EMBRYOLOGICAL MECHANISM & TERATOLOGY

ANA 308

Department of Anatomy

ABUAD 2020

Adekeye AO (Ph.D)

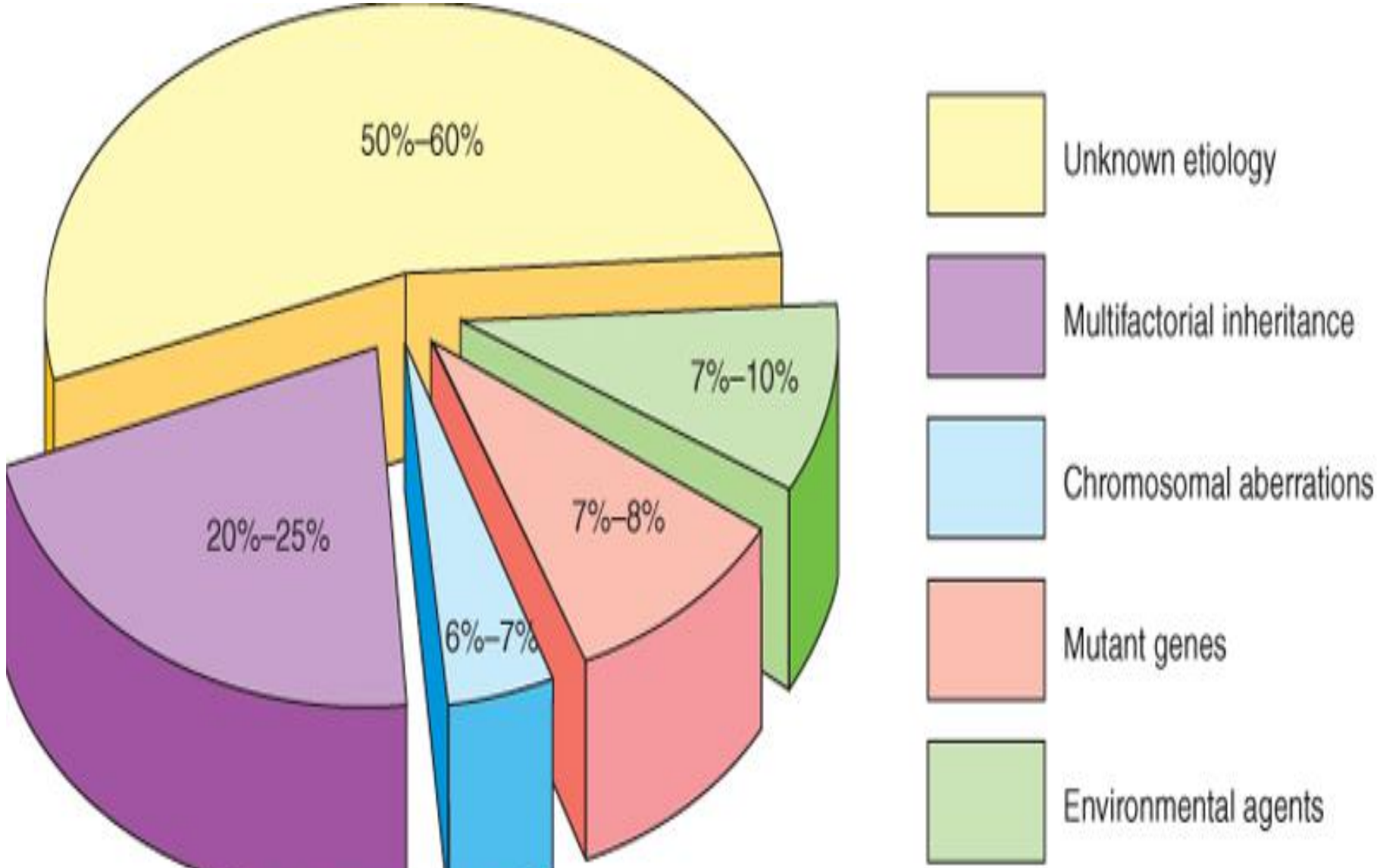
Teratology

- This is the branch of science that studies the causes, mechanisms, and patterns of abnormal development
- *Any agent that can produce a congenital anomaly or increase the incidence of an anomaly in the population is called a* ***teratogen***

➢ ***causes of congenital anatomic anomalies*** or birth defects are often divided into:

1. ***Genetic factors*** such as chromosome abnormalities
2. ***Environmental factors*** such as drugs and viruses

- *However, many common congenital anomalies are caused by multifactorial inheritance (genetic and environmental factors)*

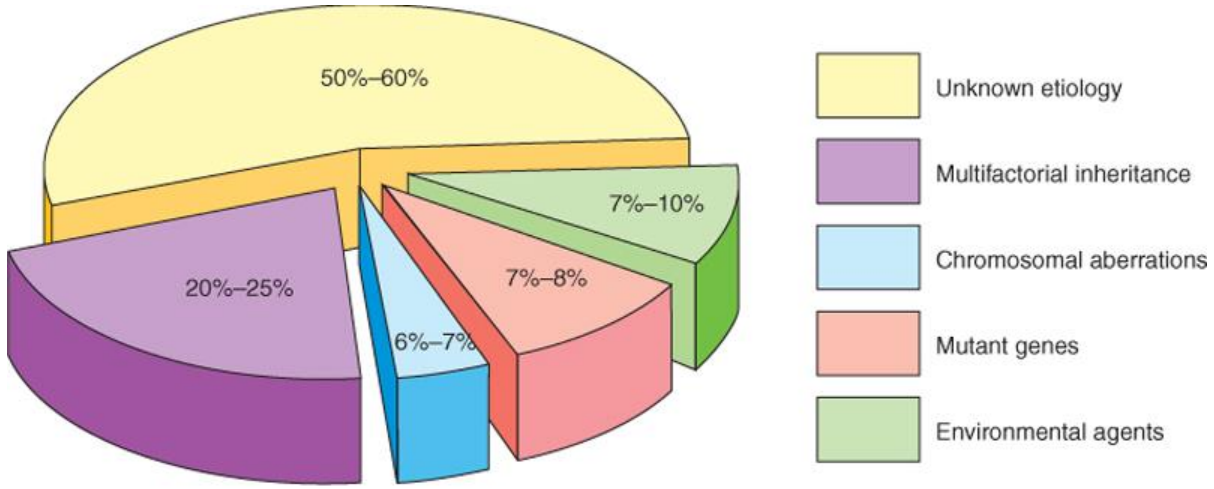

50%–60%
7%–10%
20%–25%
7%–8%
6%–7%
Unknown etiology
Multifactorial inheritance
Chromosomal aberrations
Mutant genes
Environmental agents

COMMON BIRTH DEFECT

- OTHER NAMES INCLUDE CONGENITAL DISORDER/ANOMALY
- A Birth defect is a problem that occurs when a baby is developing in utero (in the womb).
- Approximately 1 out of every 33 babies is born with a birth defect (USA).
- Birth defects can be **Minor or severe**

- These defects may affect appearance, organ function, physical and mental development.
- Most birth defects are present within the first three months of pregnancy when the organs are still forming.
- Some birth defects are harmless while some requires long term medical treatment.

- The **causes of congenital anatomic anomalies** or birth defects are often divided into:
- **Genetic factors** such as chromosome abnormalities
- **Environmental factors** such as drugs and viruses
- **Multifactorial inheritance** (genetic and environmental factors acting together in a complex manner).
- **Mutant Genes**
- **Unknown Etiology**



Graphic illustration of the causes of human congenital anomalies or birth defects. Note that the causes of most anomalies are unknown and that 20% to 25% of them are caused by a combination of genetic and environmental factors (multifactorial inheritance).

Genetics

- The mother or father may pass on genetic abnormalities to their baby.
- Genetic abnormalities occur when a gene become flawed due to mutation.
- In some cases, a gene or part of a gene might be missing.
- A particular defect may be present throughout the family history of one or both parents

Non genetic causes

- The causes of some birth defects can be difficult or impossible to identify.
- However, certain behavior greatly increase the risk of birth defects.
- These include smoking, using illegal drugs and drinking alcohol while pregnant.
- Other factors such as exposure to toxic chemical or viruses also increase the risk.

What are the risk factors for birth defects

- All pregnant women have some risk of delivering a child with a birth defect.
- Risk increases under any of the following conditions:
  - Family history of birth defects or other genetic disorder
  - Drug use, alcohol consumption or smoking during pregnancy
  - Maternal age of 35 years or older
  - Inadequate prenatal care
  - Untreated viral or bacterial infections including sexually transmitted infections
  - Use of certain high-risk medication such as **isotretinoin and lithium**

Genetic factors

Chromosomal abnormalities

May be:

✓numerical

✓ structural

❖***note***

- The normal human somatic cell contains 46 chromosomes; the normal gamete contains 23
- Normal somatic cells are **diploid, or 2*n***; ***normal gametes*** are **haploid, or *n***
- ***Euploid refers to any exact multiple of n, e.g. diploid or*** triploid

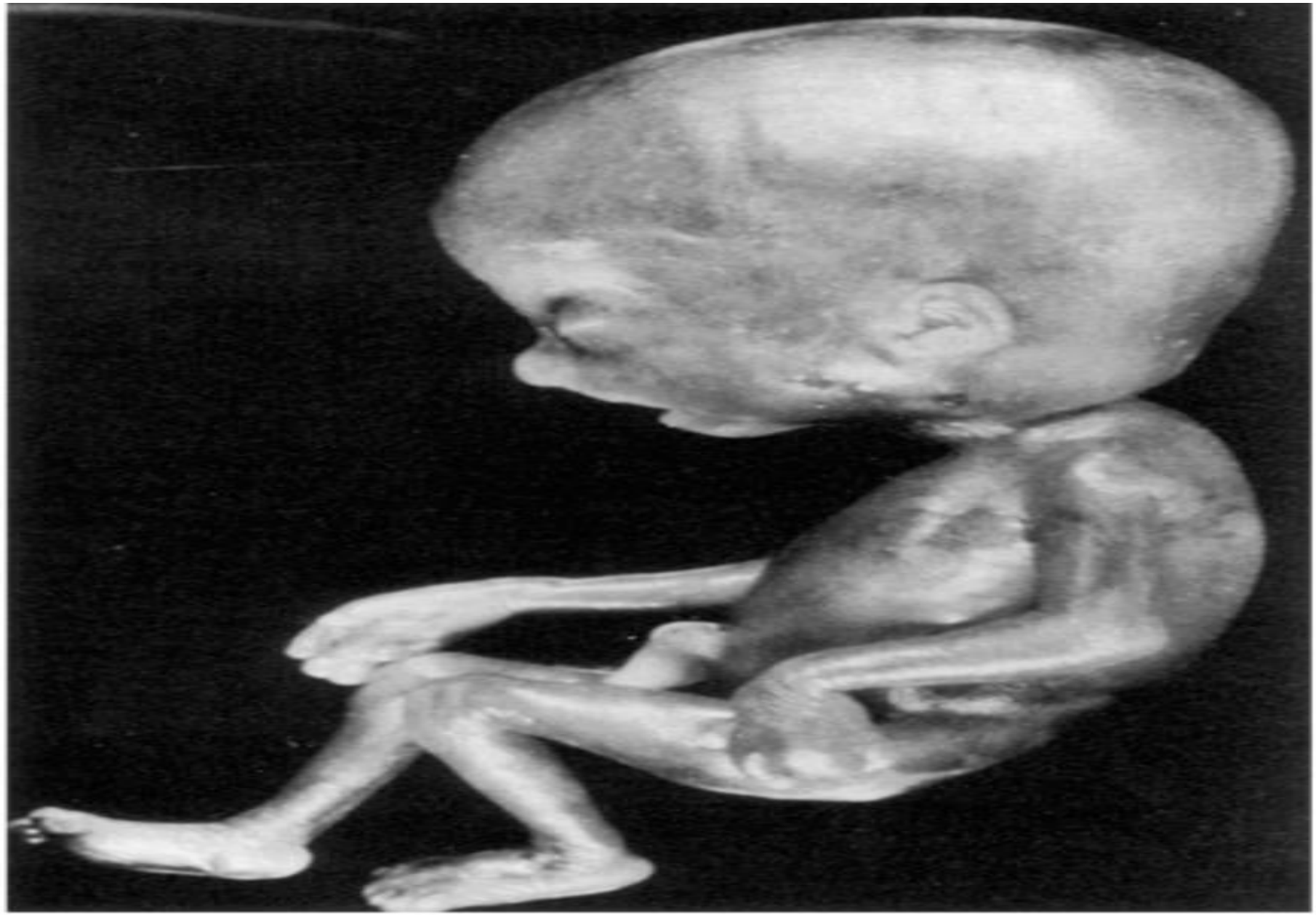
Numerical Abnormalities

Polyploidy

- *Polyploidy is the addition of **an extra haploid set** or **sets of chromosomes** (i.e., 23) to the **normal diploid set of chromosomes** (i.e., 46)*

A. Triploidy

- *is a condition in which cells contain 69 chromosomes*
- *The most common type of polyploidy is **triploidy***
- *Triploid fetuses have severe intrauterine growth retardation with a disproportionately small trunk*
- *Triploidy could result from the second polar body failing to separate from the oocyte during the second meiotic division; **but more likely triploidy results** when an oocyte is fertilized by two sperms (dispermy) almost simultaneously*



Triploid fetus illustrating severe head-to-body disproportion. Triploidy is characterized by a complete extra set of chromosomes. Triploid fetuses account for nearly 20% of chromosomally abnormal miscarriages

- *Triploidy occurs in approximately 2% of embryos, but most of them abort spontaneously*
- *Triploid fetuses account for approximately 20% of chromosomally abnormal miscarriages.*
- *Although triploid fetuses have been born alive, this is exceptional.*
- *These infants all died within a few days because of multiple anomalies and low birth weight*

B *Tetraploidy**:***

- *is a condition in which cells contain **92 chromosomes***
- *Usually due to failure of first mitotic division*
- *chromosomes replicate and divide, but all end up in the same nucleus*
- *Tetraploid embryos abort very early, and often all that is recovered is an empty chorionic sac, which used to be referred to as a "blighted embryo."*

Aneuploidy

- *Aneuploidy is the addition of one chromosome (**trisomy**) or loss of one chromosome **(monosomy)***

