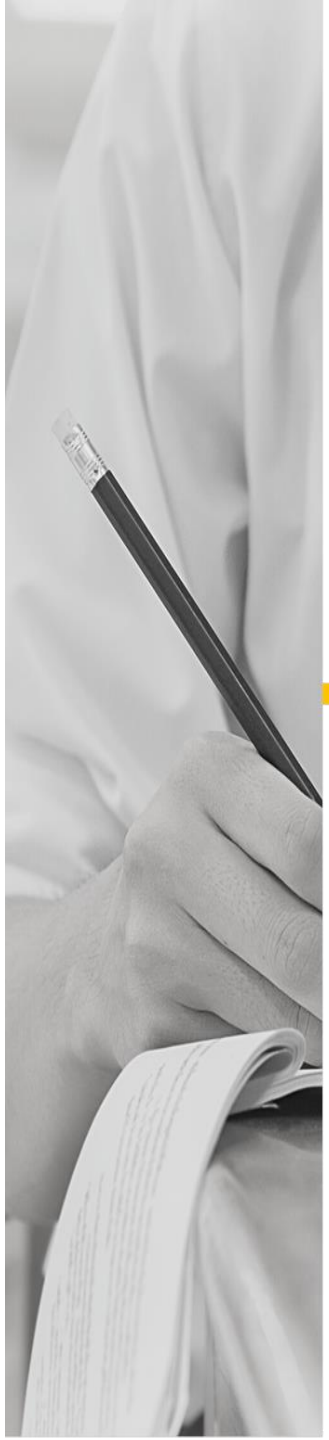

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Subject name: DRUG EVALUATION

Subject year: MSc - PHARMA

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PHARMACOLOGY MASTER COURSE – DRUG EVALUATION

Study of Drug Teratogenicity

أ د حسام الدين النجار

In Western countries, more than half of pregnant women take prescription medication, and nearly all pregnant women use over-the-counter medications, vitamins or other dietary supplements.

Drugs that are safe for adults may be teratogenic for the developing fetus.

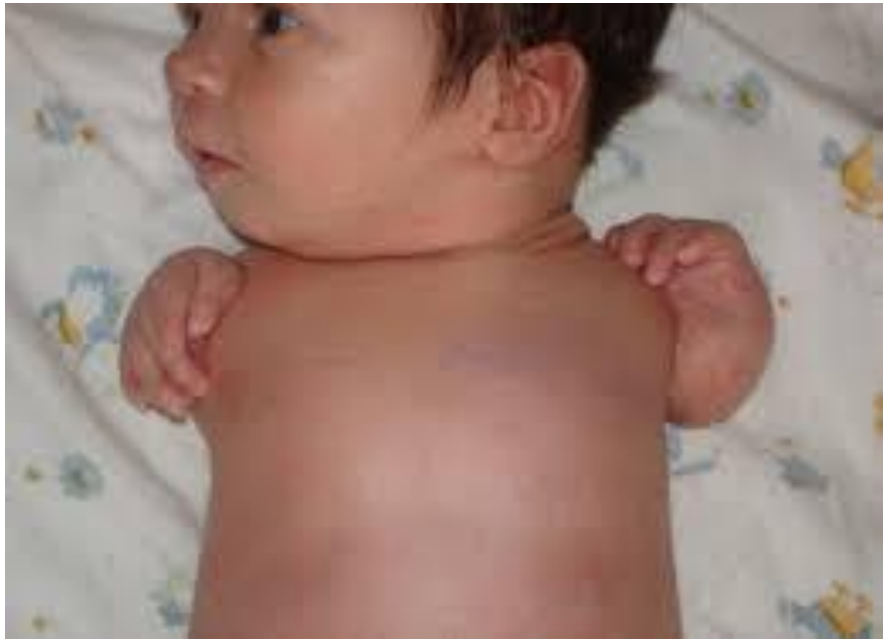
The majority of drugs or their metabolites cross the placental barrier,– and metabolites may be more fetotoxic than their source substances, as was noted in the case of thalidomide-induced phocomelias.

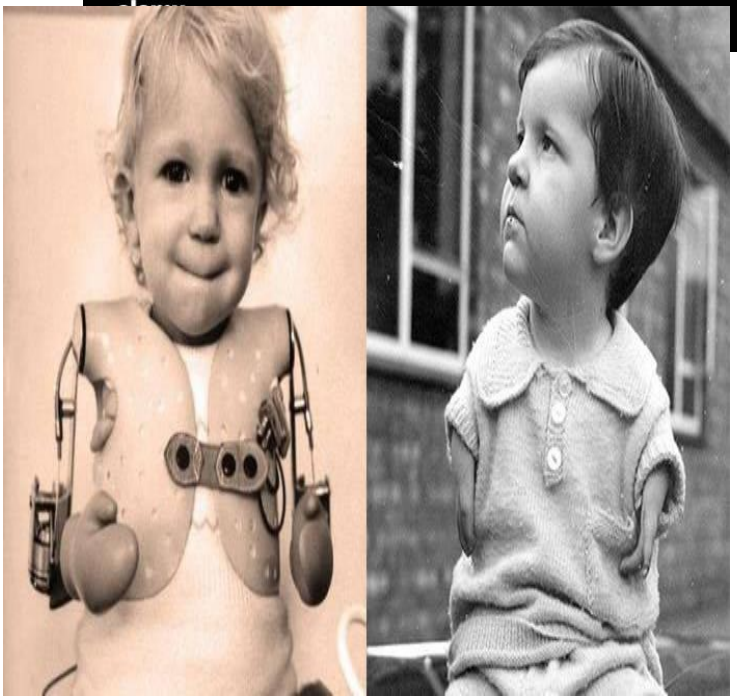
Because pregnant women rarely participate in randomized studies of medicines, evidence from observational studies is central in establishing safety of prenatal drug exposure.

