DRUGS IN PREGNANCY AND THEIR EFFECTS ON FOETUS

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Over the last two decades many reports have been published about various drugs given to pregnant women causing unexpected and undesirable effects on the foetus and the newborns. Though primarily a problem of the obstetricians and paediatricians this hazard concerns all clinicians who have to administer drugs to the pregnant women for some systemic disease.

Despite the rapid development of the field of teratology, our knowledge of congenital malformations in human has increased relatively little. About 2.3% of all live born infants show one or more significant congenital malformations at birth and at the end of one year this figure is doubled by discovery of malformations which are not found at birth.

With our present knowledge aetiology of human malformations can be divided into four categories :

1. Genetic —e.g. Haemophilia, achondroplasia.
2. Chromosomal —e.g. Downs syndrome, Turner's syndrome, Klinefelter's syndrome.
3. Environmental factor —Infectious agents : e.g. Rubella, Cytomegalovirus, herpes simplex virus etc.

   Radiation, Chemical agents : Drugs, Nutritional deficiencies, Environmental chemicals e.g. Mercury.
4. Multifactorial malformations —e.g. Congenital hypertrophic pyloric stenosis, cleft lip, cleft palate, congenital dislocation of hip, talipes equinovarus etc.

About 10% of all malformations are caused by genetic factors, 10% by chromosomal factors and remaining 80% are caused by the intricate interplay of several genetic and environmental factors.

It is very difficult to say what is the exact percentage of malformations caused by drugs, as most of the studies made in this field are retrospective and isolated. To prove teratogenic effect of one specific drug, it requires prospective investigations of thousands of pregnancies and to prove that a drug is not teratogenic is even more difficult.

The teratogenic effect of thalidomide was discovered only because it produced a rare and striking deformity like compete or partial (amelia and meromelia) absence of the extremities. Had thalidomide produced a common congenital abnormality like heart disease or cleft lip etc., teratogenic association of

the drug might have been overlooked easily and we still have been in use today of the drug for treatment of vomiting in pregnancy.

The work on laboratory animals has little relevance to the effects which can be expected in man. Many common drugs, such as salicylates and penicillin are teratogenic in animals but so far as we know they are not teratogenic in human when used in therapeutic doses. Thalidomide, a potent teratogenic agent in man is apparently safe in rat.

Hence a prospective study carried out on animals does not hold good on human beings.

There are few conditions which influences the actions of teratogenic agents.

A. **Period of Gestation:** The ill effects on the foetus of any drug administered to a pregnant woman depends to a large extent on the period of gestation at which the drug is given.

1. Blastogenesis or Segmentation Period: (5-6 days after ovulation) —The blastocyst is 5-6 days old embryo, which has not yet embedded the uterine mucosa. There is rapid cell division during blastogenesis. The blastocyst is very fragile. This is the period of maximum lethality. Effects of teratogenic agents is complete destruction of embryo. However, slight injuries can be overcome without obvious harmful consequences to growing embryo, as damaged cells can be repleced quickly by newly formed cells. During this stage many cells retain their totipotency. LSD (Lysergic acid diethylamide) and radiation may cause chromosomal damage at this stage.
2. Embryogenesis or Morphogenetic Period: All major organs and systems are formed during the fourth to eight weeks. Hence this period is also called the period of organogenesis. During this period embryo is most susceptible to teratogens. Most congenital malformations seen at birth find their origin during this critical period.

Gross Malformation	Days
Brain	15-27
Eye	24-39
Heart	20-39
Limbs	24-36
Genitalia	38-60

If a child is presented with anencephaly, one can quickly calculate that this abnormality must have started betwen 15th and 27th day. Thalidomide, causing amelia, must have affected the limb buds in the 5th week of development.

3. Foetogenesis or period of rapid development—(3rd to 9th month a development) : There is general increase of all parts of the body resulting from cellular division as well as from increase of the cellular size. As the foetus grows and develops and structural differentiation become more or less complete, anatomical malformations are less likely. But at this time drugs may lead to intrauterine growth retardation or other abnormalities which become apparent in later life only, such as metabolic disorders.

Differentiation of some organs such as external genitalia and the central nervous system continues for the whole of the foetal period. Hence severe cases of pseudoher-

maphroditism and various encephalopathies may also be produced in this period.

B. **Genetic Susceptibility :** The reaction of the embryo to specific drugs varies not only from species to species but also within a given species, between each strain and sometimes also between individuals of the same strains. Exogenous agents which are generally considered harmless for great majority of women can produce a malformation in some of them who have a genetic instability.

C. **Maternal Conditions :** The noxious effects of the drugs on the foetus depends also on the physiological status of mother.