➢*Trisomy results in spontaneous abortion of the conceptus*

❖ *However,*

I. trisomy 13 (Patau syndrome),

II. trisomy 18 (Edwards syndrome),

III. trisomy 21 (Down syndrome),

IV. Klinefelter syndrome (47, XXY)

V. And Triple X syndrome (47, XXX) are found in the liveborn population

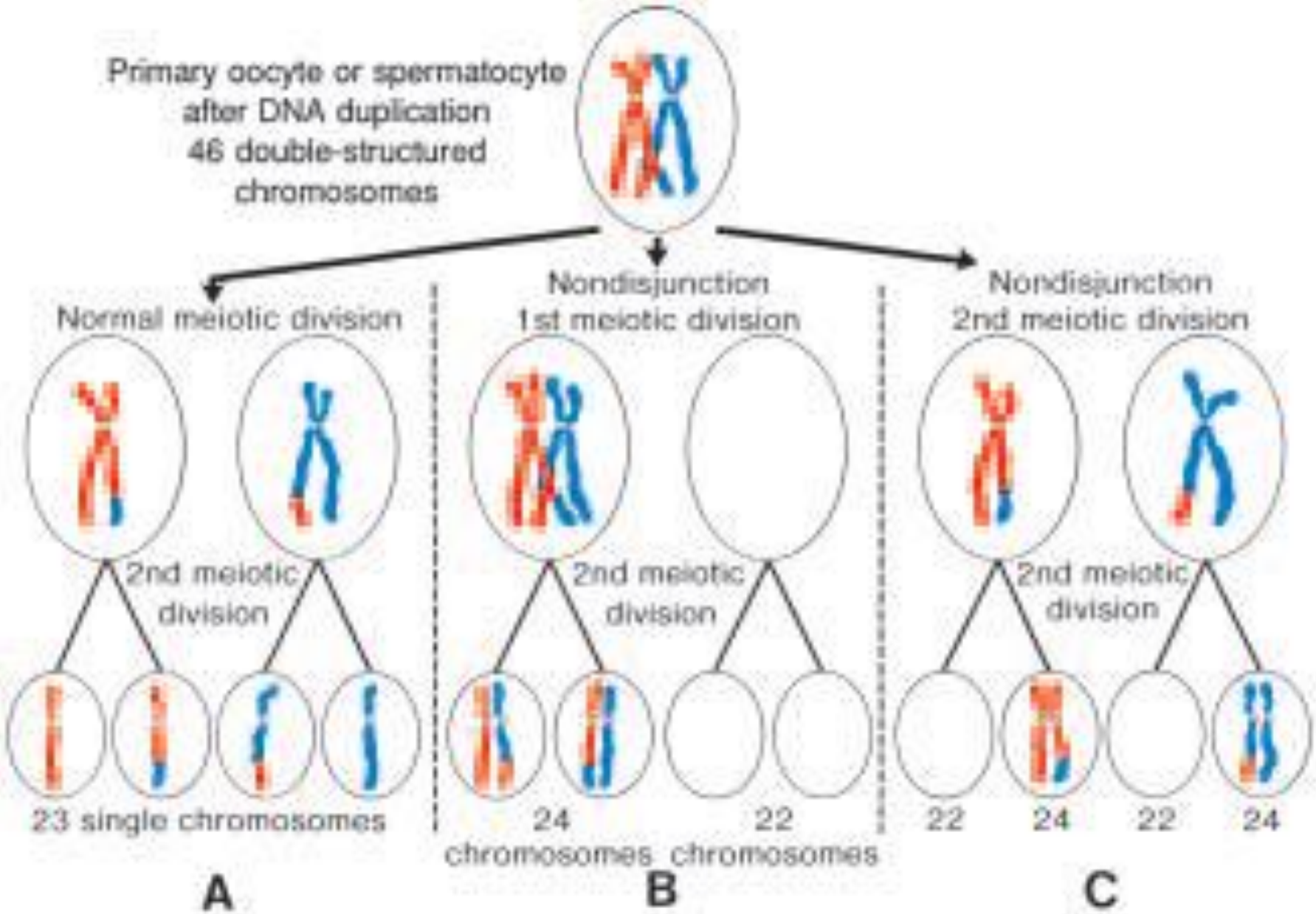
➢*Monosomy also results in spontaneous abortion of the conceptus*

❖ *However, monosomy X chromosome (45,X; Turner syndrome) is found in the liveborn population*

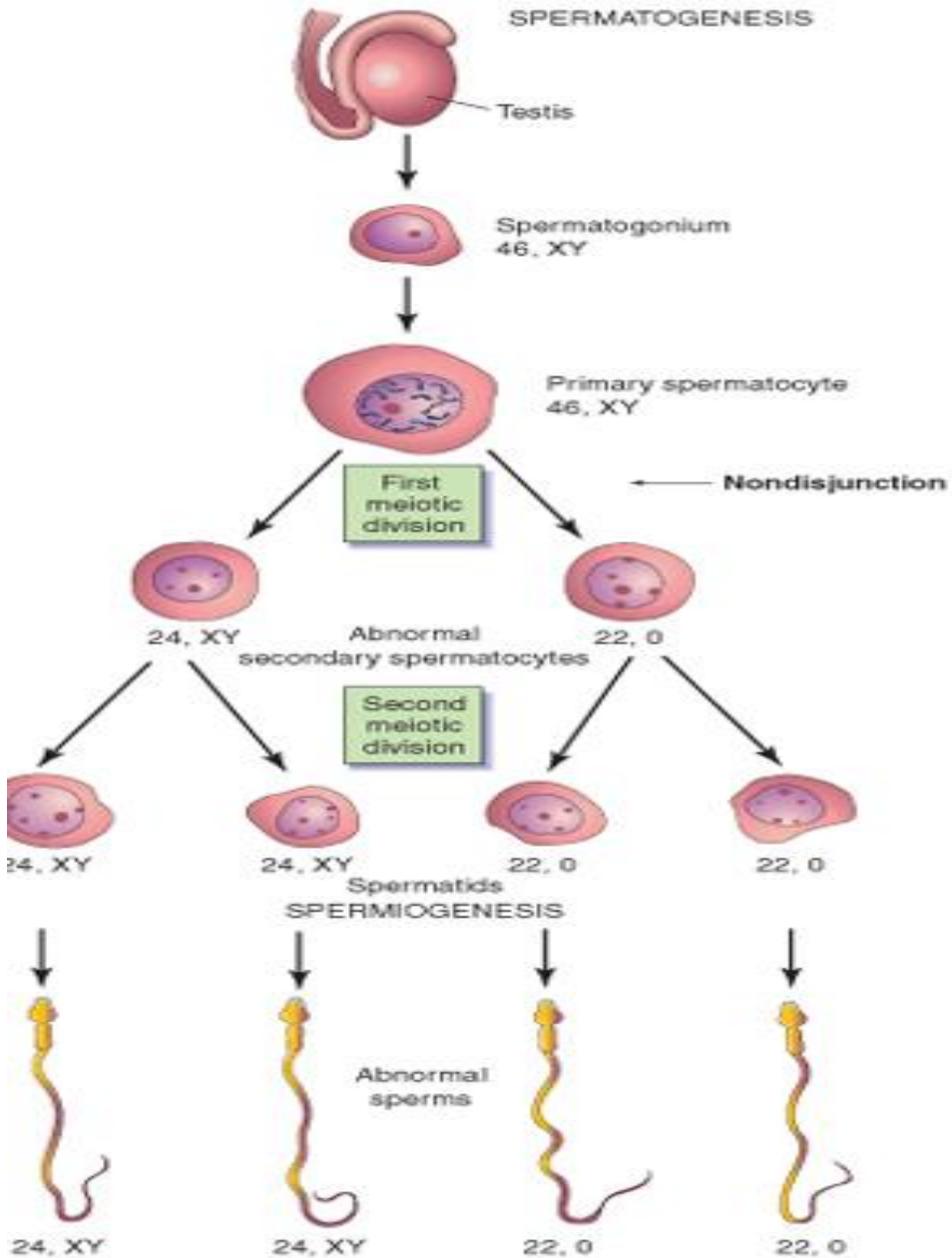
cause

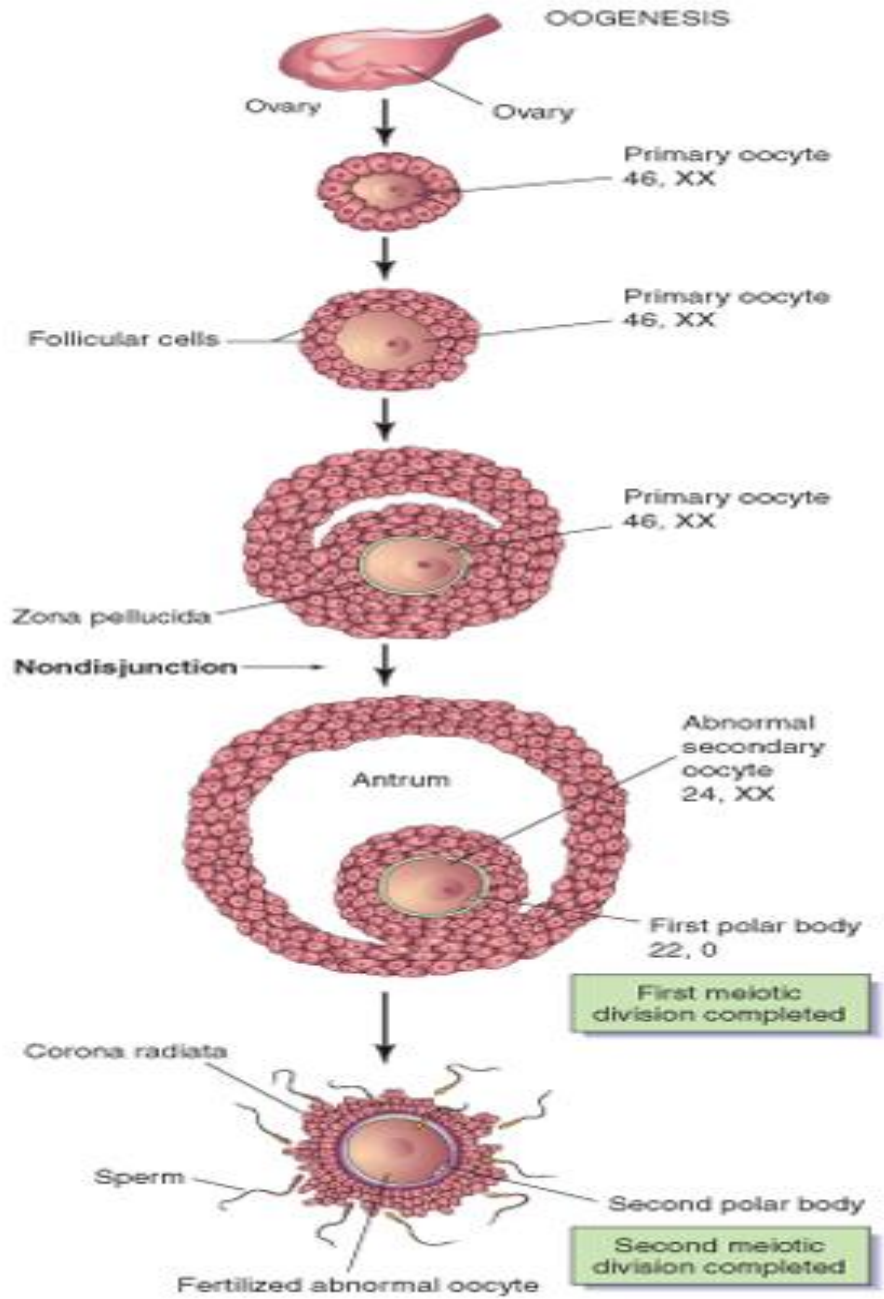
- *Aneuploidy occurs as a result of non-disjunction during meiosis*

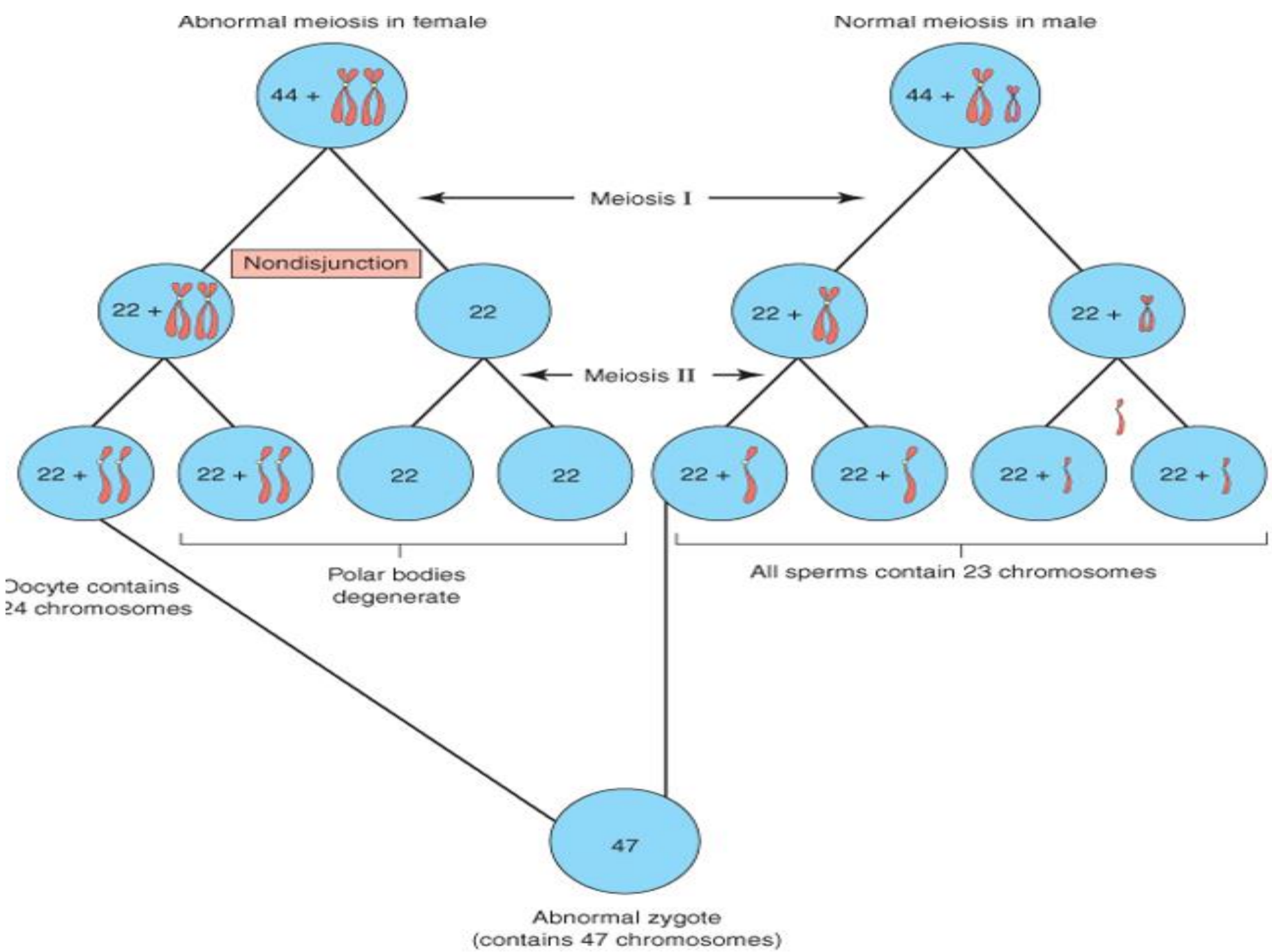
- *In **meiosis, two members of a pair** of homologous chromosomes normally separate during the first meiotic division so that each daughter cell receives one member of each pair*
- *Sometimes, however, separation does not occur (**nondisjunction), and both** members of a pair move into one cell*
- *As a result of nondisjunction of the chromosomes, one cell receives 24 chromosomes, and the other receives 22 instead of the normal 23*
- *When, at fertilization, a gamete having 23 chromosomes fuses with a gamete having 24 or 22 chromosomes, the result is an individual with either **47 chromosomes(trisomy)** or **45 chromosomes (monosomy)***


