Objective:
Enabling the medical student to understand:
- The terms that are used for birth defects
- Types of birth defects
- Causes of birth defects
- Prevention of birth defects

Birth defects, congenital malformation, and congenital anomaly are synonymous terms used to describe structural, behavioral, functional, and metabolic disorders present at birth.

Teratology & Dysmorphology
are Terms used to describe the study of these disorders.
Dysmorphologists are usually within a department of clinical genetics.

Major structural anomalies:
Occur for a total of 4% to 6%.
2% to 3% of live born infants, and
2% to 3% are recognized in children by age 5 years.
Birth defects are the leading cause of infant mortality, (approximately 21% of infant deaths).

Causes Of Birth defects
15%: Genetic factors, such as chromosome abnormalities and mutant genes,
10%: environmental factors
20% to 25%: a combination of genetic and environmental influences (multifactorial inheritance)
0.5% to 1%: twinning causes.
In 40% to 60% of persons with birth defects, the cause is unknown

Minor anomalies
occur in approximately 15% of newborns. minor anomalies serve as clues for diagnosing more serious underlying defects. For example, the presence of a single umbilical artery alerts the clinician to the possible presence of cardiovascular and renal anomalies. Microtia (small ears), pigmented spots, and short palpebral fissures, are not themselves detrimental to health but, in some cases, are associated with major defects.

Types of Abnormalities
Malformations
Disruption
Deformation
Dysplasia

Malformations
A morphologic defect of an organ, part of an organ, or larger region of the body that results from an intrinsically abnormal developmental process. Intrinsic implies that the developmental potential of the primordium is abnormal from the beginning, such as a chromosomal abnormality of a gamete at fertilization.

Disruption
A morphologic defect of an organ, part of an organ, or a larger region of the body that results from the extrinsic breakdown of, or an interference with, an originally normal
develpmental process. Thus, morphologic alterations after exposure to teratogens—agents such as drugs and viruses—should be considered as disruptions.

**Deformations**
An abnormal form, shape, or position of a part of the body that results from mechanical forces. Intraterine compression that results from oligohydramnios produces an equinovarus foot or clubfoot. Deformations often involve the musculoskeletal system and may be reversible postnatally.

**Dysplasia**
An abnormal organization of cells into tissue(s) and its morphologic result(s) e.g., congenital ectodermal dysplasia.

**Syndrome**
Is a group of anomalies occurring together and have a specific common cause. This term indicates that a diagnosis has been made and that the risk of recurrence is known.

**Association**
Is the non random appearance of two or more anomalies occur together more frequently but whose cause has not been determined.

VACTERL : Vertebral, Anal, Cardiac, trachea, Esophageal, Renal and limb abnormalities.

The times in gestation versus the risks of birth defects:
The most sensitive time for risks of birth defects is the embryonic period during the third to eighth weeks.

During the fetal period, the risk for gross structural defects being induced decreases, but organ systems may still be affected. For example, the brain continues to differentiate during the fetal period, such that toxic exposures may cause learning disabilities or mental retardation.

**Teratology**

is the branch of science that studies the causes, mechanisms, and patterns of abnormal development.

**A teratogen** is a factor that has an adverse effect on an embryo or fetus from fertilization to birth.

The term teratogen is usually limited to environmental agents e.g. drugs and viruses.

**Principles of teratology**

1. **The conceptus and maternal genome**
Susceptibility to teratogenesis depends on the genotype of the conceptus and the manner in which this genetic composition interacts with the environment. The maternal genome is also important with respect to drug metabolism, resistance to infection, and other biochemical and molecular processes that affect the conceptus.

2. **The developmental stage at the time of exposure**
Susceptibility to teratogens varies with the developmental stage at the time of exposure. While most abnormalities are produced during embryogenesis, defects may also be induced before or after this period; no stage of development is completely safe.

Each organ system may have one or more stages of susceptibility e.g. cleft palate can be induced at the blastocyst stage (day 6), during gastrulation (day 14), at the early limb bud stage (fifth week), when the palatal shelves are forming (seventh week).
3. Mechanisms And pathogenesis
Teratogens act in specific ways (mechanisms) on developing cells and tissues to initiate abnormal embryogenesis( pathogenesis) .
Mechanisms may involve inhibition of a specific biochemical or molecular process; pathogenesis may involve cell death, decreased cell proliferation, or other cellular phenomena .