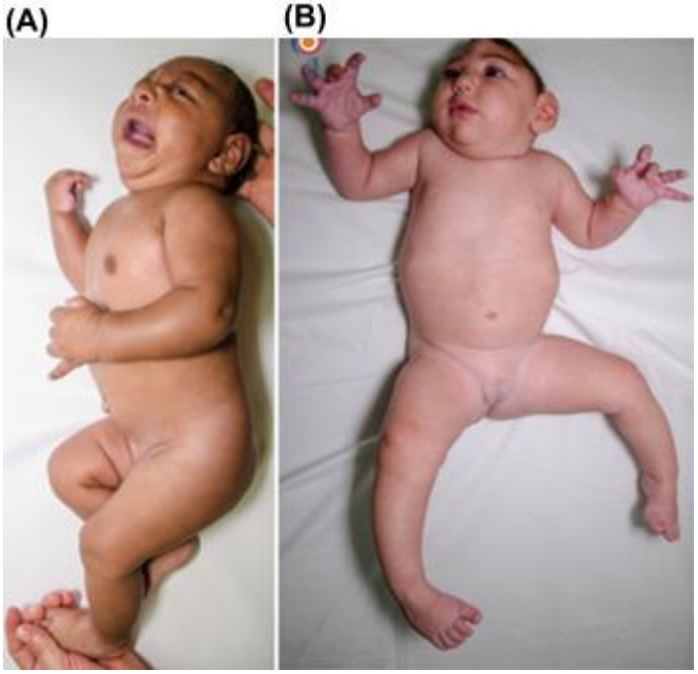
During the last decades, it has become deeply understood that drugs administered to the mothers during pregnancy might have detrimental effects on the physical development of the fetus.

Thalidomide is a well-described example of how a seemingly innocent, over-the-counter medication for the morning sickness could exert such a deleterious effect on the fetus, such as miscarriages, and physical deformities