Primary oocyte or spermatocyte
after DNA duplication
46 double-structured
chromosomes
Normal meiotic division
Nondisjunction
1st meiotic division
Nondisjunction
2nd meiotic division
2nd meiotic
division
2nd meiotic
division
2nd meiotic
division
23 single chromosomes
24
chromosomes
22
chromosomes
22
24
22
24
A
B
C

ABNORMAL GAMETOGENESIS





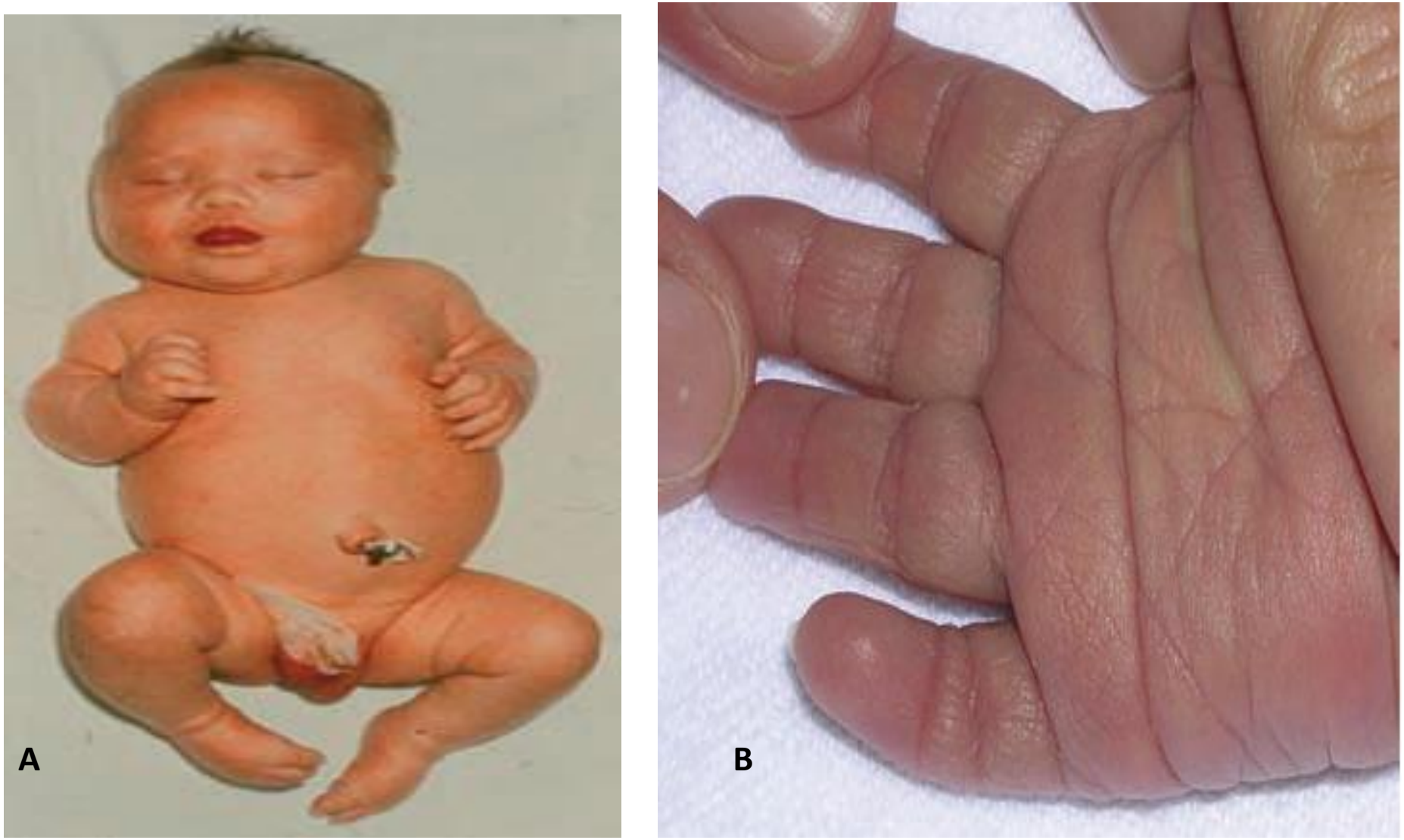

Abnormal meiosis in female
Normal meiosis in male
44 +
44 +
Meiosis I
Nondisjunction
22 +
22
22 +
22 +
Meiosis II
22 +
22 +
22
22
22 +
22 +
22 +
22 +
Polar bodies degenerate
All sperms contain 23 chromosomes
Oocyte contains 24 chromosomes
47
Abnormal zygote (contains 47 chromosomes)

➢ ***Trisomy 21 (Down syndrome)***

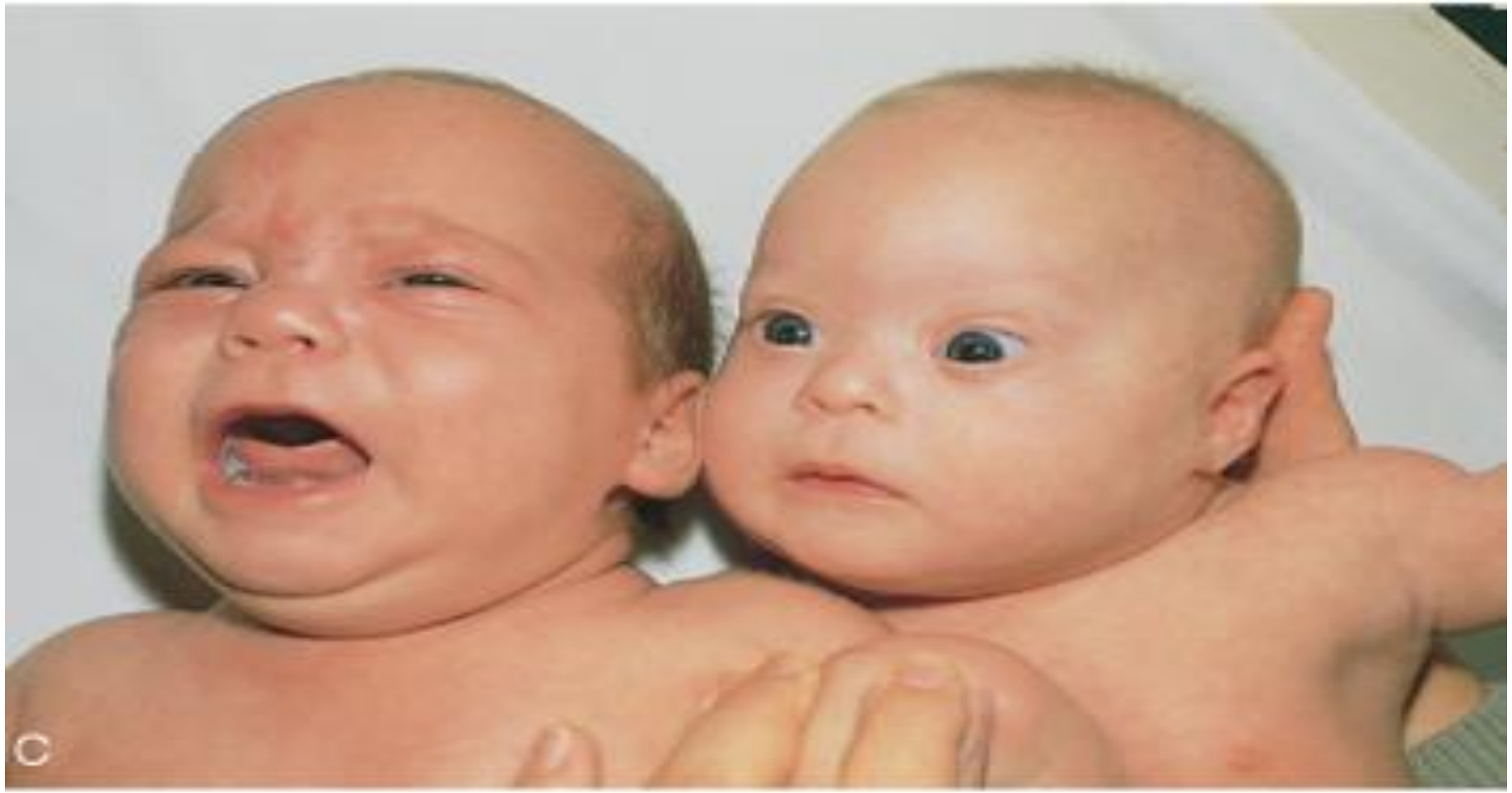
- *Down syndrome is usually caused by an extra copy of chromosome 21 (trisomy21)*

- ***features of children with down syndrome include***

- *Physical growth retardation*
- *varying degrees of mental retardation (Down syndrome IQ is around 50, compared to children without the condition with an IQ of 100 (Mental retardation has historically been defined as an IQ below 70)*
- *craniofacial abnormalities, including upward slanting eyes, epicanthal folds (extra skin folds at the medial corners of the eyes), flat facies, and small ears; protruding tongue, gastroinstestinal abnormalities*
- *cardiac defects; and hypotonia*



(A) Child with Down syndrome, which is characterized by a flat broad face, oblique palpebral fissures (B) broad hand with a single transverse (simian) crease



Anterior view of the faces of *dizygotic male twins* that are discordant for Down syndrome (trisomy 21). The one on the right is smaller and hypotonic compared with the unaffected twin. The twin on the right developed from a zygote that contained an extra 21 chromosome. Note the characteristic facial features of Down syndrome in this infant: upslanting palpebral fissures, epicanthal folds, and flat nasal bridge

- *Single simian crease*
- *high incidences of leukemia,*
- *infections,*
- *thyroid dysfunction,*
- *A short, wide neck: The neck may have excess fat and skin*
- *Short, stocky arms and legs: Some children also have a wide space between the big toe and second toe*
- *Irregular and crooked teeth: Teeth often come in late and not in the same order that other children's teeth come in*
- *Brachycephaly*
- *Clinodactyl of the fifth digit*
- *and premature aging*
- *nearly all develop signs of Alzheimer's disease (progressive mental deterioration manifested by loss of memory) after age 35*
- *Develop behavioral problems associated with ADHD or autism*

Incidence rate

➢The incidence of Down syndrome is approximately

- 1 in 2000 conceptuses for women under age 25
- This risk increases with maternal age to 1 in 300 at age 35
- and 1 in 100 at age 40

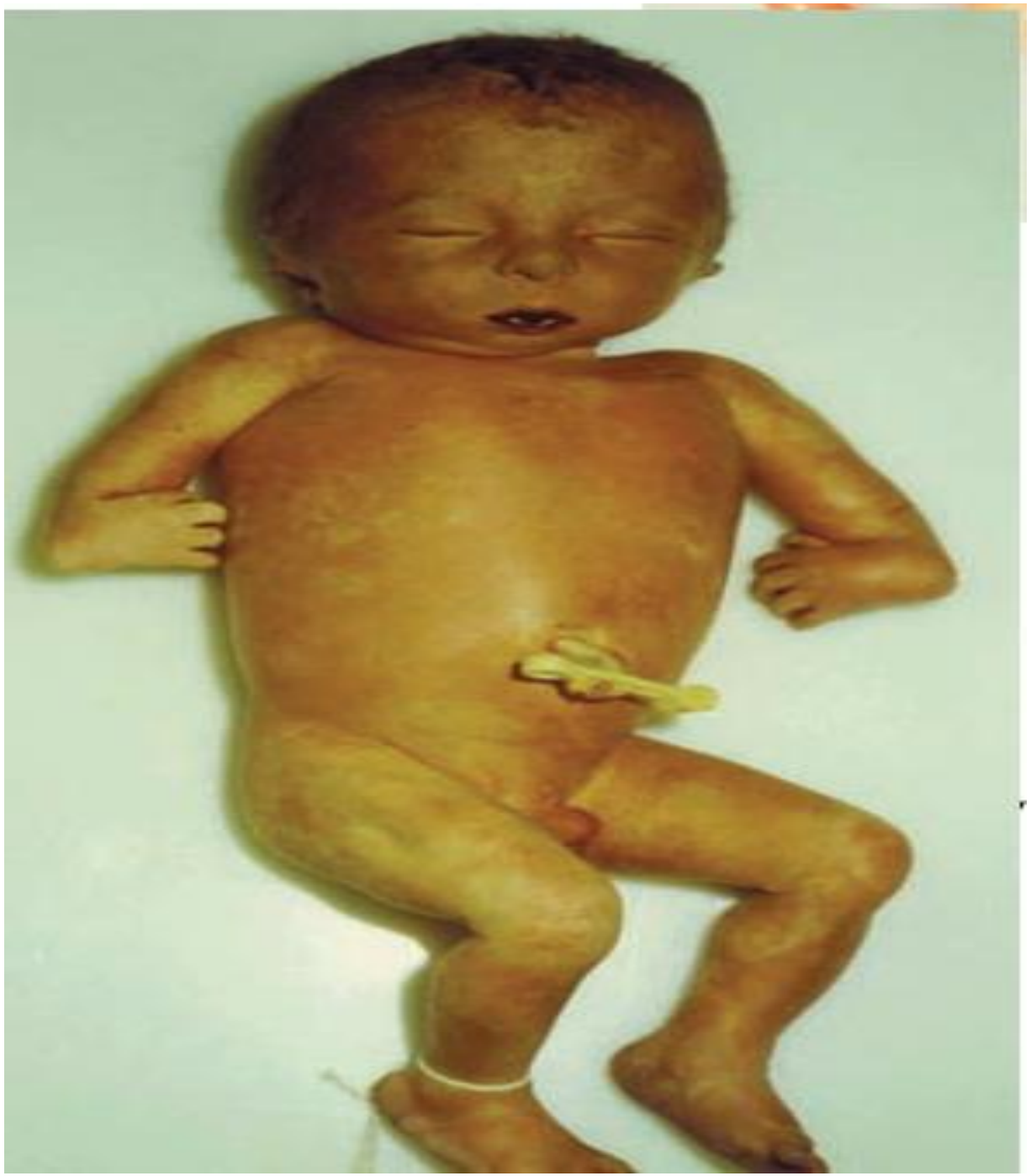
Incidence of Down Syndrome in Newborn Infants

