Prescribing of Antiepileptic Drugs (AEDs) during pregnancy

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ABSTRACT

This article combines the results of literature reviews conducted for two separate but related topics, namely "General principles of medication use during pregnancy" and "Anti-epilepitc drug use during pregnancy". This has allowed the provision of a more comprehensive coverage of this important topic i.e. the general principles and a demonstration of these principles by a specific class of drugs.

KEYWORDS

Pregnancy, Epilepsy, Anti-epileptic Drugs (AEDs)

INTRODUCTION

A recent survey has shown that 83% of mothers took medicines throughout their pregnancies.[1] Most medicines given in pregnancy are for the benefit of the mother and the foetus is the unintended recipient. All drugs diffuse across the placenta to some extent and many can have harmful effects on the foetus.[2] This review aims to provide a broad overview of medicine usage during pregnancy and to focus specifically on the management of epilepsy during pregnancy.

GENERAL PRINCIPLES OF MEDICATION USE DURING PREGNANCY

What is a teratogen?

A teratogen is any agent which when administered to a pregnant mother directly or indirectly causes structural or functional abnormalities (*i.e.* teratogenic effects) which present both in the foetus and congenitally.[2,3]
Examples of teratogenic effects are [2]:

- Chromosomal abnormalities
- Resorption or abortion of the early embryo
- Structural malformations
- Intrauterine growth retardations (IUGR)
- Death of foetus
- Functional impairment in neonate *e.g.* Deafness
- Behavioural abnormalities
- Mental retardation

Medications and the foetus: how do medications reach the foetus?

Medications taken by pregnant women reach the foetus by crossing the placenta which is the same route taken by oxygen and nutrients, which are needed for the foetus' growth and development.[4, 5, 9.]

Nearly all medications, except those with a very high molecular weights such as insulin and heparin, cross the placenta to the foetus. Lipid soluble, un-ionised medications cross more rapidly than polar medications. All medications have the potential to affect the foetus.

Factors influencing teratogenesis: timing of medication exposure

How a medication affects a foetus depends on the foetus' stage of development and the dose of medication given.[2] (refer to Table 1).

During the pre-embryonic period, which lasts until 14 days post-conception (Table 1), exposure to a teratogen has an all-or-nothing effect. Damage to all or most of the cells results in death of the foetus. If only a few cells are injured then normal development is likely.

The foetus is most vulnerable to teratogens during the embryonic period *i.e.* 3-8 weeks after conception, when the major organ systems are formed. Some medications have a specific time period of highest risk for a particular defect *e.g.* exposure to sodium valproate during the time when the neural tube closes *i.e.* 17-30 days after conception, may result in spina bifida.

From week nine post-conception to birth (foetal period) the foetus is less susceptible to teratogenic effects, although some organs such as the cerebellum and some urogenital structures are still forming. A medication given during this time is more likely to cause general growth retardation or interfere with the functional development within specific organ systems. For example warfarin may cause intracranial haemorrhage in the foetus after exposure in the second and third trimesters of pregnancy.

Medications taken close to term can cause predictable pharmacological effects in the neonate. For example, non-steroidal anti-inflammatory drugs (NSAIDs) taken in the last six weeks of pregnancy can cause premature closure of the ductus arteriosus giving rise to neonatal pulmonary hypertension.[2, 3]

Dose-response relationship and polypharmacy

Teratogenic effects are usually dose-dependent. Studies have shown a significant relationship between the incidence of neural tube defects and total daily dose of sodium valproate.[3, 6]

Exposure to multiple medications is more likely to result in abnormalities than exposure to a single medication. A study of malformations among babies born to women with epilepsy found that the incidence of birth defects increased with the number of anit-epileptic drugs (AEDs) taken. There was a 4% incidence of birth defects in babies born to women taking one antiepileptic medication and a 23% incidence in babies whose mothers took four or more medications. Further evidence of such synergistic teratonergic effects is lacking but polypharmacy should be avoided whenever possible.[3]

Genetic factors

Risk of teratogenicity can differ among individuals. There is increasing evidence from studies involving AEDs that genetic factors are an important determinant of teratogenic effects.[3,7] Most AEDs are converted by hepatic microsomal enzymes to epoxide intermediates which are then detoxified by the enzyme epoxide hydrolase. Studies suggest that malformation rates correlated with high levels of epoxide intermediates. Phenytoin teratogenicity can be linked with high levels of these metabolites occurring in individuals with low activity of the enzyme epoxide hydrolase, the activity of which is genetically determined.[7]

Pregnancy induced pharmacokinetic changes

The following pharmacokinetic changes occur during pregnancy affecting the way the body handles medications:

- Renal function increases leading to renally eliminated medications such as gentamicin and digoxin being eliminated faster.

