Birth Defects and Prenatal Diagnosis

Monday, August 11, 2025 4:58 PM

BIRTH DEFECTS & PRENATAL DIAGNOSIS

Key Terms & Definitions

- Birth defect / congenital malformation / congenital anomaly → *Structural, behavioral, functional, or metabolic disorders present at birth.*
- Teratology → Study of causes, mechanisms, and patterns of abnormal development (*Gr. teratos = monster*).
- Dysmorphology → Clinical study of congenital anomalies; dysmorphologists usually work in clinical genetics departments.

Epidemiology & Significance

- Major structural anomalies: ~3% of liveborn infants.
- Leading cause of infant mortality → ≈ 25% of infant deaths.
- Rank: 5th leading cause of years of potential life lost before age 65.
- Global consistency: Equal frequencies across

ethnicities.

- Disability impact: Major contributor to lifelong disabilities.

Causes of Birth Defects

Cause	% of Cases
Unknown	40–45%
Genetic factors (chromosomal abnormalities, mutant genes)	~28%
Environmental factors	3–4%
Multifactorial inheritance (genetic + environmental)	20–25%
Twinning	0.5–1%

Minor Anomalies

- Occur in ~15% of newborns.
- Examples:

- Microtia (small ears)
- Pigmented spots
- Short palpebral fissures

- Usually harmless but may indicate major defects:
  - 1 minor anomaly → 3% risk of major defect
  - 2 anomalies → 10% risk
  - ≥3 anomalies → 20% risk

- Ear anomalies = strong clue → seen in almost all syndromic malformations.

Types of Abnormalities

1. Malformations
   - Occur during formation of structures (organogenesis).
   - May cause complete/partial absence or altered configuration.
   - Causes: environmental and/or genetic factors.
   - *High-yield fact*: Most originate during 3rd–8th weeks of gestation.

2. Disruptions
   - Alteration of already formed structures due to destructive processes.

- Examples:
  - Vascular accidents → transverse limb defects
  - Amniotic bands → constrictive defects

3. Deformations

- Caused by mechanical forces over prolonged periods.
- Example: Clubfoot from uterine compression.
- Often musculoskeletal; may be reversible postnatally.

4. Syndrome

- Group of anomalies with a known common cause.
- Risk of recurrence known.
- *Example*: Down syndrome.

5. Association

- Nonrandom occurrence of ≥2 anomalies without known cause.
- Example: VACTERL association *(Vertebral, Anal, Cardiac, Tracheoesophageal, Renal, Limb anomalies)*.
- Recognition helps search for other anomalies in the group.

Environmental Factors in Birth Defects

- Before 1940s → Believed mostly hereditary.
- 1941 – Rubella discovery (N. Gregg): Maternal rubella early in pregnancy → congenital defects.
- 1961 – Thalidomide disaster (W. Lenz): Sedative → limb defects; showed drugs can cross placenta and cause malformations.
- Teratogens = environmental agents causing birth defects (e.g., infections, drugs, chemicals, radiation, hyperthermia, maternal diseases).

Exam Tip / Key Points to Remember

- 3rd–8th weeks = most sensitive period for structural malformations.
- Minor anomalies are important diagnostic clues for hidden major defects.
- Ear anomalies often point toward syndromic conditions.
- Multifactorial inheritance accounts for a large proportion → important in counseling.

- Always distinguish between:
    - Malformation (developmental failure)
    - Disruption (destruction of formed tissue)
    - Deformation (mechanical force)

Principles of Teratology

Teratology studies how environmental agents (teratogens) cause abnormal development. The following principles determine whether and how a teratogen will cause a birth defect:

1. Genotype–Environment Interaction

- Susceptibility depends on:
    - Genotype of conceptus → how its genetic makeup interacts with environmental factors.
    - Maternal genome → influences drug metabolism, infection resistance, biochemical pathways.
- *Key point*: The same teratogen can cause severe damage in one conceptus but minimal/no effect in another due to genetic differences.

2. Timing of Exposure

- Most sensitive period = 3rd–8th weeks (embryogenesis/organogenesis).

