Sem – VI (UG)

CC-13: Developmental Biology

C13T: Unit -5, Implications of Developmental Biology

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Teratogenesis: Teratogenic agents and their effects on embryonic development

Teratogenesis:

Teratogenesis or teratogenicity is the process by which congenital birth defects occur by some biological infections (viral, protozoan etc.), physical agents (ionizing radiations, excessive heat etc.), pharmacological drugs (thalidomide, corticosteroids, antiepileptic or antimalarial drugs etc.), industrial pollutants (toluene, cadmium etc.), tipsiness of mother (alcohols, nicotine etc.), maternal health problems (diabetes mellitus, rheumatoid arthritis etc.).

Teratology is the science that investigates the congenital malformations and their causes (how environmental agents disrupt normal development).

Teratogenic Agents:

The agents which are responsible for causing congenital malformations are called Teratogenic Agents.

1) Infectious agents:

Some infections during pregnancy are teratogenic like viral infections (e.g. **rubella, herpes simplex and cytomegalovirus**), spirochetal infections (e.g. **syphilis**), and protozoal infestations

(e.g. **toxoplasmosis**). First trimester maternal **influenza** exposure is associated with raised risk of a number of non-chromosomal congenital anomalies including neural tube defects, hydrocephalus, congenital heart anomalies, cleft lip, digestive system abnormalities and limb defects.

2) Physical agents:

Radiation is teratogenic and its effect is cumulative. The degree of ionizing radiation needed for health testing (checking) procedures is very close to the threshold for teratogenicity, especially in the first trimester. There is a basic assumption that risk prediction for human radiation exposure is proportional to the total radiation dose.

3) Chemical agents:

- **Placental transporter proteins** are involved in the pharmacokinetics of drugs and have an effect on drug level and foetal drug exposure. There is an association between P-glycoprotein polymorphisms and the risk of foetal birth defects induced by medications during pregnancy. Six underlying teratogenic mechanisms are stated to be associated with medication use. They include folate antagonism, neural crest cell disruption, endocrine disruption, oxidative stress, vascular disruption and specific receptor- or enzyme-mediated teratogenesis.
- **Antiepileptic drugs (AEDs)** are frequently used to treat epilepsy, headaches, and psychiatric disorders in women of childbearing age. In many instances, clinicians are obliged to stop these drugs or switch to another category of medications. Discontinuation of AEDs during pregnancy is not advised due to the risk of seizures that may be fatal to both mother and fetus. Hepatic mixed oxidase system and other systems like epoxide hydrolase, glutathione reductase and superoxide dismutase as well as toxin-

scavengers are important modifiers that lower the teratogenic risk of the drug. In utero exposure to some AEDs can lead to significant cognitive and behavioural teratogenic risks for the foetal outcome. Valproate obviously induces impaired cognitive development and increased risk rate of autism incidence. Exposure to other AEDs as carbamazepine, lamotrigine, levetiracetam, or phenytoin mono therapy is mentioned to be associated with more favourable cognitive and behavioural foetal outcomes than valproate. All old-generation AEDs are considered as teratogenic. The teratogenic effects of sodium phenytoin (PTH) to include toe and finger, renal, and facial malformations as well as neural tube closure-defects. Valproic acid (VPA) is an anticonvulsant and mood-stabilizer used to treat epilepsy, bipolar disorder and migraine. It is known to induce teratogenicity in the form of neural tube anomalies in humans. The teratogenic effects of VPA could involve altered micro RNAs expression. Various forms of VPA, and more importantly, newer generation of AEDs like lamotrigine, topiramate, and gabapentin show signals for either congenital jaw or oral malformation.

- **Retinoic acid (RA)** or **retinol** is the active metabolite of vitamin A and is responsible for all of the bioactivity associated with this vitamin. It plays essential signalling roles in mammalian embryogenesis. Excess intake of vitamin A often results malformations to foetus's skulls, faces, limbs, eyes and central nervous system. The RA catabolic CYP26 enzymes prevent the teratogenic consequences caused by uncontrolled distribution of RA particularly on the RA-sensitive tissues like the limbs and the testis.

- **Isotretinoin** is a very effective oral medicine (a byproduct of vitamin A) for the treatment of severe acne. In greater amount intake, it can cause foetal abnormalities including cleft lips, ear and eye defects, and mental retardation.
- **Mefloquine (MQ)** is a potent effective antimalarial drug against *Plasmodium falciparum*. It is safe during the second and third trimesters. In early gestation in Wistar rats, MQ induce minimal extension of lateral brain ventricles and renal pelvis together with delayed ossification in the foetuses.
- **Miltefosine** a drug used in the treatment of visceral leishmaniasis but its use is hampered by its potential teratogenicity. Its excess use hamper the development of foetus.
- **Ritodrine** is a drug used to stop premature labor. Its excess use cause cardiovascular problems in foetus. **Nifedipine** (Adalat) is used to manage angina, hypertension, Raynaud's phenomenon and premature labour. Its overdose can cause vascular dilation in both the uterus and the placenta. However, ritodrine + nifedipine combination had reduced the toxic and teratogenic effects of nifedipine alone on embryos.

