Drugs during pregnancy*

Drugs and pregnancy

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As around a third of pregnancies are unplanned, pregnant women conceive while taking a wide variety of both prescription and over-the-counter medications.

It is reported that approximately 50% of women will take medications during pregnancy.

As many pregnant women require medication for specific pregnancy- and non-pregnancy-related conditions.

Furthermore, the large majority of drugs cross the placenta, and some drugs have significant fetal effects. For these reasons, most drugs are not licensed for use in pregnancy, thus prescribing in pregnancy often lies outside licensed indications.

General principles for using drugs

- The benefits from continuing medication in pregnancy and when breast-feeding often outweigh the potential risks.

- Prepregnancy assessment should be offered to all women of childbearing age on regular medication with the option to change to alternative medication where possible.

- Try to avoid 1st trimester use if possible.
- Use drugs already used in pregnancy rather than new ones.
- Use the minimum dose to achieve the desired effect.

Drug trials in pregnancy:

- Drug trials are difficult to carry out in pregnancy because of concern over the fetus.

As such, many drugs have not been validated for use or safety in human pregnancy.

- Recommendations often rely on data from animal models. The occurrence of thalidomide-associated embryopathy has led to the belief that human teratogenicity cannot be predicted by animal studies.

However, every drug that has since been found to be teratogenic in humans has caused similar effects in animals.

Pharmacokinetics during pregnancy:

- Pharmacokinetics is the study of how a drug moves through the body.
- Drug absorption is altered in pregnancy. Gastric emptying and gastric acid secretion are reduced. Intestinal motility is decreased.

Pulmonary tidal volume is increased which may affect the absorption of inhaled drugs.

The volume of distribution changes in pregnancy. *

Plasma volume rises by 40%, total body water increase 7-8L, and body fat increases 20–40%. Despite these changes (which would be expected to decrease drug levels), albumin concentrations decline, and free fatty acid and lipoprptein values rises.

As a result, protein binding of many drugs is lower in pregnancy, leading to an increase in circulating free (biologically active) drug levels.

- Metabolism and elimination are also altered in pregnancy.

High steroid hormone levels affect hepatic metabolism and prolong the half-life of some drugs. Glomerular filtration rate rises 50–60%, thereby increasing the renal clearance of other drugs.

Drug transfer across the placenta:

The majority of drugs are able to cross the placenta to the fetus to some degree, and there are very few that demonstrate no placental transfer.

Transfer of drugs across the placenta can occur by passive transfer, active transport, facilitated diffusion, phagocytosis and pinocytosis.

By far the commonest method is passive diffusion, or movement of a molecule down a concentration gradient, and this is determined by the lipid solubility, polarity and molecular mass of the drug.

Heparin (both unfractionated and low molecular weight) is the best example known to be unable to cross the placenta due to its large molecular mass.

Active transport is an other mechanism for transport of drugs through the placenta, as there are a lot of energy –requiring drugs transport systems within the placenta.

These include: P-glycoprotein (multidrug-resistant gene MDR-1 product) that is able to transport digoxin and dexamethasone; MDR proteins 1-3,

able to transport methotrexate and ampicillin; and the monocarboxylate and sodium/ multivitamin transporters, able to transport valproate

and carbamazepine.

Teratogenicity:

- Teratogenicity is the study of abnormal fetal development, and refers to both structural and functional abnormalities.

- With the exception of large molecules (such as heparin), all drugs given to the mother cross the placenta to some degree.
The effect of a given drug on a fetus depends on dose, time, and* duration of exposure, and as yet poorly defined genetic and environmental factors that interact to determine the susceptibility of any individual fetus for structural injury.