- Organ systems have specific susceptibility windows:

    - Cleft palate can be induced:
        - Day 6 – blastocyst stage
        - Day 14 – gastrulation
        - 5th week – early limb bud stage
        - 7th week – palatal shelf formation

- *Key point*: No stage is completely safe — defects may occur before (e.g., gametogenesis, preimplantation) or after embryogenesis.

3. Dose–Duration Relationship

- Severity of abnormality increases with higher dose or longer duration of teratogen exposure.

- *Exam tip*: Dose threshold varies for different teratogens.

4. Specific Mechanisms of Action

- Teratogens disrupt development via specific molecular/cellular mechanisms:

    - Inhibiting a biochemical pathway

- Inducing cell death
- Reducing cell proliferation
- Altering cell migration/differentiation

- This disruption leads to abnormal pathogenesis → structural or functional defects.

5. Possible Outcomes of Teratogenesis

- Death
- Malformation
- Growth retardation
- Functional disorders (e.g., cognitive impairment, sensory deficits)

Infectious Agents as Teratogens (High-Yield for Exams)

Remember TORCH group (Toxoplasma, Other [syphilis, varicella, parvovirus], Rubella, CMV, Herpes)

Rubella Virus

- Causes Congenital Rubella Syndrome → previously a major cause of defects.

- Vaccine programs have almost eliminated CRS in many countries.

Cytomegalovirus (CMV)

- Most common viral teratogen.
- Mother often asymptomatic.
- Effects:
    - Severe illness at birth → sometimes fatal.
    - Delayed-onset: hearing loss, visual impairment, intellectual disability.
- *Key fact*: CMV can be symptomatic or silent at birth but still cause late damage.

Herpes Simplex Virus (HSV)

- Teratogenic cases are rare.
- Transmission usually during delivery → severe neonatal illness, possible death.

Varicella (Chickenpox)

- Intrauterine infection → skin scarring, limb hypoplasia, eye and CNS defects.
- Risk depends on timing:
    - Infection before 13 weeks → 0.4% risk of malformation.

    - Infection 13–20 weeks → risk rises to 2%.

- Later pregnancy infections less likely to cause anomalies but can cause neonatal varicella.

Exam Pointers

- Always link timing of teratogen exposure to the specific anomaly (especially in MCQs/SAQs).
- CMV = most common viral cause of congenital defects.
- Varicella timing risk % is a favorite MCQ.
- Know that dose, duration, and timing together determine teratogenic impact.

Other Viral Infections & Hyperthermia

Non-teratogenic Viral Infections

- Measles, mumps, hepatitis (A, C, E), poliomyelitis, echovirus, coxsackie virus, influenza:
    - No direct malformations, but can cause:
        - Spontaneous abortion
        - Fetal death
        - Neonatal infection

- Coxsackie B virus → ↑ spontaneous abortion.
- Measles & mumps → ↑ early & late fetal death, neonatal measles/mumps.
- Hepatitis B → high transplacental transmission → fetal/neonatal hepatitis.
- Hepatitis A, C, E → rarely transmitted to fetus.
- Echoviruses → no adverse fetal effects.
- Vaccinations for these viruses → no evidence of fetal harm.

Hyperthermia

- Cause: Fever (pyrogenic infections) or external heat (hot tubs, saunas).
- Teratogenic effect: Disrupts neurulation → Neural tube defects (NTDs) like:
    - Anencephaly
    - Spina bifida
- *High yield*: NTD risk especially high in early embryogenesis.

Toxoplasmosis (Protozoan: *Toxoplasma gondii*)

- Sources:
  - Poorly cooked meat
  - Cat feces
  - Contaminated soil
- Classic fetal feature: Cerebral calcifications.
- Other possible features at birth:
  - Microcephaly / Macrocephaly
  - Hydrocephalus
- Later complications (even if normal at birth):
  - Visual impairment
  - Hearing loss
  - Seizures
  - Intellectual disability
- *Similar to CMV* in late-onset effects.

Radiation as a Teratogen

- Mechanism: Kills rapidly dividing cells → can cause virtually any defect depending on dose and stage.

- Sources:
    - Medical imaging (high dose)
    - Nuclear explosions
    - Reactor accidents (e.g., Chernobyl)
- Hiroshima & Nagasaki survivors (pregnant women):
    - 28% → spontaneous abortion
    - 25% → child died in 1st year
    - 25% → severe CNS defects
- Chernobyl → large regional increase in birth defects.
- Also mutagenic → genetic alterations in germ cells → future malformations.