4) Environmental pollutants:

- **Toluene** is an organic solvent necessary for industry. Many women of childbearing age are increasingly exposed to toluene in occupational settings (i.e. long-term, low-concentration exposures) or through inhalation abuse (e.g. episodic, binge exposures to high concentrations). High levels of toluene exposure may lead to retardation of mental health and growth in foetus.
- **Cadmium (Cd)** is a heavy metal pollutant and teratogen. Cd mediated teratogenicity, in a chick embryo, had occurred

because of impaired endogenous nitrous oxide (NO), increased oxidative stress, and activated apoptotic pathways. Cd significantly decreases foetal body weight, forelimb and hindlimb bone lengths. It also may cause abortion.

5) Tipsiness of mother:

- **Alcohol** (prenatal) is considered as a teratogenic agent. Genetic factors seem to influence foetal alcohol spectrum disorders in both humans and animals. Micro RNAs and their target genes are involved in the pathogenesis of foetal alcohol syndrome. Some sociobehavioral risk factors (e.g. low socioeconomic status) are permissive for foetal alcohol syndrome (FAS). These permissive factors are related to biological factors (e.g. decreased antioxidant status) which together with alcohol, provoke FAS/ alcohol-related birth defects (ARBDs) in vulnerable foetuses.
- N**icotine** consumption by mother is teratogenic leading to increased incidence of attention hyperactivity disorder. There is a correlation of teratogenic effects of alcohol and tobacco, and the risk of anorectal atresia. Smoking increases risk for SIDS (Sudden Infant Death Syndrome) which is the sudden and unexpected death of an infant under 12 months of age that occurs typically while sleeping, also related to failure of auto-resuscitation, normal heart rate and breathing.
- **Cocaine** abuse significantly reduces foetal weight, increases the malformation rate, and augments the stillbirth rate due to abrupt placentae. Cocaethylene or ethylbenzoylecgonine is formed in the liver when cocaine and alcohol are simultaneously ingested; each is a potent stimulant and dopamine uptake blocker that is more toxic to myocardial cells than cocaine alone.

6) Maternal health problems:

- **Diabetes mellitus** of mother are of great concern during pregnancy. Teratogenesis is associated with pre-existing and gestational diabetes. The risk of congenital anomalies increases in the offspring of obese diabetic women.
- **Oral antihyperglycemic agent** use is not recommended during pregnancy. Healthy diet and regular exercise may help optimize pre-pregnancy weight and reduce the risk of congenital anomalies. Cardiac and neural tube defects are the most common malformations observed in foetuses of pre gestational diabetic mothers.
- **Multiple sclerosis (MS)** of pregnant mother should carefully consider the risks and benefits of ongoing therapy for the health of both the mother and the foetus. The immunosuppressant **mitoxantrone** and **fingolimod** are teratogenic and should be prescribed only with strict effective contraception.
- For pregnant women suffering from **rheumatoid arthritis (RA)**, the use of immune modulating medications has low risk allowing for optimal outcomes. Some women with RA may have a risk of miscarriage or low-birth-weight babies.

Table : Drugs with proven teratogenic effects

Sl. No.	Drugs	Teratogenic Effects
1.	Aminopterin, Methotrexate	CNS and limb malformations
2.	Anticholinergic drugs	Neonatal meconium ileus
3.	Anti-thyroid drugs (propylthiouracil and methimazole)	Foetal and neonatal goiter and hypothyroidism, aplasia cutis
4.	Angiotensin-converting – enzyme inhibitors	Prolonged renal failure , decreased skull ossification, renal tubular dysgenesis
5.	Carbamazepine	Neural tube defects
6.	Danazol & other androgenic drugs	Masculinization in female foetuses
7.	Hypoglycemic drugs	Neonatal hypoglycemia
8.	Lithium	Ebstein's anomaly
9.	Misoprostol	Moebius sequence
10.	Nonsteroidal anti-inflammatory drugs	Constriction of the ductus arteriosus, necrotizing enterocolitis
11.	Phenytoin	Growth retardation, CNS deficits
12.	Psychoactive drugs (e.g. barbiturates, opioids and benzo-diazepines)	Neonatal withdrawal syndrome when drug is taken in late pregnancy
13.	Systemic retinoids (isotretinoin & etretinate)	CNS, craniofacial, cardiovascular defects
14.	Tetracycline	Anomalies of teeth and bone
15.	Thalidomide	Limb-shortening defects, internal organ defects
16.	Valproic acid	Neural-tube defects
17.	Warfarin	Skeletal and CNS defects, Dandy-Walker syndrome