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'Teratogenicity in prenatal stages - A review'

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Abstract:

Teratology is the study of causes, mechanisms, and patterns of abnormal development. Many of the teratogenic effects occur because of chemical and physical factors like drugs, infection and radiation respectively. Agents which causes teratogenicity known as teratogens. During the first two weeks of gestation, teratogenic agents usually affect the embryo. There are basic cell behaviours during embryo development that may serve as targets for exposures. Cell populations in the embryo transfer to targeted locations, and interference with transfer may cause abnormal development. The reproductive toxicity includes the death of the developing organism, structural abnormality, altered growth, and functional deficiency. Teratogenicity depends on the capacity of the agent to cross the placenta. The original focus of this work was on physical malformations and more recently has referred to malformations that result from exposure to chemicals such as lead, mercury, or other compounds. The present view-point is to explore and review the teratogenic mechanism and common teratogenic effects of teratogenic compounds. The basis of this review was 'to implicate the teratogenic effects of drugs and other chemical factors. That is the behaviour or functional variation of the offspring to its environment'.

Keywords:

Teratogens, defects, congenital malformations, factors, embryo, development Alcohol, Thalidomide, Spina bifida

Introduction

Teratogenicity is a defect in a developing fetus. It is a potential side effect of many drugs such as thalidomide, captopril, methotrexate, etc [1]. Teratogenicity also called as reproductive toxicity. It broadly refers to the occurrence of biologically adverse effects on the productive system that may result from chemical exposure to several environmental agents. Fetal damage such as growth retardation, dysplasia, goitre, or the asymmetrical Teratology is the study of abnormal development in embryos and causes birth defects. The reproductive toxicity includes the death of the developing organism, structural abnormality, altered growth, and functional deficiency. [2] Teratogenicity depends upon the ability of the agent to cross the placenta.

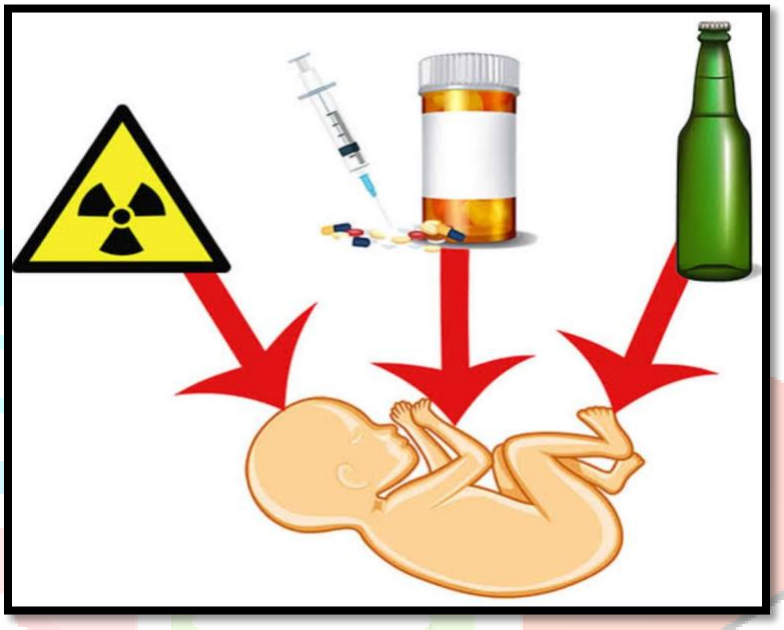


Fig No.1 Teratogenicity

Prenatal development

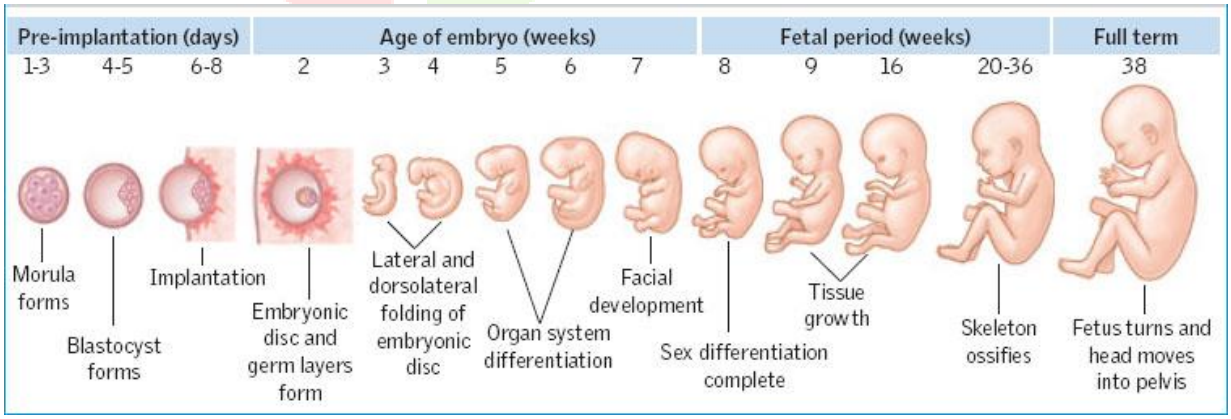


Fig No.2 Prenatal Development of fetus

Teratogen

The term teratogen is used to describe an agent that can produce structural or functional abnormalities in a developing embryo. Teratogen causes Teratogenicity. A teratogen is defined as any environmental factor that can produce a permanent abnormality in structure or function, restriction of growth, or death of the embryo or fetus. [3] Teratogenic chemicals induce their adverse effects indirectly on the fetus and some teratogens directly affect fetal development by crossing the placental barrier and entering fetal circulation. Teratogens affect the embryo or fetus in a various ways, causing physical malformations, problems in the behavioural or emotional growth of the child, and decreased intellectual quotient (IQ) in the child. As well, teratogens may also affect pregnancies and causes difficulties such as preterm labors, unplanned abortions, or miscarriages. Factors comprise medications, drugs, chemicals, and maternal conditions or diseases, including infections. The human teratogen is may be a chemical drug, metabolic state, physical agent or psychological alteration throughout development that produce a permanent pathologic or pathopsychologic alteration in the children at exposures or conditions that commonly occur [4].

History

As congenital disabilities are detected, medical professional must consider most congenital disabilities stem from teratogens [5]. At the first time, teratology was discovered in the 1930s after various experiments were performed on pregnant pigs. In these experiments, pigs were feed with a vitamin A deficiency diet. Ultimately, all those piglets experienced disturbing malformations, the major loss of eyes. The first human teratogen identified in 1941 by an ophthalmologist, Norman Gregg, was maternal rubella infection in pregnancy, which created a triad of defects (cataracts, heart malformations, and deafness) in the infants. [6] As science developed, the effect of xenobiotic agents on embryos was established by experimenting on animals with congeners of biologically predominant molecules, likely amino acid analogue azaserine. In the 1950s, aminopterin was used to terminate the pregnancy.