Pharmaceutical Drugs & Chemical Agents

Challenges in Assessing Risk:

1. Most studies are retrospective (maternal recall bias).
2. Pregnant women use many drugs:
    - Avg. 4 medications per pregnancy.
    - Only ~20% use no drugs during pregnancy.

- Safety unknown for ~90% of drugs.

Proven Drug Teratogen: Thalidomide

- Use: Antinauseant & sedative (1960s).
- Discovery: West Germany (1961) → sudden rise in amelia & meromelia (total/partial limb absence).
- Mechanism: Affects early limb development (limb buds).
- *Exam tip*: The teratogenic link was only noticed because limb absence was rare. If it caused common defects (e.g., cleft lip, CHD), the link might have been missed.

High-Yield Quick Facts Table

Agent	Key Effects	Timing Sensitivity
Hyperthermia	Neural tube defects	Early neurulation
Toxoplasmosis	Cerebral calcifications, hydrocephalus, visual/hearing loss	Any trimester

Radiation	CNS defects, growth retardation, abortion	All stages, most severe early
Thalidomide	Amelia, meromelia	Limb bud stage (4–5 weeks)
Hepatitis B	Fetal hepatitis	Any trimester
CMV	Sensorineural deficits	Any trimester

Drug Teratogens – Detailed High-Yield Notes

1. Thalidomide

- Original use: Antinauseant & sedative (1960s) → caused amelia/meromelia (limb defects).
- Modern use: Immunomodulator for AIDS, leprosy, lupus, GVHD.
- Now known effects (if taken in pregnancy):
    - Limb defects
    - Heart malformations
    - Orofacial clefts
    - Intellectual disability, autism

- Urogenital and gastrointestinal defects

- Key point: Still causes defects if given during critical limb development (4–5 weeks gestation).

2. Anticonvulsants

- Phenytoin (Diphenylhydantoin) → *Fetal hydantoin syndrome*:
  - Growth deficiency, developmental delay
  - Facial clefts
  - Distinct facial appearance

- Trimethadione → *Trimethadione syndrome*:
  - Facial clefts common
  - Broad dysmorphogenesis pattern

- Valproic acid:
  - ↑ Risk: ASD, cleft palate, hypospadias, polydactyly, craniosynostosis
  - Highest risk → Neural tube defect (esp. spina bifida)

- Carbamazepine → ↑ risk for neural tube defects

3. Antipsychotics & Antianxiety

- Phenothiazines → Evidence conflicting for teratogenicity

- Lithium → Associated with congenital heart defects, especially Ebstein anomaly (but risk is small)

4. Antidepressants

- SSRIs (fluoxetine, paroxetine, others):
    - Heart defects
    - ↑ spontaneous abortion risk
    - Possible mechanism: Disruption of serotonin (SHT) → affects laterality & heart development

5. Immunosuppressants

- Mycophenolate mofetil (MMF):
    - Spontaneous abortion
    - Birth defects: Cleft lip/palate, microtia, microcephaly, heart defects

6. Anticoagulants

- Warfarin → *First trimester* exposure:
    - Skeletal defects: Nasal hypoplasia, abnormal epiphyses, limb hypoplasia

- Heparin → Not teratogenic

7. Antihypertensives

- ACE inhibitors (2nd/3rd trimester exposure):
    - Growth retardation
    - Renal dysfunction
    - Fetal death
    - Oligohydramnios
- *First trimester* → effects less clear

8. Other Medications of Concern

Drug	Key Effects
Propylthiouracil, Potassium iodide	Goiter, intellectual disability
Streptomycin	Hearing loss
Sulfonamides	Kernicterus
Imipramine	Limb deformities
Tetracyclines	Bone/tooth anomalies

Amphetamines	Orofacial clefts, CV defects
Quinine	Hearing loss

9. Social / Recreational Drugs

- LSD → Reported limb & CNS defects, but large reviews suggest no proven teratogenicity in moderate doses

- Marijuana, PCP, cocaine → No conclusive teratogenic evidence

- Alcohol → Most important preventable teratogen:
    - Fetal Alcohol Spectrum Disorder (FASD) = broad term
    - Fetal Alcohol Syndrome (FAS) = severe end:
        - Growth deficiency
        - Intellectual disability
        - Facial anomalies (short palpebral fissures, smooth philtrum, thin upper lip)
        - Brain anomalies (microcephaly, holoprosencephaly)
        - Heart defects
    - Alcohol-Related Neurodevelopmental Disorder (ARND) = CNS involvement without full FAS

features
    - Incidence: FAS + ARND ≈ 1 in 100 live births
    - No safe dose; binge drinking (>5 drinks/session) during critical stages ↑ risk, including orofacial clefts.