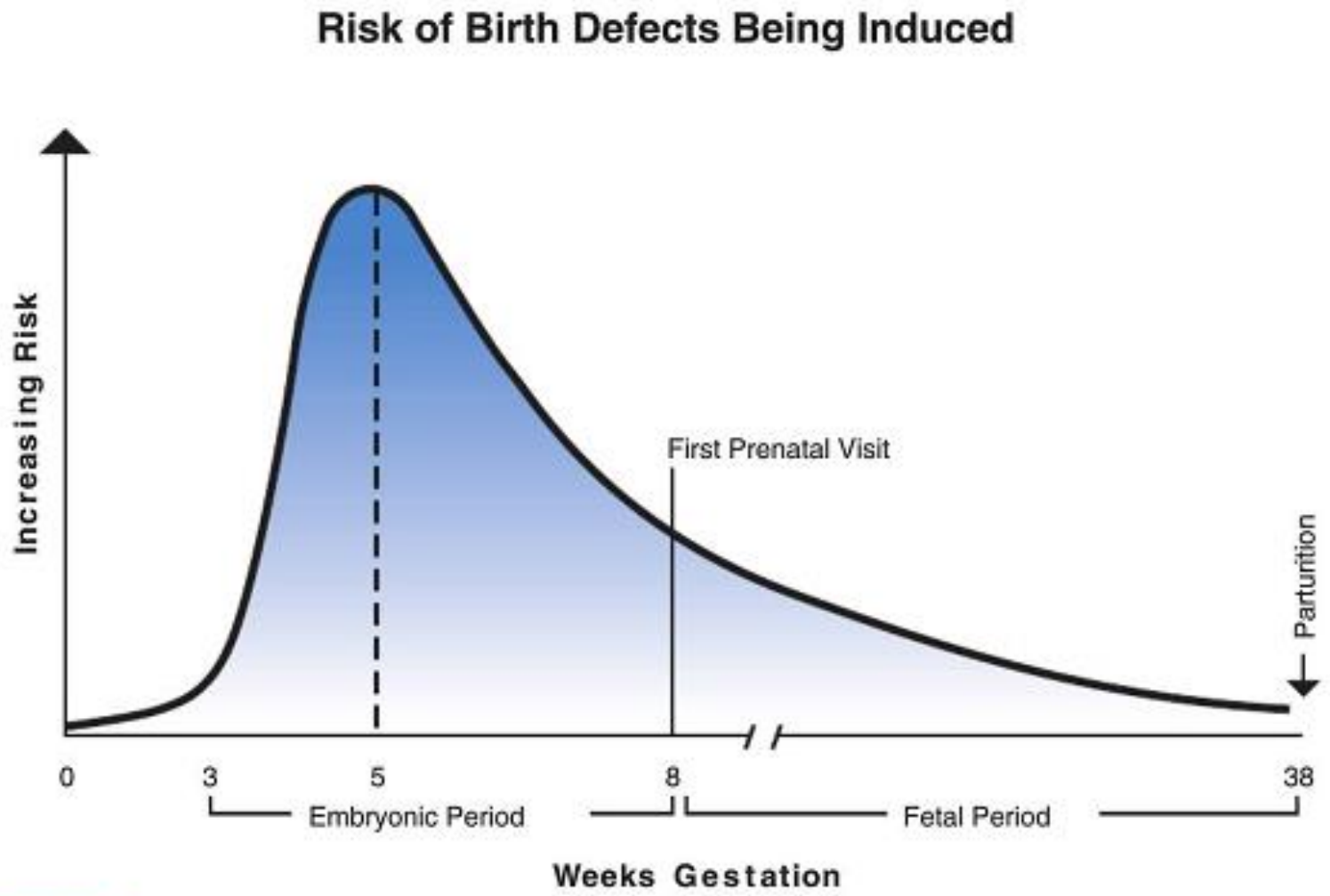


FIGURE 9.2 Graph showing the times in gestation versus the risks of birth defects being induced. The most sensitive time is the embryonic period during the third to eighth weeks. The fetal period begins at the end of the eighth week and extends to term. During this time, the risk for gross structural 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 intellectual disability. The fact that most birth defects occur prior to the eighth week makes it imperative to initiate birth defects prevention strategies prior to conception. Unfortunately, most women do not appear for their first prenatal visit until the eighth week, which is after the critical time for prevention of most birth defects.

Susceptibility to teratogens varies with the developmental stage at the time of exposure.

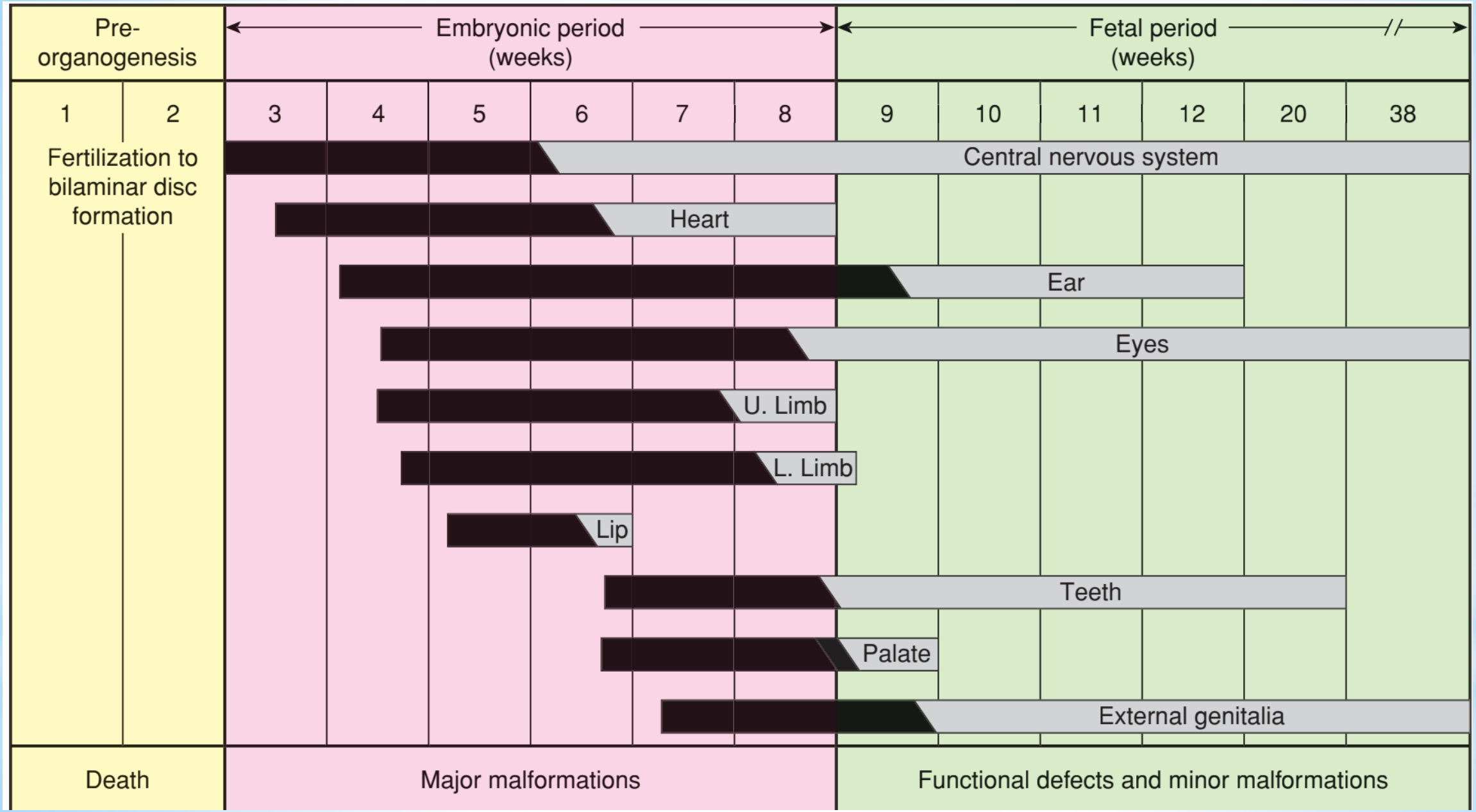
The most sensitive period for inducing birth defects is the third to eight weeks gestation, the period of embryogenesis.