General mode of action of teratogen

Mammalian fetal development passes throughout three main phases: blastocyst formation, organogenesis, histogenesis and maturation of purpose. Many teratogens have capacity to inhibit cell division and kill embryo during cell division, which was implicated in blastocyst formation. Administration of teratogen during the period of organogenesis (Day 17-60) leads to malformations. The type of malformation produced by teratogen involves defect in eye and brain, skeleton and limbs, heart and major vessels, palate, and genitourinary system. Teratogens and teratogenic effects may generate mutagenic effect such as vitamin A derivatives (retinoids), which are occupied in morphogenesis and are potent teratogens.

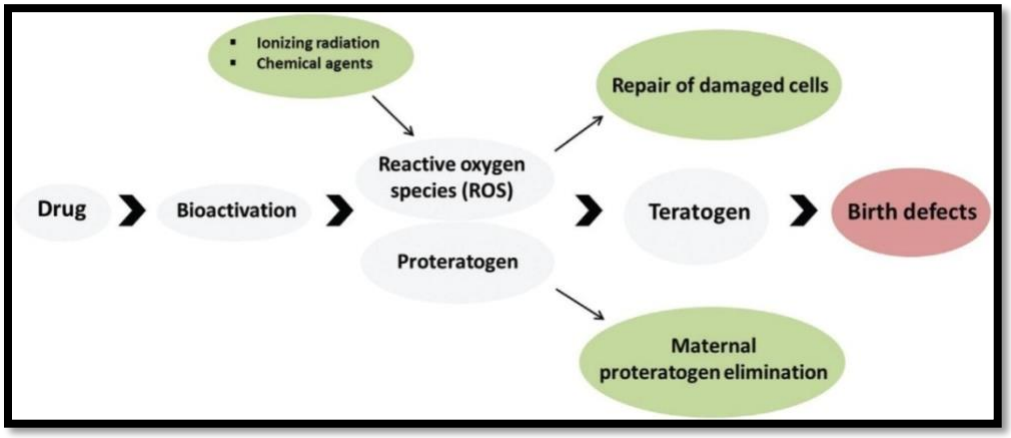


Fig No.3 Mode of action of teratogen

Teratogenic factors:

Teratogens are mainly classified into four types:

Drugs, chemicals, maternal factors, Physical factors

Sr. No.	Factors	Medication
A.	**Drugs**	ACE Inhibitors (captopril, enalapril) NSAID (Diclofenac), Thalidomide, Androgen hormone(oestrogen),Antineoplastic agents (methotrexate), Warfarin, Valproic acid, Retinoic acid
B.	**Chemicals**	Alcohol, Cocaine, Methylmercury, Lead Acetate
C.	**Maternal Factors**	Diabetes Mellitus, Epilepsy
D.	**Physical Agents**	Cigarette smoking, Ionizing radiation

Table no.1 Teratogenic factors

A. Drugs

1) ACE inhibitors: (captopril and Enalapril)

Angiotensin-converting enzyme inhibitors (ACEIs) are the mainly indicated medications in the treatment of cardiovascular and renal diseases, with heart failure, acute coronary syndrome, nephrotic syndrome, diabetes, and hypertension.[7]

The ACE inhibitors are competitive inhibitors of kininaseII

⇩

They affect both the Angiotensin/aldosterone and bradykinin/prostaglandin systems

⇩

Fetal wastage

Administration of ACE inhibitors during pregnancy leads to fetal wastage. Specifically, these drugs were associated with increase infant risks for cardiovascular and nervous system anomalies. [8] They cause severe renal and other problems during the second and third trimesters; these drugs should be avoided during pregnancy. [9]

Fetotoxic effects of ACE inhibitors consist of fetal hypotension, renal tubular dysplasia, anuria and oligohydramnios, growth restriction, hypocalvaria, and death when used in the second and third trimesters of pregnancy. [10]

2) Non - steroidal anti-inflammatory agents: Diclofenac

Diclofenac is a nonsteroidal anti-inflammatory drug and usually used by reproductive age women for the treatment of variety of conditions. Because of its low molecular weight diclofenac can readily crosses the human placenta during the first trimester.

Diclofenac can readily crosses the human placenta

⇩

Accumulates in fetal tissue

⇩

Induce skeletal and heart defects and fetal growth retardation

Pregnant women treated with high toxic doses of non-selective cyclooxygenase inhibitors show bone developmental variations in fetus. Drugs of this class like aspirin inhibit synthesis of vasodilator prostaglandin, causing temporary vasoconstriction and provoking malformations and cellular death. [11] Administration of NSAIDs during the latter part of pregnancy may cause premature closure of the fetal ductus arteriosus, fetal renal impairment, embarrassment of platelet aggregation, and delay labor and delivery.

3) Thalidomide

Thalidomide used as a sedative to treat morning sickness in pregnant women. Thalidomide is effective for lepra patients. Thalidomide can inhibit the production of tumour necrosis factor-α (TNF-α) in stimulated human monocytes. In addition, thalidomide and its derivatives can regulate the production of several cytokines, interleukin-2 and interferon γ. Thalidomide inhibit angiogenesis.

Thalidomide causes injure to the forming embryo in a short time susceptible window also known as the "critical period." The time susceptible window extends among days 20 and days 36 after fertilization (34–50 days after last menstrual cycle). [12] It has been established that thalidomide administration during the early stage of pregnancy significantly increases the incidence of miscarriage and the birth of malformed newborns with limb reduction anomalies and other defects, as well as congenital heart disease, ear and eye damage, and internal organ injure.

4) Androgen hormones: oestrogen

Androgens are a group of sex hormones. Natural androgens are steroidal hormones produced by gonands and adrenal glands. They help begin puberty and play a role in reproductive fitness and body development. Testosterone is the generally common androgen [13].