Key Exam Tip – Teratogenicity Patterns

- Timing is critical: Most major structural defects occur if exposure is during organogenesis (3–8 weeks).

- CNS is vulnerable throughout gestation.

- Some teratogens have very specific hallmark defects (e.g., Lithium → Ebstein anomaly, Valproic acid → NTD).

Teratogens – Part 2

1. Cigarette Smoking

- Effects:

    - ↑ Risk of orofacial clefts (cleft lip, cleft palate)
    - Intrauterine growth retardation (IUGR)
    - Premature delivery

- Mechanism: Likely due to fetal hypoxia (carbon

monoxide + nicotine → vasoconstriction).

2. Isotretinoin (Accutane) & Vitamin A Derivatives

- Use: Severe cystic acne, chronic dermatoses.
- Highly teratogenic → Isotretinoin embryopathy:
  - Craniofacial malformations
  - CNS defects
  - Cardiovascular defects
  - Thymic abnormalities
- Even topical retinoids (e.g., etretinate) may be teratogenic.
- Vitamin A itself:
  - High doses (>10,000–25,000 IU) → possible teratogenicity (controversial threshold).
  - Multivitamins usually safe (2,000–8,000 IU).
- Key fact: Related to embryopathy risk if taken during early pregnancy.

3. Androgenic Agents

- Old practice: Synthetic progestins used to prevent abortion (e.g., ethisterone, norethisterone).

- Effect in female fetuses:
    - Masculinization of genitalia: Enlarged clitoris, partial fusion of labioscrotal folds.

4. Endocrine Disrupters

- Definition: Exogenous agents altering normal hormonal regulation during development.
- Most common target: Estrogen receptors.
- Classic example: Diethylstilbestrol (DES):
    - Female fetuses:
        - ↑ Risk of vaginal and cervical clear cell carcinoma in adulthood.
        - Reproductive tract malformations: uterus, uterine tubes, upper vagina.
        - Infertility, reproductive dysfunction.
    - Male fetuses:
        - Testicular malformations, abnormal sperm analysis.
        - No increased carcinoma risk.
- Environmental estrogens (pesticides, industrial chemicals):

- Possible ↑ in:
  - Testicular cancer
  - Hypospadias
  - Reproductive tract anomalies
- CNS sex differentiation abnormalities (e.g., masculinization of female brain, feminization of male brain in animal studies).

5. Oral Contraceptives

- Low teratogenic potential.
- Discontinue if pregnancy suspected (precautionary due to hormone-related risks).

6. Corticosteroids

- Animal data: Cortisone at critical stages → high % cleft palate.
- Human data: Modestly ↑ risk of orofacial clefts with corticosteroid use in pregnancy.

Exam Buzzwords & Triggers

Teratogen	Classic Defect / Association	Mnemonic Cue
Cigarette	Orofacial clefts,	"Smoke cuts the

smoking	IUGR, prematurity	face & growth"
Isotretinoin	Isotretinoin embryopathy (craniofacial, CNS, heart, thymus)	Acne drug = All defects
Androgenic agents	Female genital masculinization	"Progestin makes girl into boy"
DES	Vaginal clear cell carcinoma + uterine anomalies	"DES = Daughter's Endangered S-system" (uterus + cervix)
Cortisone	Orofacial clefts	"C for Cleft"

Maternal Disease as Teratogenic Factor

1. Diabetes Mellitus

Pregestational Diabetes (Type 1 & Type 2 diagnosed before pregnancy)

- Risks:
    - ↑ Stillbirths, neonatal deaths
    - Macrosomia (abnormally large infants)

- Congenital malformations (risk ↑ 3–4×; up to 80% in long-standing disease)
  - Neural tube defects
  - Congenital heart defects
  - Caudal dysgenesis / Sirenomelia

- Mechanism:
  - Altered maternal glucose levels → teratogenic; insulin itself not teratogenic

- Key correlation: Risk ↑ with severity & duration of disease.

