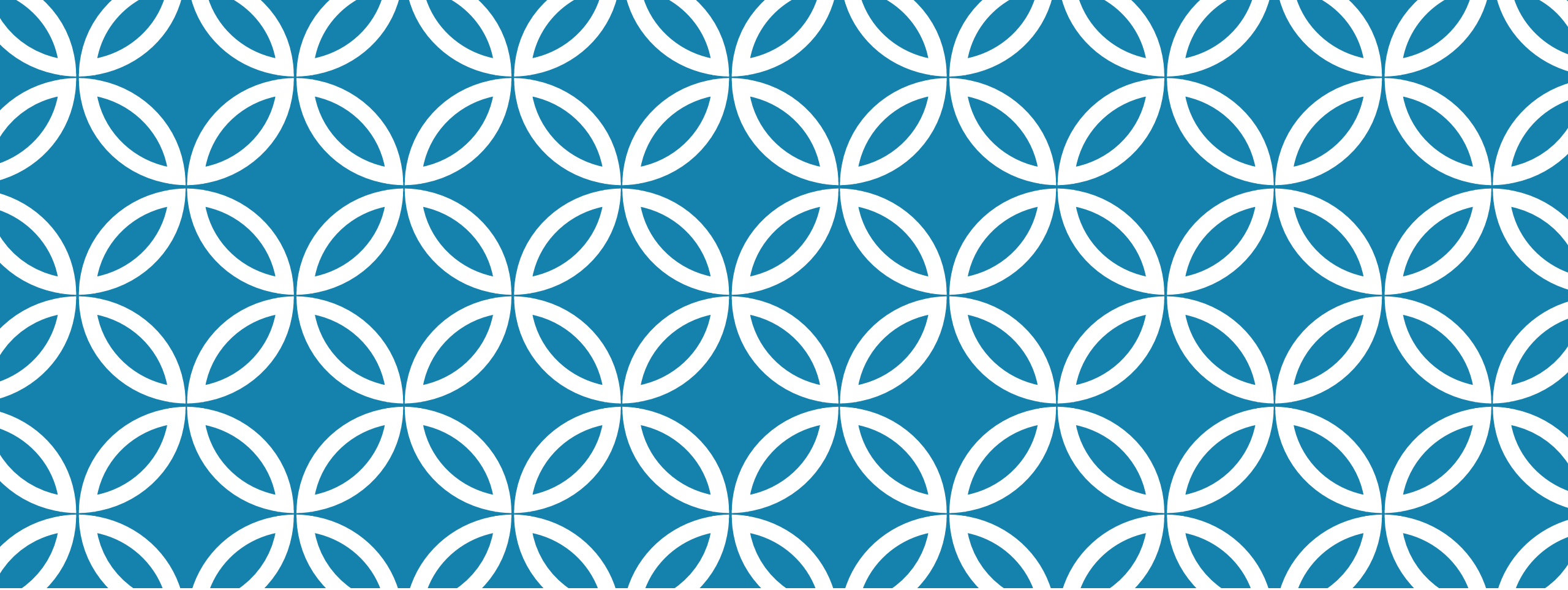


DRUGS USED DURING PREGNANCY & LACTATION

PREGNANCY PHYSIOLOGY AND ITS EFFECTS ON PHARMACOKINETICS

Absorption

1. Gastrointestinal motility is decreased but there appears to be no major affect in drug absorption except that reduced gastric emptying delays the appearance in the plasma of orally administered drugs, especially during labor.
2. Absorption from an intramuscular site is likely to be efficient because tissue perfusion is increased due to vasodilatation.

DISTRIBUTION:

1. Total body water increases by up to 8 Litres, creating a larger space within which water soluble drugs may distribute.
2. As a result of haemodilution, plasma albumin (normal 33-55 g/1) declines by some 10 g/1. Thus there is scope for increased free concentration of drugs that bind to albumin.
3. Unbound drug, is free to distribute, metabolized and excreted; e.g. the free (and pharmacologically active) concentration of phenytoin is unaltered, although the total plasma concentration is reduced.