thalidomide






(A)
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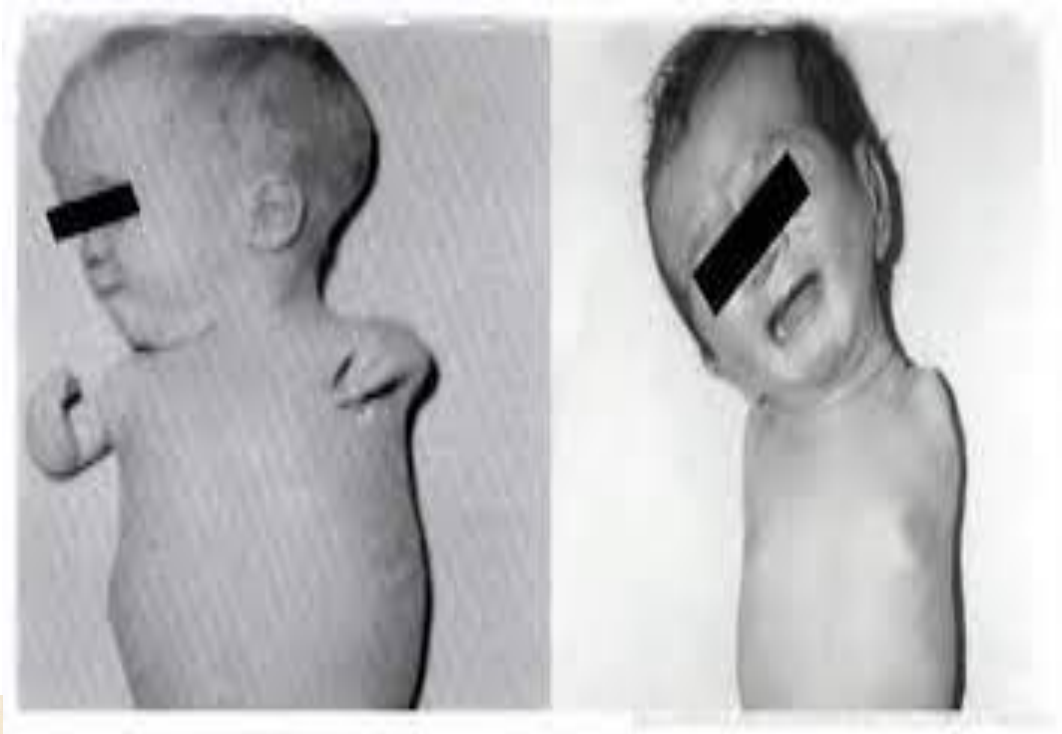
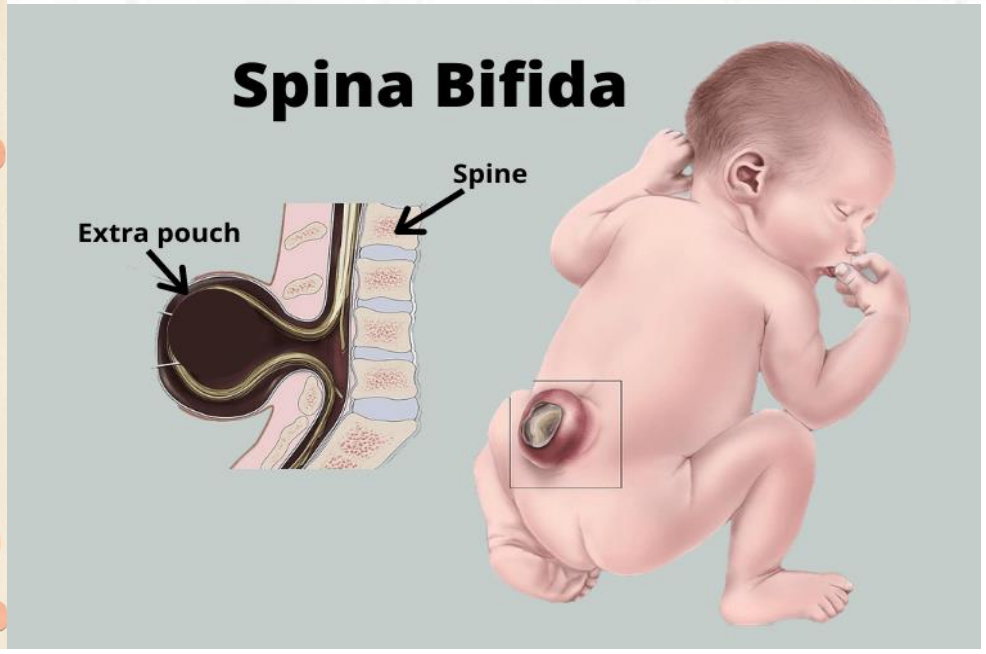
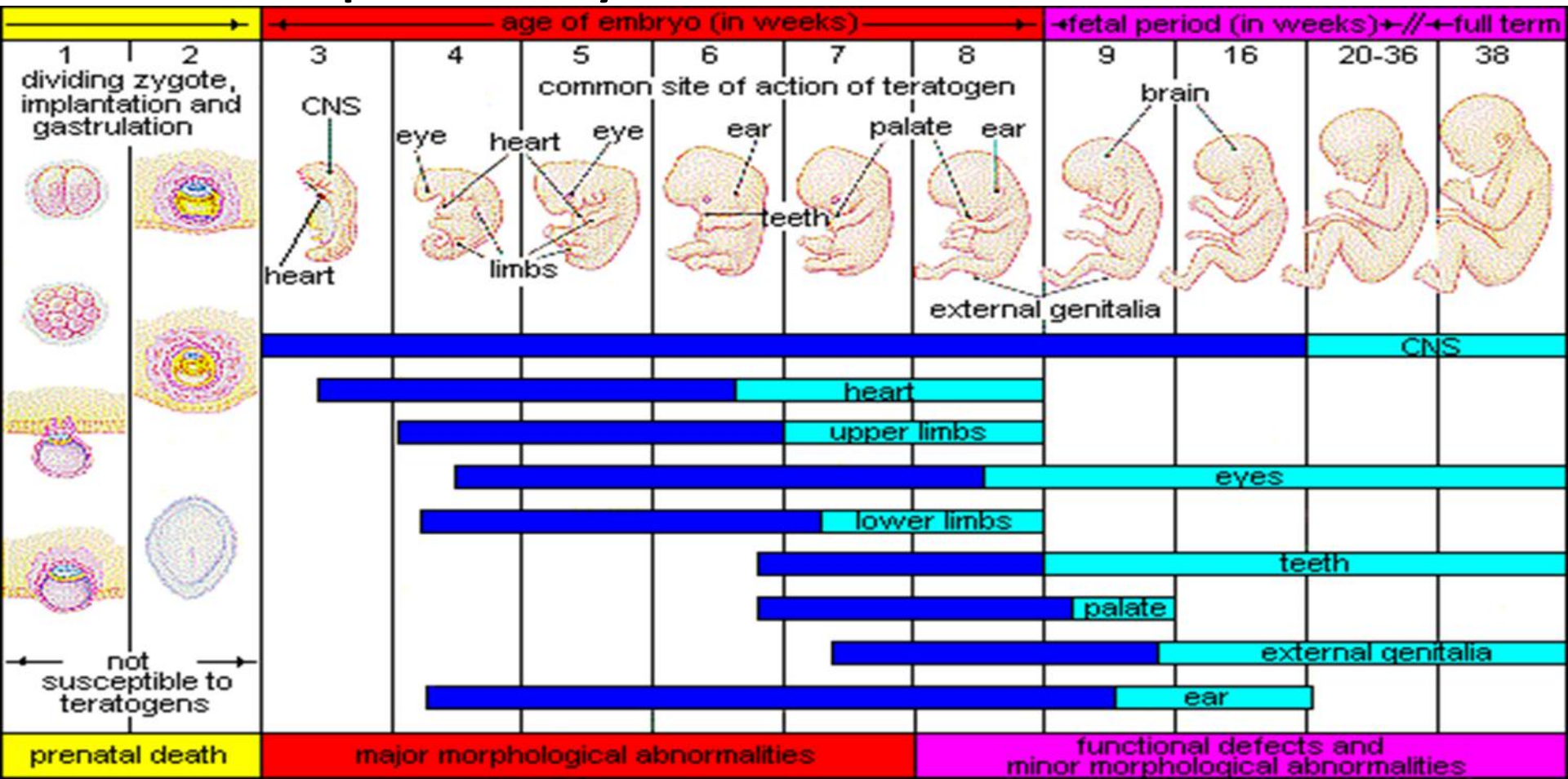
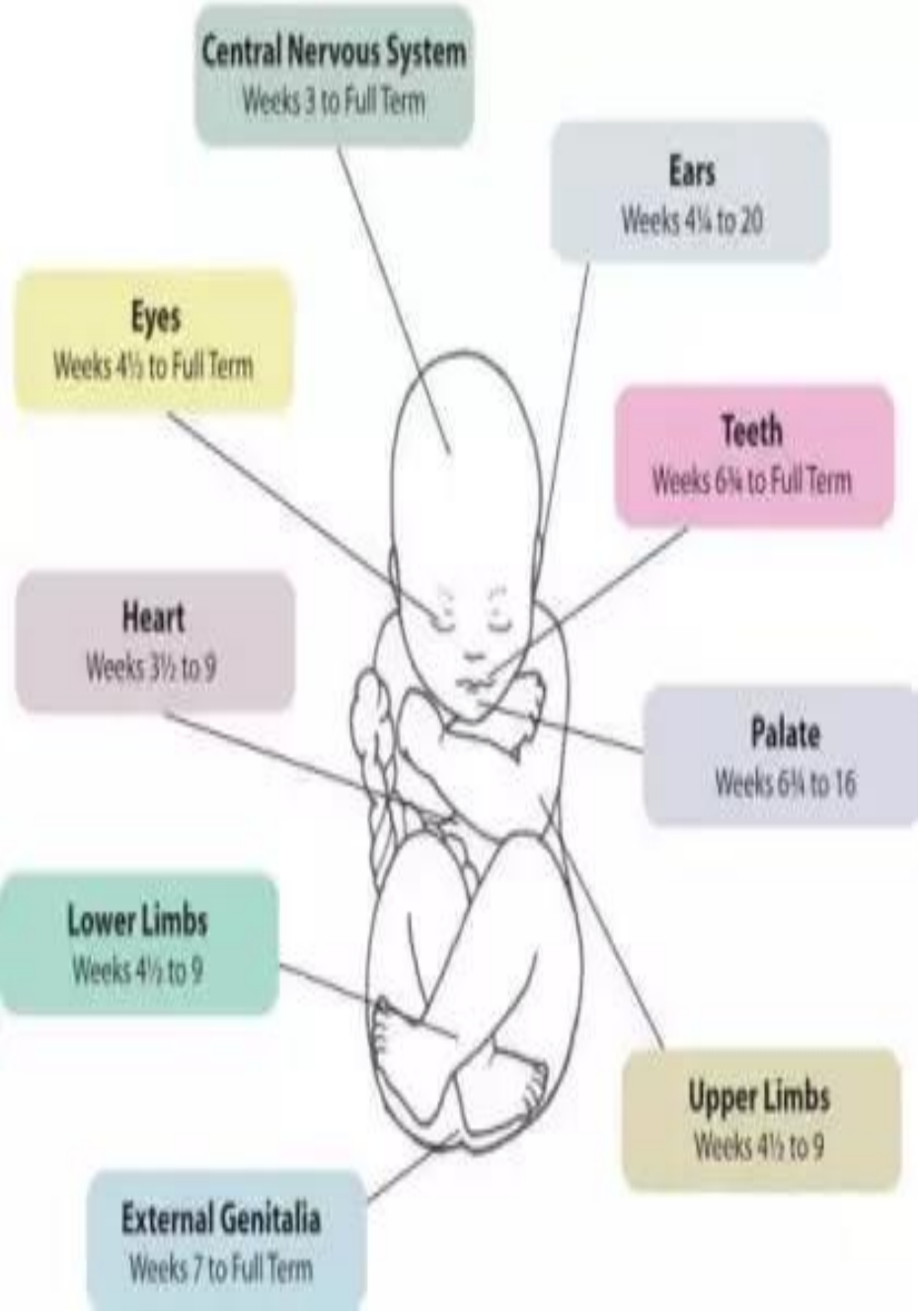