- Prevention: Strict glucose control before conception & during pregnancy ↓ malformation rate to baseline.

Gestational Diabetes

- Risk for structural birth defects less clear:
  - Onset usually after organogenesis (3–8 weeks), so structural anomalies less likely.
  - Possible increased risk if undiagnosed pregestational diabetes present.

2. Phenylketonuria (PKU)

- Cause: Deficient phenylalanine hydroxylase → ↑ serum phenylalanine.

- Effects on fetus:
    - Intellectual disability
    - Microcephaly
    - Cardiac defects
- Prevention: Low-phenylalanine diet before conception & throughout pregnancy normalizes risk.

3. Nutritional Deficiencies

- Iodine deficiency:
    - Endemic cretinism → stunted mental & physical growth.
- Methyl-deficient diets:
    - Alter expression of imprinted genes → birth defects, ↑ cancer risk postnatally.
- Poor maternal nutrition:
    - Low birth weight
    - Structural birth defects
- Severe starvation during pregnancy:

- 2–3× ↑ risk of schizophrenia in offspring.

4. Obesity

- Definition: BMI >30 before pregnancy.
- Risks (↑ 2× for NTDs):
  - Neural tube defects
  - Congenital heart defects
  - Omphalocele
  - Multiple congenital anomalies
- Possible mechanism: Maternal metabolic disturbances (glucose, insulin, other factors).

5. Hypoxia

- Animal studies: Causes malformations.
- Humans:
  - High altitude → low birth weight & smaller infants (no ↑ malformation rate).
  - Cyanotic heart disease → small infants but usually no gross malformations.

6. Heavy Metals

- Example: Minamata disease (Japan)

- Cause: Organic mercury contamination from industrial waste in Minamata Bay.
- Source: Fish consumption.
- Effects: Multiple neurological symptoms in newborns (resembles cerebral palsy).
- Key feature: Mothers often asymptomatic despite fetal effects.

Buzzword Table for Rapid Revision

Maternal Condition	Key Defect(s)	Memory Aid
Pregestational DM	NTDs, CHDs, caudal dysgenesis, macrosomia	"Diabetic baby = Big body, bad back, bad heart"
PKU	ID, microcephaly, CHDs	"PKU → Phenyl Kills Understanding"
Iodine deficiency	Endemic cretinism	"Iodine → IQ"
Obesity	NTDs, CHDs, omphalocele	"Overweight → Over defects"
Hypoxia	Small infant (no	"Thin air → Thin

	major malformation)	baby"
Mercury	Neuro defects (CP-like)	"Minamata Mercury Mind damage"

Environmental & Paternal Factors in Teratogenesis

Heavy Metals

Mercury

- Fetal sensitivity > maternal — mothers may remain asymptomatic.
- Sources & outbreaks:
  - Japan (Minamata disease) → fish contaminated with organic mercury from industrial waste.
  - USA → seed corn treated with mercury fungicide → hog meat → pregnant women.
  - Iraq → grain treated with mercury fungicide.
- Effects:
  - Severe neurological symptoms in newborns (resembles cerebral palsy).
  - Multiple developmental abnormalities.

Lead

- Associated with:
    - ↑ Abortions
    - Growth retardation
    - Neurological disorders.

Male-Mediated Teratogenesis

- Mechanism: Mutations or damage to male germ cells from exposures.
- Teratogens affecting males:
    - Ethylnitrosourea
    - Radiation
    - Mercury, lead, solvents
    - Alcohol
    - Cigarette smoke
- Effects on offspring:
    - Spontaneous abortion
    - Low birth weight
    - Birth defects
- Paternal age effects:
    - Advanced age → ↑ risk for structural birth

defects, Down syndrome, new autosomal dominant mutations.
    - <20 years: some studies show ↑ risk (inconclusive evidence).

- Other pathways:
    - Paternal toxins in seminal fluid
    - Household contamination from work clothes.

