WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES

Volume 3, Issue 3, 72-83. Review Article ISSN 2278 – 4357

TERATOGENIC HEROES – A REVIEW

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Article Received on
04 January 2014

Revised on 29 January 2014,
Accepted on 24 February 2014

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ABSTRACT

Pregnancy is a unique physiological condition where drug treatment plays a major role. Most women take a medicine at some point during pregnancy, and especially more than 80% of this includes at least one prescribed medication. Some women enter pregnancy with medical conditions like asthma, epilepsy, schizophrenia, hypertension, etc., that requires treatment. But every drug administered or taken by pregnant women may affect the health of both the mother and fetus. Various drugs like antiepileptic, antipsychotics, vitamin A, purine derivatives, antidepressants with benzodiazepines, flavonoids, caffeine, alcohol consumption, smoking and substance abuse causes significant congenital malformations and other perinatal complications. Also a significant rise in the incidence of polytherapy with two or more antidepressants, antipsychotics and sedative-hypnotics have a great impact. On the other hand, this review highlighting the importance of Preconception counseling which will increase women's knowledge related to the teratogenic drug use and its effects during pregnancy that helps to protect the unwanted birth defects.

Key words: FDA, Major Congenital Malformations, Preconception counseling, Pregnancy, Teratogenic.

INTRODUCTION

Most women take a medicine at some point during pregnancy, and for more than 80% this includes at least one prescribed medication[1]. During pregnancy, the average fetus is exposed to four physician-prescribed and five self-prescribed drugs. Every drug administered or taken by a pregnant woman presents the mother with both risks and benefits. The risks include the drug's potential as a teratogen or as a cause of toxicity in the fetus. It has been estimated that up to 10% of congenital anomalies may be caused by environmental exposures–that is, exposures to medications, alcohol, or other exogenous factors that have adverse effects on the developing embryo or fetus[2]. The concern on medication use during pregnancy and lactation has been influenced by historical events, including thalidomide crisis in the 1960s and the teratogenic effects discovered, related to the use of diethylstilboestrol in 1971. These events led the US Food and Drug Administration to establish strict regulations regarding drug labeling, the use of medications in pregnancy, requiring demonstrations on safety and efficacy of any drug before it became commercially available[3].

Many medicines involved are associated with substantial experience of safe use in pregnancy, but there is significant prescribing of drugs known to be associated with fetal risks, with 1–4% of women being prescribed medicines considered contraindicated[4] and a larger proportion prescribed medicines where information on safety in pregnancy is incomplete. These figures are in the context of over 650 000 maternities in England annually[5], up to 50% of which may be unplanned[6]. Commonly used medicines include analgesics, antibiotics, antiemetics and there is also evidence of increasing use of antidepressants during pregnancy in UK[7] and USA[8].

Also due to the changes in cardiovascular, pulmonary, gastrointestinal, renal, and hepatic function during pregnancy[9], there are also changes in the expression and activity of transport proteins and enzyme systems, such as cytochrome P450 (CYP) enzymes leading to PK alterations which may change the metabolic profile of a drug. The presence of the fetal-placental unit further distinguishes the pregnant state from a nonpregnant adult, and offers significant complexity to determining a drug's safety profile[10-12]. Developmental toxicity (death, structural malformations, functional abnormalities, growth restriction, or premature birth) is a concern throughout gestation[13], and certain drugs or exposures may interfere with the development and function of the placenta[14]. The placenta may change the metabolic

profile of a drug during pregnancy, for example, the placenta may be responsible for new metabolites, not observed in the nonpregnant adult, as recently observed for glyburide[15]. Hence careful consideration of the benefit to the mother and the risk to the foetus is required, while prescribing drugs during pregnancy. Reducing medication errors and improving patient safety are of utmost importance[16].

DRUGS USED DURING THE PERIOD OF PREGNANCY

In a recent study, majority of drugs used during pregnancy belonged to USFDA category A, such as vitamins and mineral supplements. This was followed by category B drugs, which included paracetamol, diclofenac sodium, ibuprofen, antacids, dicyclomine, ranitidine, omeprazole, pantoprazole, ampicillin, amoxicillin, cephalosporins, metronidazole, methyldopa, which were prescribed for diseases encountered during pregnancy. There were some conditions where category C and D drugs like Nifedipine, insulin, clotrimazole, fluconazole, digoxin, chloroquine, isoxsuprine, betamethasone, phenobarbitone, and carbamazepine were prescribed to prevent complications caused by various disease conditions. The only Category X drug, Progesterone, was prescribed in cases of threatened miscarriages, missed abortions and preterm labour[17].