Each organ system may have one or more stages of susceptability.

For example, cleft palate can be induced at the blastocyst stage (day 6)

during gastrulation (day 14), at the early limb bud stage (fifth week), or when the palatal shelves are forming (seventh week).

Furthermore, whereas most abnormalities are produced during embryogenesis, defects may also be induced before or after this period; no stage of development is completely safe.


Pre-organogenesis
Embryonic period (weeks)
Fetal period (weeks)
1
2
3
4
5
6
7
8
9
10
11
12
20
38
Fertilization to bilaminar disc formation
Central nervous system
Heart
Ear
Eyes
U. Limb
L. Limb
Lip
Teeth
Palate
External genitalia
Death
Major malformations
Functional defects and minor malformations

Risk categories for drugs in pregnancy :

The Food and Drug Administration (FDA) in the USA has defined five risk categories for drug use in pregnancy: A,B,C,D,X.

Individual agents are assigned to a risk category according to their risk-benefit ratio,

eg, although oral contraceptives are not teratogenic, they are classified as category X because there is no benefit on the pills the women being pregnant.

Category A:

Controlled studies in women fail to demonstrate a risk to the fetus and the possibility of fetal harm appears remote.

Example:

- Vitamin C, folate, L-thyroxine

Category B:

- Either animal studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal studies have shown an adverse effect that was not confirmed in controlled studies in women.

Examples:

Hydrochlorothiazide, α-methyldopa, ampicillin.

Category C:

Either studies in animals have revealed adverse effects on the fetus and there are no controlled studies in women, or there are no controlled studies in animals or women.

Only use if potential benefit justifies risk to fetus.

Example:

theophylline, nifedipine, digoxin,

ß-blockers, verapamil, zidovudine (AZT), acyclovir.

Category D:

Positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk.

Example:

spironolactone, ACE inhibitors, methotrexate, phenytoin.

Category X:

Positive evidence of animal or human fetal abnormalities, or the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. Contraindicated in women who are or may become pregnant. Example:

Aminopterin, isotretinoin (vitamin A), radioisotopes, oral contraceptives.

Some Examples*

Thalidomide:

an antinauseant and sleeping pill.

In 1961, it was noted in West Germany that the frequency of amelia and meromelía (total or partial absence of the extremities), a rare abnormality that was usually inherited, had suddenly increased.