1. *Age* — The risks of malformations and perinatal mortality are higher in very young mothers and even more in the older age groups.
2. *Social Status* — Deficiency or excesses of the foodstuffs can modify the deliterious effects of drugs. The large number of malformations observed in lower social groups are generally ascribed to malnutrition, alcoholism and chronic diseases.
3. *Pathological Status* — Various pathological status of the mother, including metabolic diseases such as diabetes, obesity, hypertension, toxaemia and liver dysfunction — enhances the harmful effects of drugs and increase the frequency of foetal damage. Hypertension & toxaemia has definite damaging effect on placenta and certain drugs, which are normally arrested by the placental barrier, may reach the foetus when this barrier is damaged.

Effects of few common drugs used in pregnancy are mentioned here. But it must again be emphasised that our knowledge of this aspect of pharmacology is rudimentary and the only safe course is to avoid prescribing any drug casually or without very good reason to a pregnant woman.

1. CYTOTOXIC DRUGS :

Cytotoxic drugs such as aminopterin, mercaptopurine, methotrexate, chlorambucil, cyclophosphamide, bisulphan etc produce teratogenic effects. (I.U.G.R. hypoplasia of mandible, cleft palate, cranial dysostosis, ear defects and club foot). These drugs inhibit normal cell division and interfere with DNA synthesis & hence produce teratogenic effects.

2. ADRENO-CORTICAL STEROIDS :

There have been many reports of cause of cleft palate in infants whose mothers had received large doses of cortisone, ACTH or hydrocortisone in early pregnancy on account of collagen disorders, bronchial asthma or arthritis. This is the summation of individual case records and at present there are no reports available of large scale prospective investigations into the action of these drugs on the human embryo. Corticosteroids in replacement dosage are harmless even in the earliest weeks of pregnancy but therapeutic dosage at this time should be avoided unless the mother's clinical condition makes it imperative and then they should be employed in the smallest doses which will achieve the desired effect.

The flourinated steroids such as dexamethasone is thought to be more teratogenic than others and are so best avoided during pregnancy. Female

infants of mothers treated with ACTH may show partial pseudohermophroditism at birth and as a rule it is better to use corticosteroids rather than corticotrophins for treatment during pregnancy.

3. THYROTOXICOSIS :

There are three drugs commonly used for thyrotoxicosis. These are carbimazole, methyl thiouracil and pottasium perchlorate. These drugs pass freely across the placenta and inhibit foetal thyroid gland which leads to release of T.S.H. from foetal pituitary. Due to action of TSH, foetal thyroid becomes hypertrophic and the infant is born with goiter. In some cases the enlargement of the thyroid can produce obstruction of the trachea with serious respiratory problems (T.S.H. and thyroxin do not cross placenta). The thyroxine of foetus is essential for foetal nervous and skeletal maturation in later pregnancy. Hence antithyroid drugs also lead to mentally and growth retarded babies. During pregnancy doses of antithyroid drugs should be kept as less as possible and they should be reduced immediately once the patient becomes euthyroid.

It has been observed that if mother is kept euthyroid and drugs are used to a minimum the slight thyroid enlargement of foetus disappears within two weeks of birth. As antithyroid drugs get excreted through breast milk, mothers receiving these drugs should not feed her baby on breasts.

4. DIABETES :

Oral hypoglycaemic agents can be divided in two groups. (1) Sulphonyl urea derivatives like tolbutamide, chlorpropamide, glybenclamide, glynase (gipizide) etc. (2) Biguanides, like phenformin, metformin etc. All these oral hpyoglycaemic agents cross the placenta. These drugs are definitely teratogenic in animals but there is at present no proof that they interfere with embryogenesis in man hence is best to avoid their use in the first trimester. During pregnancy we deal with mostly juvenile onset, brittle diabetics who develop ketosis easily and as a general rule these drugs are unsuitable for such patients. Chlorpropamide, may cause profound hypoglycaemia in neonates since they are poorly metabolised in the immature foetal and neonatal liver. This drug should, therefore, be discontinued at least 7 days before delivery and insulin should be started. Jackson and her colleagues (1962) reported a 73% perinatal mortality amongst 22 pregnant diabetic women who had been treated with 500mg of chlorpropamide daily. Insulin hardly crosses the placenta and whatever amount enters foetal circulation is rapidly metabolised by foetus & does not have any effect on foetal state and hence should be the choice of drug in pregnancy.

5. TUBERCULOSIS :

Most of the anti-tuberculosis drugs cross the placenta to enter foetal circulation. Isoniazide, PAS, themibutol appears to cause no harm to the foetus but streptomycin may do so. Isolated cases of congenital deafness and permanent otic damage have been reported in the infants of mothers who were on long term streptomycin therapy. Impairment of hearing in the infants of such mothers may be more frequent than we realise and be discovered only on special testing in the second or third year of life.