MATERNAL AGE (YEARS)	**INCIDENCE**
• 20-24	1:1400
• 25-29	1:1100
• 30-34	1:700
• 35	1:350
• 37	1:225
• 39	1:140
• 41	1:85
• 43	1:50
• 45+	1:25

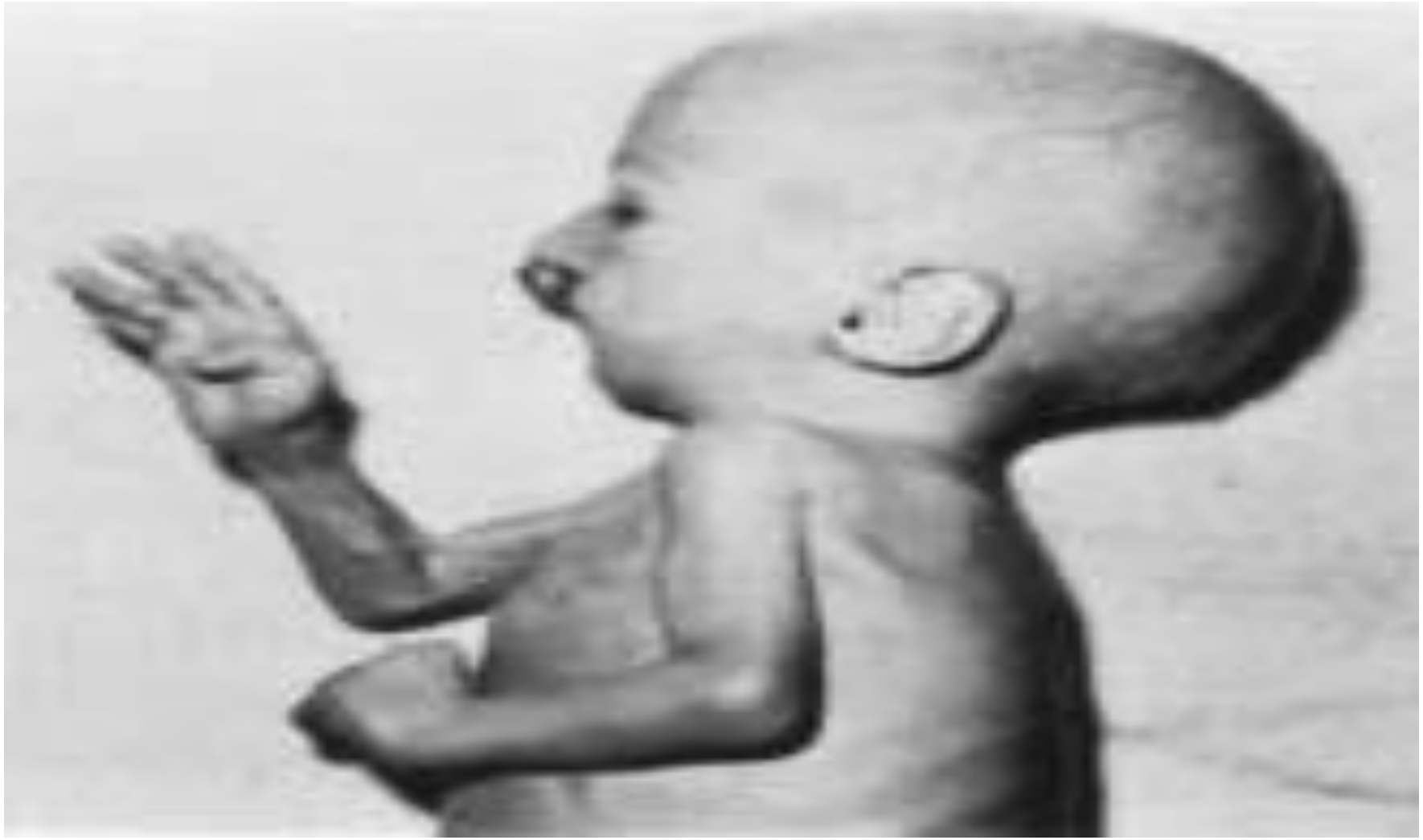
Trisomy 18 *(Edwards syndrome)*

➢ *Patients with trisomy 18 show the following features:*

- *mental retardation,*
- *growth retardation*
- *prominent occiput*
- *congenital heart defects*
- *low-set ears,*
- *flexion of fingers and hands*
- *sheild chest or short and prominent sternum*
- *Micrognathia, cleft lip*
- *renal anomalies , low birth weight*
- *Syndactyly (webbing or fusion of fingers or toes)*
- *malformations of the skeletal system (absent or hypoplasia of the radius and ulna/ deformed hands and feet)*

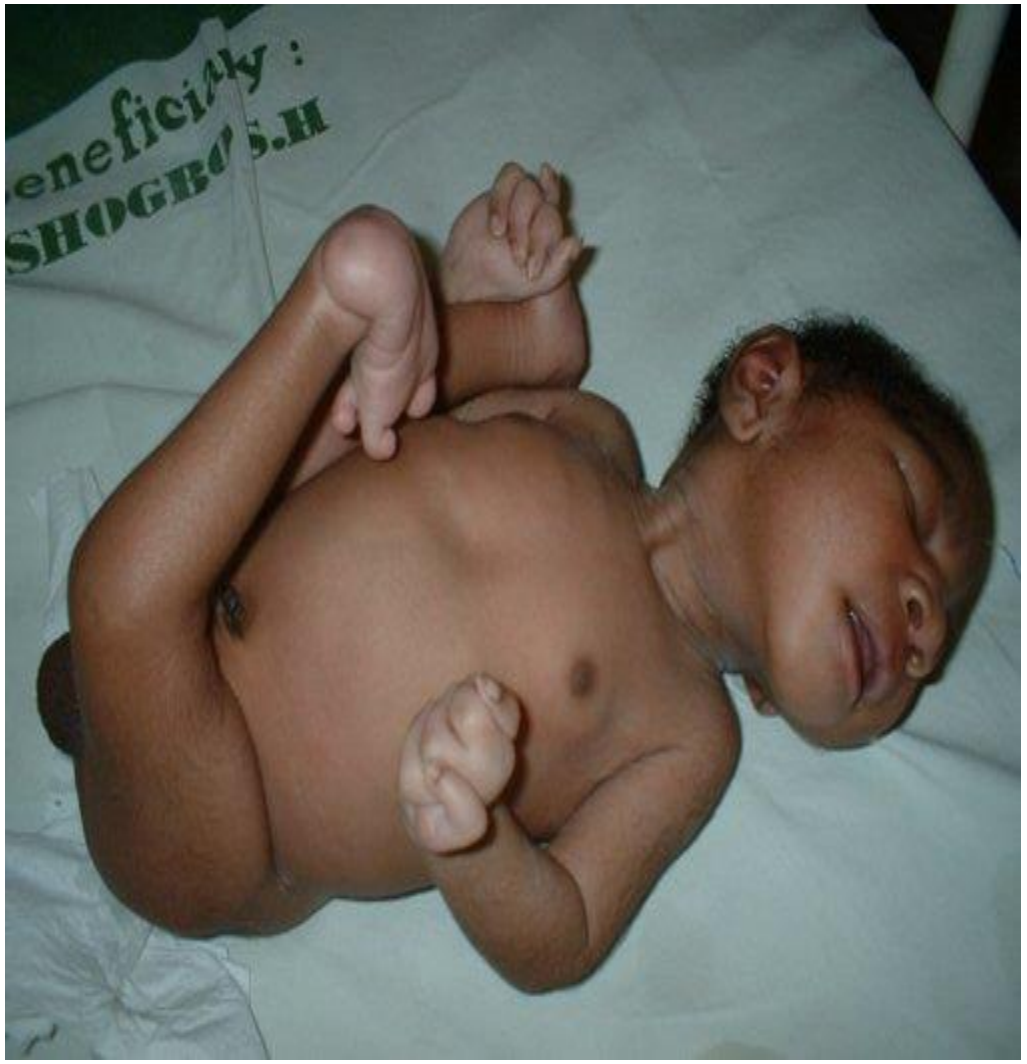


Child with trisomy 18. Note the low sets ears, small mouth, deficient mandible (micrognathia) flexion of the hands, and absent/ or hypoplasia of thr radius and unla



Photograph of child with trisomy 18. Note the prominent occiput, cleft lip, micrognathia, low-set ears, and one or more flexed fingers

CLEFT LIP

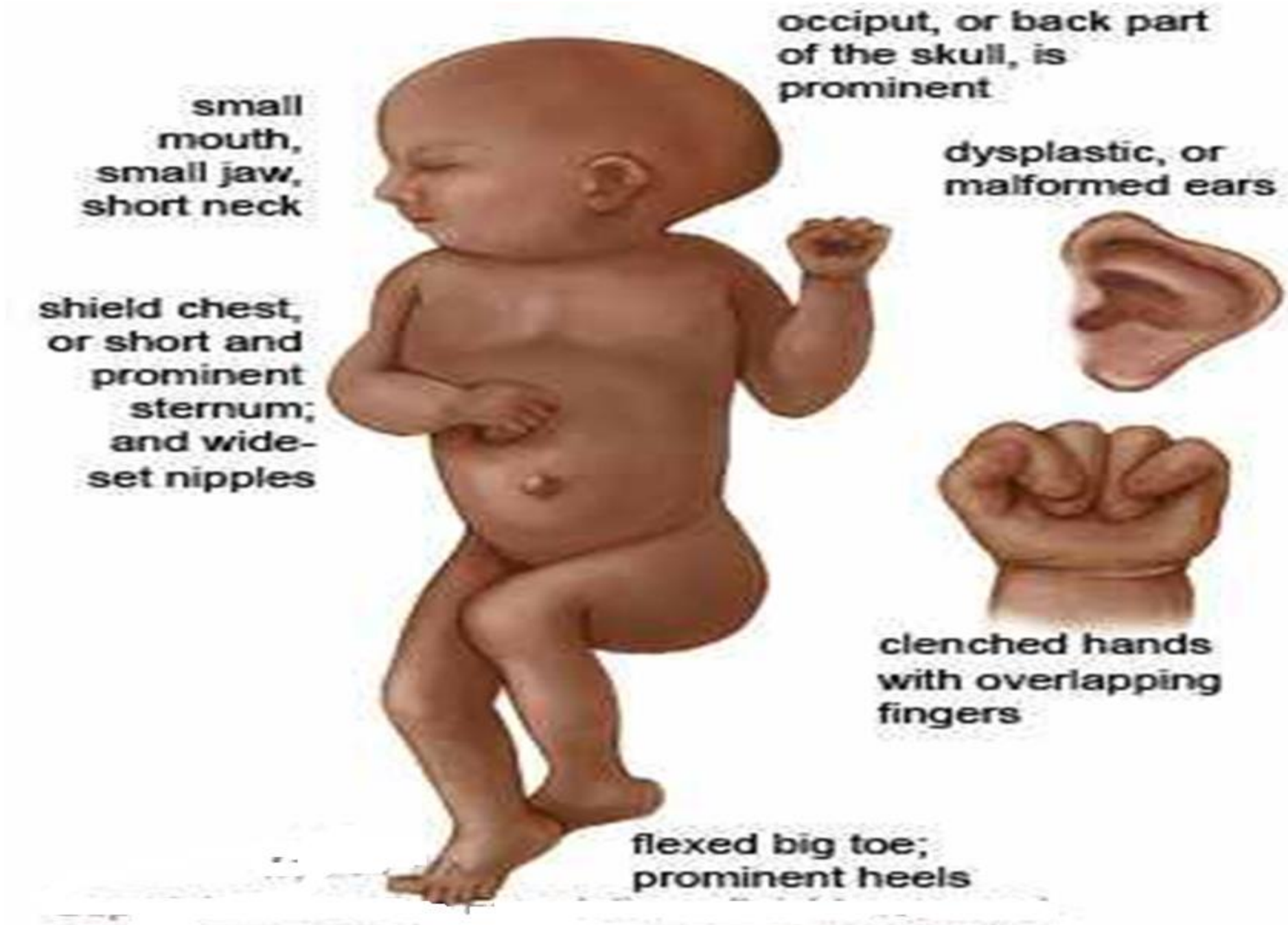


deformed hands and feet

incidence rate

incidence rate of this condition is approximately 1 in 5000 newborns.