Increased level of androgenic hormones during pregnancy causes masculinisation of a female foetus. Masculinisation means to cause male characteristics in female and pseudohermaphroditism in pregnant mother. The androgenic progestin administered to the mother is changed to an oestrogen that does not protect the foetus from the masculinisation effect and causes cornification of the vagina. Testicular testosterone produced during a critical prenatal period is thought to masculinize and defeminise the male brain from the inherent feminization program. These actions of testosterone show to be exerted not through its androgenic activity, but rather throughout its conversion by brain aromatase into oestrogen, with the ensuing activation of oestrogen receptor mediated signalling. [14]

5) Antineoplastic Agents

Antineoplastic drugs are medications used to treat cancer. Other names for antineoplastic drugs are anticancer, chemotherapy and cytotoxic drugs. The use of antineoplastic agents in pregnant women poses noticeable risks to both the patient and the developing fetus, particularly during organogenesis. Congenital malformations can occur in just about 20% of cases if chemotherapy using cytotoxic anticancer drugs is administered through the first trimester. [15]

If the patient is pregnant while receiving chemotherapy, termination of pregnancy is an option as there is an enlarged risk of drug-induced fetal malformations. Patients with breast cancer sensitive to premenopausal hormones may miss their chance to become pregnant, as the postoperative administration of tamoxifen may be extended term. [16]

Methotrexate It is a synthetic analogue of dihydrofolate and acts as competitive inhibitors of dihydro folate reductase (DHFR) enzyme. Methotrexate causes trouble in folate metabolism and may have a teratogenic effect through inhibition of the folate methylation cycle. Birth defects in children born to women who have been treated with methotrexate contain skeletal defects, low birth weight, and a wide range of developmental abnormalities

6) Anticoagulant Agents: Warfarin

Warfarin is the competitive inhibitor of vitamin K. Warfarin can easily cross the placental barrier and enters the fetal bloodstream. It has a lower molecular weight, causing fetal warfarin syndrome-children. Warfarin crosses the placenta and is related with increased rates of fetal loss. Warfarin taken throughout the second and third trimester causes central nervous system anomalies.[17] Consuming higher doses of warfarin greater than 5mg daily can immediately result in fetal death.

Warfarin syndrome can be prevented by not prescribing the warfarin drug to the women trying to suppose and avoid it before five days of conception.

7) Valproic Acid

Valproic acid (VPA) is a commonly prescribed drug for those affected by epilepsy and bipolar disorders. VPA has a well known teratogenic prospective, causing a variety of birth defects with neural tube defects (NTDs) and other congenital malformations, when women are treated with this medication during pregnancy. [18] Valproic acid causes valproate syndrome. It increases in the rate of developmental problems, manifested by decreased verbal intelligence often with communication problems of the autistic spectrum disorder (ASD). [19]

8) Retinoic Acid

Retinoids are vitamin A i.e retinol derivatives. Vitamin A (retinol) is an essential vitamin that helps to regulate cellular differentiation of epithelial tissue. [20] Excess of vitamin A can concern embryonic development and result in teratogenesis in a developing embryo.. The concerned organs are the fetal skull, face, limbs, eyes, central nervous system due to excess retinoids. Avoiding the retinoids excess during pregnancy can make the baby sleep in this world as an entire human with no defects. [21]

Factors	Time period	Defects

Angiotensin inhibitors	First trimester	Hypotension, Renal dysplasia, anuria or oliguria, pulmonary hyperplasia ,Spina bifida, intrauterine or neonatal death
Thalimomide	First trimester	Malformed intestines, hearing defects, absent ears/ocular and renal anormalies
Oestrogens	Second trimester	Possible cardiovascular defects, hypospadia
Antineoplastic	Second and Third trimester	Cleft palate, renal agensis,cardiac anomalies, cleft lip and palate, anencephaly, low-set ears
Epileptics	First trimester	Facial dysmorphia, gingival hyperplasia, Neurological hyper excitability and multiple malfomations
Valproic acid	First and Second trimester	Lumbosacral Spina bifida, with menigomyelbceq, Prominent heart disease and decrease postnatal growth
Warfarin	First trimester	Deformities of the axial and appendicular skeleton, hypoplastic nose, eye abnormalities, mental retardation, scoliosis

Table No.2 Teratogenic effect of drugs

B. Chemical Factors

a. Unnecessary chemical

1) Alcohol

During the primary four weeks of pregnancy, the baby develops organ systems in their body, such as the heart, central nervous system, eyes, arms, and legs. The baby's brain starts developing about the third week of its intrauterine life and gradually matures together with the pregnancy.

Alcohol exposure during pregnancy can have direct toxic and teratogenic effects on a fetus, Ethanol diffuses through the placenta and distributes quickly into the fetal compartment, accumulating in the amniotic fluid [22]

MOA:

The mother consumes alcohol

⇩

It can easily bypass through the placenta

⇩

Interfere with growth factor that regulate cell division in cerebral cortex of foetus

⇩

Preventing the normal growth and fetal brain development

⇩

Developmental exposure can result in fetal alcohol spectrum disorders (FASDs)

The maternal and fetal endocrine systems are also reported to be affected by alcohol in a number of ways, and the maternal-fetal endocrine balance may also be disrupted. [23] Alcohol is a known as toxicant it causes cell death in a fetus, and a teratogen, altering cell cycle and function in a developing fetal brain, with PAE having instant and persisting effects on an individual among FASDs. [24]

Prevention: One can barrier these changes by avoiding alcohol expenditure during pregnancy and protecting the baby from fetal alcohol spectrum disorder.

2) Cocaine:

Cocaine is an alkaloid and nitrogen-based natural compound. It is a drug with probable local anaesthetic effect and properties like painkiller and antidepressant.

Cocaine works as a central nervous system stimulant by interfering with the nervous cells reuptake of nor epinephrine and dopamine. Nor-epinephrine and dopamine are chemicals involved in the transmission of neurological signals, or neurotransmitters. Slowed reuptake causes raise in levels of neurotransmitters like Dopamine. [25] Increased levels of nor-epinephrine enable cocaine to accumulate at nerve terminals, which in

pregnant women results vasoconstriction and hypertension at the site where the uterus and placenta attach together. This disturbance of blood flow to the uterus and placenta may also result in maternal tachycardia, a condition that manifests in an abnormally high heart rate, an amplified risk for ventricular arrhythmias, and amnion rupture, which in turn causes limb defects in the fetus .The effective vasoconstrictive effects of cocaine when exposed during the first trimester may increase the risk of structural abnormalities.

b. other chemicals

1) Methylmercury

Methylmercury is generally known for its variable toxicity such as neurotoxin, endocrine disruptor and teratogen. Exposure of methylmercury produces changes in behaviour and health in humans. Prenatal exposures of methylmercury in humans at high concentration outcome in neurobehavioral effects such as cerebral palsy and severe mental retardation. It is also associated with decreased birth weight and early sensor motor dysfunction such as late onset of walking.. It also produces developmental neurotoxic effects in fetus and infant. To avoid these teratogenic effects, pregnant women and women of childbearing age are possible to avoid exposure of methylmercury.