Congenital toxic labyrinthine damage may also occur. Rifampicin is found to be teratogenic in most animals and until more is known of its effect on the human embryo its use in the first trimester is best avoided. It is, however, an extremely potent antituberculous drug and can be employed later in pregnancy.

Thiacetazone, pyrazinamide, ethionamide, cycloserine are not known to have any teratogenic effect & can be tried whenever necessary.

6. ANTIMALARIAL DRUGS :

Chloroquine : Chloroquine is harmless to the foetus, but long term therapy can cause systemic lupus erythematosus, mental retardation etc.

Quinine : It can cause abortion, congenital deafness, thrombocytopenia in new borns. It has got an oxytocic action on the uterus and is directly toxic to embryo.

Primaquine : It could cause serious effects in foetus with Glucose 6-phosphate dehydrogenase deficiency.

7. AMOEBICIDAL DRUGS :

Metronidazole, iodochlorhydroxyquinoline, phanquone are known to be not teratogenic when used for short periods.

8. ANTICONVULSANTS :

Recently a large number of reports have been published regarding the various anomalies seen in infants born to epileptic mothers who were on anticonvulsant therapy during gestation. Most commonly reported malformation are cleft lip, cleft palate, hydrocephaly, anencephaly, intra-uterine growth retardation etc. Cleft lip and palate were five times more with dilantin which suggest its definite teratogenic relationship.

The drugs which are commonly used for grand-mal epilepsy are phenobarbitone and phenytoin. Since convulsions itself, especially grandmal, may cause foetal anoxia and brain damage, it is not permissible to discontinue antiepileptic therapy during pregnancy. If the drugs have to be started for the first time during pregnancy, she should be given small dose first and can be increased gradually until the seizures are controlled.

Anticonvulsant drugs may cause folic acid deficiency. It may be justifiable to add folic acid to the therapy.

9. PROGESTOGENS :

Progestogens are frequently used during pregnancy for treatment of threatened abortion. Ethisterone and norethisterone have considerable androgenic activity and may masculinize a genetically female foetus and produce female pseudohermaphroditism. All synthetic progestogens which are administered orally may have this effect and when progestogen therapy is considered necessary in early pregnancy, the patient should receive parenteral treatment with 17 α— hydroxyprogesterone acetate (proluton depot), which is safe in pregnancy.

10. OESTROGENS :

Oestrogens if given for long time, may also cause masculinisation of the female foetus. Administration of Diethyl-stilboestrol in pregnancy carries the risk of vaginal adenosis or carcinoma 20 years later in the female offsprings of women so treated.

Use of pregnancy test tablets/ injections containing oestrogen and progestogens should be restricted and more reliance should be put on urine

examination for diagnosis of early pregnancy.

11. ANALGESICS :

Salicylates are highly teratogenic in laboratory animals. Their teratogenic effect in human has not been proved. It is better not to use heavy dose of salicylates in pregnancy. Administration of aspirin in second part of pregnancy can prolong the duration of gestation and of parturition. A prospective study was carried out in women taking aspirin regularly and it was found that 16% of them have prolonged gestation periods, as compared to 2% in the control group. Postnatal bleeding and prolonged labour ending in caesarean section were 7 times more frequent than normal.

Morphine, meperidine, scopolamine, chloral hydrate are not teratogenic. Administered in last month of pregnancy morphine, pethidine have a definite depressant action on the foetus.

For fever and simple headache etc., paracetamol is safest of all.

12. ANAESTHESIA :

All volatile anaesthetic agents are lipid soluble and cross the placenta. There is on evidence to suggest that any of the commonly used anaesthetics are teratogenic when given in the course of surgical operation. Surgical procedure under anaesthesia should be differed until 6th week of gestation to avoid spontaneous abortions.

13. TRANQUILISERS :

Commonly used tranquilisers like diazepam, chlordiazepoxide, nitraze, pam cross the placenta readily. These can be used in small doses. Their use should be restricted in first trimester and just before delivery. Their prolong use can depress neurological activity in the foetus at birth.

14. HYPOTENSIVE DRUGS :

Ganglion blocking agents can cause paralytic ileus in the newborns. Adrenergic blocking agents like guenethidine, bethanidine etc., may cause postural hypotension with consequent effect on the foetus. Reserpine produce lethargy, bradycardia, nasal blocking and nasal discharge causing respiratory difficulty in newborn. Reserpine should be discontinued at least seven days before delivery.

Methyldopa seems to be safest of all.

15. DIURETICS :

Thiazide diuretics used for the treatment of preeclampsia, heart failure or in hypertension may cause thrombocytopenic purpura in the neonates. However risk of neonatal bleeding is very small and value of the drug to the mother may be great.

16. ANTICOAGULANTS :

Oral anticoagulants such as dicoumarol and warfarin easily cross the placenta giving rise to the risk of haemorrhage in foetus. Heparin is the ideal anticoagulant in pregnancy as it does not cross the placenta.