METABOLISM

- **Hepatic metabolism** increases, but not the blood flow to liver.
- So, increased clearance of drugs such as phenytoin and theophylline (elimination rate depends on liver enzyme activity)
- Drugs that are so rapidly metabolized that their elimination rate depends on their delivery to the liver, i.e. on hepatic blood flow, have unaltered clearance, e.g. pethidine.

ELIMINATION:

- Renal plasma flow almost doubles
- So there is rapid loss of drugs that are excreted by kidney
- e.g. amoxycillin, dose of which should be doubled for systemic infections (but not for urinary tract infections as penicillins are highly concentrated in urine).

PLACENTAL TRANSFER OF DRUGS

1. The placenta is not a perfect barrier to drugs and chemicals administered to mother.
2. Thalidomide tragedy, showed that placenta was capable of transferring drugs ingested by mother to fetus, with potential for great harm.
3. On other hand, placental transfer of drugs administered to mother has been used to treat fetal arrhythmias, congestive heart failure, & other conditions.

FACTORS AFFECTING PLACENTAL DRUG TRANSFER & FETAL TISSUE

(1) Physicochemical properties of drug

(2) Rate at which drug crosses placenta & amount of drug reaching the fetus

(3) Duration of exposure to drug

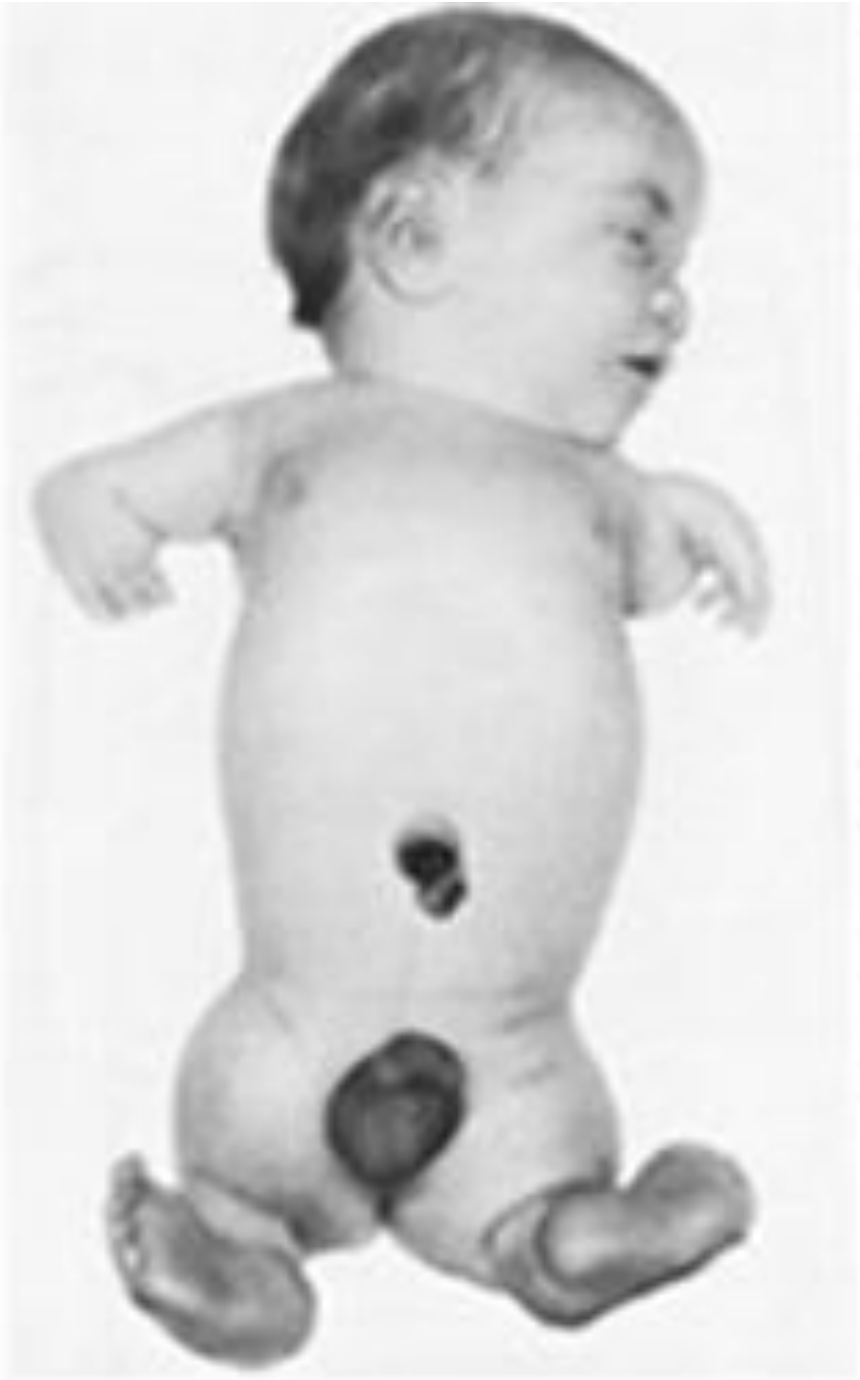
(4) Distribution characteristics in different fetal tissues