2) Lead acetate

Lead is common industrial and public health problem that causes numerous adverse effects in both men and women. A woman who has lead poisoning can pass lead to her fetus if she becomes pregnant. The term “lead poisoning” refers to blood Pb levels ≥50 µg/dl. Harmful effects of lead exposure have not been credibly shown to occur at blood Pb levels ≤20 µg/dl. Lead crosses the placenta as early as the 12th to 14th weeks of gestation and accumulates in fetal tissue. [26] The adverse effects of lead consist of spontaneous abortion and stillbirth. A small but most important increase in minor malformations, including haemangioma, lymph-angiomas, skin tags, skin papillae, and was seen in infants with elevated lead levels in the umbilical blood. The VACTERL (vertebral, anal, cardiac, tracheoesophageal fistula, renal and limb abnormalities) organization has been reported with prenatal exposure to high lead levels. [27] Serious effects of lead exposure include increased prevalence of menstrual disturbances, spontaneous abortion and threatened abortion.

c.Maternal Factors

1) Diabetes Mellitus

Diabetes mellitus is an assembly of physiological dysfunctions categorized by hyperglycaemia resulting directly from insulin resistance, insufficient insulin secretion, or extreme glucagon secretion. Insulin is a hormone in the body of human. Insulin helps to obtain enough glucose into the body cells to be used as fuel whenever there is no exterior food source.

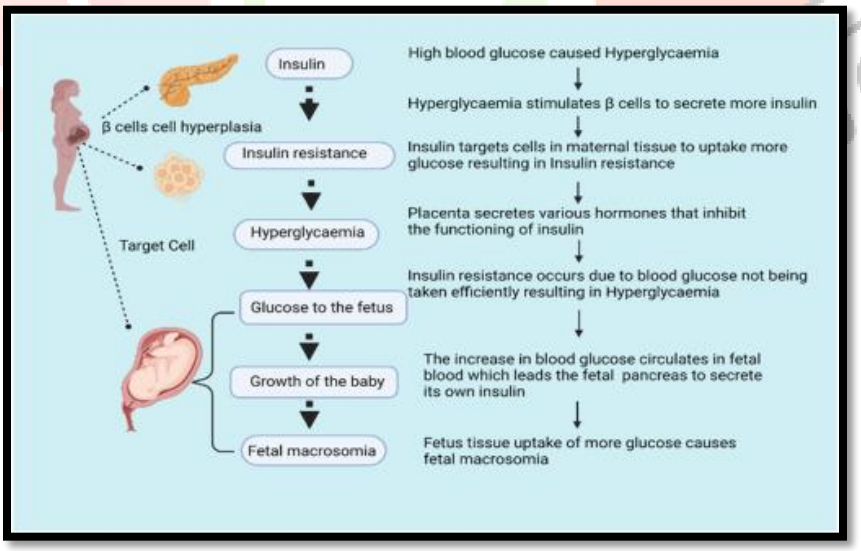
Types of Diabetes Mellitus are:

a) Type 1 diabetes (T1D)
b) Type 2 diabetes (T2D)
c) Type 3 gestational diabetes

Gestational diabetes in which blood glucose levels rise and various diabetic symptoms rapidly appear through pregnancy, as the same women may not be diagnosed as diabetic before. This is general for pregnant women.

Diabetes is responsible for a defeat of normal homeostasis not only of carbohydrate but of fat and protein metabolism as well. [28] The placenta is an organ that provides the baby with all the nutrients and oxygen essential to grow, lactogen, and cortisol. All the mentioned hormones can block the insulin. This blockade is known as insulin resistance. It is insulin resistance that results in excess amounts of insulin in the mother's body and can produce surplus sugar levels in the blood giving rise to gestational diabetes. women has type II diabetes, has difficulties with multiples or with twins, lack of physical activity, polycystic ovarian syndrome, before given birth to a baby of weight greater than nine pounds. Difficulties for the infant of a diabetic mother are stillbirth, birth anomalies mainly in the first trimester of pregnancy, macrosomia, birth injury, hypoglycemia, respiratory distress and preeclampsia.

Fig No.2 Mechanism of Diabetes Mellitus



Precautions: Even though a woman had gestational diabetes before, the risk can also be lowered for the next pregnancy if they follow a healthy way of living and eating foods advanced in fibre content, low fat, and calories. Devouring fruits, vegetables, and whole grains, along with watching the portion sizes, is suggested. Exercising daily for 30 min of a moderate workout can help you plan for your pregnancy at a healthy weight, not more

than the recommended weight during pregnancy. All the above mentioned factors will help to defeat gestational diabetes.

2) Epilepsy

Epilepsy is a disorder in which nerve cell activity in the brain is anxious, causing seizures. Epilepsy may occur as a result of a genetic disorder or an acquired brain damage, such as a trauma or stroke. Epilepsy and pregnancy interrelate in a complicated way. Antiepileptic drugs (AEDs) have usual chronic teratogenic effects, the most common of which are congenital heart disease, cleft lip/palate, urogenital defects, and neural tube defects [29] Phenytoin is most commonly used antiepileptic medications. If phenytoin is administered by the mother in the first trimester, there is approximately a 5 to 10 percent chance that the baby could be born with a combination of birth defects known as the Fetal Hydantoin Syndrome that includes abnormalities like short nose, low or broad nasal bridge, epicanthic folds, hypertelorism, microcephaly, abnormal ears, wide mouth, oral clefts, hypoplasia of distal phalanges, short/webbed neck, low hairline, irregular mental development and abnormal motor development.

Valproic acid (VPA) is a usually prescribed drug for those affected by epilepsy and bipolar disorders. VPA has a well known teratogenic potential, causing a range of birth defects including neural tube defects (NTDs) and other congenital malformations, when women are treated with this medication during pregnancy.

Precautions: In spite of these risks, seizure control through pregnancy is very important. Therefore, when a woman with epilepsy is planning a pregnancy, it is important for her to meet with both her neurologist and her obstetrician, before conception, to discuss the definite treatment to be used to manage seizures while pregnant.

D.Physical agents

1) Cigarette smoking

Cigarette smoking by the mother is one of main reasons of general developmental abnormalities. Reduced development in fetus is observed. The range of chemicals like nicotine, carbon monoxide and cyanide released during tobacco smoking obstruct with the transport of amino acids across the placenta.

