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Teratogenesis - Area of Toxicological Research

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Introduction- Birth defects affect three to five percent of all newborns, but account for 20% of infant deaths. In the 1950s, the field of teratology discovered that environmental agents, called teratogens, could affect the developing foetus. An estimated ten percent of birth defects are caused by teratogens rather than genetic disorders. However, 65% of congenital disorders have no known cause.

What is Teratogenesis ?

Exposure to drugs or Medicines in Pregnancy may be accidental or self induced. It results damage to unborn body. If structural damage takes place in foetus is called "Teratogenesis." & Study of its disorders is referred to "Teratology."

Teratology refers to the study of malformations, usually in regard to the deleterious effects of environmental agents or external exposures on the developing embryo. Birth defects due to teratogenesis can include cleft palate, missing or malformed limbs, and deformities of the brain and heart.

This definition is broadened now a days, as it include any birth defects e.g. morphological ,biochemical ,behavioral .The placenta doesnot strictly constitute a barrier so any drug can cross it to greater or lesser extent & drugs effects on foetus & these effects are irreversible. Drugs can affect the foetus at 3 stages-

- a) Prior to implantation – (0 to 17 days) During early embryogenesis drug reach to conceptus , deleterious effects on blastocyst is usually death.
- b) During organogenesis – (2 to 12 weeks) drugs can produce gross congenital malformation & even death.
- c) From second trimester onwards – the principle transfer from mother to foetus is through utero-placental circulation , because of lowered serum albumin concentration . so free drug is available for placental transfer.

Most of the drugs enter in maternal circulation will reach the foetal blood in varying concentration. The foetus is less capable of eliminating drugs than adult because of immature kidney, Liver & inadequately developed Enzyme System So teratogenic effect may develop. There are Several Physiological changes takes place in Pregnancy.

Some Physiological Changes in Pregnancy are :

- 1) Decrease in rate of stomach Emptying
- 2) Increase in total body water
- 3) Increase in body fat
- 4) Increase in half life of drug
- 5) Decrease in Protein binding
- 6) Increase in Glomerular Filtration rate.

Some Teratogenic Drugs & Their target sites :

Drugs	Teratogenic Site
1. Androgens, progestin	- Reproductive organ
2. Ethanol	- Brain
3. Folic Acid antagonist	- Spine
4. Heavy Metals	- Brain
5. Phenytoin	- Brain & Limbs
6. Tetracycline	- Teeth, bones
7. Thalidomide	- Limbs
8. Warfarin	- Nose

If Pregnant lady comprises about the drugs abuse like :Alcohol, Nicotine, Cocaine it will produce harmful effect on the foetus.

- **Alcohol Dependant Women** Can Cause "**Foetal Alcohol Syndrome**" Characterized by growth retardation, Microcephally, Maxillary hypoplasia, Cleft palate, CNS abnormality especially "Mental Retardation."
- **Chain smoker Woman** may cause Low Birth wt baby or SIDS (Sudden Infant Distress Syndrome).
- "**Neonate withdrawl syndrome**" May develop with addiction with morphine, heroine, pethidine, Barbiturate & benzodiazepines.
- **Folic acid deficiency** in pregnancy may cause **spina bifida**.
- **Mercury & teratogenesis** –Methylmercury, a worldwide contaminant of seafood and freshwater fish, is known to produce adverse nervous system effects, especially during brain development. Eating fish is the main source of mercury exposure in humans and some fish may contain enough mercury to harm the developing nervous system of an embryo or fetus, sometimes leading to learning disabilities.
- **Lead & teratogenesis**- Neurological toxicity is observed in children of exposed women as a result of the ability of lead to cross the placental barrier. A special concern for pregnant women is that some of the bone lead accumulation is released into the blood during pregnancy. Several studies have provided evidence that even low maternal exposures to lead produce intellectual and behavioral deficits in children.
- **Cocain** - causes Attention deficit syndrome in foetus
- **Marijuana**- causes hole in heart of baby, poor eye sight, learning disability, fearfulness in later life.
- **Air pollution**-Compounds such as carbon monoxide, sulphur dioxide and nitrogen dioxide all have the potential to cause serious damage when inhaled by an expecting mother. Low birth weight, preterm birth, intrauterine growth retardation, and congenital abnormalities have all been found to be associated with foetal exposure to air pollution.

Congenital Malformations are common in 2 to 3% of all live born infants & even more in still born .