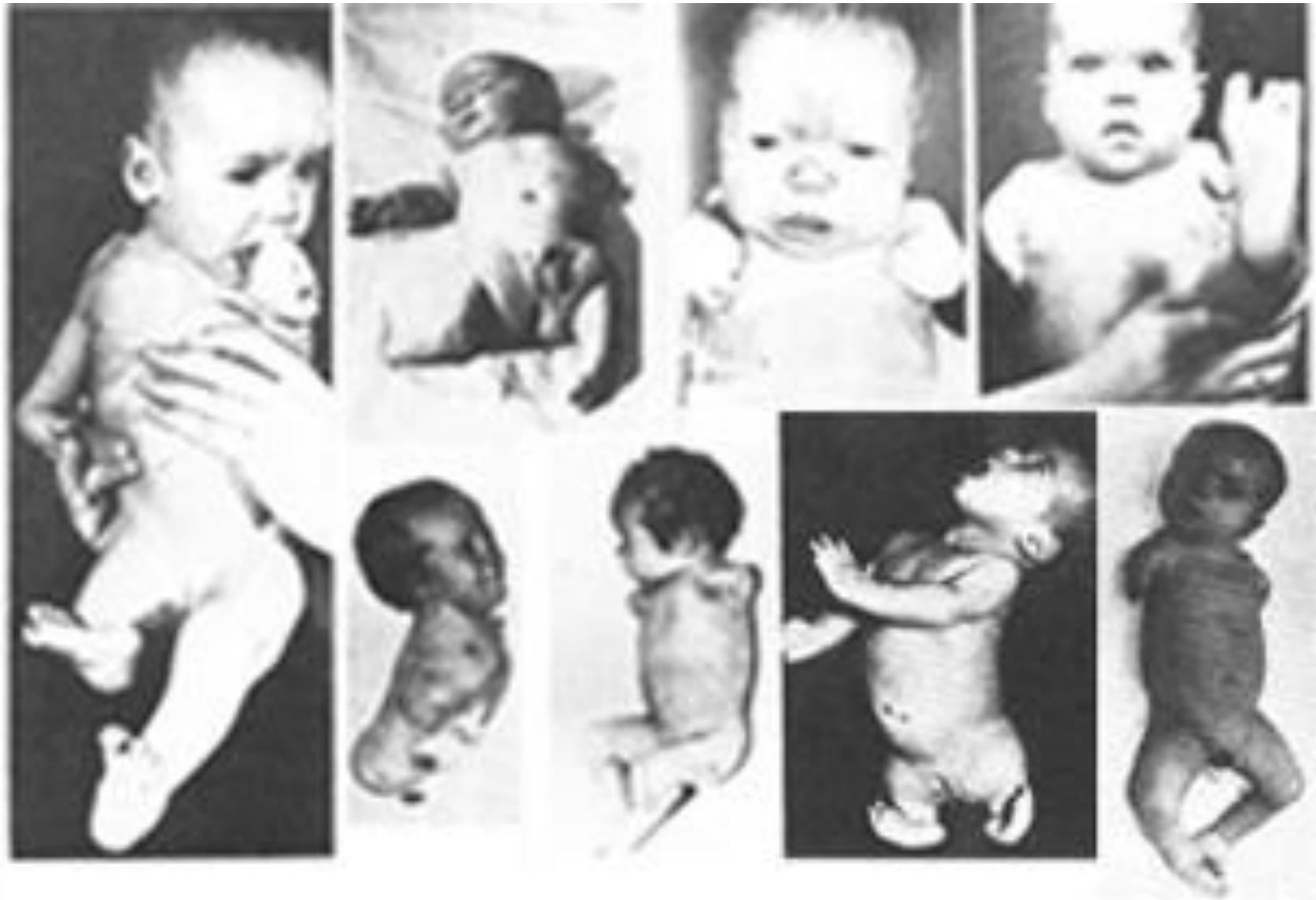
(5) Stage of placental & fetal development at time of exposure to the drug