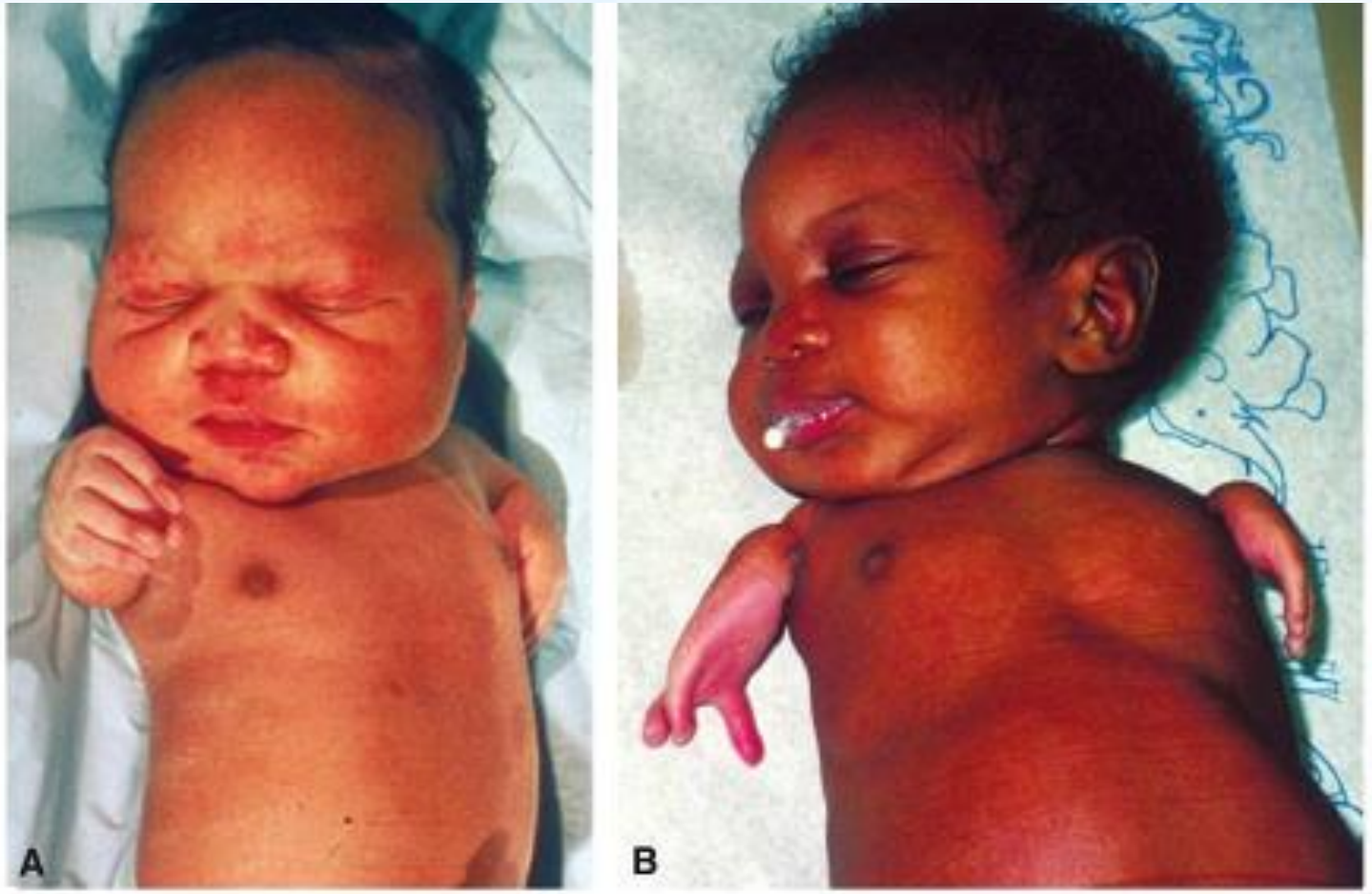
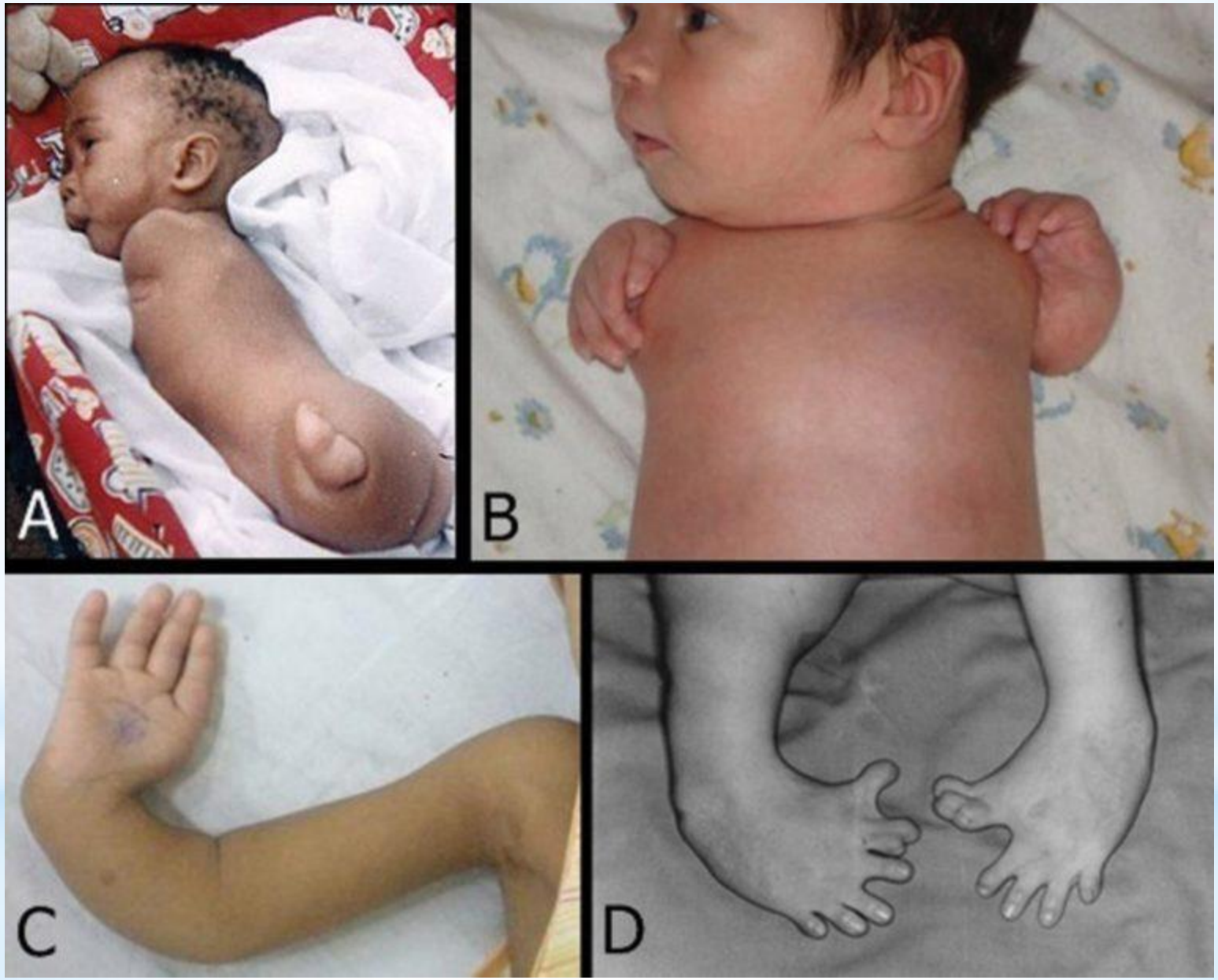


FIGURE 9.5 **A,B.** Examples of phocomelia. Limb defects characterized by loss of the long bones of the limb. These defects were commonly produced by the drug thalidomide.


A
B
C
D

*

The discovery that a drug like thalidomide could cross the placenta and cause birth defects was revolutionary and led to the Science of teratology.

Today, thalidomide is still in use as an immunomodulatory agent in the treatment of people with AIDS and other immunopathological diseases such as leprosy, lupus erythematosus, and graft versus host disease.

Limb defects still occur in babies exposed to the drug, but it is now clear that other malformations are produced as well.

These abnormalities include heart malfomations, orofacial orofacial clefts, intellectual disability, autism, and defects of the urogenital and GIT systems.

Isotretinoin (Accutane)

an analogue of vitamin A,

has been shown to cause a characteristic pattern o f malformations known as the isotretinoin embryopathy.

The drug is prescribed for the treatment o f cystic acne and other chronic dermatoses, but 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 itself may be teratogenic at high doses, based on animal studies and the fact that isotretinoin is a closely related compound.