4. Manifestations of abnormal development
Are death, malformation, growth retardation, and functional disorders. depend on: dose and duration of exposure to a teratogen.

Environmental factors
1. drugs, hormons and vitamins
The role of pharmaceutical drugs in the production of abnormalities in humans is difficult to assess for two reasons
1. studies are retrospective, relying on the mother’s memory for a history of exposure and
2. pregnant women take a large number of pharmaceutical drugs .
Few of the many drugs used during pregnancy have been positively identified as being teratogenic
Thalidomide: an antinauseant and sleeping pill. In 1961, it was noted in West Germany that the frequency of amelia and meromelia (total or partial absence of the extremities), a rare hereditary abnormality, had suddenly increased.
This observation led to examination of the prenatal histories of affected children and to the discovery that many mothers had taken thalidomide early in pregnancy.

Anticonvulsants diphenylhydantoin (phenytoin), valproic acid , and trimethadione , which are used by epileptic women produce a broad spectrum of abnormalities Phenobarbital is considered to be a safe, antiepileptic drug for use during pregnancy. Magnesium sulfate and diazepam are also widely used for seizure prophylaxis; however, more controlled clinical trials are required to establish whether these combinations are free of teratogenic risks.
Antipsychotic agents Are major and minor tranquilizers. they are suspected producers of congenital malformations. The antipsychotics: phenothiazine and lithium carbonate have been implicated as teratogens .

Antianxiety agents meprobamate, chlordiazepoxide, and diazepam (Valium)
A prospective study showed that: severe anomalies occurred in 12% of fetuses exposed to meprobamate and in 11% of those exposed to chlordiazepoxide, compared with 2.6% of controls. fourfold increase in cleft lip with or without cleft palate in offspring whose mothers took diazepam during pregnancy.
The anticoagulant agents All anticoagulants except heparin cross the placental membrane and may cause hemorrhage in the embryo or fetus. Warfarin and other coumarin derivatives are antagonists of vitamin K. Warfarin is used for the treatment of thromboembolic disease and in patients with artificial heart valves. Warfarin is definitely a teratogen.
Antihypertensive agents that inhibit angiotensin-converting enzyme (ACE inhibitors) produce growth retardation, renal dysfunction, fetal death, and oligohydramnios.

Antibiotics
- Tetracyclines cross the placental membrane and are deposited in the embryo’s bones and teeth at sites of active calcification.
- Deafness has been reported in infants of mothers who have been treated with high doses of streptomycin and dihydrostreptomycin as antituberculosis agents.
- Penicillin has been used extensively during pregnancy and appears to be harmless to the human embryo and fetus.

Thyroid Drugs
- Potassium iodide in cough mixtures and large doses of radioactive iodine may cause congenital goiter. Iodides readily cross the placental membrane and interfere with thyroxin production. They may also cause thyroid enlargement and cretinism (arrested physical and mental development and dystrophy of bones and soft parts). Maternal iodine deficiency may also cause congenital cretinism.
- Propylthiouracil interferes with thyroxin formation in the fetus and may cause goiter.
The administration of antithyroid substances for the treatment of maternal thyroid disorders may cause congenital goiter if the mother is given the substances in excess of the amount required to control the disease.

Aspirin (salicylates) Epidemiologic studies indicate that aspirin is not a teratogenic agent but large doses should be avoided, especially during the first trimester.

Isotretinoin (An analogue of vitamin A) is used for treatment of skin conditions such as cystic acne. It is highly teratogenic and can produce virtually any type of malformation. Even topical retinoids, such as etretinate, may have the potential to cause abnormalities. Vitamin A is a valuable and necessary nutrient during pregnancy, but long-term exposure to large doses is unwise.
Pregnant women should avoid high levels of vitamin A because an increased risk of birth defects among the offspring of women who took more than 10,000 IU of vitamin A daily has been reported.

a number of other compounds that may damage the embryo or fetus:
- sulfonamides (kernicterus), the antidepressant imipramine (limb deformities),
- amphetamines (oral clefts and cardiovascular abnormalities), and quinine (deafness).
- Social drugs LSD (lysergic acid diethylamide), PCP (phencyclidine, or “angel dust”): marijuana, alcohol, and cocaine. In the case of LSD, limb abnormalities and malformations of the central nervous system have been reported. Cocaine has been reported to cause a number of birth defects, possibly due to its action as a vasoconstrictor that causes hypoxia.