(6) Effects of drugs used in combination

TERATOGENESIS

A *teratogen* is a chemical substance that can induce a malformation during development.





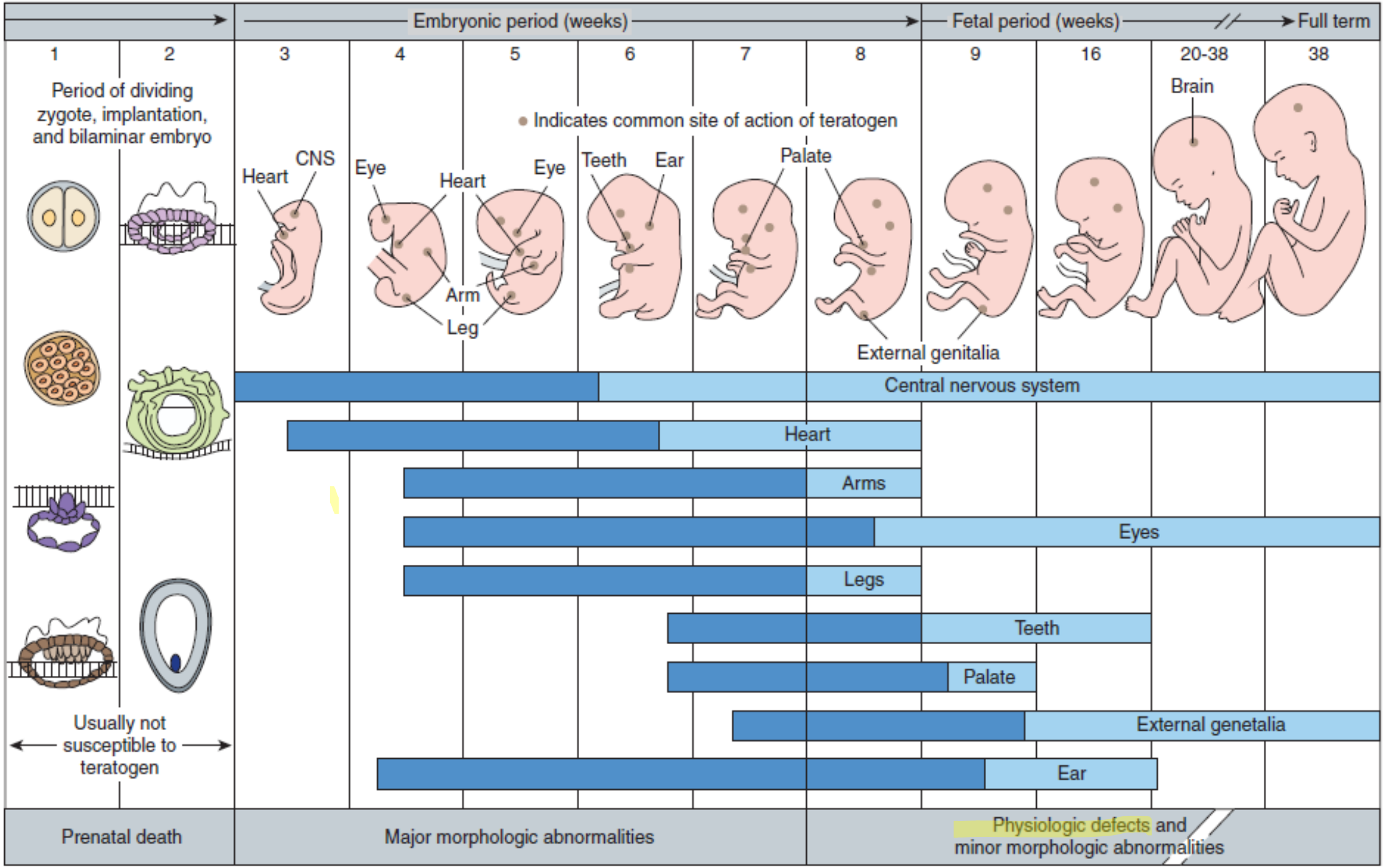
Malformations due to maternal ingestion of thalidomide (Schardein 1982 and Moore 1993).