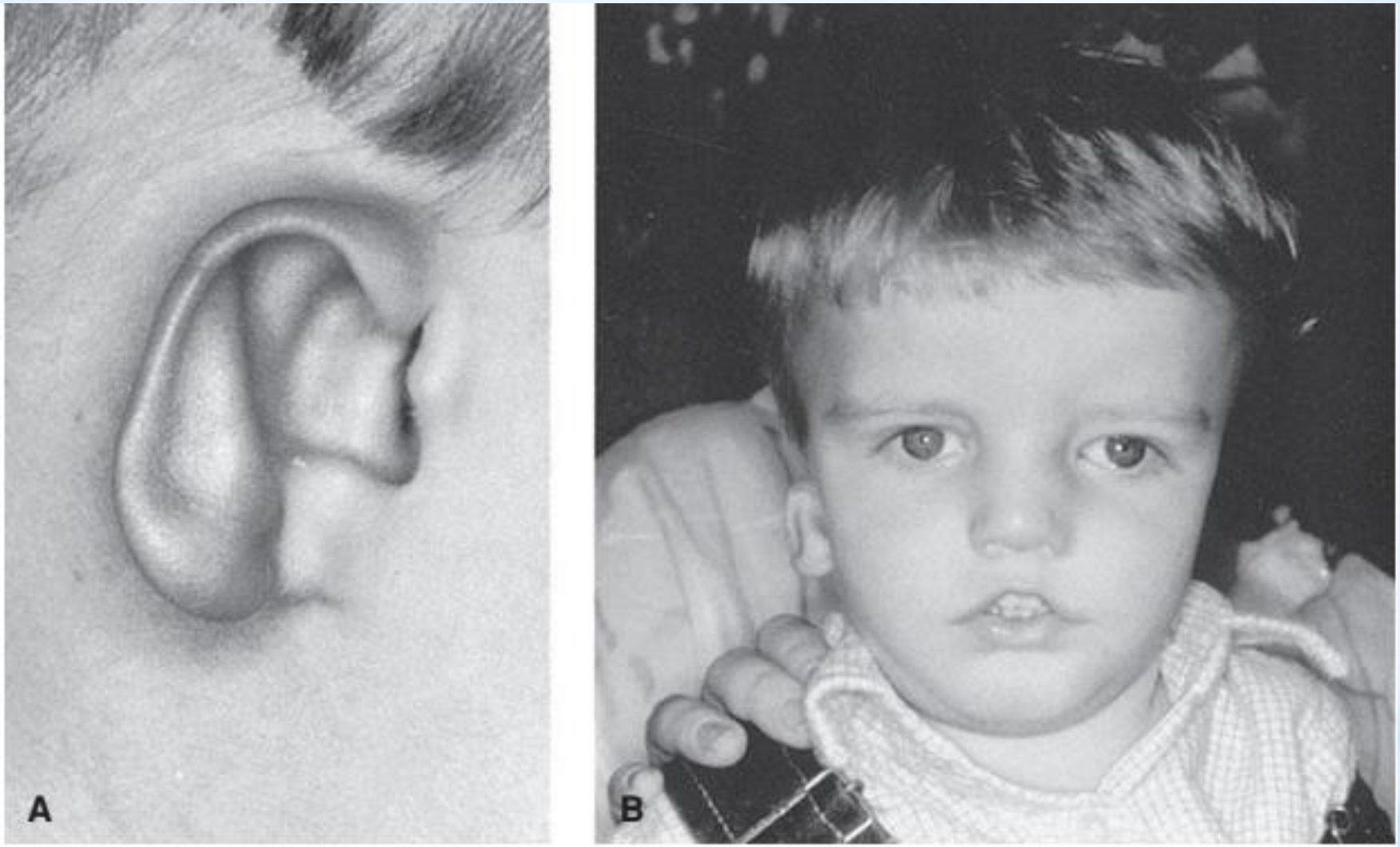
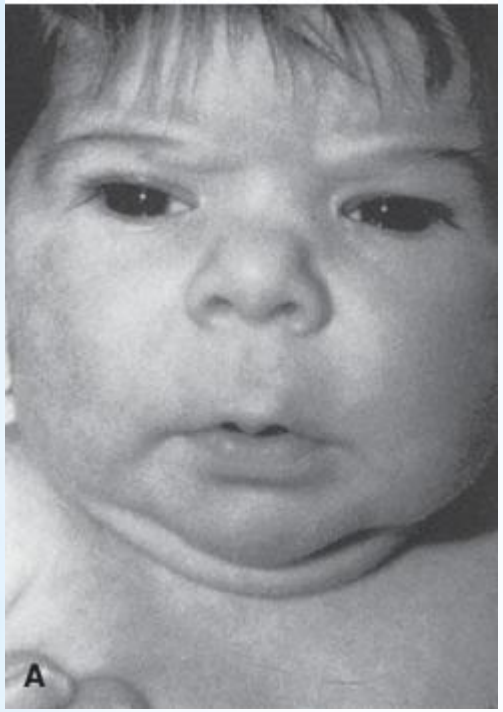
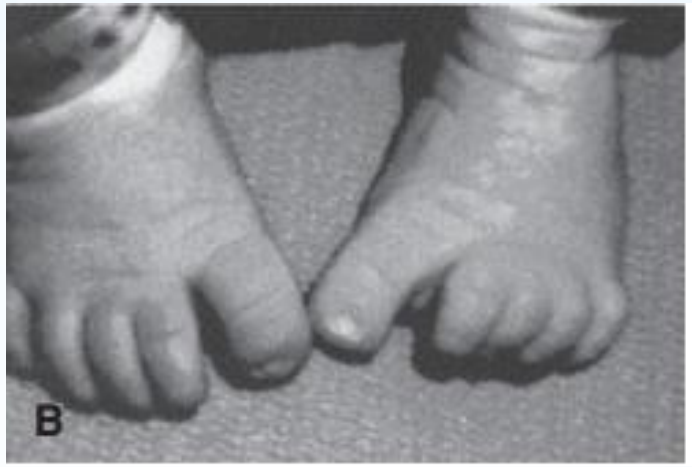


FIGURE 12-4 Isotretinoin embryopathy. **A.** Bilateral microtia or anotia with stenosis of external ear canal. **B.** Flat, depressed nasal bridge and ocular hypertelorism. (Photograph contributed by Dr. Edward Lammer.)