Spina Bifida
Spine
Extra pouch

The gestational age of the embryo at the time of exposure is the determining factor for the nature of the defect, making the first trimester, the period of organogenesis, the most precarious period for significant malformations._ The scope of this article is to present the most important teratogenic medications and their mechanism of action comprehensively.





Timing

- The effect of teratogens depends upon the timing of exposure.
- The first trimester of pregnancy is the critical period of organ and limb development in the fetus.
- The fetal brain develops throughout pregnancy and can be affected at any time.
- Exposure to a teratogen during the two weeks following conception is unlikely to cause birth defects.

Neurological Medications

Medications for neurologic conditions are among the drugs with the highest teratogenic potential.

One of the most commonly prescribed drug categories in pregnant women is antiepileptic drugs (AEDs), used primarily to prevent seizures, but also for neuropathic pain, migraines, and psychiatric disorders.

AEDs in low doses can cause cognitive defects and, in higher doses, cause structural malformations.

Phenobarbital, an inducer of CYP450 2B and 3A genes, at a molecular level, produces free radicals and causes DNA bases transversion while macroscopically, results in impaired growth, motor development, and fetal mortality.

Valproate poses a higher teratogenic threat compared to the other AEDs and potentially can distort the development of the fetus.

It can lead to cardiac anomalies, neural tube defects, dominantly spina bifida, and developmental delay.

It may also cause the fetal valproate syndrome, a rare clinical condition consisting of characteristic facial dysmorphisms linked to valproate exposure, limb abnormalities, lip/cleft palate, and urinary tract defects.

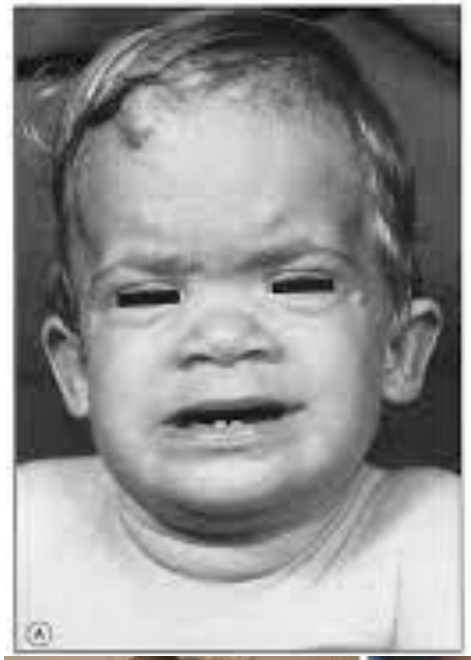
The teratogenicity of valproic acid is exerted via the inhibitory actions of folate and histone deacetylase, through increased accumulation in embryonic circulation, as well as by the production of reactive oxygen species (ROS).