- Body water increases by about 8 litres and plasma volume may also increase. As a result, there is a decrease in the serum concentration of many medications, especially those with a small distribution volume.

- Protein binding of medications falls due to a decrease in serum albumin concentration. This leads to an increase in the unbound (free) fraction of the medication. The protein binding of several antiepileptic medications such as phenytoin and sodium valproate has been shown to decrease in the last trimester of pregnancy.

- Some medications have lower serum concentrations during pregnancy. This can

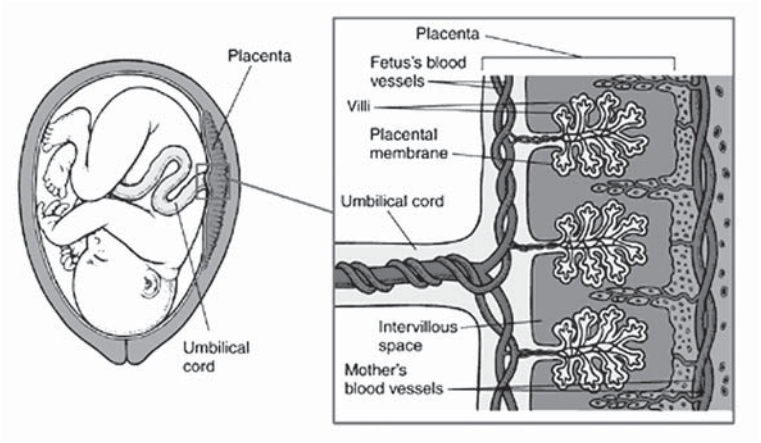
Table 1: Summary of Foetal Development during pregnancy[5]

Weeks	Development	Organs vulnerable to drug effects
0-3 After conception	Limb buds and a primitive central nervous system forms. Heart develops and starts to beat.	Brain and skeleton are sensitive to teratogenic effects from week 3 until the end of pregnancy (week 40 post conception). Heart is most sensitive to teratogenic effects during 3-4 weeks.
3-8 Embryonic period	Cell division is rapid. Major organ system formation occurs. Head and facial features develop. Foetus shows early movements. External genitalia are present but sex is not distinguishable. From 6 weeks onwards the foetus is visible on ultrasound.	Foetus is very vulnerable to birth defects during this period as major organ formation is occurring. e.g. neural tube defects and spina bifida occur during this time.
8-12	Eyelids fuse and sex is apparent. Fetal circulation starts functioning. Sucking and swallowing begins and the foetus moves freely. Kidneys begin to function – foetus passes urine from 10 weeks.	External genitalia are most sensitive to teratogenic effects during 8-9 weeks.
12-16	Rapid skeletal development. Nasal septum and palate fuse. Lanugo (a fine downy hair) appears on body.	
16-20	Mother feels fetal movements. Fetal heartbeat can be heard with stethoscope Fingernails can be seen and skin cells begin to be renewed.	
20-24	Most organs are capable of functioning. Foetus goes through periods of sleep and activity and responds to sound.	Medications taken after organ development is complete may alter growth and function of normally formed organs.
24-28	Eyelids reopen and there are respiratory movements. Survival may be expected if baby is born prematurely.	
28-32	Foetus begins to store fat and iron. Skin becomes paler and less wrinkled.	
32-36	Fat storages makes the body more rounded. Nails reach the tip of the fingers. Lanugo disappears from the body and head hair lengthens.	
36-40 post conception	Baby's contours are rounded and its skull is firm. Term is reached and birth is due.	

Adapted from: Every M, Hallam C. **Overview of Pregnancy.** *Pharmaceutical Journal*. 2003;270:194-196.[5]

Figure 1: How drugs cross the placenta

Some of the foetus' blood vessels are contained in tiny hairlike projections (villi) of the placenta that extend into the wall of the uterus. The mother's blood passes through the space surrounding the villi (intervillous space). Only a thin membrane (placental membrane) separates the mother's blood in the intervillous space from the foetus' blood in the villi. Drugs in the mother's blood can cross this membrane into blood vessels in the villi and pass through the umbilical cord to the foetus.



