UNIT 3 TERATOGENESIS

Structure

3.0 Introduction

3.1 Objectives

3.2 Definition and Concepts

- 3.2.1 Definition
- 3.2.2 Principles in Teratology
- 3.2.3 Stage of Exposure to Teratogens

3.3 Sources of Teratogens and their Effects

3.4 Teratogenesis

- 3.4.1 Basic Principles in Teratogenesis
- 3.4.2 Mechanism of Action

3.5 Let Us Sum Up

3.6 Key Words

3.7 References and Suggested Further Readings

3.8 Answers to Check Your Progress

3.0 INTRODUCTION

We have learnt about toxicants and toxins in the previous units and how they exert deleterious effects on the organs. Some toxic substances can penetrate the placental barrier and bring about birth defects with malformations in the developing embryo and foetus. They can cause mental retardation, paralysis of the limbs, congenital heart defects, cleft palate, visual and auditory disturbances. There have been numerous reports which have shown that the drug Thalidomide used to treat morning sickness in women caused teratogeny and birth defects in the children born to these women. Bhopal gas tragedy and endosulfan pesticide poisoning induced teratogeny among the human population. Let us now learn about teratogens, some concepts in teratogeny and their mechanism of action.

3.1 OBJECTIVES

After reading this unit, you should be able to:

- define teratogens and teratogenesis;
- understand the principles underlying teratogenic effects;
- explain the various sources of teratogens and their effects; and
- describe the mechanism of teratogenesis.

3.2 DEFINITIONS AND CONCEPTS

Dear Learners, you will read about definitions and concepts in the following sentences:

3.2.1 Definitions

Let us now learn about some definitions and terms commonly used in teratogeny.

a) *Developmental toxicity:* It is caused due to any morphological or functional alteration caused by chemical or physical insult that interferes with normal growth, homeostasis, development, differentiation, and/or behavior.

b) *Teratology:* It is a specialized area of embryology that focuses on the study of the etiology of abnormal development. It is otherwise known as the study of birth defects.

c) *Teratogens:* They are toxic agents, xenobiotics that cause malformations in the developing foetus.

d) *Malformation*: This is referred to a primary structural defect resulting from a localized error of morphogenesis.

e) *Disruption*: It is a particular abnormality that arises from disruption of normal developmental processes. This is dependent on time and not on an agent.

f) *Deformation*: This refers to an alteration in shape or structure of previously normally formed part.

g) *Syndrome*: It is a recognized pattern of malformations with a given etiology.

h) *Congenital malformation:* These are structural defects present at birth. They may be gross or microscopic, on the surface of the body or within it, familiar or sporadic, hereditary or nonhereditary, single or multiple. (Warkany, 1947)

Some examples of teratogens are therapeutic drugs, drugs of abuse, hormones found in contraceptive agents, components found in cigarette, nicotine, alcohol, heavy metals, viral agents and so on.

3.2.2 Principles in Teratology

Teratogens can be organ specific, dose specific and species specific. There are six principles in teratology that was proposed by James Wilson in 1959. They are given below.

1) The susceptibility of a foetus to teratogenesis depends on the genotype of the embryo which interacts with adverse and toxic environmental factors.

2) Teratogenesis is related to the stage of development of the foetus when exposed to the toxicant.

3) Teratogenic agents have well defined mechanisms for producing toxic effects.

4) The type of the teratogenic compound is an important factor that determines its path to the developing foetus.

5) Teratogenesis is mainly characterized by death, malformation, growth retardation, and functional deficits.

6) The extent of altered development increases with increasing dose.

3.2.3 Stage of Exposure to Teratogens

In most cases the stage of exposure of the developing foetus or the stage of pregnancy is important for the effects of teratogens. The process of embryogenesis

is highly complex. It involves: cell migrations, proliferation, differentiation and organogenesis. It can also be classified as: pre-implantation stage, implantation to organogenesis stage, and the foetal to neonatal stage. The outcomes associated with exposure during each of these stages differ. Exposure during the pre-implantation stage causes embryonic lethality. Exposure to teratogens during implantation to time of organogenesis leads to morphological defects. Exposure to teratogens during the foetal to neonatal stage leads to functional disorders and growth retardation. The most critical period is the time of organogenesis when organs formation takes place.