Prenatal Diagnosis

Ultrasonography

- Principle: High-frequency sound waves reflect from tissues → image.
- Approach:
    - Transabdominal
    - Transvaginal (higher resolution).
- Capabilities:
    - Detect fetal blood flow, heart valve motion, tracheal/bronchial fluid flow.
- Usage: ~80% of U.S. pregnancies receive ≥1 scan.

- Information provided:
    - Fetal age & growth
    - Presence/absence of anomalies
    - Amniotic fluid volume
    - Placental position & umbilical blood flow
    - Detection of multiple gestations
- Impact: Ultrasound-guided management in low-birth-weight cases ↓ mortality by 60%.
- Age & growth estimation:
    - 5–10 weeks: Crown-rump length
        - 10 weeks: Biparietal diameter (BPD), femur length, abdominal circumference.
- Detectable anomalies:
    - NTDs (anencephaly, spina bifida)
    - Abdominal wall defects (omphalocele, gastroschisis)
    - Heart defects
    - Facial defects (cleft lip/palate).
- Special screening: Nuchal translucency (11–14 weeks) → ↑ risk for Down syndrome & other chromosomal abnormalities.

- Combined with maternal serum screening + maternal age → risk estimate.
- High-risk → offer amniocentesis for confirmation.

Prevention of Birth Defects

- Iodine supplementation → prevents cretinism (intellectual disability, bone deformities).
- Strict metabolic control in diabetes & PKU before conception → reduces birth defect risk.
- Folic acid supplementation:
  - ↓ NTD incidence (spina bifida, anencephaly).
  - ↓ hyperthermia-induced defects.
- Alcohol avoidance in all pregnancy stages → prevents fetal alcohol spectrum disorders.
- Pre-conception interventions essential.
- Drug teratogenicity caution:
  - Always consider pregnancy risk when prescribing to women of childbearing age.
  - Isotretinoin (Accutane):
    - Potent teratogen → "isotretinoin

embryopathy".

- Used for cystic acne — high risk in sexually active young women.
- Must be used with extreme caution.

Buzzword & Exam Tip Table

Agent / Factor	Key Defect / Outcome	High-Yield Clue
Mercury	CP-like neuro defects	Minamata, asymptomatic mother
Lead	Abortions, growth retard, neuro issues	Environmental exposure
Paternal radiation / toxins	Miscarriage, LBW, anomalies	Male germ cell mutations
Advanced paternal age	AD mutations, Down syndrome	>40 yrs risk
Nuchal translucency ↑	Down syndrome risk	11–14 weeks
Folate deficiency	NTDs	Preconception

		prevention
Isotretinoin	Severe craniofacial, cardiac, CNS defects	Acne drug caution

Maternal Serum Screening & Prenatal Diagnostic Procedures

I. Maternal Serum Screening (MSS)

- Purpose: Detect biochemical markers in maternal blood indicating fetal abnormalities.
- Key marker: α-fetoprotein (AFP)
  - Produced by: Fetal liver.
  - Physiology: Peaks ~14 weeks → enters maternal circulation via placenta → rises during 2nd trimester → declines after 30 weeks.
- AFP levels:
  - ↑ Increased in:
    - Neural tube defects (anencephaly, spina bifida)
    - Abdominal wall defects (omphalocele, gastroschisis)
    - Bladder exstrophy
    - Amniotic band syndrome
    - Sacrococcygeal teratoma

        - Intestinal atresia
    - ↓ Decreased in:
        - Down syndrome (Trisomy 21)
        - Trisomy 18
        - Sex chromosome abnormalities
        - Triploidy

- Improved detection with quadruple test in 2nd trimester:
    - AFP
    - Human chorionic gonadotropin (hCG)
    - Unconjugated estriol (uE3)
    - Inhibin A

2. Amniocentesis

- Procedure:
    - Needle insertion → amniotic cavity (ultrasound-guided).
    - Fluid withdrawn: 20–30 mL
    - Usually after 14 weeks (enough fluid to avoid fetal risk).

- Risks:
    - Fetal loss: ~1 in 300–500 (lower in skilled hands).

- Tests on fluid:
    - Biochemical: AFP, acetylcholinesterase (for neural tube defects).
    - Genetic: Fetal cells cultured → metaphase chromosomes → karyotyping (translocations, breaks, trisomies, monosomies).
    - Advanced: PCR, genotyping assays for molecular detection.
- Drawback: Results take 1–2 weeks (cells need culture to divide).