Anticonvulsants diphenylhydantoin (phenytoin), valproic acid, and trimethadíone.

Specifically, trimethadione and diphenylhydantoin produce a broad spectrum of abnormalities that constitute distinct patterns of dysmorphogenesis known as the known as the trimethadione and fetal hydontoin syndrome.



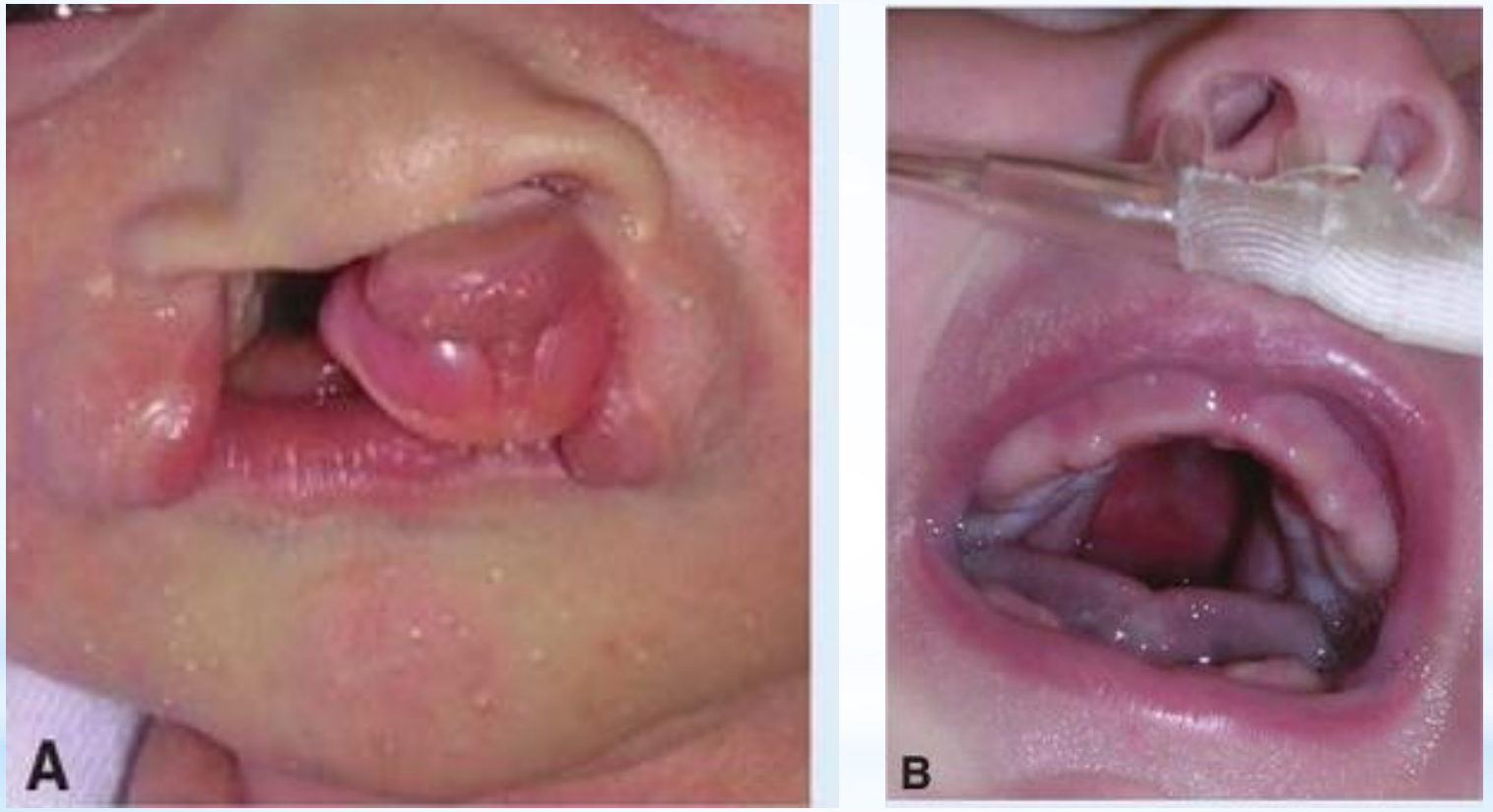


Fetal hydantoin syndrome. **A.** Facial features including upturned nose, mild midfacial hypoplasia, and long upper lip with thin vermilion border. **B.** Distal digital hypoplasia. (From

valproic acid increases the risk for several defects, including atrial septal defects, cleft palate, hypospadias, polydactyly, and craniosynostosis, but the highest risk is for the neural tube defect, spina bifida.

The anticonvalsant carbamazepine also has been associated With an increased risk for neural tube defects and possibly other types o f malformations.

Even newer anticonvulsant drugs like Topamax (topiramate) increase the risk for cleft lip and/or cleft palate.