- *85% are lost between 10 weeks of gestation*
- *whereas those born alive usually die by age 2 months*
- *Approximately 5% live beyond 1 year*


occiput, or back part of the skull, is prominent
small mouth, small jaw, short neck
dysplastic, or malformed ears
shield chest, or short and prominent sternum; and wide-set nipples
clenched hands with overlapping fingers
flexed big toe; prominent heels

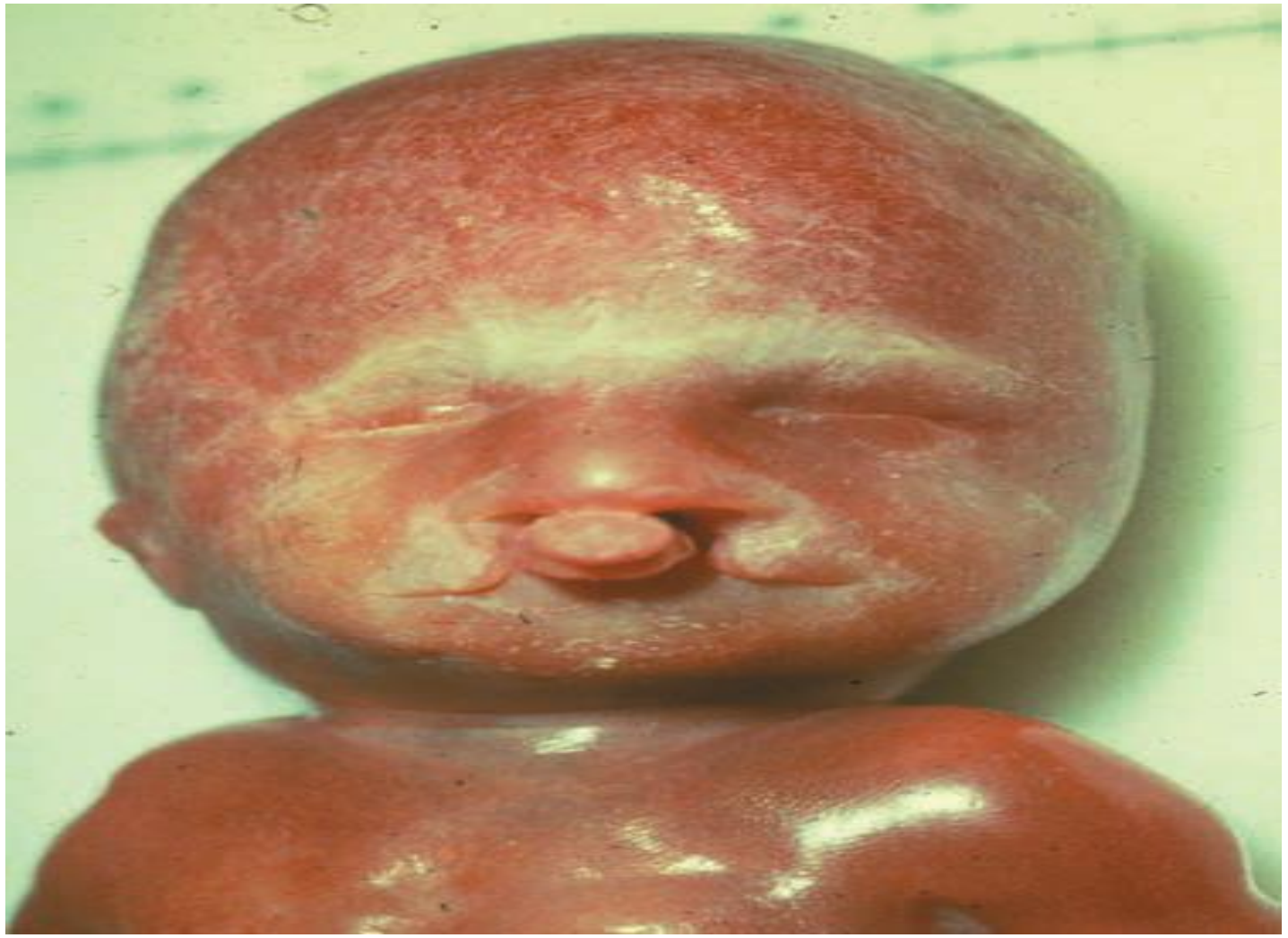
Trisomy 13(Patau syndrome)

➢ *The main abnormalities of trisomy 13 are*

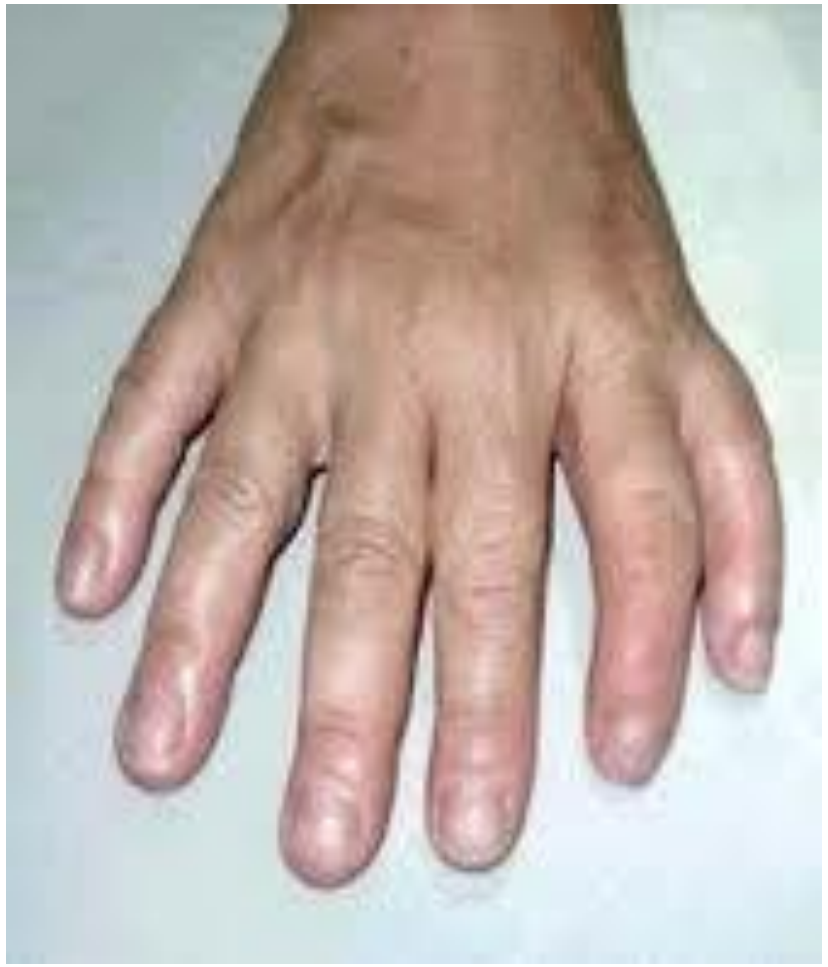
- *mental retardation*
- *severe central nervous system malformations*
- *congenital heart defects*
- *sloping forehead; malformed ears*
- *scalp defects*
- *bilateral cleft lip and/or palate;*
- *Polydactyly (presence of more than 5 digits on hand or foot)*
- *eye defects, such as :*
- *Microphthalmia*
- *anophthalmia (congenital absence of tissue of the eyes)*

Incidence rate

- *The incidence of this abnormality is approximately 1 in 20,000 live births,*
- *over 90% of the infants die in the first month after birth*
- *Approximately 5% live beyond 1 year*



Child with trisomy 13, note the bilateral cleft lip, the sloping forehead, and anophthalmia



Trisomy 13: The syndrome is commonly accompanied by polydactyly

➢ ***Turner syndrome***

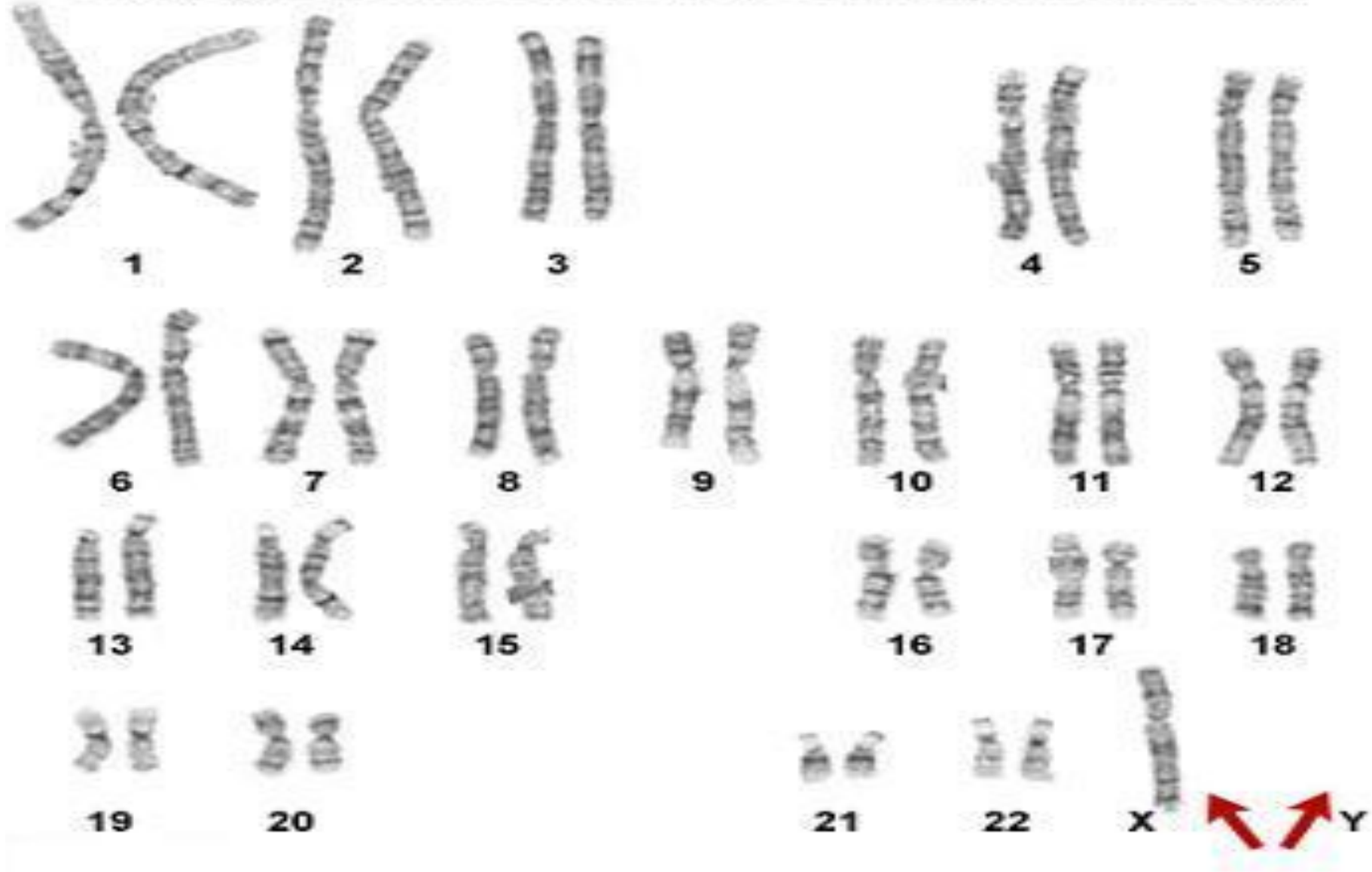
- *Turner syndrome, with a 45,X karyotype, is the only monosomy compatible with life*
- *Even then, 98% of all fetuses with the syndrome are spontaneously aborted*
- *The few that survive are unmistakably female in appearance*
- *Characteritics features are*

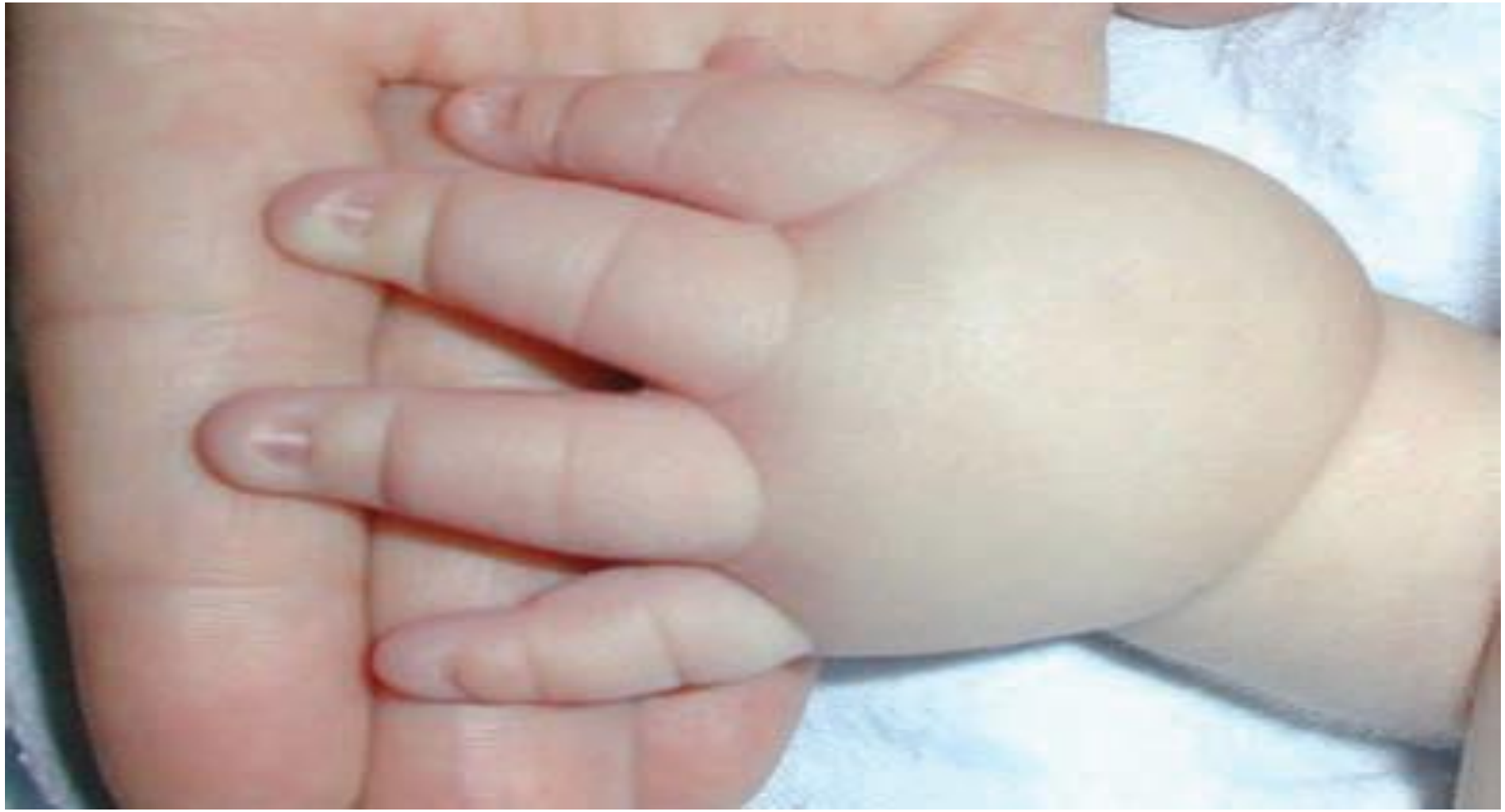
✓*the absence of ovaries (gonadal dysgenesis)*

✓*short stature*

- *Webbed neck*
- *lymphedema of the extremities,*
- *skeletal deformities*
- *and a broad chest with widely spaced nipples*
- *Poor breast development*
- *No menstruation*