3. Chorionic Villus Sampling (CVS)

- Procedure:
    - Needle (transabdominal/transvaginal) → placental villi aspirated (5–30 mg tissue).
    - Cells from mesenchymal core cultured for genetic analysis.
    - Culture time: 2–3 days → faster than amniocentesis.
- Risks:
    - Pregnancy loss (similar to amniocentesis in experienced hands).
    - Possible ↑ risk of limb reduction defects (digits).

- Limitation: High rate of chromosomal errors in placenta → mesenchymal core cells used for accuracy.

4. ACOG Recommendations (since 2007)

- Invasive testing (amniocentesis or CVS) for aneuploidy offered to all pregnant women.

- High-risk factors:

    1. Advanced maternal age (≥35 years).

    2. Family history of genetic problem (e.g., Down syndrome, neural tube defect).

    3. Maternal disease (e.g., diabetes).

    4. Abnormal ultrasound or serum screening results.

Exam Tip:

- AFP ↑ → think *open defects* (NTD, abdominal wall).

- AFP ↓ + abnormal hCG/uE3 → think *chromosomal abnormalities*.

- Amniocentesis vs CVS:
    - Amniocentesis → after 14 wks, slower results, less limb defect risk.
    - CVS → after 10–12 wks, faster results, small risk of limb defects.

Fetal Therapy

1. Fetal Transfusion

- Indication: Fetal anemia (commonly due to maternal antibodies — e.g., Rh incompatibility — or other causes).

- Procedure:
    - Ultrasound-guided needle insertion into umbilical cord vein.
    - Direct transfusion of compatible blood into fetus.

2. Fetal Medical Treatment

- Indirect treatment:
    - Drugs given to the mother → cross placenta → reach fetus.
    - Examples: Antibiotics for infections,

antiarrhythmics for fetal cardiac arrhythmia, thyroid hormones for hypothyroidism.

- Direct treatment:
    - Intramuscular injection into fetal gluteal muscle.
    - Umbilical vein administration.

3. Fetal Surgery

- Indication: Only when no reasonable alternatives & performed in specialized centers.
- Types:
    - Shunt placement: Removes fluid from organs/cavities.
        - Example: Obstructive urinary disease → shunt from fetal bladder to amniotic sac (prevents renal damage if diagnosed early).
    - Ex utero surgery (open fetal surgery):
        - Uterus opened → direct fetal repair.
        - Used for:
            - Congenital diaphragmatic hernia repair.
            - Removal of cystic adenomatous lung lesions.
            - Repair of spina bifida.
        - Also: Interventions for certain congenital heart defects.

- Status: Most procedures are experimental; under randomized clinical trials to assess benefit.

- Risks: Maternal, fetal, and future pregnancy complications.

4. Stem Cell Transplantation

- Rationale: Fetus lacks immunocompetence before 18 weeks → no rejection risk if transplanted early.

- Current research:

    - Hematopoietic stem cells for immunodeficiency and hematologic disorders.

5. Fetal Gene Therapy

- Aim: Correct inherited metabolic diseases in utero.

- Examples under investigation: Tay-Sachs disease, cystic fibrosis.

- Approach: Viral vectors or other delivery systems introduced before immune competence develops.

Exam Tip Table: Fetal Therapy Modalities

Therapy	Route	Indication	Special Notes
Fetal transfusion	Umbilical vein	Fetal anemia	Ultrasound guided
Medical treatment (indirect)	Mother → placenta	Infections, arrhythmias, hypothyroidism	Placental transfer required
Medical treatment (direct)	IM injection into fetus / umbilical vein	When rapid effect needed	More invasive
Shunt placement	In utero	Obstructive urinary disease, hydrothorax	Prevents organ damage
Ex utero surgery	Open uterus	Diaphragmatic hernia, lung lesions, spina bifida	Experimental, high risk
Stem cell transplanta	Direct into	Immunodeficienc y, hematologic	No rejection if before

tion	fetus (<18 wks)	disorders	immune maturity
Gene therapy	Direct delivery system	Inherited metabolic disorders	Still research phase