Alcohol There is a well-documented association between maternal alcohol ingestion and congenital abnormalities.

the term fetal alcohol spectrum disorder (FASD) is used to refer to any alcohol-related defects ranging from mental retardation to structural abnormalities.

Fetal alcohol syndrome (FAS) represents the severe end of the spectrum and includes structural defects, growth deficiency, and mental retardation.
Alcohol-related neurodevelopmental disorder (ARND) represents a less severe example of alcohol-related abnormalities.

**Cigarette smoking**

Maternal smoking during pregnancy is a well-established cause of **intrauterine growth restriction** (IUGR). There is some evidence that maternal smoking may cause urinary tract anomalies, behavioral problems, and decreased physical growth. **Nicotine** constricts uterine blood vessels, causing a decrease in uterine blood flow, lowering the supply of oxygen and nutrients available to the embryo/fetus from the maternal blood in the intervillous space of the placenta. The resulting deficiency impairs cell growth and may have an adverse effect on mental development. High levels of carboxyhemoglobin, resulting from cigarette smoking, appear in the maternal and fetal blood and may alter the capacity of the blood to transport oxygen. As a result, **chronic fetal hypoxia** (low oxygen levels) may occur and affect fetal growth and development.

**Hormones**

**Androgens** (testosterone) causes masculinization of the external genitalia of female infants

**Synthetic estrogens** (diethylstilbesterol): Female embryos exposed to the drug in utero cause raised the incidence of carcinomas of the vagina and cervix, high percentages of reproductive dysfunction due impart to congenital malformation of the uterus, uterine tubes, and upper vagina

Male embryos exposed to the drug in utero produce malformations of testis and abnormal sperm analysis. In contrast to women, however, men do not demonstrate an increased risk of developing carcinomas of the genital system.

**Environmental estrogens**: Decrease sperm count and increase incidence of testicular cancer, hypospadias, abnormalities of the human reproductive tract together with CNS abnormalities (masculinization of female brains and feminization of male brains)

**ORAL CONTRACEPTIVES**: Containing estrogens and progestogens, appear to have a low teratogenic potential. Use of oral contraceptives should be discontinued if pregnancy is suspected.

**Cortisone**

In mice and rabbit, causes a high percentages of cleft palate. In human, not documented

**2. Maternal disorders**

- age of pregnant
- Maternal diabetes
- phenylketonuria
- nutritional deficiencies

**Age of pregnant** Congenital abnormalities of the CNS and abdominal walls are more frequent in infants of mothers under 20 or more than 40 years

**Maternal diabetes** Disturbances in carbohydrate metabolism during pregnancy in diabetic mothers cause a high incidence of stillbirths, neonatal deaths, abnormally large infants, and congenital malformations. Evidence suggests that altered glucose levels play a role and that insulin is not teratogenic. Oral hypoglycemic agents (the sulfonylureas and biguanides) have been implicated as teratogens.
Numerous animal studies have shown that during gastrulation and neurulation, mammalian embryos depend on glucose as an energy source, so that even brief episodes of low blood glucose are teratogenic. Therefore, caution must be exercised in managing the pregnant diabetic woman. Strict control of maternal metabolism with aggressive insulin therapy prior to conception reduces the occurrence of malformations. Such therapy, however, increases the frequency and severity of hypoglycemic episodes.

**Phenylketonuria** Mothers with Phenylketonuria (increase serum concentration of phenyl aniline due to deficient phenyl aniline hydroxylase) are at risk of having infants with mental retardation, microcephaly and cardiac defects. Women with Phenylketonuria should maintain in diet with low phenyl aniline prior to conception to reduce the risk of these abnormalities.

**Nutritional deficiencies**
Vitamin deficiency have been proven to be teratogenic in laboratory animals, the evidence in human is sparse with the exception of iodine deficiency (endemic cretinism).

Poor maternal nutrition prior to and during pregnancy contributes to low birth weight and birth defects.