Check Your Progress 1

Note: a) Write your answer in about 50 words.

b) Check your progress with possible answers given at the end of the unit.

1) Define a teratogen.

.....

.....

.....

.....

.....

.....

2) What are the principles in teratology?

.....

.....

.....

.....

.....

.....

3.3 SOURCES OF TERATOGENS AND THEIR EFFECTS

There are many sources of teratogens which can be harmful. They can be therapeutic drugs, alcohol and even drugs of abuse. Let us learn some of them in detail.

1) Therapeutic Drugs

a) *Thalidomide:* This is a sedative drug that was used in Europe from 1957 to 1961. The drug was actually used for insomnia (sleeping disorders), nausea, vomiting and morning sickness associated with pregnancy. It was widely used by women in Europe, Australia, Asia, Africa, and America. Later on it was observed that the women who had consumed this drug in the first trimester gave birth to children who had abnormalities. The birth defects were amelia (absence of limbs), phocomelia (severe shortening of limbs), absence of the auricles,

deafness, muscular defects of eye and face, malformations of the heart, bowel, uterus, and the gallbladder. The effect was disastrous with more than 10,000 affects. So finally the compound was withdrawn from the market in 1961.

b) *Accutane (Isotetrinoin):* This drug belongs to the retinoid group of drugs. It is related to vitamin A. The drug is supposed to cure severe and painful acne. The pregnant women who took this drug were reported to have children with birth defects including facial deformities, heart defects, and mental retardation.

c) *Diethylstilbestrol:* This drug is synthetic estrogen which inhibits ovulation by affecting release of pituitary gonadotropins. It is used in the treatment of hypogonadism.

d) *Tetracycline*: This antibiotic has the ability to go across the placental barrier and constituents are deposited in the bones and teeth of the growing foetus. It can cause yellow stained teeth and bone disorders.

e) *Anticonvulsant agents*: The therapeutic drug phenytoin causes foetal hydantoin syndrome. It results in microcephaly, mental retardation and intrauterine growth retardation.

f) *Anti-neoplastic or chemotherapeutic agents*: These drugs can stop the rapidly dividing cells during foetal growth formation. So it should be totally avoided during pregnancy.

2) Alcohol

Women who consume alcohol during pregnancy give birth to children with mental and physical retardation. The foetal alcohol syndrome is also observed when the foetus is exposed to alcohol in utero. The most critical period for this defect is the first trimester. The babies born have small body size, low birth weight, craniofacial defects, psychomotor defects, microcephaly (small head), scoliosis, small eye openings, and other neurological problems. They may also have visceral defects associated with the heart and kidney. Learning disabilities may also be present.

3) Non Chemical Teratogens

There may be other non chemical agents also that can be teratogens. This also can harm the developing foetus. For example Rubella virus that causes german measles is hazardous and causes teratogenic effects. It was reported as early as 1941 in Austria. The defects produced vary with thie stage of gestation (pregnancy). Exposure to this virus during the first two months of pregnancy causes heart and eye anomalies. Exposure during the third month of gestation induced hearing anomalies in the growing foetus. Other biological infectious teratogens include cytomegalovirus, varicella, herpes simplex, toxoplasma, syphilis, human immunodeficiency virus (HIV).

4) Physical Agents

Some physical agents induce teratogenecity. They include: ionizing radiations, hyperthermia and so on. Ionizing radiation can harm the growing embryo. It results in cellular death and injury to chromosomes. Some women exposed to the radiations in the Hiroshima atomic bombing during 10 – 18 weeks

of gestation had children with brain defects. In the same way x-rays can also cause risk to the developing foetus.