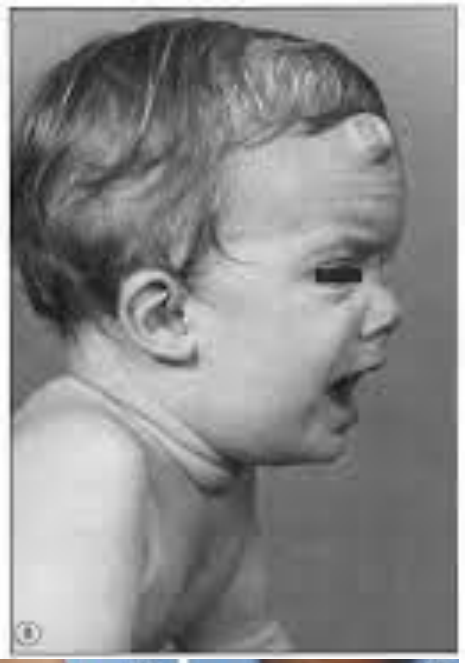
Mnemonic for Valproic Acid

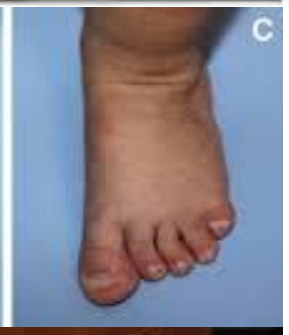
Adverse effects

Fetal Valproate Syndrome - Facial Features

- Tall forehead
- Medial eyebrow deficiency
- Flat nasal bridge
- Broad nasal root
- Shallow philtrum
- Long upper lip
- Thin vermillion border







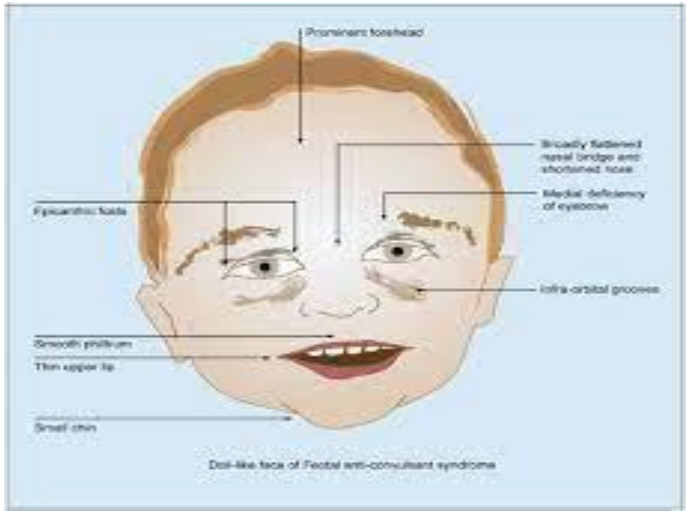
Carbamazepine is useful for the treatment of epilepsy and bipolar disorder during pregnancy.

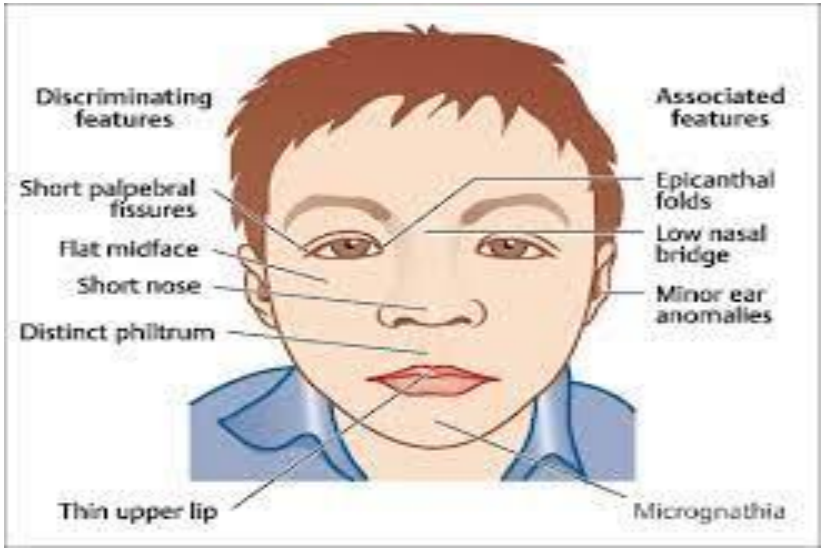
Carbamazepine is metabolized into carbamazepine-10, 11-epoxide, damages DNA, and could be associated with craniofacial defects, abnormal IQ, and growth retardation.