A
B

Anticoaggulants:

Both UFH and LMWH do not cross the placenta and are not associated with teratogenicity or fetal bleeding. In contrast, vitamin K antagonists such as **warfarin**, cross the placenta and, with exposure between 6 and 12 weeks of gestation, are associated with a characteristic embryopathy:

* Mid-facial, particularly nasal, hypoplasia
* Stippled chondral calcification
* Short proximal limbs
* Short phalanges
* Scoliosis

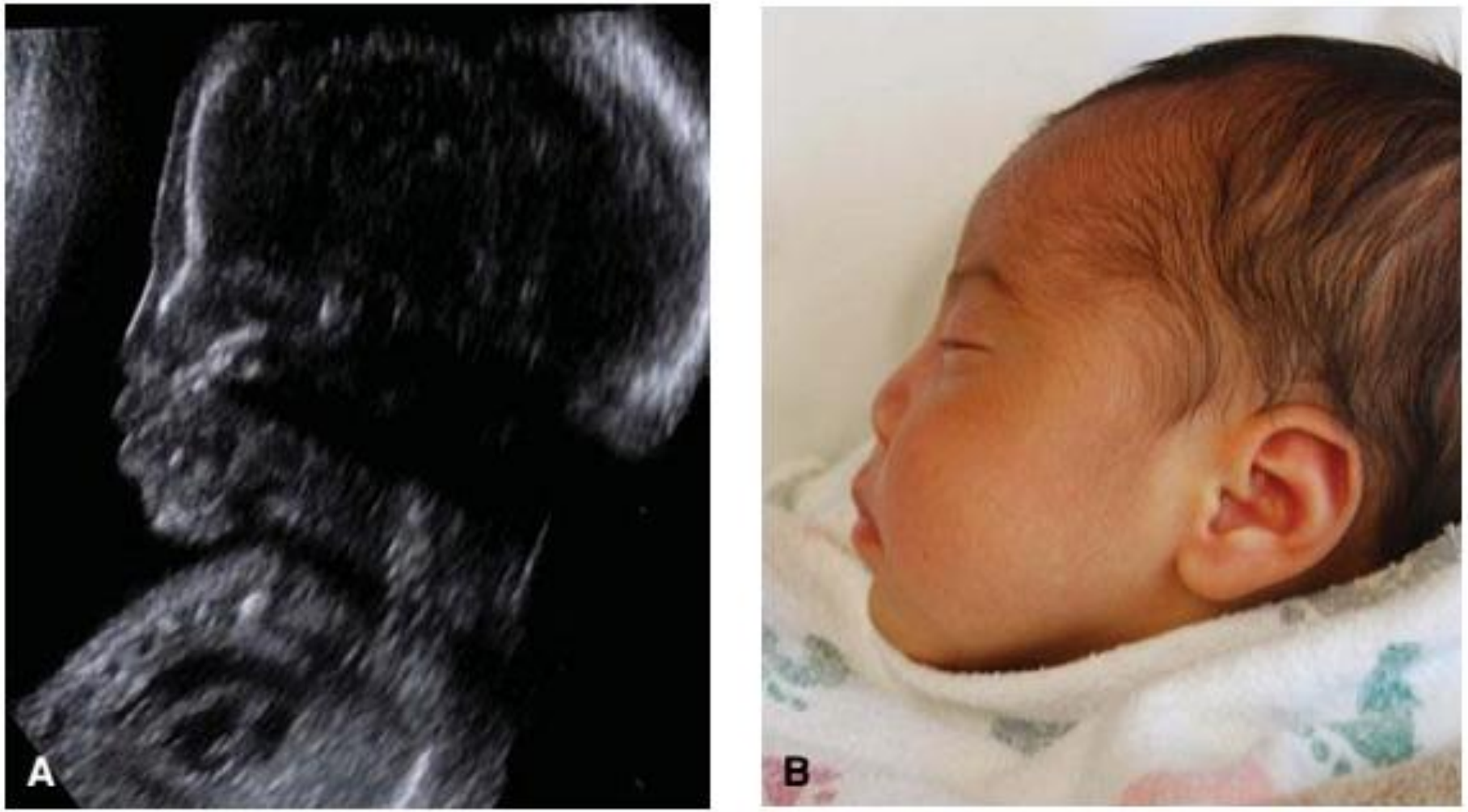


FIGURE 12-5 Warfarin embryopathy or fetal warfarin syndrome: nasal hypoplasia and depressed nasal bridge seen in a fetal sonographic image **(A)** and in the same newborn **(B)**.

The risk of embryopathy may be higher with doses of warfarin over 5 mg/day.
Warfarin is also associated with fetal and neonatal haemorrhage.

With fetal liver immaturity, maternal therapeutic warfarin (INR 2-3) is likely to result in excessive anticoagulation in the fetus. Warfarin during the second and third trimesters may also result in neurodevelopmental problems.

Antipsychotic and antianxiety agents

(major and minor tranquilizers, respectively)

are suspected producers of congenital malformations. The antipsychotics phenothiazine and lithium have been implicated as teratogens.

Although evidence for the teratogenicity of phenothiazines is conflicting, an association between lithium and congenital heart defects, especially Ebstein anomaly, is better documented.