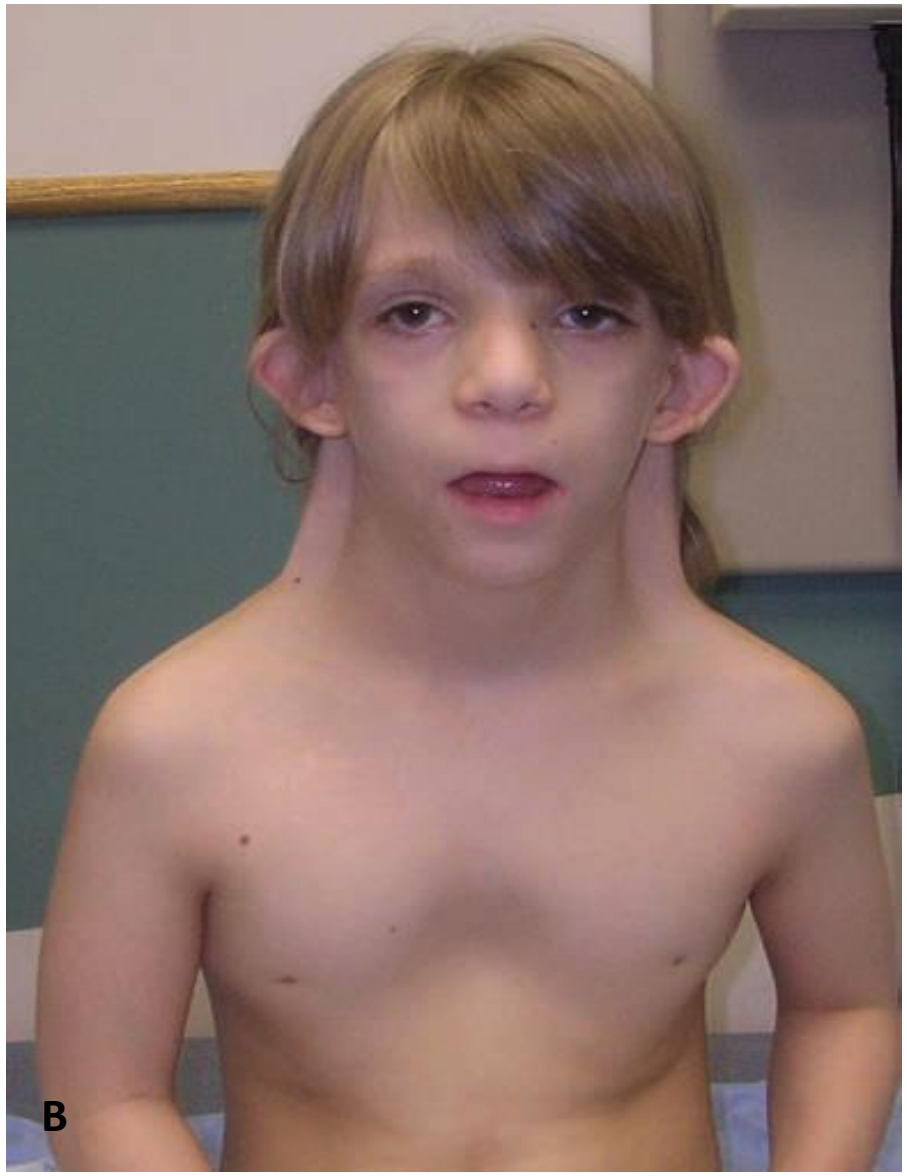
Karyotype From a Female With Turner syndrome (45,X)

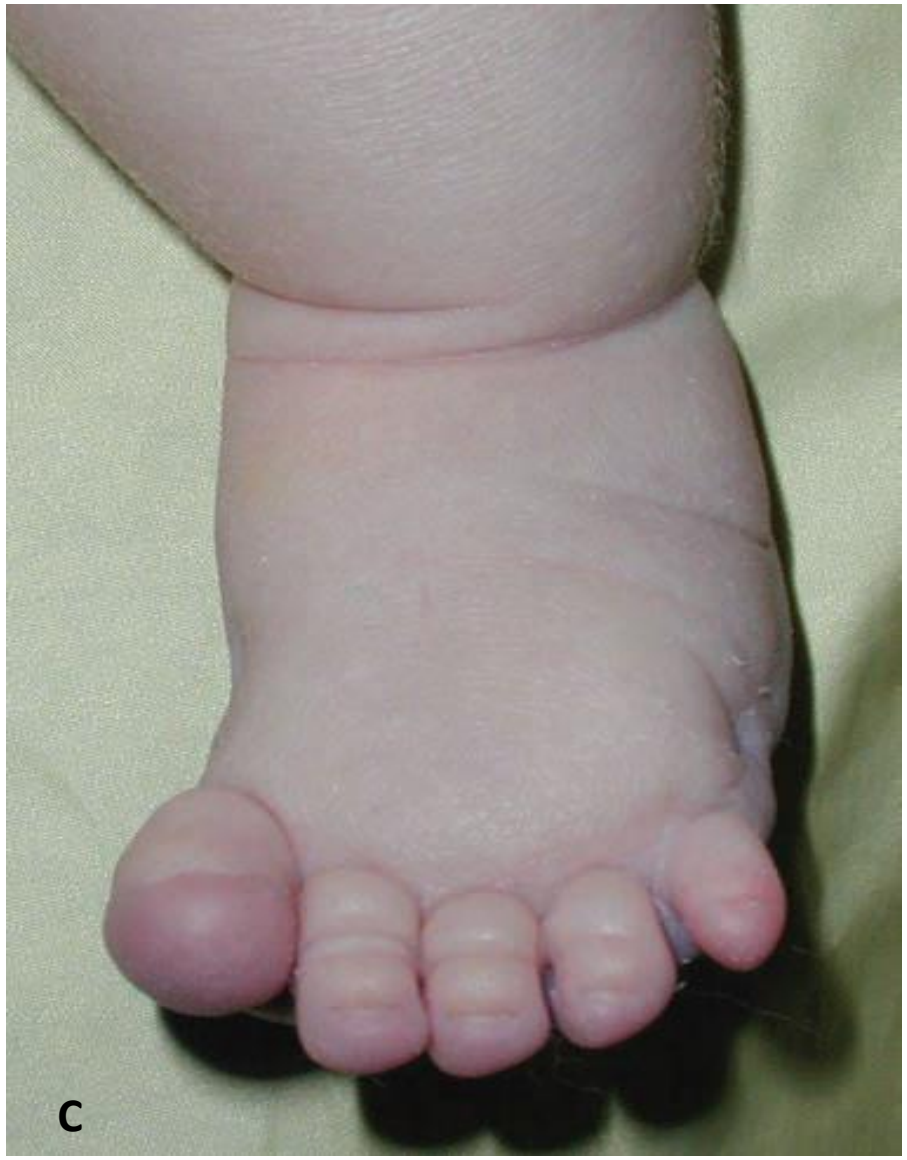




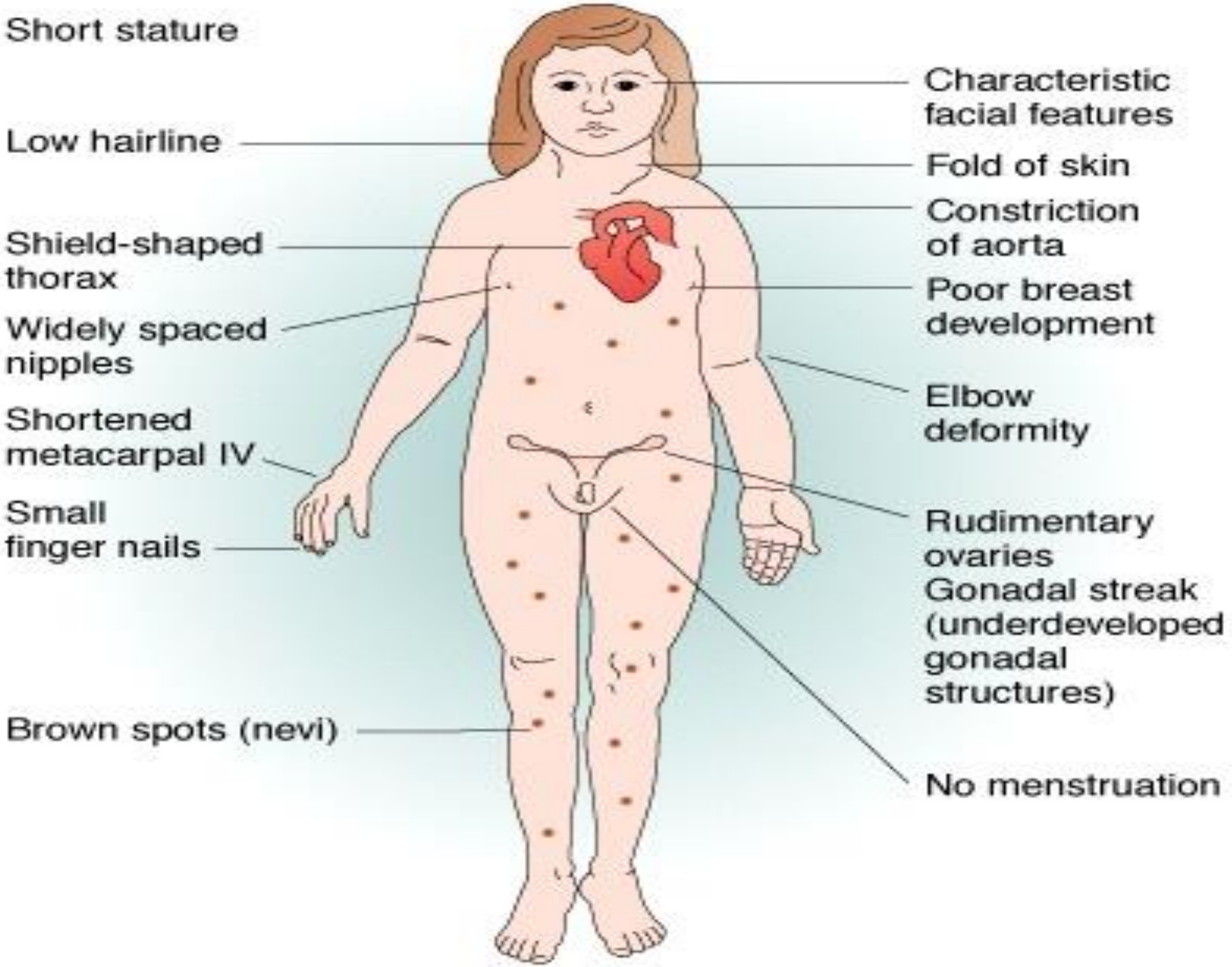
A

Patients with Turners syndrome (A) swelling in the hand





Patients with Turners syndrome (B) prominient webbed neck and widely spaced nipples with a broad chest (C) Caused by lymphedema


Short stature
Low hairline
Shield-shaped thorax
Widely spaced nipples
Shortened metacarpal IV
Small finger nails
Brown spots (nevi)
Characteristic facial features
Fold of skin
Constriction of aorta
Poor breast development
Elbow deformity
Rudimentary ovaries
Gonadal streak (underdeveloped gonadal structures)
No menstruation

Klinefelter's syndrome (47, XXY)

- found only in males
- The non disjucntion of XX homologues is the most causative event

features

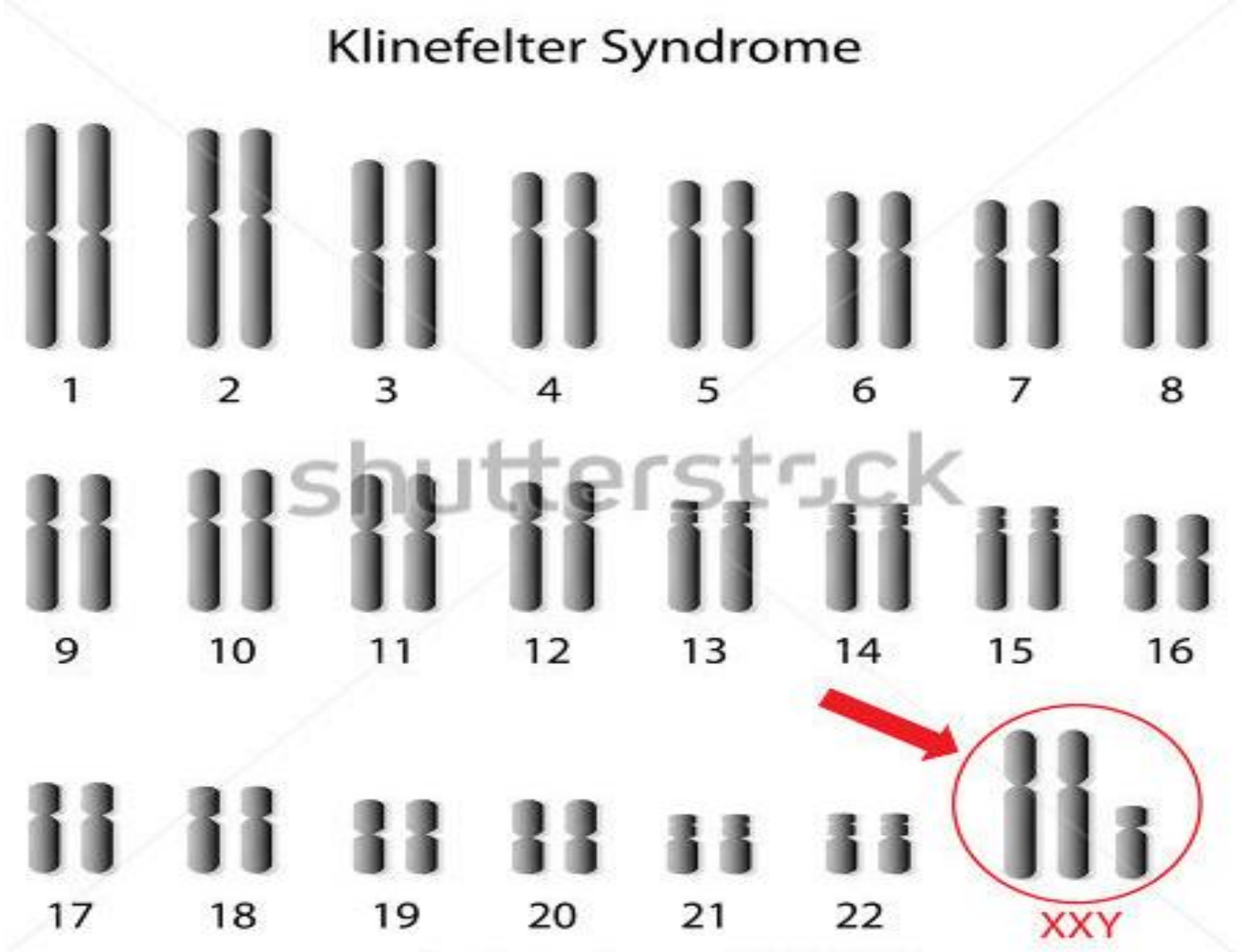
- small testes, narrow shoulders, tendency to grow fewer chest hairs
- hyalinization of seminiferous tubules
- sterility
- often tall with disproportionately long lower limbs
- Intelligence is less than in normal siblings
- Wide hips
- Female type pubic hair pattern
- Approximately 40% of these males have **gynecomastia**

Note: XXY males can have normal sex lives, but they usually make little or no sperm.