Lamotrigine, a new anti-epileptic medication, has been established as the safest mood stabilizer during pregnancy, although it carries an increased risk for facial malformations in fetuses, especially facial cleft


A


B

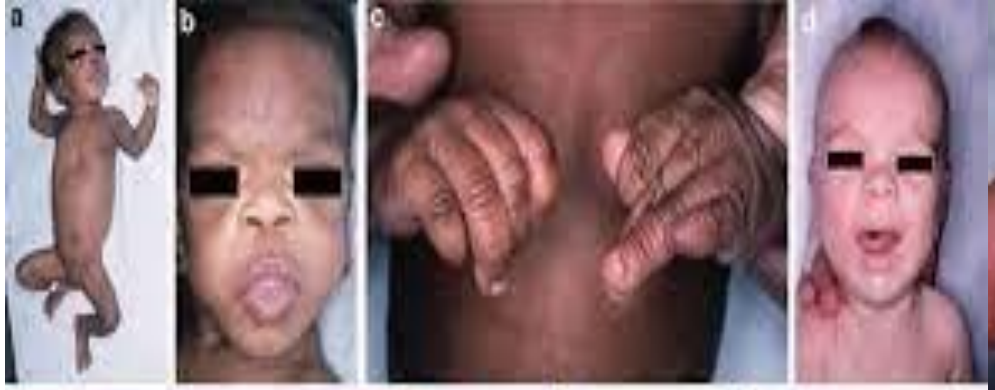

Prominent forehead
Epicanthic folds
Smooth philtrum
Thin upper lip
Small chin
Doll-like face of Foetal anti-convulsant syndrome


Discriminating features
Associated features
Short palpebral fissures
Flat midface
Short nose
Distinct philtrum
Epicanthal folds
Low nasal bridge
Minor ear anomalies
Thin upper lip
Micrognathia

When the fetus suffers exposure in utero to **phenytoin**, it increases the risk of developing fetal phenytoin syndrome (FHS), characterized by growth deficiency, mental retardation, epicanthic folds, hypertelorism, and a short nose with anteverted nostrils.

Phenytoin gets bioactivated by embryonic prostaglandin H synthase to a free radical, resulting in DNA oxidative damage.

Topiramate is a drug used for epilepsy and migraines, and it has been interlinked with hypospadias and oral clefts to newborns, especially in pregnant women who received higher doses

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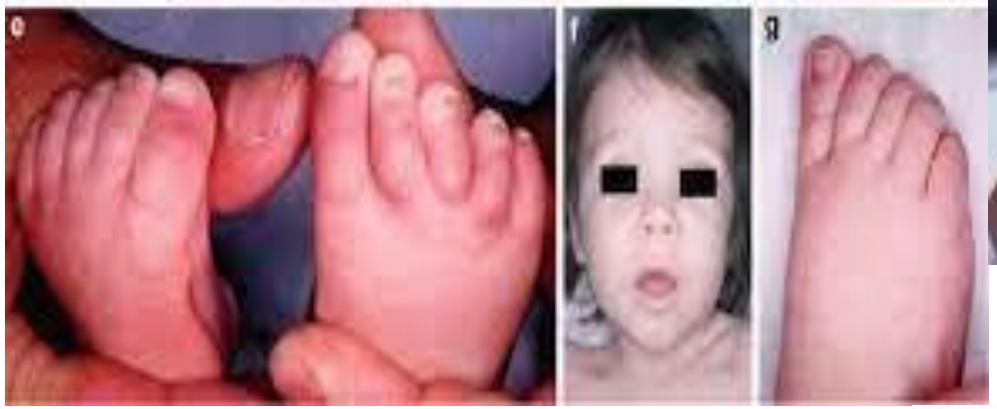
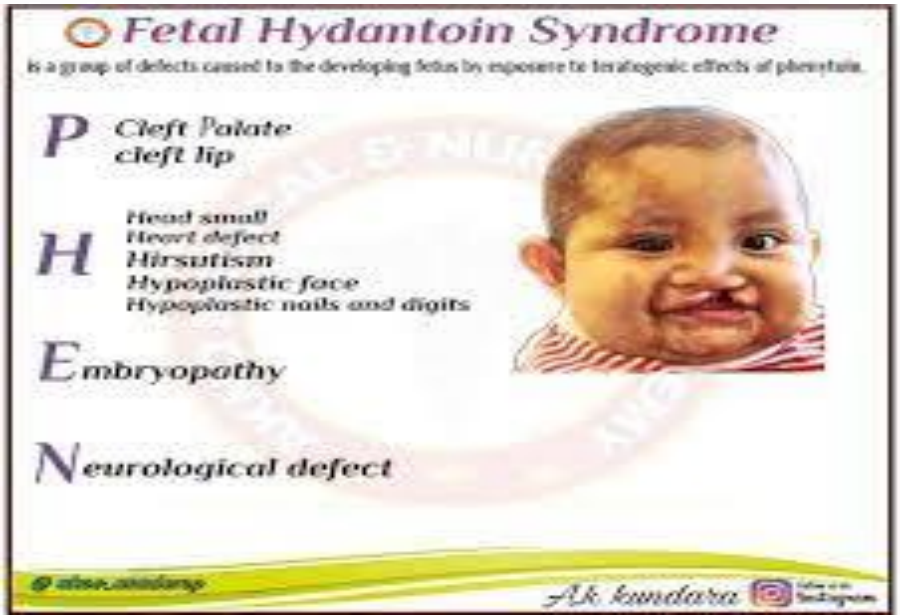
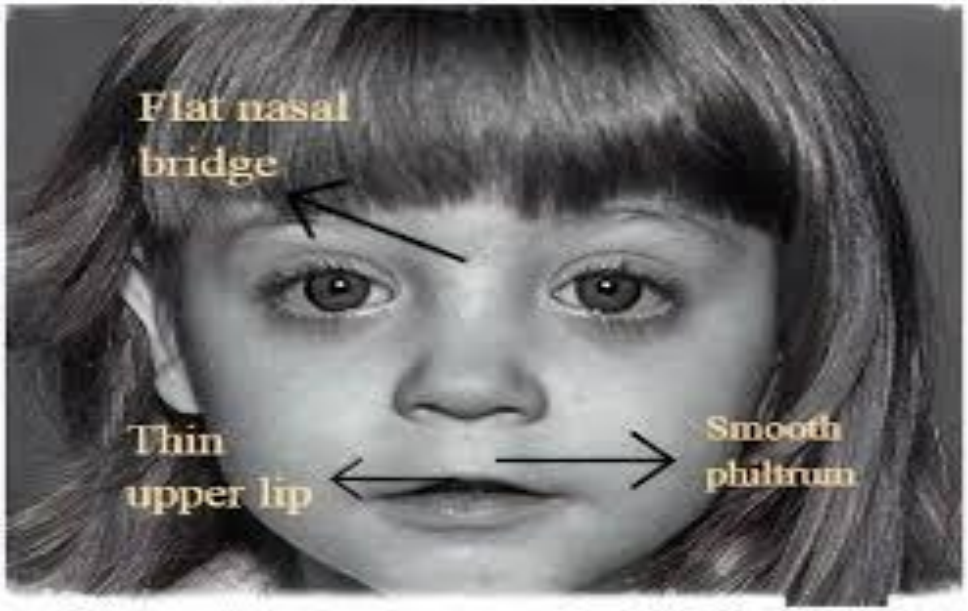