3. **Infectious Agents.**
Infectious agents that cause birth defects include a number of viruses. The complicating factor introduced by these infectious agents is that most are pyrogenic and hyperthermia is teratogenic causing disturbances of neural tube closure. In addition to febrile illnesses, use of hot tubs and saunas can produce sufficient temperature elevations to cause birth defects. **Rubella** used to be a major problem, but today approximately 85% of women are immune.

**Cytomegalovirus** is a serious threat. Often, the mother has no symptoms, but the effects on the fetus can be devastating. The infection is often fatal, and if it is not, meningoencephalitis caused by the virus produces mental retardation.

**Herpes simplex virus, varicella virus,** and **human immunodeficiency virus (HIV)** can cause birth defects.

**Toxoplasmosis** is particularly dangerous during trimester II produce congenital toxoplasmosis characterized by cerebral calcifications and chorioretinitis. Syphilis in mother cause syphilitic visceral and cutaneous lesions in fetus as well as hydrocephaly after birth

4. **Radiation**
Ionization radiation is potent teratogen. It kills rapidly proliferating cells. Radiation is also mutagenic (genetic alteration of germ cells and subsequent malformation). Radiation from nuclear explosions is also teratogenic. Observations of Japanese atomic bomb survivors and their children suggest that 8 to 16 weeks after fertilization (10-18 weeks after LNMP) is the period of greatest sensitivity for radiation damage to the brain, resulting in severe mental retardation.

By the end of the 16th week, most neuronal proliferation is completed, after which the risk of mental retardation decreases. It is generally accepted that large doses of radiation (>25,000 mrad) are harmful to the developing CNS. Accidental exposure of pregnant women to radiation is a common cause for anxiety.

5. **Obesity**
Prepregnancy obesity, defined as having a body mass index (BMI) >30 kg/m². Causation has not been determined but may relate to maternal metabolic disturbances affecting glucose, insulin, or other factors.

**Prepregnancy obesity is associated with:** a two- to threefold increased risk for having a child with a neural tube defect. Increases the risk for having a baby with a heart defect, omphalocele, and multiple anomalies.

6. **Hypoxia**

At higher altitude, children born are usually lighter in weight and smaller than those born near or at sea level with no increase in incidence of congenital anomalies.

Women with cyanotic heart disease often give birth to small infants but usually without gross congenital abnormalities.

7. **Heavy Metals**

Researchers in Japan noted that a number of mothers with diets consisting mainly of fish had given birth to children with multiple neurological symptoms resembling cerebral palsy. Further examination revealed that the fish contained an abnormally high level of **organic mercury**. In the United States, similar observations were made when seed corn sprayed with a **mercury**-containing fungicide was fed to hogs and the meat was subsequently eaten by pregnant women. Similarly, in Iraq, several thousand babies were affected after mothers ate grain treated with **mercury**-containing fungicides.

**Lead** has been associated with increased abortions, growth retardation, and neurological disorders.

**Male–mediated teratogenesis**

Exposure to chemicals and other agents such as ethylnitrosurea and radiation can cause mutations in male germ cells. There is a link between **paternal occupation** and environmental exposures to mercury, lead, solvents, alcohol, cigarette smoking and incidence of spontaneous abortion, low birth weight and birth defects. Advanced **paternal age** is a factor for an increase risk of limb and neural tube defects and Down syndrome. Men younger than 20 years also have a high risk of having children with birth defects.

**Prevention of birth defects**

- Mental retardation can be eliminated by supplementation of salt or water with **iodine**.
- Placing women with diabetes and phenylketonuria under strict metabolic control prior to conception in order to reduce the incidence of birth defects in their offspring.
- Folate supplementation lowers the incidence of neural tube defects.
- Avoidance of alcohol and other drugs during all stages of pregnancy.

**Prenatal diagnosis**

**1. Ultrasonography**

Important parameters revealed by ultrasound include characteristics of **fetal age** and growth; presence or absence of **congenital anomalies**; status of the **uterine environment**, including the amount of amniotic fluid; **placental position** and **umbilical blood flow**; and whether **multiple gestations** are present.
Fetal age and growth are assessed by: **crown-rump length** during the 5th to 10th weeks of gestation. After that, a combination of measurements—including the **biparietal diameter (BPD)** of the skull, **femur length**, and **abdominal circumference**—are used.

**Congenital malformations that can be determined by ultrasound include** the neural tube defects anencephaly and spina bifida, abdominal wall defects, such as omphalocele and gastrochisis and **heart and facial defects**, including cleft lip and palate.