Carbon monoxide formed during smoking crosses placenta and increases carboxyhemoglobin levels in blood which has longer half-life in fetal blood than in maternal blood. Nicotine released during cigarette smoking has vasoconstriction effect that grades in uterine vascular constriction and intrauterine growth retardation because of decreased perfusion of fetal tissues. It also increases the risk of prenatal death. The prenatal mortality that is death recognized to abruption placenta, placentaprevia, impulsive abortion, prematurity and intrauterine growth retardation, preterm delivery, prenatal mortality, sub fertility, unusual placentation, childhood morbidity and mortality, congenital malformations, gastroschisis, cardiac defects, chromosomal abnormalities and central nervous system problems.

2) Ionizing radiation

The cell loss or chromosome injury is the ordinary reasons of embryo injury by ionizing radiation. Exposure of radiations 8-15 weeks after fertilization is the mainly critical exposure period vital to toxicity. The exposure leads to numerous effects such as human embryos abortion, malformations, and intrauterine growth retardation and has early- or late-stage onset genetic disease of which permanent growth retardations additional severe. The CNS is mainly affected by radiation exposure and leads to CNS abnormalities like early microcephaly, mental retardation and later increases incidence of hematopoietic malignancies and leukaemia. Excessive exposure to radiation causes chromosomal fragmentation, and alters DNA structure main to mutations

Teratogenic Defects in infants

1. Spina bifida

Spina bifida is a birth defect in which a developing baby's spinal cord fails to develop appropriately. It's a form of neural tube defect. Spina bifida is a congenital malformation in which the spinal column is split as a result of failed closure of the embryonic neural tube, during the fourth week post-fertilization. In its commonest and most severe form, myelomeningocele (MMC) the spinal cord is open dorsally, forming a placode on the back of the fetus or newborn baby that normally rests on a meningeal sac. Individuals with MMC often reveal motor and sensory neurological shortage. This may result in lower limb weakness or paralysis that prevents walking, and lack of sensation. Urinary and fecal incontinence occur commonly.

Mechanisms and pathophysiology

The primary disorder in the pathogenesis of MMC is failed neural tube closure in the embryonic spinal region, which leads to prolonged exposure of the open neural tube to the amniotic fluid environment. The bifid neuroepithelium initially undergoes relatively normal neuronal differentiation, with development of spinal motor and sensory function even below the lesion level. As gestation progresses, however, the uncovered spinal cord becomes haemorrhagic and neurons expire as a effect of toxicity of the amniotic fluid. Axonal connections are interrupted, and function is lost Hence, neurological disability in MMC is often measured a ‘two-hit’ process: failed neural tube closure followed by neurodegeneration in utero. [30]

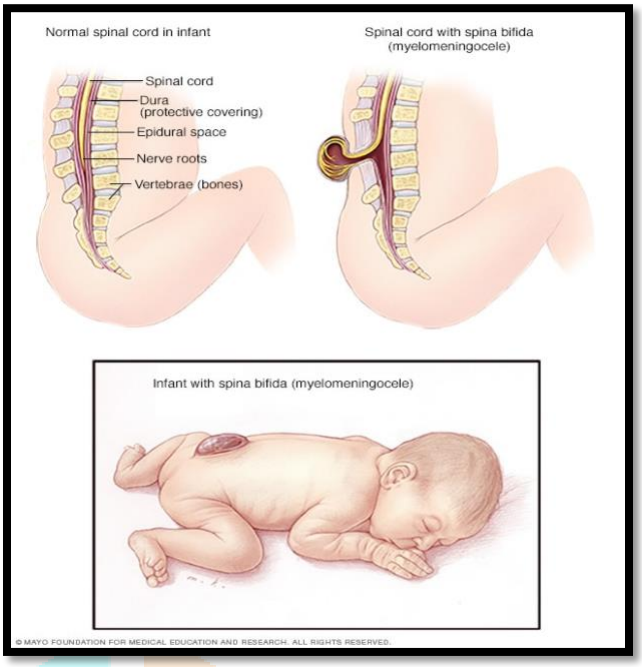


Fig No.3 Spina bifida

Treatment- Spina bifida treatment depends on the rigorousness of the condition.

The two major Spina bifida treatment options are fetal surgery in the duration of pregnancy or surgery on the baby after birth. Prenatal surgery for Spina bifida takes place previous to the 26th week of pregnancy.

2. Hypocalvaria

The calvaria are the top part of the skull. It is the superior part of the neurocranium and covers the cranial cavity containing the brain. It forms the main component of the skull roof. The calvaria are made up of the superior portions of the frontal bone, occipital bone, and parietal bones. Hypocalvaria is a condition in which the skull is absent. It happens often after using ACE Inhibitors while pregnancy. Hypocalvaria is its hypoplastic alternative where the skull bones are moderately produced. Due to such a exceptional incidence, it has been given the status of an orphan disease. The cause of the hypoplastic calvaria found with ACE inhibitor exposure is unknown. Endochondral bone and membrane bone grow and develop in entirely different ways. Long bones require low oxygen tension because nutrition takes place by diffusion through the cartilaginous epiphyses. Membrane bones, on the other hand, have the high degree of vascularity necessary for their own growth, and high oxygen tension is required. The presumed hypotension produced by ACE inhibitor exposure may result in hypoxic effects and thus hypoplastic calvaria. [31

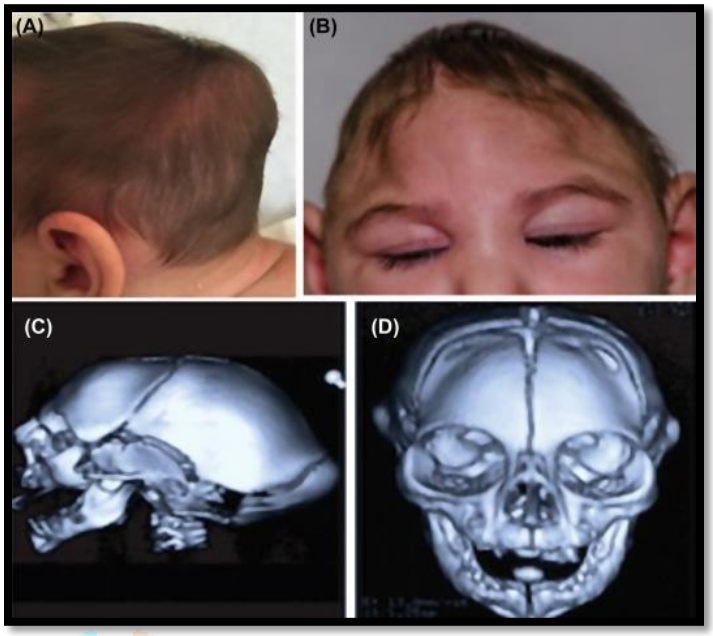


Fig No.4 Hypocalvaria

Precautions- a lesser amount of exposure or avoidance of ACE inhibitor can avoid hypocalvaria.