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be important for medications showing good correlation between plasma levels and therapeutic effect e.g. phenytoin, carbamazepine, lithium and digoxin. Women taking these medications should have their serum concentrations monitored and dose adjusted during and after pregnancy.[3]

FDA Classification of risk in pregnancy

The United States of America (USA) Food and Drug Administration (FDA) has developed the most widely used system to grade the teratogenic effects of medications. FDA assigns a safety category for use of medications in pregnancy using a 5 letter system: A, B, C, D and X. Category A indicates no demonstrable risk, B to D indicate increasing level of risk while category X indicates extreme risk [8] (see Table 2).

Table 2: FDA Classification of risk in pregnancy[8]

Category	Definition
A	Controlled studies in women fail to demonstrate risk to the foetus in the first trimester (and there is no evidence of a risk in later trimesters) and the possibility of fetal harm appears remote.
B	Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal reproduction studies have shown an adverse effect that was not confirmed in controlled studies in women in the first trimester (and there was no evidence of a risk in later trimester).
C	Either studies in animals have revealed adverse effects on foetus and there are no controlled studies in women, or studies in women and animals are not available.
D	There is positive evidence of foetal risk, but the benefits from use in pregnancy may be acceptable despite the risk.
X	Studies in animals or humans have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of use of medication in pregnant woman clearly outweighs any possible benefit. The medication is contraindicated in women who are or may become pregnant.

Evaluation of studies

Data on human exposure to medications during pregnancy is limited because drugs are not tested in the pre-marketing phase on women of child bearing age or pregnant women. Many drug companies and independent agencies have established pregnancy registries which prospectively collect information on drug exposure during pregnancy. Some examples of pregnancy registries are listed below:

• Australian Pregnancy Register for Women on Antiepileptic Medication – reports on pregnancy outcomes for women taking AEDs.

• Northern American Epilepsy and Pregnancy Registry – women with epilepsy taking AEDs who are pregnant are encouraged to contact the registry voluntarily and pregnancy outcomes are then reported.

• Lamotrigine Pregnancy Registry – set up by the manufacturer of Lamotrigine to monitor pregnancy outcomes in women exposed to lamotrigine.

• EURAP – Central Registry of Antiepileptic drugs – an international antiepileptic drugs and pregnancy registry. A number of health professional groups world-wide with an interest in AED use during pregnancy contribute information on pregnancy outcomes to this registry.

• Motherisk programme (Hospital for Sick Children, Toronto, Canada) – prospectively enrol patients who contact their teratology information service and follow the pregnancy. The pregnancy outcome data is then compared to non-exposed cohort and the results are published as prospective cohort studies. The Motherisk programme has a website, containing useful information and abstracts of studies undertaken by their organisation, available on URL: http://www.motherisk.org/drugs/index.php3

Table 3 outlines the possible study types used to investigate the teratogenic properties of drugs and their advantages and disadvantages.

Table 3: Evaluation of study types used to investigate teratogenic risk[10]

Study type	Advantages	Disadvantages
Animal/ in vitro	Can provide clues concerning safety of drugs in humans	Extrapolation of findings to human pregnancy is questionable
Case reports	Have been useful indicators in proving the teratogenicity of certain drugs	Findings may be due to chance or influenced by a combination of factors e.g. genetics, environment, other drugs taken, recall bias
Case control studies	Cost efficient, fast, allows analysis of rare malformation	Retrospective exposure assessment Recall bias
Prospective cohort studies	Prospective exposure & outcome assessment Allows analysis of rare exposures Temporal relationship between drug exposure and gestational age can be accurately determined No recall bias Results can be extrapolated to a defined population	Time consuming More expensive than case-control studies Loss to follow-up Low numbers obtained
Retrospective cohort studies	Less time consuming than prospective cohort	Retrospective exposure assessment Loss to follow-up
Randomised controlled trials	Most reliable methodological approach	Not ethical Rarely used for the evaluation of teratogenic properties of drugs
Systems based on voluntary or spontaneous reporting	Possibility to investigate drugs in a real life setting	Incomplete data, the outcome assessment often retrospective Potential for under-reporting

MANAGEMENT OF EPILEPSY DURING PREGNANCY

Case

Mrs R is a 27 year old pregnant female who presented to the Women's Health clinic for prenatal care at 15 weeks gestation. This is her first pregnancy. She has been an epileptic since the age of 8 suffering from tonic clonic seizures. Her epilepsy has been well controlled over the past five years during which she has been taking Phenytoin at a dose of 100mg twice daily. She has no other medical problems and is not using any other medications.

Mrs R has voiced her concerns about phenytoin use during pregnancy and wants to know:

"What are the risks associated with taking phenytoin during pregnancy?"

Continued on page 36