### 2. Maternal Serum Screening

A non-invasive technique for an initial assessment of fetal well-being.

1. **Alpha-fetoprotein (AFP)** concentrations
2. **Human chorionic gonadotropin (hCG)** and
3. Unconjugated estriol

**Serum alpha-fetoprotein (AFP) concentrations** are produced normally by the fetal liver, peaks at approximately 14 weeks, and "leaks" into the maternal circulation via the placenta. Thus, AFP concentrations increase in maternal serum during the second trimester and then begin a steady decline after 30 weeks of gestation.

**AFP levels increase in amniotic fluid and maternal serum in cases of neural tube defects** and several other abnormalities, including omphalocele, gastrochisis, bladder exstrophy, amniotic band syndrome, sacrococcygeal teratoma, and intestinal atresia.

**AFP concentrations decrease**, as, for example, in Down syndrome, trisomy 18, sex chromosome abnormalities, and triploidy. These conditions are also associated with lower serum concentrations of human chorionic gonadotropin (hCG) and unconjugated estriol.

### 3. Amniocentesis

A needle is inserted transabdominally into the amniotic cavity (identified by ultrasound) and approximately 20 to 30 mL of fluid is withdrawn. The procedure is usually performed after 14 weeks gestation, when sufficient quantities of fluid are available without endangering the fetus. The risk of fetal loss as a result of the procedure is 1%, The amniotic fluid itself is analyzed for

1. Biochemical factors, such as AFP and acetylcholinesterase.
2. Fetal cells, sloughed into the amniotic fluid, can be recovered and used for metaphase karyotyping and other genetic analyses. Unfortunately, the harvested cells are not rapidly dividing, and therefore, they must be cultured for 8 to 14 days, and consequently, making a diagnosis is delayed.

### 4. Chorionic villus sampling (CVS)

Inserting a needle transabdominally or transvaginally into the placental mass and aspirating approximately 5 to 30 mg of villus tissue. Cells may be analyzed immediately and because of the large number of cells obtained, only 2 to 3 days in culture are necessary to permit genetic analysis. Thus, the time for genetic characterization of the fetus is reduced compared with amniocentesis. The risk of fetal loss from CVS is approximately twofold greater than with amniocentesis.

**Indications for prenatal diagnostic tests**

1. **Advanced maternal age** (35 years and older);
2. **Previous family history of a genetic problem**, such as the parents having had a child with Down syndrome or a neural tube defect;
3. **The presence of maternal disease**, such as diabetes; and
(4) an abnormal ultrasound or serum screening test.

**Fetal Therapy**

**Fetal Transfusion**
Is performed in cases of fetal anemia produced by maternal antibodies or other causes. Ultrasound is used to guide insertion of a needle into the umbilical cord vein, and blood is transfused directly into the fetus.

**Fetal Medical Treatment**
Treatment for infections, fetal cardiac arrhythmias, compromised thyroid function, and other medical problems is usually provided to the mother and reaches the fetal compartment after crossing the placenta.

In some cases, however, agents may be administered to the fetus directly by intramuscular injection into the gluteal region or via the umbilical vein.

**Fetal Surgery**
Because of risks to the mother, infant, and subsequent pregnancies, procedures are only performed in centers with well-trained teams and only when there are no reasonable alternatives. Several types of surgeries may be performed, including placing shunts to remove fluid from organs and cavities. Repairs of hernias and lung lesions have good outcomes if proper selection criteria for cases are employed, and one of these is the fact that without surgery, fetal demise is almost certain.

**Surgery for neural tube defects** is more controversial because the abnormalities are not life threatening. Because of risks to the mother, infant, and subsequent pregnancies, procedures are only performed in centers with well-trained teams and only when there are no reasonable alternatives. Several types of surgeries may be performed, including placing shunts to remove fluid from organs and cavities.

**Stem Cell Transplantation and Gene Therapy**
Because the fetus does not develop any immunocompetence before 18 weeks’ gestation, it may be possible to transplant tissues or cells before this time without rejection. Research in this field is focusing on hematopoietic stem cells for treatment of immunodeficiency and hematologic disorders. Gene therapy for inherited metabolic diseases, such as cystic fibrosis, is also being investigated.

**Thank you**