5) Environmental Toxicants

Some environmental toxicants like organic mercury compounds, polychlorinated biphenyl, agricultural herbicides and industrial solvents are reported to cause teratogenic effects. People affected by consumption of organic methyl mercury contaminated fishes in Japan had children born with birth defects.

6) Maternal Health Factors

Another important factor is the health of the mother during pregnancy. Mothers who have diabetes can have an increased risk of having children with congenital heart disease, renal, gastrointestinal, and central nervous system anomalies. Women with phenylketonuria have an increased risk of giving birth to children with mental retardation, low birth weight, and congenital heart disease. Also genetic factors play important role in teratogeny.

7) Drugs of Abuse

Drugs used for abuse are highly risky to the developing embryo.

a) *Cocaine:* Cocaine or benzoylmethylecgonine is a teratogen. It is an alkaloid extracted from the plant *Erythroxylum coca*. Expsoure to this drug causes gastrointestinal anomalies, cardiac problems, craniofacial anomalies, tissue death due to disruption in blood supply to the developing embryo. It can also cause limb anomalies.

b) *Opioids:* This can cause preterm deliveries, chorioamnionitis, neural tube anomaly and foetal death.

c) *Cannabis:* This drug can cause low birth weight children and shorter gestation periods.

d) *Amphetamines:* This can cause microcephaly, oral cleft defects and so on.

e) *Hallucinogens*: They include phencyclidine, lysergic acid diethylamide (LSD), and 3,4-methylenedioxymethamphetamine. Phencyclidine causes microcephaly and intracranial abnormalities. LSD causes limb defects and eye abnormalities.

8) Inhalants

They include industrial solvents, such as toluene; fuels; anesthetics; nitrous oxide; and alkyl nitrites. Women may be exposed to these substances at the industrial workplaces. Toluene causes preterm labor, intrauterine growth retardation, microcephaly, craniofacial abnormalities, wide nasal bridge, blunt fingertips and abnormal palmar creases.

These are some sources and effects of teratogens. You can see how much damage they can do to the developing embryo. So during pregnancy utmost care has to be taken by the mother and she should avoid drugs (both therapeutic

as well as of abuse) and non chemical agents. She should be careful about the food she eats, the water she drinks and the air she breathes as environmental toxicants are also detrimental.

Check Your Progress 2

Note: a) Write your answer in about 50 words.

b) Check your progress with possible answers given at the end of the unit.

1) List the different sources of teratogens.

.....

.....

.....

.....

.....

.....

.....

2) Describe the effects caused by therapeutic drugs.

.....

.....

.....

.....

.....

.....

.....

3) Describe the effects caused by drugs of abuse and non chemical teratogens.

.....

.....

.....

.....

.....

.....

.....

.....

3.4 TERATOGENESIS

We have seen the sources of teratogens and the effects caused by them. They are present even in the environment as toxicants. These can induce embryotoxicity. Teratogenicity refers to the manifestation of developmental toxicity representing a particular case of embryo/foetotoxicity by inducing structural disorders in the foetus.

3.4.1 Basic Principles in Teratogenesis

The fundamental principles involved in teratogenesis include the following.

a) Critical stages of foetal development;

b) dosage of the drug, chemical, non chemical agent; and the

c) genotype (genetic constitution) of the embryo and mother are important factors.

Teratogens cause toxicity to the growing foetus. Broadly they can cause:

a) death of the developing foetus in utero;

b) malformation of foetus;

c) intrauterine growth retardation; and

d) functional defects in the newborn.

3.4.2 Mechanism of Action

A teratogen can cause effects on different intracellular components during the various stages of pregnancy. In general there can be four main levels or areas where the action can take place. They are given below.

a) Teratogens can act on the intracellular compartment which is between the nucleus and the cytoplasm.

b) They can act on the cell surface giving rise to structural and functional anomalies.

c) They can act on the extracellular matrix.

d) They can act on the foetal environment at the organismal level or in the foeto-maternal relation.