Some of the selected drug's teratogenic effects are as follows

Teratogenic exposure to Antiepileptic drugs (AED)

Antiepileptic drug (AED) exposure *in utero* has been associated with major congenital malformations and adverse cognitive outcomes in the offspring of women with epilepsy[18,19]. The use of older-generation AEDs during pregnancy is known to be associated with a two- to threefold increased risk of birth defects in the offspring and possibly also other adverse outcomes in the exposed infant. Much less has been known about newer-generation AEDs[20]. A systematic review by using meta-analysis of published pregnancy registries and cohorts found that the highest rates of births with congenital malformations (CMs) were seen for valproate (10.73%; 95% CI = 8.16, 13.29) and phenytoin (7.36%; 95% CI = 3.60, 11, 11). But AEDs like Carbamazepine (4.62%; 95% CI = 3.48, 5.76), phenobarbital (4.91%; 95% CI = 3.22, 6.59), and lamotrigine (2.91%; 95% CI = 2.00, 3.82) were slightly lower. Also they found that the highest rate of births with CM for polytherapy regimens including the individual drugs plus one other AED were seen for phenytoin (11.47%; 95% CI = 6.65, 16.30), phenobarbital (9.19%; 95% CI = 5.88, 12.50), and valproate (9.79%; 95% CI = 7.57,

12.02). Hence they concluded that across AEDs, valproate was associated with the highest risk of malformations[21].

Long term Teratogenic exposure to Vitamin A derivative

Isotretinoin, a commonly used medication for severe acne. It has severe teratogenic effects, as serious craniofacial, cardiovascular, thymic and central nervous system malformations. Generally patients in treatment with isotretinoin avoid eventual pregnancy, and after its stopping, fertility and foetal development are normal once circulating isotretinoin levels return to normal. But a study stated that a 32 year-old healthy nullipara pregnant woman, with an uneventful past gynaecological history, was admitted in Hospital, with a severe depressive syndrome in a 18 weeks malformed pregnancy for thoraco-omphalopagus conjoined twins. She only assumed isotretinoin, at dose of 1 mg/kg a day, for a severe and scarring acne for 7 months. But unfortunately even after 3 months of pharmacological wash out, patient become pregnant and manifested this severe malformation. Woman interrupted gestation, by labour induction. Hence the authors concluded that the isotretinoin has a possibility to develop foetal malformations even after a long term wash out from isotretinoin therapy[22].

Teratogenic exposure to Purine derivatives

Kozenko M et al, reported a case of a multiple congenital anomalies in a newborn infant whose mother was on allopurinol treatment through the pregnancy. The pattern of congenital anomalies that was noted in their patient was similar to the pattern described in a number of published reports following mycophenolate mofetil [CellCept®] treatment during pregnancy. The anomalies present in their patient include: diaphragmatic hernia, unilateral microtia and absence of external auditory canal, micrognathia, microphthalmia, optic nerve hypoplasia, hypoplasia of the corpus callosum, unilateral renal agenesis, pulmonary agenesis, and cleft lip and palate. Since both allopurinol and mycophenolate mofetil act by disrupting purine biosynthesis and given the similarities in anomalies seen after prenatal exposure, the authors suggested that allopurinol should also be considered as a teratogen[23].

Teratogenic exposure to Antipsychotics

Many First-generation antipsychotics (FGAs) (including haloperidol, chlorpromazine, fluphenazine, thioridazine) have been associated with perinatal complications, particularly when exposure is later in pregnancy. These include but are not limited to withdrawal symptoms, unstable body temperature, extrapyramidal signs, respiratory distress, seizures and

transient neurodevelopmental delay. Conclusions regarding other FGAs are limited due to either poor methodology or incomplete reporting[24].

Various studies found that exposure to second generation antipsychotics (SGAs) is associated with a significantly increased risk of low birth weight[25,26] and small for gestational age infants, in comparison to healthy controls[26].

A study has shown a significant rise in the incidence of polytherapy with two or more antidepressants, antipsychotics and sedative-hypnotics, as well as an increase in the concomitant prescription of an antidepressant and antipsychotic[25].