Between 95 percent and 99 percent of XXY males are infertile because their bodies don't make a lot of sperm.

- incidence rate:

1 in 500 males


Klinefelter Syndrome
1
2
3
4
5
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9
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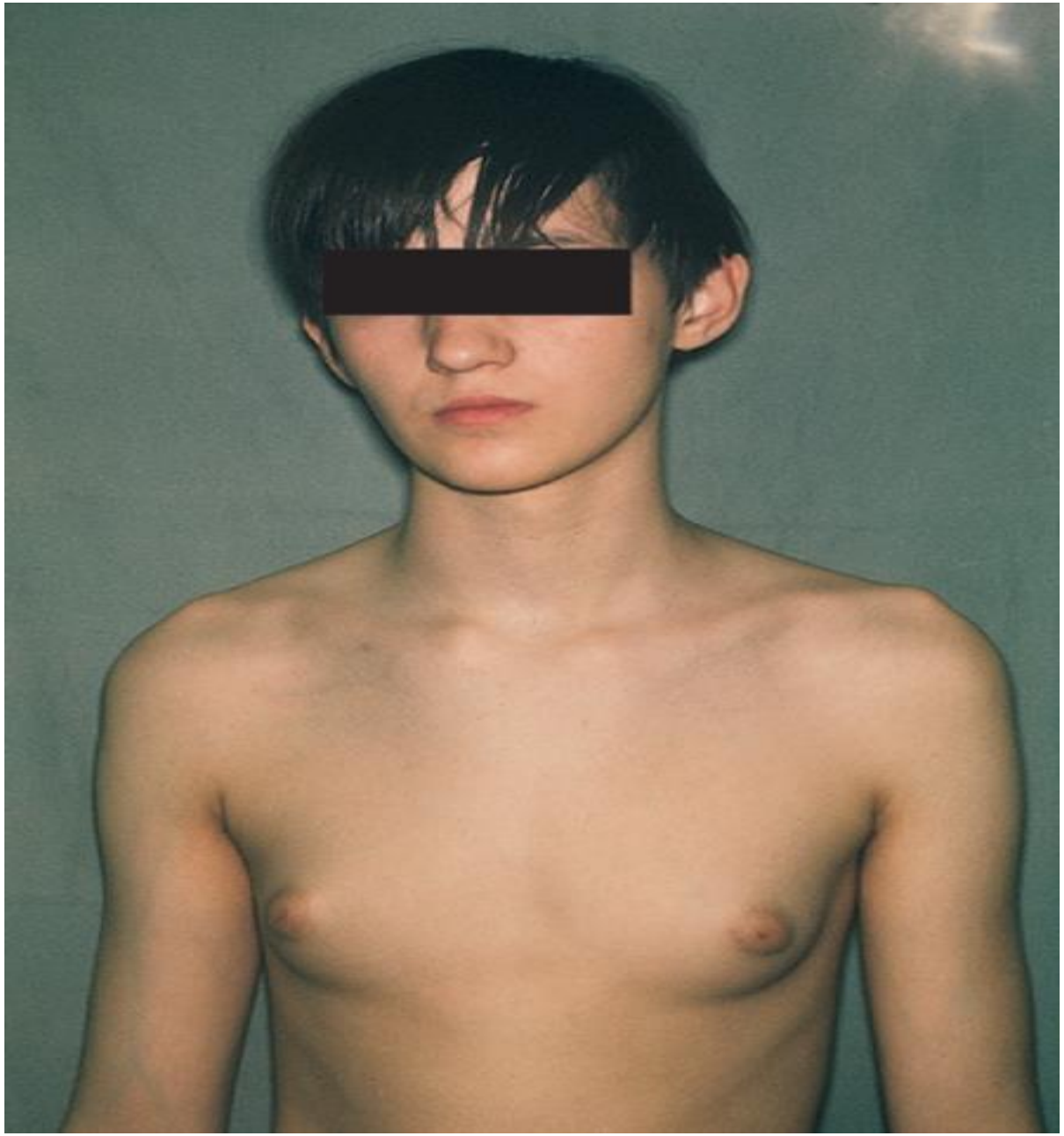
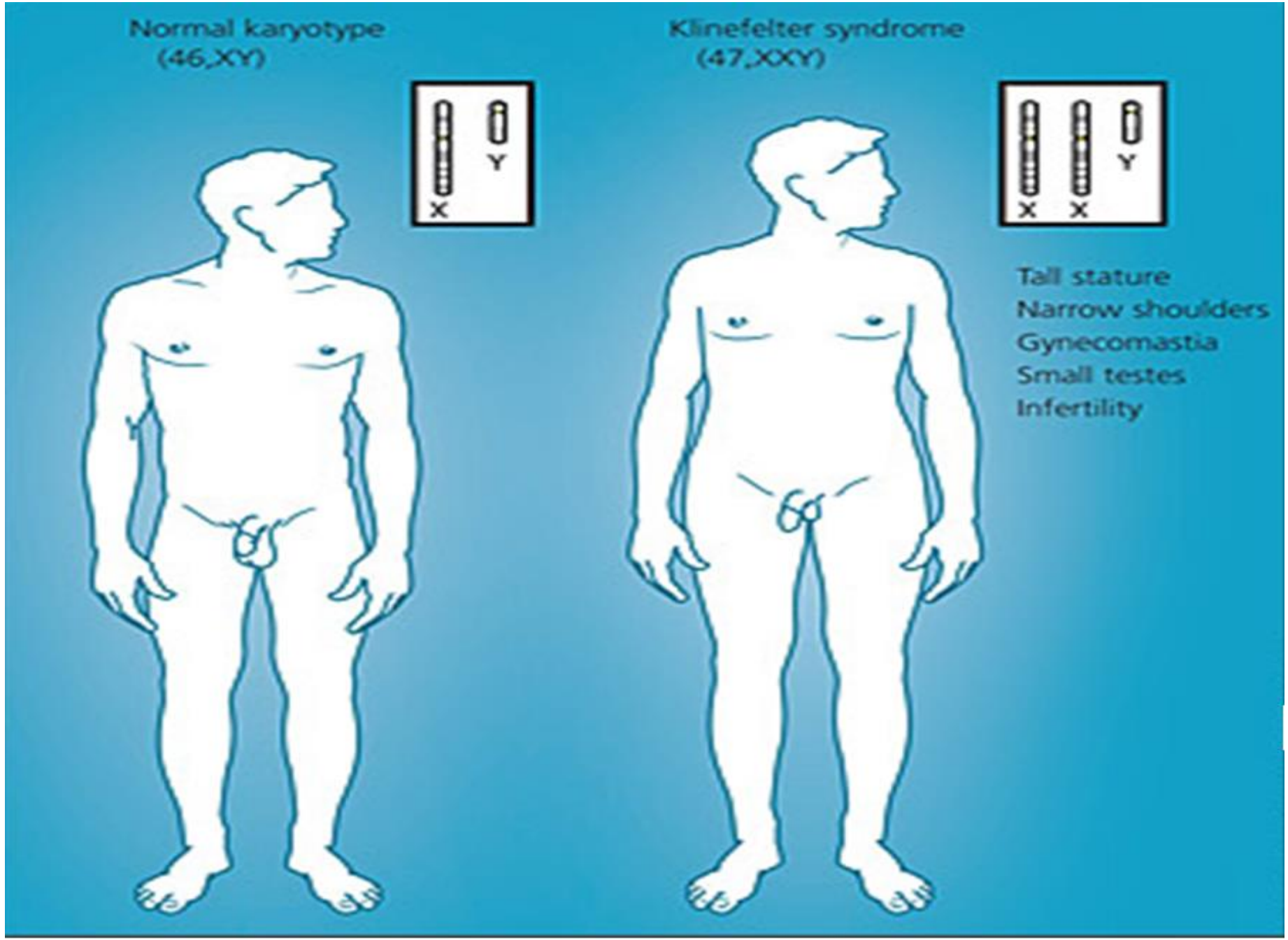
11
12
13
14
15
16
17
18
19
20
21
22
XXY



Adolescent male with Klinefelter's syndrome (XXY trisomy)

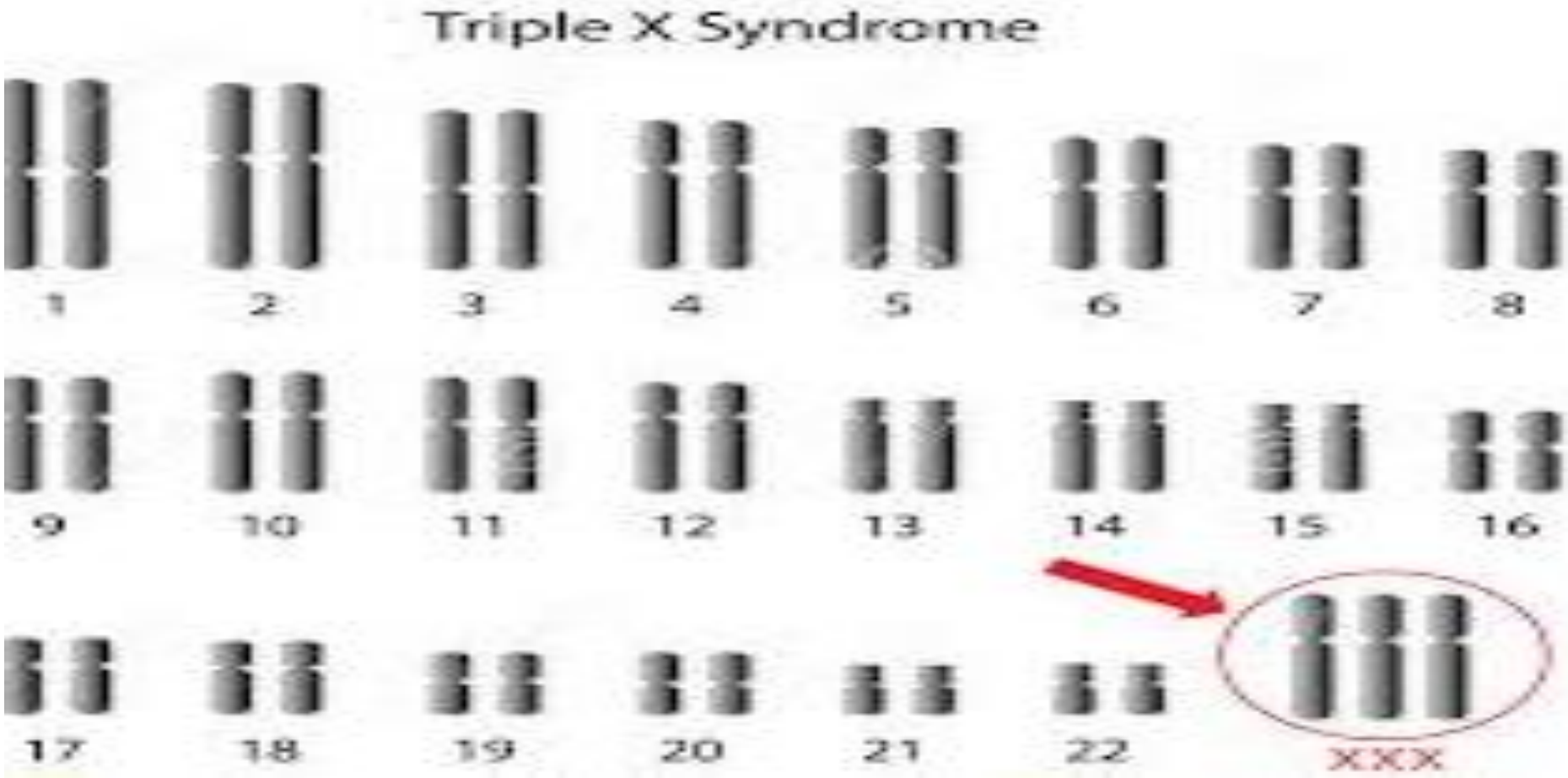
Note the presence of breasts; approximately 40% of males with this syndrome have *gynecomastia* (development of mammary glands) and small testes


Normal karyotype
(46,XY)
X
Y
Klinefelter syndrome
(47,XXY)
X
X
Y
Tall stature
Narrow shoulders
Gynecomastia
Small testes
Infertility


Frontal baldness absent
Tendency to grow fewer chest hairs
Breast development
Female-type pubic hair pattern
Small testicular size
Poor beard growth
Narrow shoulders
Wide hips
Long legs

TRIPLE X SYNDROME (47 XXX)

- Patients with ***triple X syndrome are infantite, with scanty menses and some*** degree of mental retardation
- These girl have frequent problems with speech and self esteem
- They have two sex chromatin bodies in their cells



Structural chromosome abnormalities

Structural chromosome abnormalities

- involve one or more chromosomes usually result from chromosome breakage

Breaks are caused by:

✓Environmental factors, such as viruses, radiation, and drugs

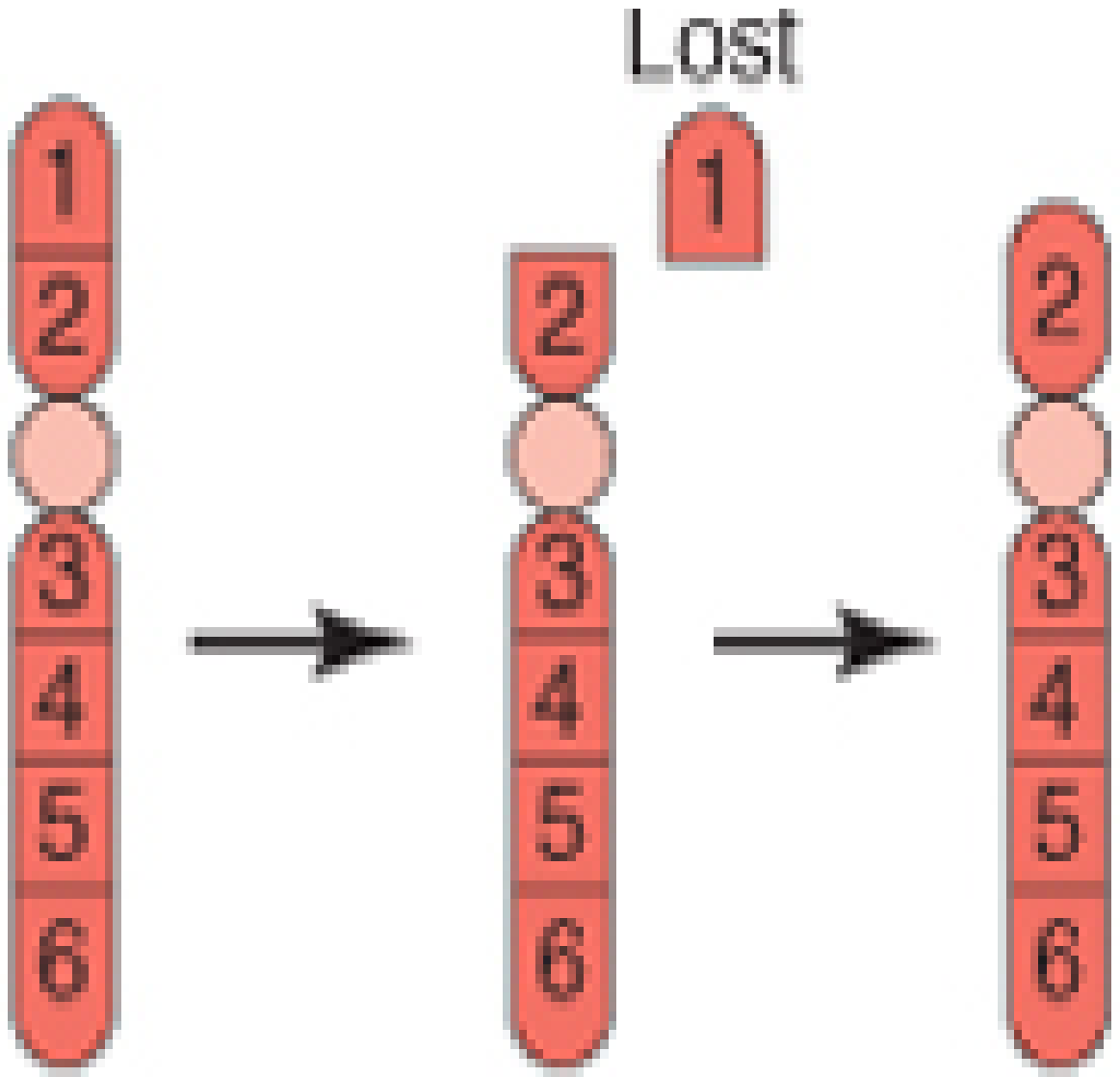
- The result of breakage depends on what happens to the broken pieces
- In some cases, the broken piece of a chromosome is lost, and the infant with **partial deletion** chromosome is **abnormal**
- A well-known syndrome, caused by partial deletion is the **cri-du-chat syndrome**

➢**Cri-du-chat syndrome**

- caused by partial deletion of the short arm of chromosome 5
- children have a catlike cry, microcephaly, mental retardation, and congenital heart disease, poor growth, behavioral problems such as hyperactivity, aggression, tantrums, and repetitive movements;
- unusual facial features which may change over time;
- feeding problems because of difficulty swallowing and sucking

Other features include;

- Downward slant to the eyes
- Low birth weight and slow growth
- Low-set or abnormally shaped ears
- Intellectual disability
- Partial webbing or fusing of fingers or toes
- Single line in the palm of the hand
- Skin tags just in front of the ear
- Slow or incomplete development of motor skills
- Small head (microcephaly)
- Small jaw (micrognathia)
- Wide-set eyes (hypertelorism)
- Hypotonia
- excessive drooling (excessive flow of saliva from the mouth)


Lost
1
2
3
4
5
6
1
2
3
4
5
6
2
3
4
5
6

Microdeletions

Microdeletion: Loss of a tiny piece that may be too small to be seen readily through a microscope'from a chromosome

Disorders caused by microdeletions include Angelman, DiGeorge, Prader-Willi, and Williams syndromes.

- This takes place in a few contiguous genes
- This may result in microdeletion syndrome or contiguous gene syndrome
- They can be detected only by high resolution chromosome banding, (high resolution banding allows detection of very small terminal deletions in a number of disorders), , molecular chromosome analysis or DNA analysis

➢Examples of microdeletion include occurs on the long arm of chromosome 15

- if the defect is inherited on the paternal chromosome, it is called ***Prader-Willi syndrome***
- if the defect is inherited on the maternal chromosome , it is called ***Angelman syndrome***

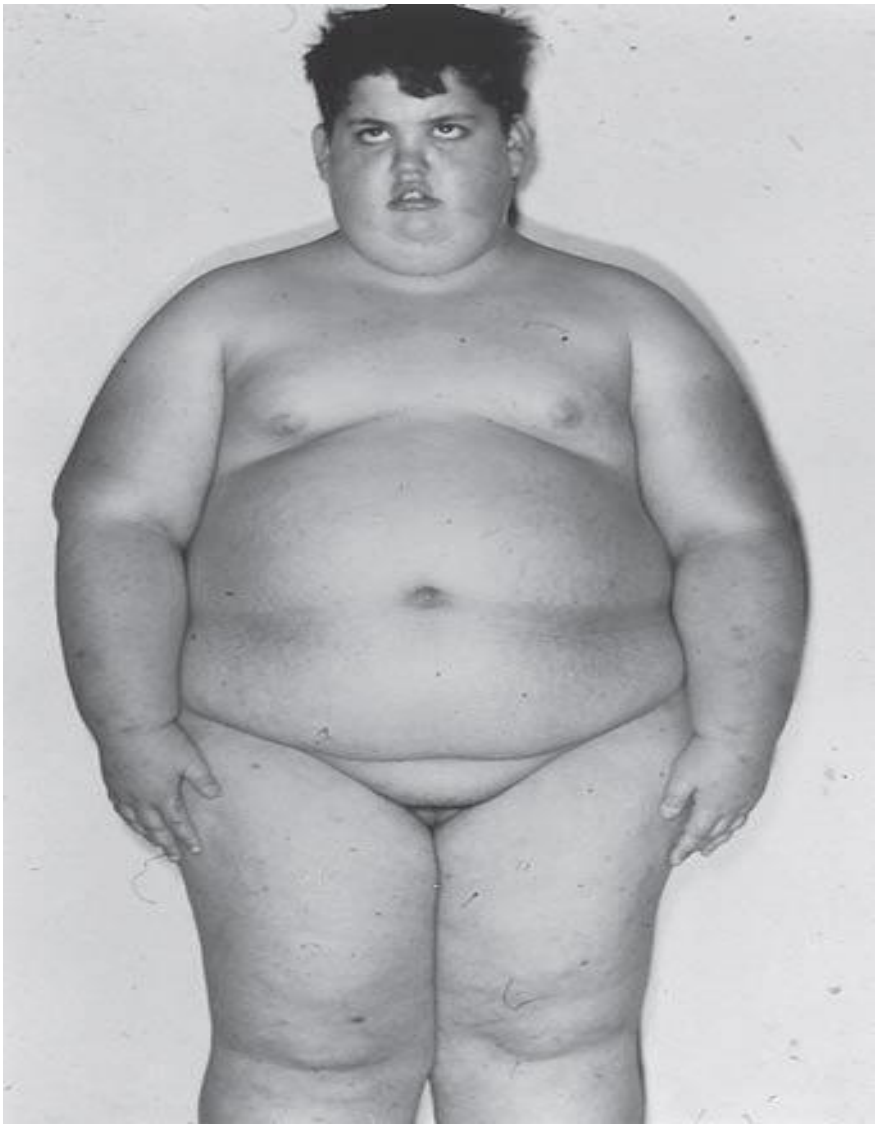
Prader-Willi syndrome

- affected individuals are characterized by hypotonia, obesity, mental retardation, hypogonadism, and cryptorchidism (undescended testes)

Angelman syndrome

- affected individuals are characterized by mentally retardation, inability to speak, exhibition of poor motor development, and are prone to unprovoked and prolonged periods of laughter

Patient with Angelman syndrome resulting from a microdeletion on maternal chromosome 15



Patient with prader willi syndrome resulting from a microdeletion on paternal chromosome 15

William syndrome: developmental disorder that affects many part of the body.

Environmental factors

- *Environmental factors, such as infection and drugs, may simulate genetic conditions*
- *Some of them include:*

Maternal Cigarette Smoking

causes

- Intrauterine growth retardation(IUGR)
- In heavy cigarette smokers premature delivery is twice as frequent as in mothers who do not smoke,
- Low birth weight (<2000 g) is the chief predictor of infant death
- heart defects and limb deficiencies
- may cause urinary tract anomalies, behavioral problems, and decreased physical growth
- **chronic fetal hypoxia** (low oxygen levels) as a result of high level of high levels of carboxyhemoglobin

Thalidomide:

Causes;

- Abnormal development of limbs. Examples are;

✓ meromelia (partial absence) of limbs

✓ amelia (complete absence) of limbs

- facial anomalies
- systemic anomalies; e.g., cardiac and kidney defects

Tetracycline

- Stained teeth
- hypoplasia of enamel

Cocaine

- IUGR
- prematurity
- microcephaly
- cerebral infarction
- urogenital anomalies, neurobehavioral disturbances

Oral contraceptives

- oral contraceptives containing progestogens and estrogens, taken during the early stages of an unrecognized pregnancy, are suspected of being teratogenic agents
- The infants of 13 of 19 mothers who had taken progestogen-estrogen birth control pills during the critical period of development exhibited the **VACTERL syndrome**

The acronym VACTERL stands for

Vertebral

Anal

Cardiac

Tracheal

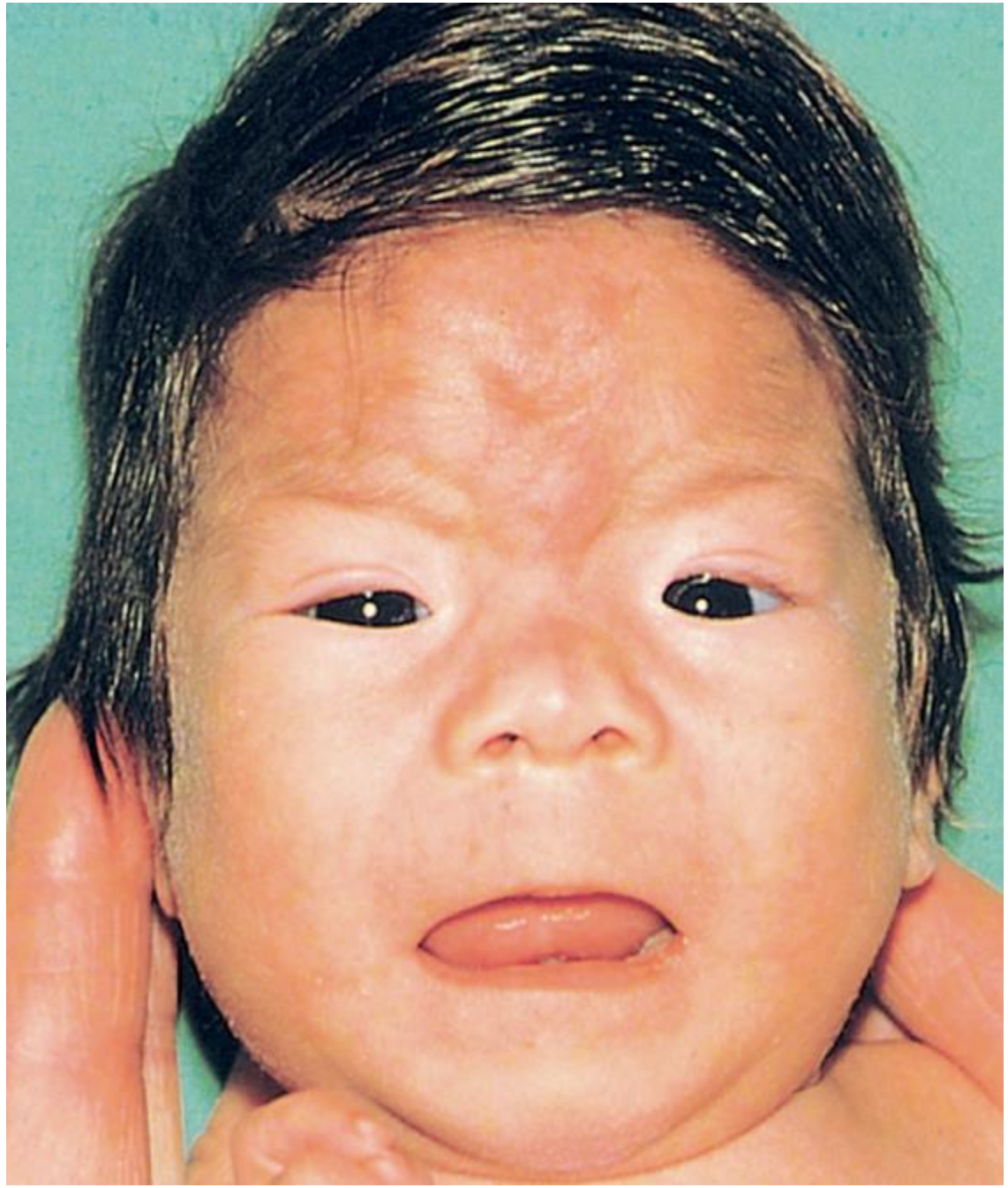
Esophageal

Renal

Limb anomalies

Alcohol

- Both moderate and high levels of alcohol intake during early pregnancy may result in alterations in growth and morphogenesis of the fetus. The greater the intake is, the more severe the signs
- Infants born to chronic alcoholic mothers exhibit ;
- prenatal and postnatal growth deficiency
- mental and other anomalies
- Microcephaly
- short palpebral fissures,
- epicanthal folds, maxillary hypoplasia, short nose, thin upper lip
- abnormal palmar creases, joint anomalies, and congenital heart disease are also present in most infants
- This pattern of anomalies is refered to as **fetal alcohol syndrome** (FAS)



Fetal alcohol syndrome in an infant.

Note the thin upper lip, elongated and poorly formed philtrum (vertical groove in medial part of upper lip), short palpebral fissures, flat nasal bridge, and short nose