These can further be divided into genetic and non-genetic types.

1) **Intracellular Region**

Genetic: They are known as 'inborn errors of metabolism'. It was named by Sir Archibald Garrod. In this mainly a mutant gene leads to deficiency of an enzyme activity. So the metabolic pathway is blocked. An example is Hurler's syndrome due to deficiency of the lysosomal enzyme a-L-iduronidase, and the accumulation of heparin sulfate and dermatan sulfate in the cells. The excess metabolite accumulation in cells leads to growth retardation, mental regression, skeletal defects, cardiac problems and hepatosplenomegaly (Leroy & Crocker, 1966).

Non-genetic: In this the nucleocytoplasmic interactions are blocked by inhibitors. The inhibitors prevent the process of reading genetic information. Thereby they cause hereditary disorders. An example is Actinomycin D which is reported to be teratogenic to early brain and causes severe eye defects (Diethelm & Schowing, 1974). The drug Cycloheximidine stops both protein synthesis and morphogenesis.

2) **Extracellular Matrix**

Teratogens can also affect the function of a tissue by interfering with the production or maturation of this extracellular material.

Genetic: One example is Dermatosparaxis. It is a hereditary disease recently

detected in cattle with fragile skin with an inelastic dermal tissue. This is due to abnormal or insufficient production of collagen in the dermal connective tissue. Similar defects were observed in patients suffering from Ehlers-Danlos syndrome (Lichtenstein et al. 1973).

Non-genetic: The example of the antibiotics of tetracycline group comes under these effects. They act on the extracellular compounds. The drug tetracyclines get into the mineralizing tissues causing hypoplasia and growth retardation. The action is well known on the bone mineral tissues.

3) **Fetal Environment**

Embryogenesis and foetal development is controlled by various factors. They include maternal, placental and autogenous factors. They are the hormonal factors, immune mechasisms and nutritional factors. Teratogens can cause changes in the foetal environment even without crossing the placenta. These agents can block the supply of nutrition or vital necessities to the growing foetus. Thus they bring about birth anomalies.

Genetic: Hereditary disorders can cause teratogeny in foetus. The endocrine disorders come under this category. An example is Pendred's syndrome characterized by congenital deafness and hypothyroidism.

Nongenetic: These include factors like nutritional deficiencies, placental insufficiency, altered maternal endocrine status and immunization following feto-maternal incompatibility. Brent in 1971 showed that rabbit antisera when injected into pregnant rats caused congenital abnormalities in the offspring. What was surprising is that the antibodies did not cross the placenta. But they accumulated in the yolk-sac epithelium (structure present in placenta of rodents and rabbits). It was in this region the immunoglobulins impaired the placental function by disrupting the transport of nutrition to the growing foetus. Azo dyes are also known to cause similar actions without entering the foetus (Beck, 1967).

Counseling and proper care by qualified practitioners is very important for pregnant women. Community based services, parenting education is also very important.

3.5 LET US SUM UP

In this unit we have studied about the various teratogens and the effects of teratogens. A congenital malformation can be anatomical or structural abnormality observed at birth. These can be due to teratogenic agents like therapeutic drugs, alchohol, drugs of abuse or even radiations. The health condition of the mother is also very important for a healthy child to be born. The first two weeks of pregnancy is important as most teratogens can destroy or kill the embryo at this stage. During the period of organogenesis major organ defects are formed. Hence understanding the action of teratogens and their mechanism of action is essential to rule out and prevent these anomalies.

3.6 KEY WORDS

Teratology : It is a specialized area of embryology that focuses on the study of the etiology of abnormal development. It is otherwise known as the study of birth defects.

Teratogens : They are toxic agents, xenobiotics that cause malformations in the developing foetus.

Toxicant : Any toxic material or substance is termed as a toxicant. They are hazardous and poisonous. Toxicants are generally man-made and artificial products introduced into the environment due to human activity. They include bisphenol, insecticides and a number of industrial chemicals.