PRINCIPLES OF TERATOLOGY

- Teratogens act with specificity. A teratogen produces a specific abnormality or constellation of abnormalities. Eg. thalidomide produces phocomelia, and valproic acid produces neural tube defects.
- Teratogens demonstrate a dose-effect relationship.
- Teratogens must reach the developing conceptus in sufficient amounts to cause their effects.
- The effect that a teratogenic agent has on a developing fetus depends upon the stage during development when the fetus is exposed.

MECHANISMS OF TERATOGENESIS

- Genetic interference, gene mutation, chromosomal breakage, interference with cellular function, enzyme inhibition, and altered membrane characteristics.
- The response of the developing embryo to these insults is failure of cell–cell interaction crucial for development, interference with cell migration, or mechanical cellular disruption.


Embryonic period (weeks)
Fetal period (weeks)
Full term
1
2
3
4
5
6
7
8
9
16
20-38
38
Period of dividing zygote, implantation, and bilaminar embryo
Indicates common site of action of teratogen
Heart
CNS
Eye
Heart
Eye
Arm
Leg
Teeth
Ear
Palate
External genitalia
Brain
Central nervous system
Heart
Arms
Eyes
Legs
Teeth
Palate
External genetalia
Ear
Usually not susceptible to teratogen
Prenatal death
Major morphologic abnormalities
Physiologic defects and minor morphologic abnormalities