Teratogenic exposures to Serotonin reuptake inhibitor antidepressants and benzodiazepines

A study performed to determine a population-based incidence of congenital anomalies following prenatal exposure to serotonin reuptake inhibitor antidepressants used alone and in combination with benzodiazepines. In this study, population health data, maternal health, and prenatal prescription records were linked to neonatal records, representing all live births in British Columbia during a 39-month period (1998-2001). Even after controlling for maternal illness profiles, infants exposed to prenatal serotonin reuptake inhibitors in combination with benzodiazepines had an increased incidence of congenital heart disease versus controls who had not been exposed. Serotonin reuptake inhibitor monotherapy was not associated with an increased risk for major congenital anomalies, but was associated with an increased incidence of atrial septal defects, and researchers did not associate risk with first trimester medication dose/day[27].

Another study concluded that antidepressants do not seem to be associated with increased risk of congenital malformations, but evidence showed a statistical significance for cardiovascular malformations[28].

Teratogenic Exposure to substance abuse

Children, adolescents, and adults with prenatal exposure to alcohol were often exposed to substances in utero, including tobacco, cocaine, methamphetamines, marijuana, and opiates all of which are substances known to affect brain structure[29-31].

Teratogenic exposure to flavonoids

Hydroxyethylrutoside (HER), a flavonoid derivate drug, used frequently in pregnant women for the treatment of vascular diseases. A case-control study evaluated the teratogenic potential of oral HER treatment in the Hungarian population. In this study they compared the exposure (HER treatment) during pregnancy in the mothers of cases with congenital abnormalities and matched with the control newborns without any defect. Of the 22 843 cases with congenital abnormalities, 567 (2.5%) had mothers with HER treatment while of 38 151 matched controls, 1143 (3.0%) were born to mothers with HER treatment (OR with 95% CI: 0.8, 0.7–0.9). However, an association of HER treatment during the second and/or third month of pregnancy was found with the higher risk of unilateral ocular coloboma (OR with 95% CI: 5.4, 2.2–12.9) and a new congenital abnormality syndrome including anotia/microtia, poly/syndactyly and caudal (genital and anal) defects (OR with 95% CI: 3.0, 1.3–27.4). Hence the authors concluded that oral HER treatment during early pregnancy associates with a higher risk for ocular coloboma and for a newly delineated congenital abnormality syndrome[32].

Teratogenic Exposure to caffeine

Greenwood et al. studied caffeine exposure during pregnancy, late miscarriage, and stillbirth. According to the authors, ‘‘there are no large well conducted effectiveness studies’’. They included 2643 pregnant women, aged 18 to 45 years of age who were admitted to the study between 8 and 12 weeks gestational age. The pregnancies were monitored for late SAs and stillbirth. Total caffeine intake was estimated from all possible sources in the first trimester and throughout pregnancy. The adjusted data revealed a strong association between caffeine intake in the first trimester and subsequent late miscarriage between 12 and 24 weeks and stillbirth after 24 weeks. The cases ingested an average of 145mg of caffeine per day, while the controls averaged 103mg per day. All the OR were increased for the cases, and none of the increased OR’s were statistically significant. The authors support the conclusion that caffeine intake should be limited during pregnancy. Unfortunately, the investigators did not adjust the data for the pregnancy signal. The investigators provided no mechanism for caffeine exposure in the first trimester to produce a pregnancy loss many weeks later or even in the third trimester[33].

Teratogenic exposure to the use of alcohol and smoking

Alcohol use and smoking during pregnancy can cause fetal damage. A cross-sectional study

was conducted with 326 mothers of the Fortaleza General Hospital to evaluate the use of drugs, alcohol and smoking during pregnancy and its relation to teratogenic potential in different population characteristics, between 2006 and 2007. Postpartum women who had their babies in the research site were included and those whose babies were not admitted as hospital inpatients were excluded. Chi-square tests and t-tests were used in the analysis, with a p value <0.05 considered significant. 96.6% of the mothers took medications (2.8 drugs/pregnancy) and self-medication occurred in 11.3% of the cases. Single women took more drugs with high teratogenic potential (p=0.037). A total of 11 cases of fetal malformation were observed, five of them were exposed to high teratogenic risks. Smoking occurred in 11.3% and alcohol use in 16%. The authors concluded that being single was found to be a risk factor for exposure to high teratogenic potential. Quality of prenatal care and other sociodemographic variables weren't related to exposure to teratogenic risks[34].

