal dose.

It is the responsibility of all clinicians including pharmacist to counsel pregnant women with complete, accurate and current informations on the risk and benefit of using medications during pregnancy. Counselling women who have had exposure

to drugs about risk of teratogens involves accurately identifying exposure and quantifying the magnitude of exposure. This may be straightforward task for the prescribed drugs but it can be much more difficult with OTC or other drug abuse. Also when selecting drugs to be used in pregnancy effectively, drugs that have been in use for a long time are often preferable because fetal safety has been established even though newer alternatives may be available.

CONCLUSION

Various approaches have been used to study the association between the drugs and teratogenicity. Animal studies and observational studies have contributed a lot to the understanding of teratogenicity. FDA preganacy risk categorization has also helped in the safe drug prescribing in pregnancy. Case reports has contributed to establishment of the pregnancy and drug use association. Though randomized trials can pave the way to finding the association between various drugs and teratogenicity, they have been rarely used due to the ethical reasons.

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