17. ANTIBIOTICS :

It is an established fact that all antibiotics can freely cross the placenta and indirect evidence is available to prove that toxic and unusual side effects could occur in the foetus or neonates after administration of antimicrobial drugs.

a. **Tetracyclines :** Tetracyclines have an affinity for metallic ions, combine readily with calcium and are deposited in foetal teeth and bones. During first

trimester tetracyclines will enter the calcifying hyaline cartilage of the bones, depressing the rate of foetal growth. During foetal period, tetracyclines discolour deciduous teeth and cause hypoplasia of enamel and predisposes teeth to dental caries. Usually only the deciduous teeth are involved but when treatment is continued to late stages of pregnancy the colour of permanent teeth may also be affected. Tetracyclines are also deposited in the foetal nails which may become discoloured but this is rectified as the nails grow.

It is best to avoid the use of tetracyclines throughout the pregnancy.

b. **Chloramphenicol :** No teratogenic action have been reported when given in therapeutic dosage. Chloramphenicol therapy should not be continued for long periods, as it inhibits protein synthesis. It is advisable not to give chloramphenicol to mother near term and during lactation. 'Grey syndrome' a serious and potentially fatal manifestation produced by this drug in infants is well known.

c. **Streptomycin, Kanamycin, Gentamycin** : All aminoglycosides like streptomycin, kanamycin, gentamycin are ototoxic and hence should only be used in pregnancy when specifically essential.

d. **Sulphonamides :** They may produce dental malformation and skeletal defects. They tend to occupy the protein binding sites in the foetus and prevent inactivation of bilirubin and hence there is a risk of kernicterus in newborns specially when long acting preparations (sulphametapyrazine, Sulphafurazole, trimethoprim) are employed. Free bilirubin may then diffuse more rapidly into central nervous system and exert toxic effects.

e. **Nitrofurantoin :** This drug should not be used in first trimester. This is supposed to cause haemolysis in the newborn if administered to mother near term and during lactation.

f. **Novobiocin :** Novobiocin, if administered to mother at term has shown to affect neonatal bilirubin metabolism causing hyperbilirubinaemia but more studies are needed to document this fact.

g. **Erythrocin :** There is no evidence of any adverse effect on foetus occurring with use of erythrocin in pregnancy. Erythrocin is effective and safe during pregnancy until proved otherwise.

h. **Cycloserin :** Cycloserin is highly teratogenic, hence should not be prescribed in pregnancy.

Most safe antibiotics during pregnancy are penicillin, ampicillin, cloxacillin, amoxycillin, cephalosporins, erythrocin.

18. VACCINATION :

Vaccinations against influenza. tetanus, poliomyelitis, and cholera are harmless for the pregnant mother and for the foetus. Antipoliomyelitis oral vaccination should be taken only in third trimester. Primary small pox vaccination should not be taken in pregnancy. Secondary small pox vaccination should be taken only when very essential and that also in second half of pregnancy. Rabies, rubella, B.C.G., antidiphtheria vaccination should be avoided during pregnancy.

In principle, any vaccine containing live viruses should be regarded as a potential teratogen until proved otherwise.

19. RADIATION :

The teratogenic effect of X-ray irradiation has been known for many years and it is well recognised that microcephaly, skull defects, spina-bifida, blindness, cleft palate and defects of the extremities may result from treating pregnant women with large doses or roentgen rays or radium. The nature of malformation depends on the doses of radiation and the stage of development at which the radiation is given. At early stages mainly central nervous system anomalies are produced. At later stages, cleft palate and skeletal deformities are observed. Small doses of radiation may cause genetic mutation leading to shortening of life, the development of cancer and cataracts, sterility and increased susceptibility to disease in future generation.

Therefore, radiological examination, particularly of the urinary and alimentary system should be avoided or kept to minimum during pregnancy.

CONCLUSION :

When prescribing a drug to a woman of child bearing age, clinician should first enquire routinely whether there is any chance that she may be pergnant. Whenever a course of treatment is started with a drug of unknown teratogenic potentiality, the patient should be warned of the need to avoid pregnancy until the therapy has been completed.

Again a careful note should be kept of all drugs prescribed for a pregnant woman in order that, should there later be found a congenital defect in the child, it may be possible to look back and see if any drug which might be incriminated was given early in pregnancy : should that be the case the coincidence should be reported to concerned authorities.

It has now been determined that most of drugs can and does pass from the mother to the foetus and placental barrier is largely a myth. Hence before prescribing a drug to expectant mother, we should remember Dr. Voltair's warning :

"DON'T POUR DRUG OF WHICH WE KNOW LITTLE INTO A PATIENT (THE FOETUS) OF WHOM WE KNOW LESS."

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