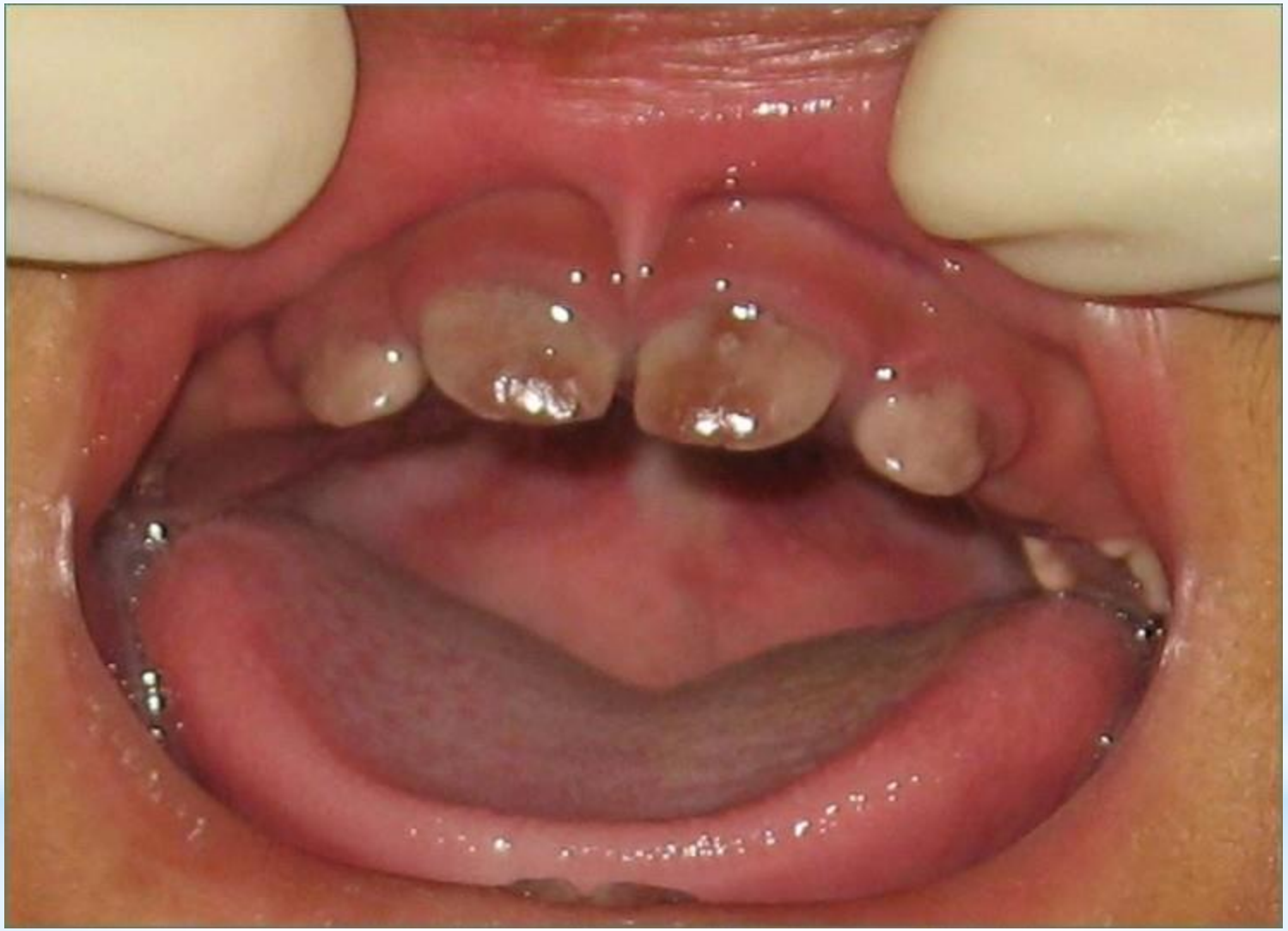
Antihypertensive agents :

that inhibit angiotensin-converting enzyme (ACE inhibitors) produce growth retardation, renal dysfunction, fetal death, and oligohydramnios if exposures occurs during the second or third trimester.

Effects of exposure to these compounds in the first trimester are less clear.

Caution has also been expressed regarding a number of other compounds that may cause damage to the fetus or the embryo.

The most prominent among these are propylthiouracil and and potassium iodide (goiter and intellectual disability), Streptomycin (hearing loss), sulfonamide (kernicterus),the antidepressant imipramine (limb deformities), tetracyclines (bone and tooth anomalies), amphetamines (oral clefts and cardiovascular abnormalities), and quinine (hearing loss).



Drug	Pre-conception	Effects of pregnancy	Fetal considerations	Lactation
Analgesics				
Paracetamol	–	–	Safe	Safe
NSAIDs	–	–	Premature closure of ductus and kidney dysfunction >32 weeks [A]	Considered safe
Codeine	–	–	Has been inconsistently associated with respiratory tract malformations but considered safe for short-term use; may cause neonatal withdrawal	advise avoidance as may cause high levels of morphine in fast metabolisers, thus risk of cardiorespiratory depression in neonates [E]
Opiates	–	–	No major effects known, fetal dependence and withdrawal [D]	As for codiene

Drug	Pre-conception	Effects of pregnancy	Fetal considerations	Lactation
Cardiovascular system				
ACE inhibitors, ARBs	Should be changed to alternative if possible	Avoid – use only if no alternative with fetal monitoring of growth and liquor volume; stop if oligohydramnios [D, E]	Teratogenic in first trimester; renal and cardiac problems in late gestation [D, E]	Considered compatible
Antihypertensives	Optimise blood pressure control	Nifedipine may demonstrate increased clearance in third trimester [D, E]	Beta blockers associated with fetal growth restriction (less so with labetalol); IV doses should be given with fetal monitoring	Present in breast milk (except nifedipine, which is >90% protein bound); infants reported normotensive, so considered safe
Statins	–	–	Usually stop as may adversely affect placental development; studies ongoing	Considered compatible

Drug	Pre-conception	Effects of pregnancy	Fetal considerations	Lactation
Antibiotics				
Penicillins/ cephalosporins	–	Increased renal excretion, lower plasma levels	Cross placenta, considered safe	Small amounts in breast milk; safe
Tetracyclines	–	–	Increased risk of NTD, cleft palate and cardiovascular effects (not doxycycline); tooth discoloration [D, E]	Found in breast milk; concerns about effects on teeth
Ciprofloxacin	–	–	Only small amounts cross placenta but has been associated with bone/ cartilage problems; however, few data	Concentrated in breast milk; neonatal *Clostridium difficile* has been reported [D]