3. Fetal Alcohol spectrum disorders

Fetal alcohol spectrum disorders (FASDs) are a set of conditions that can occur in a person whose mother drank alcohol in the duration of pregnancy. FASDs can arise when a person is exposed to alcohol prior to birth. Alcohol in the mother's blood passes to the baby throughout the umbilical cord. Symptoms includes an irregular appearance, short height, low body weight, little head size, poor coordination, behavioural difficulty, learning problems, and problems with hearing and view. The risk of FASD depends on the quantity consumed, the frequency of consumption, and the points in pregnancy at which the alcohol is consumed.

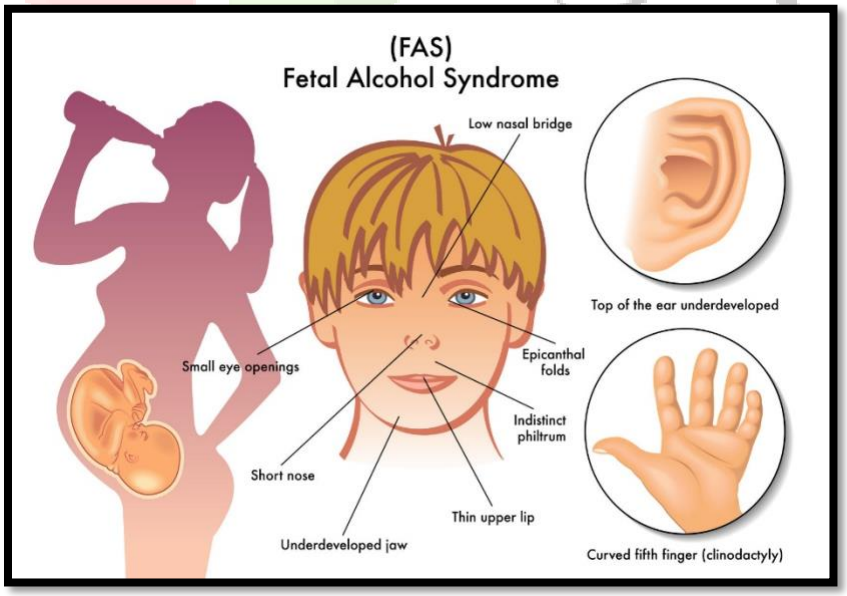


Fig No.5 Fetal Alcohol spectrum disorders

Precautions-To prevent FASDs, a woman should evade alcohol if she is pregnant or might be pregnant. FASDs are escapable if a baby is not exposed to alcohol before birth. [32]

4. Cleft lip and palate

Cleft lip and cleft palate are birth defects that arise when a baby's lip or mouth do not appears properly during pregnancy. These birth defects togetherly called as "orofacial clefts"

Cleft lip and cleft palate are caused by a grouping of genes and other factors, such as things the mother get in touch with environment, or what the mother eats or drinks, or sure medications she uses during pregnancy.

Cleft Lip - The lip forms among the fourth and seventh weeks of pregnancy. As a baby develops throughout pregnancy, body tissue and special cells from each side of the head grow toward the center of the face and join mutually to make the face. This joining of tissue forms the facial features, like the lips and mouth. A cleft lip happens if the tissue that makes up the lip does not join entirely before birth. This results in a gap in the upper lip. The opening in the lip can be small or large. A cleft lip may be one or both sides or in the middle of the lip. Children having a cleft lip may also form a cleft palate.

Cleft Palate -The palate i.e covering of mouth is formed between the sixth and ninth weeks of pregnancy. A cleft palate happens if the tissue that making the roof of the mouth does not join completely during pregnancy. In some babies, both the front and back parts of the palate are open and in some only front part of the palate is open.

Children with a cleft lip or a cleft have problems with feeding and speaking clearly and can have ear infections. They also might have hearing trouble and problems with their teeth. [33]

Following are some factors that enhance chance of baby having orofacial cleft:

1. Smoking- Women who smoke during pregnancy having more possibility baby with an orofacial cleft.
2. Diabetes- Women with diabetes diagnosed before pregnancy have a bigger risk of having a child with a cleft lip with or without cleft palate.
3. Use of certain medicines—Women who used medicines to treat epilepsy, like topiramate or Valproic acid, during the first trimester (the first 3 months) of pregnancy have an better risk of having a baby with cleft lip with or without cleft palate.

4.

Fig no.6 Cleft lip and palate

Treatment-.Surgery can repair cleft lip. Generally the surgery recommended within the first 12 months of life. Surgery to repair a cleft palate is suggested within the first 18 months of life or earlier if possible. Surgical repair can develop the look and structure of a child's face and might also develop breathing, hearing, and speech and language development.

5. Facial dysmorphia

Dysmorphic feature is a congenital disorder, genetic syndrome, or birth defect. It is isolated dysmorphic syndrome. Dysmorphic features may contain craniofacial dysmorphism, skeletal abnormalities and short proximal limbs and renal cysts in different disorders linked to peroxisomal dysfunction

1. Dysmorphic features may effect from a perturbation of human development

Dysmorphic facial features with arched eyebrows, broad nasal root, low set ears, downward sloping eyes, epicanthal folds, strabismus, and myopathic face were noticed. [35]

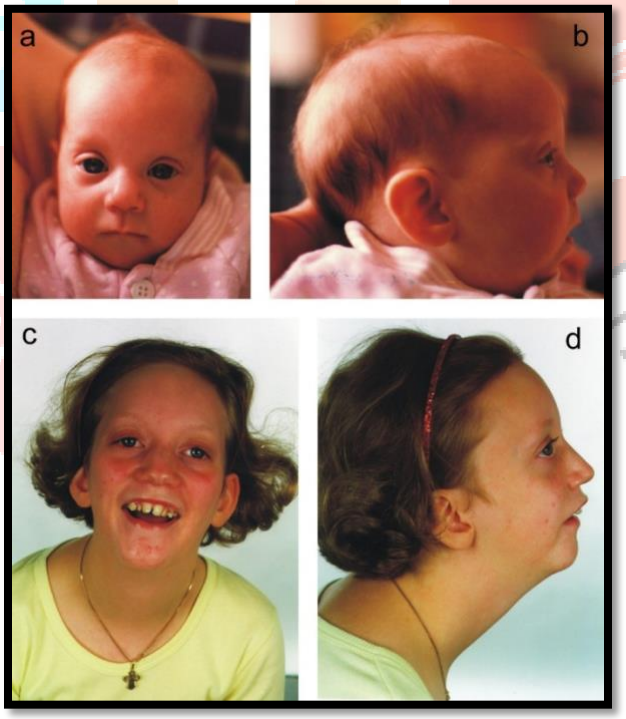


Fig No.7 Facial dysmorphia

Treatment-Treatment for body dysmorphic disorder includes a combination of cognitive behavioural therapy and medications. Medications includes selective serotonin reuptake inhibitors (SSRIs) like Lexapro, Prozac, fluvoxamine