Toxins : These are produced naturally by living organisms. For example, toxins from the mushroom plant and toxin from the venom of snake are natural toxins.

Xenobiotic is referred to a foreign substance entering the body. It is derived from the Greek word 'xeno' meaning 'foreigner'.

3.7 REFERENCES AND SUGGESTED FURTHER READINGS

Abel, P. D., ed. Water Pollution Biology. London: Taylor and Francis, 1996.

Ballantyne, B., Marrs, T. and P. Turner, eds. General and Applied Toxicology, college ed., New York: Macmillan, 1995.

Costa, D. L. Air pollution. In Casarett and Doull's Toxicology: The Basic Science of Poisons, 6th ed., C. D. Klaassen, ed. New York: McGraw-Hill, 2001, pp. 979–1012.

Doull, J. Recommended limits for occupational exposure to chemicals. In Casarett and Doull's Toxicology: The Basic Science of Poisons, 6th ed., C. D. Klaassen, ed. New York: McGraw-Hill, 2001, pp. 1155–1176.

Hodgson, E., and R. C. Smart, eds. Introduction to Biochemical Toxicology, 3rd ed. New York: Wiley, 2001.

Hodgson, E., R. B. Mailman, and J. E. Chambers, eds. Dictionary of Toxicology, 2nd ed. London: Macmillan, 1998.

Klaassen, C. D. ed. Casarett and Doull's Toxicology: The Basic Science of Poisons, 6th ed. New York: McGraw-Hill, 2001.

Timbrell, J. A. Principles of Biochemical Toxicology, 3rd ed. London: Taylor and Francis, 2000.

Wexler, P. Information Resources in Toxicology, 3rd ed. San Diego: Academic Press, 2000.

Holgate, S. T., J. M. Samet, H. Koren, and R. Maynard, eds. Air Pollution and Health. San Diego: Academic Press, 1999.

Hoffman, D. J., B. A. Rattner, G. A. Burton, and J. Cairns, eds. Handbook of Ecotoxicology, 2nd ed. Boca Raton: Lewis, 2002.

Hood, R. D. Handbook of Developmental Toxicology. Boca Raton, FL: CRC Press, 1997.

Klaassen, C. D., ed. Casarett and Doull's Toxicology: The Basic Science of Poisons, 6th ed., New York: McGraw-Hill, 2001.

Korach, K. S. Reproductive and Developmental Toxicology. New York: Dekker, 1998.

Larson, S. J., P. D. Capel, and M. S. Majewski, eds. Pesticides in Surface Waters. Chelsea, MI: Ann Arbor Press, 1998.

Thorne, P. S. Occupational toxicology. In Casarett and Doull's Toxicology: The Basic Science of Poisons, 6th ed., C. D. Klaassen, ed. New York: McGraw-Hill, 2001, pp. 1123–1140.

3.8 ANSWERS TO CHECK YOUR PROGRESS

Answers to Check Your Progress 1

1) Your answer should include the following points:

   Teratogens are toxic agents, xenobiotics that cause malformations in the developing foetus. Some examples of teratogens are therapeutic drugs, drugs of abuse, hormones found in contraceptive agents, components found in cigarette, nicotine, alcohol, heavy metals, viral agents and so on.

2) Your answer should include the following points:

   Teratogens can be organ specific, dose specific and species specific. There are six principles in teratology that was proposed by James Wilson in 1959. They are given below.

   - The susceptibility of a foetus to teratogenesis depends on the genotype of the embryo which interacts with adverse and toxic environmental factors.
   - Teratogenesis is related to the stage of development of the foetus when exposed to the toxicant.
   - Teratogenic agents have well defined mechanisms for producing toxic effects.
   - The type of the teratogenic compound is an important factor that determines its path to the developing foetus.
   - Teratogenesis is mainly characterized by death, malformation, growth retardation, and functional deficits.
   - The extent of altered development increases with increasing dose.