Fetal Hydantoin Syndrome
is a group of defects caused to the developing fetus by exposure to teratogenic effects of phenytoin.
P Cleft Palate
cleft lip
H Head small
Heart defect
Hirsutism
Hypoplastic face
Hypoplastic nails and digits
Embryopathy
Neurological defect
Ak kundara


Flat nasal bridge
Thin upper lip
Smooth philtrum

Antimicrobial Medications

Antimicrobials are among the most generously prescribed medications during pregnancy and lactation. **Hence, clinicians should demonstrate great attention to the dose and type of drug administered to pregnant women, due to pharmacokinetic alterations during this period and the potential harm they could pose to the fetus.**

Primarily, **chloramphenicol** is a bacteriostatic drug that binds to the 50s subunit of prokaryotic ribosomes and thus, interferes with protein synthesis. According to the available data regarding the toxicity of chloramphenicol to fetuses and newborns, there is a potential danger of bone marrow suppression in direct proportion to dose. **Also, it may lead to the development of gray baby syndrome, a syndrome characterized by abdominal dilatation, vomiting, hypothermia, cyanosis, and gray color of the baby's skin.**

This syndrome has a high prevalence among premature infants because of their reduced ability for renal and liver metabolism (primarily glucuronidation) of chloramphenicol.

Tetracyclines and fluoroquinolones are drug categories that should be avoided during pregnancy.

Quinolones and fluoroquinolones, a very effective group of bactericidal antimicrobials, act by inhibiting the bacterial DNA gyrase or the topoisomerase IV enzyme.

They have correlated with renal, cardiac, and central nervous system toxicity.

Fluoroquinolones inhibit DNA synthesis and possibly lead to organ agenesis or even carcinogenesis in fetuses.

Animal studies have shown that they induce articular cartilage damage. In further studies conducted on fetal embryonic tissues, in vitro, fluoroquinolones caused impairment of limb development, dose-dependent, and antimicrobial dependent.

Tetracyclines, a bacteriostatic group of antimicrobials that bind to the 30S ribosomal subunit, are contraindicated in pregnancy due to liver necrosis, bone, and teeth defects. Tetracyclines can penetrate several tissues and cross the placenta, but do not accumulate within the fetus. They can form a complex with calcium, and the organic matrix without affecting the crystal of hydroxyapatite and can result in discoloration of bones and teeth. Furthermore, in high doses, they suppress skeletal bone growth and cause hypoplasia of tooth enamel.

Antifungal agents remain a challenging type of medication to be prescribed during pregnancy since the maternal pharmacokinetics change.

Azoles inhibit the action of C14 demethylase and thus the biosynthesis of ergosterol, a substantial element of fungal cell membranes.

Fluconazole, in particular, has been shown to cause, in doses greater than 400 mg per day or above, clinical manifestations : midfacial hypoplasia

Anticoagulants

Coumarin derivatives, e.g., warfarin antagonize vitamin K, and inhibit γ-carboxylation of glutamyl residues, reducing protein binding ability with calcium.

This inhibition during fetal development could explain the skeletal abnormalities, the stippled calcification of epiphysis, and the nasal hypoplasia.

Depending on the severity of nasal hypoplasia, choanal atresia or stenosis could also be present, leading to respiratory and feeding problems.

Central nervous system malformations may also occur with the administration of coumarin anticoagulation since they cross the placenta, inhibit clotting factors, and mainly cause intracranial hemorrhage.

The risk of congenital disabilities associated with fetal warfarin syndrome (FWS) is particularly high during the 6-9 gestational weeks.

Antithyroid Medications

Maternal hyperthyroidism is still managed with antithyroid drugs during pregnancy.

Propylthiouracil (PTU), methimazole (MMI), and carbimazole inhibit the (thyroid peroxidase) TPO-mediated iodination of tyrosine residues in thyroglobulin and thus hinder the synthesis of T4.

The administration of these agents has been associated with two significant teratogenic effects on fetus; aplasia cutis and choanal/esophageal atresia, but the data remains debatable.

Vitamin A

Vitamin A, in large doses, can also be teratogenic. A pregnant woman can receive an excessive amount of vitamin A by eating excess food or by taking nutrient supplements with Vitamin A or drugs containing retinoids.

Not only the overdose but also the lack of them can cause embryonic malformations. Retinoic acid is essential for early embryogenesis and subsequently for maturation and development of tissues and organs.