6. Gastroschisis:

Gastroschisis is a congenital defect. This defect is characterised by anterior abdominal wall through which the abdominal contents freely extend beyond. There is no overlaying sac. Gastroschisis occurs during early pregnancy. The rip open is generally to the right side of the belly button. The intestines are not covered in a protective sac and are exposed to the amniotic fluid, they can become irritated, causing them to shorten, twist, or swell. Due to a teratogenic experience, rupture of the amniotic membrane at the bottom of the umbilical cord, irregular involution of the right umbilical vein, leading to impaired possibility. It leads to local necrosis of the abdominal wall at the base of the cord, abnormal folding of the embryo leading to a ventral body wall defect Gastroschisis is classified into simple and complex types based on the condition of the bowel. In simple gastroschisis, the bowel is in good condition with no intestinal problems. Complex gastroschisis is gastroschisis associated with congenital intestinal problems in the form of an atresia, perforation, ischemia, necrosis, or volvulus. [36]

Gastroschisis is occurs due to extra intake of aspirin in pregnancy.

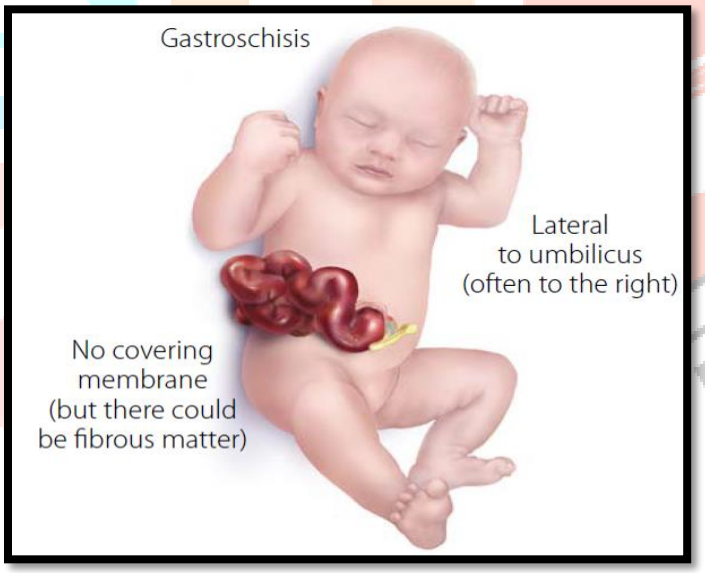


Fig No.8 Gastroschisis

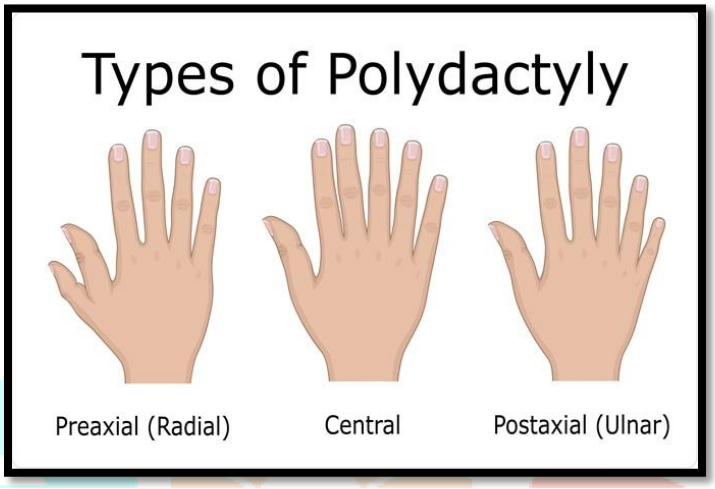
Treatment- The treatment for gastroschisis is surgery. If possible, A surgeon will put the bowel back into the abdomen and close the defect. If the abdominal cavity is too small, a mesh sack is stitched around the borders of the defect and the edges of the defect are pulled up.

If the gastroschisis defect is large renovate might be done slowly, in stages. [37] Other treatments for the baby consist of nutrients by IV and antibiotics to prevent infection.

7. Polydactyly:

Polydactyly is a condition in which a baby is born along with one or more extra fingers. It is a common condition that frequently runs in families. The extra fingers are generally small and abnormally developed. As a baby develops in their mother's womb, the hand first forms in the shape of a paddle and later divides into split fingers. If this process continues a bit longer than normal, a single finger divides again, creating an extra finger.

Fig No.9 Polydactyly



Treatment-Polydactyly is usually treated in early childhood with the removal of the extra finger or toe. If the extra digit is not attached with bones, a vascular clip may be used to remove it. The vascular clip attaches to the extra finger and cuts off blood flow to it. This usually occurs when a child is between 1 and 2 years old. At this age, children are young enough not to miss developmental milestones, such as grasping for objects, but old enough to better tolerate anaesthesia and surgery.

8. Moebius syndrome

Moebius syndrome is an infrequent congenital condition which results from underdevelopment of the facial nerves that manage some of the eye movements and facial expressions. The condition can also involve the nerves responsible for speech, chewing and swallowing.

It occurs due to lack of 6th and 7th cranial nerves, which manage eye movements and facial expression. Many of the other cranial nerves may also be pretentious. The first symptom, present at birth, is a failure to suck. Other symptoms includes: feeding, swallowing, and choking problems; crossed eyes; lack of facial expression; inability to smile; eye sensitivity; motor delays; high or cleft palate; hearing and speech problems. Children with Moebius syndrome are incapable to move their eyes back and forth. Deformities of the tongue, jaw, and limbs, such as clubfoot and absent or webbed fingers, may also occur. As children get elder lack of facial expression and incapability to smile become the leading visible symptoms.