Answers to Check Your Progress 2

1) Your answer should include the following points:

There are many sources of teratogens which can be harmful. They can be therapeutic drugs, alcohol and even drugs of abuse. Let us learn some of them in detail.

1) Therapeutic drugs
2) Alcohol
3) Non chemical teratogens
4) Physical agents
5) Environmental toxicants
6) Maternal health factors
7) Drugs of abuse
8) Inhalants

These are some sources and effects of teratogens. You can see how much damage they can do to the developing embryo. So during pregnancy utmost care has to be taken by the mother and she should avoid drugs (both therapeutic as well as of abuse) and non chemical agents. She should be careful about the food she eats, the water she drinks and the air she breathes as environmental toxicants are also detrimental.

2) Your answer should include the following points:

- *Thalidomide:* This is a sedative drug that was used in Europe from 1957 to 1961. The drug was actually used for insomnia (sleeping disorders), nausea, vomiting and morning sickness associated with pregnancy. It was widely used by women in Europe, Australia, Asia, Africa, and America. Later on it was observed that the women who had consumed this drug in the first trimester gave birth to children who had abnormalities. The birth defects were amelia (absence of limbs), phocomelia (severe shortening of limbs), absence of the auricles, deafness, muscular defects of eye and face, malformations of the heart, bowel, uterus, and the gallbladder. The effect was disastrous with more than 10,000 affects. So finally the compound was withdrawn from the market in 1961.

- *Accutane (Isotetrinoin):* This drug belongs to the retinoid group of drugs. It is related to vitamin A. The drug is supposed to cure severe and painful acne. The pregnant women who took this drug were reported to have children with birth defects including facial deformities, heart defects, and mental retardation.

- *Diethylstilbestrol:* This drug is synthetic estrogen which inhibits ovulation by affecting release of pituitary gonadotropins. It is used in the treatment of hypogonadism.

- *Tetracycline*: This antibiotic has the ability to go across the placental barrier and constituents are deposited in the bones and teeth of the growing foetus. It can cause yellow stained teeth and bone disorders.

- *Anticonvulsant agents*: The therapeutic drug phenytoin causes foetal hydantoin syndrome. It results in microcephaly, mental retardation and intrauterine growth retardation.
- *Anti-neoplastic or chemotherapeutic agents*: These drugs can stop the rapidly dividing cells during foetal growth formation. So it should be totally avoided during pregnancy.

3) Your answer should include the following points:

Non Chemical Teratogens

- There may be other non chemical agents also that can be teratogens. This also can harm the developing foetus. For example Rubella virus that causes german measles is hazardous and causes teratogenic effects. It was reported as early as 1941 in Austria. The defects produced vary with thie stage of gestation (pregnancy). Exposure to this virus during the first two months of pregnancy causes heart and eye anomalies. Exposure during the third month of gestation induced hearing anomalies in the growing foetus. Other biological infectious teratogens include cytomegalovirus, varicella, herpes simplex, toxoplasma, syphilis, human immunodeficiency virus (HIV).

Drugs of Abuse

- Drugs used for abuse are highly risky to the developing embryo.
- *Cocaine:* Cocaine or benzoylmethylecgonine is a teratogen. It is an alkaloid extracted from the plant *Erythroxylum coca*. Expsoure to this drug causes gastrointestinal anomalies, cardiac problems, craniofacial anomalies, tissue death due to disruption in blood supply to the developing embryo. It can also cause limb anomalies.
- *Opioids:* This can cause preterm deliveries, chorioamnionitis, neural tube anomaly and foetal death.
- *Cannabis:* This drug can cause low birth weight children and shorter gestation periods.
- *Amphetamines:* This can cause microcephaly, oral cleft defects and so on.
- *Hallucinogens*: They include phencyclidine, lysergic acid diethylamide (LSD), and 3,4-methylenedioxymethamphetamine. Phencyclidine causes microcephaly and intracranial abnormalities. LSD causes limb defects and eye abnormalities.