High doses of Vitamin A in pregnant rats caused neural tube defects, for instance, exencephaly, spina bifida with meningocele, hydrocephalus, eye malformations, and cleft palate.

The carboxylate group and the side chain of the molecule give the retinoids their teratogenic potency.

Hormonal Medication

Diethylstilbestrol (DES) is a nonsteroidal estrogen drug that acts by inhibiting the hypothalamic-pituitary-gonadal axis.

DES was being prescribed in pregnant women for three decades, to prevent pregnancy miscarriage. Research later showed that it could potentially be a carcinogen or even a teratogen upon prenatal exposure.

The women exposed in utero to DES developed clear cell adenocarcinoma of vagina and cervix and structural anomalies in the genital tract.

Besides, the sons of women who received DES during pregnancy developed several abnormalities of the genital tract. DES has a lower affinity for binding with sex hormone-binding globulin than estradiol, so it can easily cross the placenta.

Furthermore, DES undergoes metabolism to reactive intermediates in comparison to estradiol, and it does not bind to alpha-fetoprotein.

On the other hand, excessive androgen production or the use of anabolic-androgenic steroids, for example, by female athletes, can cause female fetuses to develop clitoromegaly and labial fusion if administered before the end of the first trimester.

FDA Pregnancy Risk Information: An Update

The former pregnancy categories, which still may be found in some package inserts, were as follows:

Category A

Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).

Example drugs or substances: levothyroxine, folic acid, liothyronine.

Category B

Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

Example drugs: metformin, hydrochlorothiazide, amoxicillin.

Category C

Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Example drugs: gabapentin, amlodipine, trazodone.

Category D

There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Example drugs: losartan

Category X

Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

Example
drugs: atorvastatin, simvastatin, methotrexate, finasteride.

FDA Pregnancy Risk Categories Prior to 2015

In 1979, the FDA established five letter risk categories - A, B, C, D or X - to indicate the potential of a drug to cause birth defects if used during pregnancy.

The categories were determined by assessing the reliability of documentation and the risk to benefit ratio.

These categories did not take into account any risks from pharmaceutical agents or their metabolites in breast milk. In the drug product label, this information was found in the section “Use in Specific Populations”.

In 2015 the FDA replaced the former pregnancy risk letter categories on prescription and biological drug labeling with new information to make them more meaningful to both patients and healthcare providers.

The FDA received comments that the old five-letter system left patients and providers ill-informed and resulted in false assumptions about the actual meaning of the letters.

The new labeling system allows better patient-specific counseling and informed decision making for pregnant women seeking medication therapies. While the new labeling improves the old format, it still does not provide a definitive "yes" or "no" answer in most cases. Clinical interpretation is still required on a case-by-case basis.

The **Pregnancy and Lactation Labeling Final Rule (PLLR)** went into effect on June 30, 2015; however, the timelines for implementing this new information on drug labels (also known as the package insert) is variable.

The A, B, C, D and X risk categories, in use since 1979, are now replaced with narrative sections and subsections to include:

Pregnancy (includes Labor and Delivery):
Pregnancy Exposure Registry
Risk Summary
Clinical Considerations
Data

Lactation (includes Nursing Mothers)
Risk Summary
Clinical Considerations
Data

Females and Males of Reproductive Potential
Pregnancy Testing
Contraception
Infertility

The **Pregnancy** subsection will provide information about dosing and potential risks to the developing fetus and registry information that collects and maintains data on how pregnant women are affected when they use the drug or biological product.

Information in drug labeling about the existence of any pregnancy registries has been previously recommended but not required until now. Contact information for the registries will also be included, and pregnant women are encouraged to enroll to help provide data on the effects of drug use or biologics in pregnancy.

If information for the subsections of Pregnancy Exposure Registry, Clinical Considerations, and Data is not available, these subsections will be excluded. The Risk Summary subheadings are always required, even if no data is available.

The **Lactation** subsection will replace the "Nursing Mothers" subsection of the old label. Information will include drugs that should not be used during breastfeeding, known human or animal data regarding active metabolites in milk, as well as clinical effects on the infant. Other information may include pharmacokinetic data like metabolism or excretion, a risk and benefit section, as well as timing of breastfeeding to minimize infant exposure.

In the subsection entitled **Females and Males of Reproductive Potential**, relevant information on pregnancy testing or birth control before, during or after drug therapy, and a medication's effect on fertility or pregnancy loss will be provided when available.

Why Did the FDA Make This Change?

Clinically, many women require drug treatment during pregnancy due to chronic conditions such as epilepsy, diabetes, hypertension (high blood pressure), or asthma.

To withhold drug treatment would be dangerous for both mother and baby. In addition, women are having babies at a later age, which can boost the number of women with chronic conditions.

Accessible and understandable pregnancy and lactation information is important for women and their health care provider's to assess risk versus benefit.

Clinicians and patients were often confused by the meaning of the pregnancy risk categories because, according to the FDA, it was overly simplistic, led to misinformation, and did not adequately address the available information.

Examples of drugs approved since June 30th, 2015 showing various new pregnancy and lactation subsections in their labels:

Addyi (flibanserin) - indicated for generalized hypoactive sexual desire disorder (HSDD) in premenopausal women.

Descovy (emtricitabine and tenofovir alafenamide fumarate) - indicated for HIV-1 infection.

Entresto (sacubitril and valsartan) - indicated for heart failure.

Harvoni (ledipasvir and sofosbuvir) - indicated for chronic viral hepatitis C infection (HCV).

Praluent (alirocumab) - indicated for heterozygous familial hypercholesterolemia, or patients with atherosclerotic heart disease who require additional lowering of LDL-cholesterol.