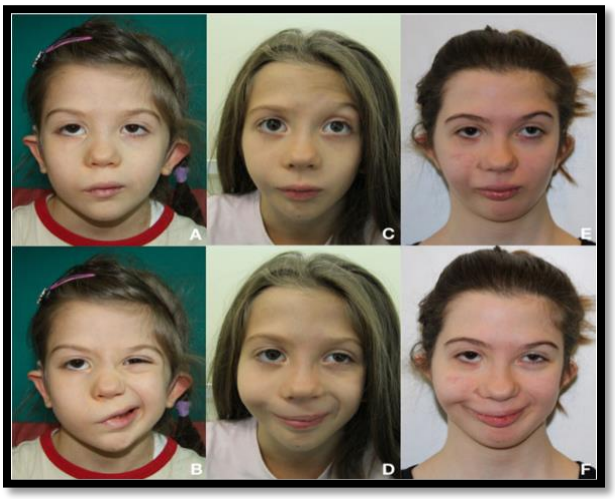


Fig No.10 Moebius syndrome

Treatment- treatment is helpful and in accordance with symptoms. Infants may need feeding tubes or special bottles to maintain sufficient nutrition. Surgery may correct crossed eyes and advance limb and jaw deformities. Physical and speech therapy often improves motor skills and management, and leads to enhanced control of speaking and eating abilities.

9. Scoliosis

Scoliosis is an irregular lateral curvature of the spine. It is a deviation of the normal vertical line of the spine, including lateral curvature with rotation of the vertebrae within the curve. There should be at least 10° of spinal angulation on the posterior-anterior radiograph connected with vertebral rotation. The causes of scoliosis are varying. They are classified generally as congenital, neuromuscular, syndrome-related, idiopathic and spinal curvature due to secondary reasons. Congenital scoliosis is due to a vertebral abnormality causing the mechanical departure of the normal spinal alignment.[39] Scoliosis can be due to neurological conditions, muscular abnormalities other syndromes due to main cause is over ingestion of various medications.

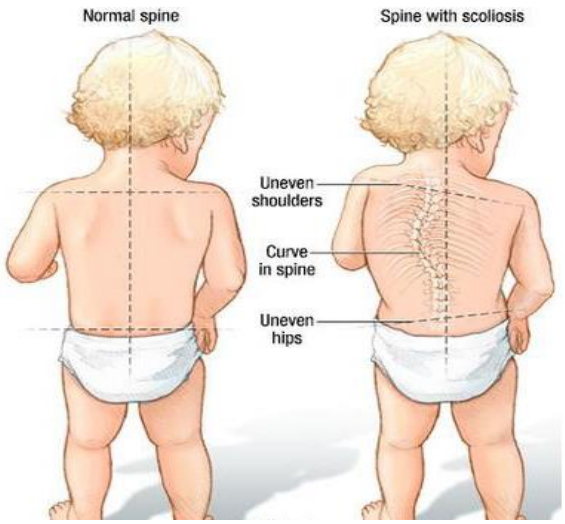


Fig No.11 Scoliosis

Treatment- General Treatment and management intend to halt the progression of the spinal defect. The goal is to boost thoracic volume, pulmonary and cardiac function.

Treatment and management of scoliosis is aimed at identifying those curves which are at hazard.

Many infants with mild scoliosis (a curve of less than 25 degrees) do well exclusive of surgery and may only require regular monitoring to make sure that the curve doesn't worsen. Monitoring may consist of regular observation, X-rays and lab tests. Most mild cases of immature scoliosis do not worsen and many correct themselves as child grows.

Other children with progressive curves may require immediate treatment to avoid chest-wall distortion and allow normal lung development.

10. Clubfoot

Clubfoot describes an array of foot abnormalities generally present at birth (congenital) in which baby's foot is twisted out of shape or position. In clubfoot, the tissues connecting the muscles to the bone and tendons are shorter than normal. Clubfoot is a quite common birth defect and is generally an isolated problem for an otherwise healthy newborn. Clubfoot may be mild or severe. About half of children with clubfoot having in both feet.

The cause of clubfoot is may be a combination of genetics and environmental agents.

Boys are about twice as likely to develop clubfoot as girls.

Risk factors includes Family history, congenital conditions, Environment, Not sufficient amniotic fluid during pregnancy**,** Smoking during pregnancy can extensively increase the baby's threat of clubfoot.

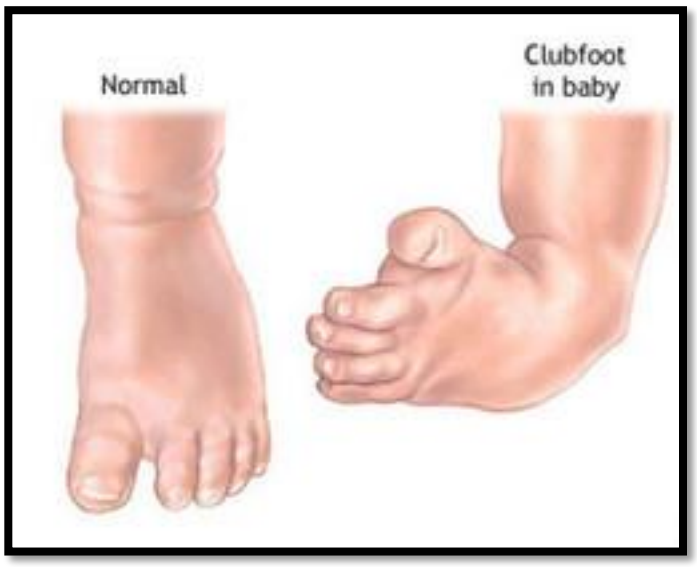


Fig No.12 Clubfoot

Treatment- Because newborn's bones, joints and tendons are very flexible, treatment for clubfoot usually begins in the first week or two after birth. The goal of treatment is to improve the way child's foot looks and works before he or she learns to walk. [43]

Treatment options includes 1.Stretching and casting

2. Surgery

Prevention-The clubfoot can be prevented by avoiding smoking, alcohol and drugs not approved by doctor.

Conclusion:

Deal with the effects of drugs during pregnancy and exposure to a variety of teratogens on developing foetus. This chapter provides some practical suggestion and direction for advising patients on the risks to the fetus from taking various recommended medicines and from being exposed to environmental toxins and illicit drugs. The risks of drug exposure to the fetus must first be precise in terms of the generally rates of malformations. The incidence of major malformations in the general population is 2% to 3%.1 These malformations consist of those incompatible with survival (e.g. anencephaly) as well as those requiring main surgery for example cleft palate or congenital heart disease or causing everlasting disability or developmental delays. The malformation rate may be as elevated as 7% to 10% if minor defects are counted (ear tags, extra digits).

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