EXAMPLES

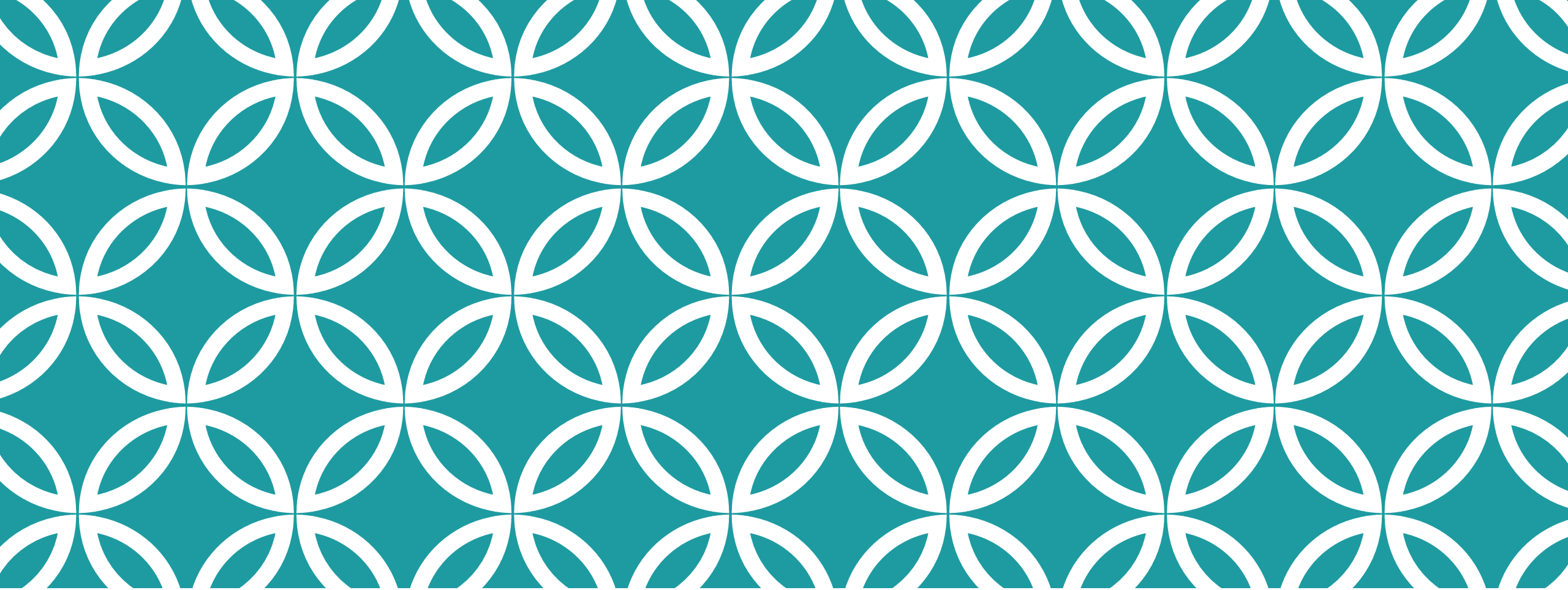
Drug	*Abnormality*
Thalidomide	phocomelia, multiple defects
Anticancer drugs (methotrexate)	cleft palate, hydrocephalus, multiple defects, foetal death
Androgens	virilization; limb, esophageal, cardiac defects
Progestins	virilization of female foetus
Stilboestrol	vaginal carcinoma in teenage female offspring
Tetracyclines	discoloured and deformed teeth, retarded bone growth
Warfarin	depressed nose; eye and hand defects, growth retardation
Phenytoin	hypoplastic phalanges, cleft lip/palate, microcephaly
Phenobarbitone	various malformations
Carbamazepine	neural tube defects, other abnormalities
Valproate sod.	spina bifida and other neural tube defects
Alcohol	low IQ baby, growth retardation, foetal alcohol syndrome
ACE inhibitors	hypoplasia of organs, growth retardation, foetal loss
Lithium	foetal goiter, cardiac and other abnormalities
Antithyroid drugs	foetal goiter and hypothyroidism
Indomethacin/aspirin	premature closure of ductus arteriosus
Isotretinoin	craniofacial, heart and CNS defects

PRESCRIBING IN PREGNANCY

- minimize prescribing;
- use ‘tried and tested’ drugs whenever possible in preference to new agents;
- use the smallest effective dose;
- remember that the fetus is most sensitive in the first trimester;
- consider pregnancy in all women of childbearing potential;
- discuss the potential risks of taking or withholding therapy with the patient;
- seek guidance on the use of drugs in pregnancy in the British National Formulary, Drug Information Services, National Teratology Information Service (NTIS);
- warn the patient about the risks of smoking, alcohol, over-the-counter drugs and drugs of abuse.

DRUG USE DURING LACTATION

- Most drugs administered to lactating women are detectable in breast milk. Fortunately, the concentration of drugs achieved in breast milk is usually low.
- Infant would receive in a day is substantially less than what would be considered a "therapeutic dose."
- If the nursing mother must take medications and the drug is a relatively safe one, she should optimally take it 30–60 minutes after nursing and 3–4 hours before the next feeding.
- Caution: Sedative-Hypnotics, Lithium Tetracyclines



THANK YOU