SAFE DRUGS DURING PREGNANCY

The FDA categories and list of safe drugs during pregnancy are mentioned below in table I and table II:

Table I: FDA categories: Teratogenic risks of drugs[35]

Category	Risk factors
A	Controlled studies showed no risk to the fetus. This group is limited to multivitamins and prenatal vitamins.
B	Either animal studies have shown no fetal risks, but there are no controlled human studies during pregnancy, or animal studies have shown adverse effect that was not confirmed in controlled studies during the first trimester. Pencillins are in this family.
C	There are no adequate studies or animal studies have shown adverse effects, but controlled studies in women are not available. Potential benefit must be greater than the risk to the fetus if these medications are used.
D	Evidence of fetal risk is proven, but potential benefit must be thought to outweigh the risks.
X	Proven fetal risks clearly outweighs any potential benefits.

Table II: Safe drugs during pregnancy[36,37]

Drugs	FDA category	Use in pregnancy	Use in nursing	Possible side effects
Analgesics				
Acetaminophen	B	Yes	Yes	Not reported
Aspirin	C	Not in 3rd trimester	No	Postpartum haemorrhage
Ibuprofen	B	Not in 3rd trimester	Yes	Delayed labour
Aproxen	B/D**	Not in 2nd ½ of pregnancy	Yes	Delayed labour
Codeine	C	With caution	Yes	Multiple birth defects
Oxycodone	B	With caution	With caution	NRD
Hydrocodone	C/D*	With caution	With caution	NRD
Morphine	B	Yes	Yes	Respiratory depression
Propoxyphene	C	With caution	Yes	Not reported
Meperidine	B	Yes	Yes	Not reported
Pentazocine	C	With caution	With caution	Not reported
Antibiotics				
Amoxicillin	B	Yes	Yes	Not reported
Metronidazole	B	Yes	Yes	Not reported
Erythromycin	B	Yes	Yes	Not reported
Penicillin V	B	Yes	Yes	Not reported
Cephalosporins	B	Yes	Yes	Not reported
Gentamycin	C	Yes	Yes	Fetal ototoxicity
Clindamycin	B	Yes	Yes	Not reported
Tetracycline	D	No	No	Maternal toxicity
Fetal death				
Chloramphenicol	X	No	No	Not reported
Chlorhexidine	B	No data	No data	Fetal toxicity
Antifungals				
Nystatin	B	Yes	Yes	Not reported
Clotrimazole	B	Yes	Yes	Not reported
Fluconazole	C	With caution	With caution	Not reported
Ketoconazole	C	With caution	No	Fetal bradycardia
Local anesthetics				
Lidocaine	B	Yes	Yes	Not reported
Mepivacaine	C	With caution	Yes	Fetal bradycardia
Prilocaine	B	Yes	Yes	Not reported
Bupivacanine	C	With caution	Yes	Fetal bradycardia
Etidocaine	B	Yes	Yes	Not reported
Corticosteroids				
Prednisolone	B	Yes	Yes	Not reported
Sedative/hypnotics				
Nitrous oxide	Not assigned	Not in 1st trimester (**)	Yes	Spontaneous abortions
Barbiturate	D	Avoid	No	NRD
Benzodiazepines	D	No	No	Clefe lip/palate

*D-indicates caution, if used for prolonged period of time or high doses.
**NRD – Neonatal Respiratory Depression

PRECONCEPTION COUNSELING

An important component of preconception counseling is informing women about medications that are potential teratogens. This requires providing information about the frequency and severity of teratogenic effects as well as alternative therapies which may have less severe fetal effects. This could be facilitated by Health care practitioners (HCPs).

Various studies demonstrated that preconception counseling can increase women's knowledge of pregnancy related risks and change women's pregnancy-related behaviors, including reducing their exposure to potential teratogens during pregnancy[38,39].

CONCLUSIONS

In conclusion, our review stated briefly about the associations between exposure to various drugs and pregnancy. Because, various drugs causing significant congenital malformations and other perinatal complications a careful prescribing behavior of prestigious physicians, with the majority of safe drugs being prescribed during pregnancy which will act as a major tool to protect future births from the broad spectrum of malformations and perinatal complications. On the other hand, this review highlights the importance of preconception counseling increase women's knowledge of pregnancy related risks and change women's pregnancy-related behaviors, including reducing their exposure to potential teratogens during pregnancy.

ACKNOWLEDGEMENT

The authors would like to thank College of Health & Medical Sciences, Haramaya University for their kind co-operation.

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