Incidence of Teratogenesis (Congenital Deformity)**Thalidomide Tragedy (1950-1961)**

Thalidomide – A Sedative drug taken by pregnant lady for relief from morning sickness. Congenital malformations was noted in their off spring, in form of absence of ears, *Amelia-*

total absence of Limbs , *Phocomelia* – absence of one or more limbs. Paralysis of cranial nerves, anorectal stenosis etc.

Tetracyclines – It chelates calcium. Teratogenic effects noted are yellow staining of teeth , Defective formation of enamel & hypoplasia of teeth.

Behavioral teratogenesis – abnormal behavior in new born.

The drugs like – reserpine , phenothiazines, barbiturates, amphetamines & cannabis leads to behavioral changes in new born. Types of malformation depends on the drugs as well as the stages of exposure to teratogens.

The main lesson to be learnt from great human tragedy is to take an extra care & precautions when prescribing the drug to pregnant woman.

Main Teratogens are :

- 1) Ionizing Radiation :** Atomic weapons, Radio Iodine, Radiation Therapy.
- 2) Infections :** CMV, Herpes viruses, Rubella Virus, Syphilis, Toxoplasmosis, Venezuelan equine encephalitis virus, vertical transmitted infections.
- 3) Metabolic Imbalances :** Diabetes, Folic Acid Deficiency, hyperthermia, lack of Nutrients.
- 4) Drugs :** Methotrexate, Tetracycline, Thalidomide, Phenytoin, ethanol, Organic mercury, Valproic Acid.

Commonly Used Drugs & Its Foetotoxicity

Drugs	Toxic effect on foetus
1. Antacids	- Metabolic Alkalosis, CHF
2. Antihistamines	- Liver Damage, Hypotension
3. Laxatives	- Renal Damage
4. Paracetamol	- Methaemoglobinaemia.
5. Pseudoephedrine	- Alkalosis.
6. Methotrexate	- CNS & Limb Malformation, cleft lip, cleft palate, hydrocephalus.
7. Tetracycline	- Anomalies of teeth & Bones
8. Thalidomide	- Limb shortening, Internal organ defect.
9. Phenytoin	- Growth Retardation.
10. Androgenic steroids	- masculinisation of female off spring.
11. Antithyroid drugs	- Goiter, Mental retardation.
12. Oral anti diabetic drugs	- Abnormalities in eyes , skeletal system, neonatal hypoglycaemia.
13. Valproate	- Increase risk of neonatal tube defect.
14. Chloramphenicol	- Grey baby syndrome,
15. Narcotics	- Depression of CNS , apnoea, bradycardia & hypothermia.
16. Aspirin	- premature closure of ductus arteriosus.

Problems With Teratogenic Effect :

- Experiments usually done on Animals & not on pregnant Lady. So results may not be wholly applicable to human foetus.
- Teratogenesis may occur mainly during first 8-12 weeks of Intrauterine life.
- Causes of structural defects mentioned in Ayurvedic science -

मातापित्रोस्तु नास्तिव्यादशुभैश्च पुराकृतैः ।
वातादीनां प्रकोपेण गर्भो वैकृतामाप्नुयात् ॥ सुशा २ / ५५

Aacharya Sushrut said : The person who not believe on veda & Abnormalities in Vata - Pita- Kapha Dosh then structural defects formed.

सर्पवृश्चिक कुष्मांड् विकृताकृतयश्च ये ।
गर्भास्त्वेते स्त्रियाश्चैव ज्ञेयाः पापकृतो भृशम् । सु.शा. २ /५३
- गर्भो वातप्रकोपेण दौहृदे वाऽवमानिते ।
भवेत् कुब्जः कुणिः पंगुः मुको मिन्मिन एवं वा ॥ २ /५४

Duo to vitiation of vata dosha or if any desire of pregnant lady is not completed then there is chances of formation of deformed baby like - kyphosis, absence of leg or deformed leg, Deaf & dumb baby etc.

Precautions while prescribing drugs to pregnant woman

1. Treat minor ailments without drugs.
2. If a drug, when prescribed to pregnant woman, It must be safe.
3. Prefer a drug which has been in use from long time.
4. Discourage the patient from self administrating over the counter (OTC) Drugs.
5. Advise the patient that absolute safety of foetus cannot be guaranteed even by not prescribing any drug to woman.
6. Only well tested & reputed drugs are to be prescribed & that to be using the minimum therapeutic dosages for shortest possible period.

Therefore do not sacrifice the mothers interest for the sake of fetus.

Conclusion –

Many teratogenic birth defects are preventable, so teratology education is important for expecting families. Teratology also helps to determine which medications are safe for pregnant women. patients should be advised to delay pregnancy for certain period of time after completing the course of teratogenic drugs. Teratogenic effects not found by herbal Ayurved medicine.

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