Cloherty and Stark's
Manual of Neonatal Care

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Summary

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Chapter 1
Fetal Assessment and Prenatal Diagnosis

I. Gestational Age Assessment

1. Importance of Gestational Age Assessment

- **Accurate timing for interventions** like chorionic villus sampling (CVS) and amniocentesis.
- **Essential in preterm delivery** for prognosis, obstetric decisions, and neonatal care planning.

2. Clinical Estimation

- **Last Menstrual Period (LMP)**: Commonly used based on the first day of the last period.
- **Physical Exam Clues**:
    - Auscultation of fetal heart sounds.
    - Maternal perception of fetal movements.

3. Ultrasound Accuracy

- **Most accurate early in pregnancy**.
- **First trimester**:
    - **Crown-rump length (CRL)** is a reliable gestational age predictor.
- **After 14 weeks**:
    - Biometric measurements used: **Biparietal diameter (BPD), Head circumference (HC), Abdominal circumference (AC), Femur length**.
- **Later gestation**: Accuracy declines, especially in cases of fetal growth restriction (FGR).

4. Due Date Adjustments

- **Stability is important**: Once established, due dates should not be changed unless **major discrepancies** exist between LMP and ultrasound dating.

II. Prenatal Diagnosis of Fetal Disease

- **General Overview**
    - Prenatal diagnosis is improving due to:
        - Advances in understanding genetic/developmental disorders
        - Increased test sensitivity and specificity

- Two main test categories:
  - **Screening tests** (noninvasive, less specific)
    - Maternal blood tests
    - Ultrasound findings
  - **Diagnostic tests** (invasive, more accurate)
    - Chorionic Villus Sampling (CVS)
    - Amniocentesis
    - Small procedural risk to mother and fetus

A. Screening tests

1. Cell-free DNA (cfDNA) Screening – Noninvasive Prenatal Testing (NIPT)

• Technology

- Analyzes fetal DNA (from placenta) in maternal blood
- **Detects:**
  - Trisomies 13, 18, 21
  - Sex chromosome aneuploidies
  - Some microdeletions/duplications and single-gene disorders (on select platforms)
- Available from as early as **9 weeks gestation**

• Fetal Fraction

- cfDNA derives from fetal apoptosis
- Fetal fraction: typically **3% to 13%**
- Low fraction → potential "no-call" result
- Low fraction linked to:
  - Early gestation
  - High maternal BMI
  - Fetal chromosomal abnormalities

• Detection & False-Positive Rates

- **Trisomy 21**: 99.7% detection
- **Trisomy 18**: 97.9% detection
- **Trisomy 13**: 99% detection
- **Combined false-positive rate**: 0.13% (excluding no-calls)

• Performance in Special Populations

- **Younger women**: lower PPV due to lower prevalence
  - PPV for Trisomy 21:

- 33% if <25 years
- 87% if >40 years

- **Twins**:
  - Lower detection rates
  - Higher false-positive rates
  - Still the most accurate available screening

• Limitations

- Targets **only common aneuploidies**
- May miss:
  - Other chromosomal abnormalities
  - Mosaicism
  - Copy number variants (CNVs)
- **17%** of fetuses with structural anomalies may have undetected chromosomal issues

• Confirmation & Next Steps

- cfDNA is a **screening**, not diagnostic, test
- Positive cfDNA → confirm with **CVS** or **amniocentesis**
- If ultrasound reveals anomalies → recommend **diagnostic testing**

2. Single-Gene cfDNA Screening

• Purpose

- Detects **fetal Rh status** (99% accuracy)
- Can screen for single-gene disorders such as:
  - Achondroplasia
  - Noonan syndrome
  - Osteogenesis imperfecta
  - CHARGE syndrome (Coloboma, Heart defects, Atresia choanae, Growth retardation, Genital/Ear anomalies)

• Status

- Not widely used in routine care
- Not yet endorsed by national guidelines
- Clinical utility and test parameters still under research

3. Maternal Serum Analysis During Pregnancy

a. MSAFP for Neural Tube Defects (NTDs)

- **Timing**: 15–22 weeks

- **Elevated MSAFP (>2.5 MoM):**
  - Detects 70–85% of open spina bifida
  - Detects 95% of anencephaly cases
- Ultrasound confirms diagnosis, evaluates gestational age
- **Signs**:
  - **Lemon sign** (head shape)
  - **Banana sign** (cerebellar deformity)

b. First-Trimester Serum Screening

- **Analytes**: PAPP-A and hCG (free or total)
- **Timing**: 9–10 weeks
- Limited sensitivity (<50% detection for Trisomy 21)

c. First-Trimester Nuchal Translucency

- Ultrasound to measure fluid at fetal neck
- **Enlarged nuchal translucency in:**
  - 70–80% of aneuploid fetuses
  - Some structural/genetic disorders (e.g. cardiac defects, Noonan syndrome

d. Second-Trimester Aneuploidy Screening (Quad Screen)

- **Includes:**
  - MSAFP
  - hCG (↑ in Trisomy 21)
  - Unconjugated estriol (uE3) (↓ in Trisomy 21)
  - Inhibin (↑ in Trisomy 21)
- **Detection Rates:**
  - Trisomy 21: 80%
  - Trisomy 18: usually low levels of all markers
- **False-positives**: 5% in women <35 years (98% are unaffected)

e. Combined First-Trimester Screening

- **Combines:**
  - PAPP-A
  - β-hCG
  - Nuchal translucency
  - Maternal age
- **Detection**: ~80% for Trisomy 21
- **False-positive rate**: ~5% in women <35 years

f. Combined First- and Second-Trimester Screening

- Goal: maximize sensitivity, minimize false-positives

- **Integrated Screening**:
  - Results disclosed after both trimesters
  - Highest detection (97%) with 2% false-positive rate

- **Sequential Screening**:
  - **Stepwise**: all women get 2nd trimester screen if 1st trimester high risk
  - **Contingent**: only intermediate-risk women proceed to 2nd trimester
  - Both approaches: ~90% detection, 2–3% false-positive rate

4. Ultrasound After Serum Screening

- Second-trimester targeted ultrasound:
  - Detects structural anomalies
  - Can reduce risk of Trisomy 21 by 50–60%

- Helps refine risk after positive first-trimester screen

B. Diagnostic Tests

Indications for Diagnostic Testing:

- Positive family history of genetic disease
- Positive screening test
- Abnormal ultrasound findings (e.g., structural anomalies)

1. Chromosomal Microarray (CMA)

- **Detects:** Aneuploidy and chromosomal copy number variations (CNVs)

- **Findings:**
  - Pathogenic CNVs in 0.4% of tests (done due to maternal age or anxiety)
  - Women <35 years have higher rates of syndromic CNVs than trisomy 21

- **Limitations:**
  - Does *not* detect:
    - Balanced translocations
    - Some structural rearrangements
    - Triploidy

- **When to Use:**
  - Recommended when fetal anomalies are found and karyotype is normal → detects additional abnormalities in 6%

- o   Offered alongside karyotyping during diagnostic testing for anomalies
- **Clinical Benefit:**
  - o   Enables early planning and potential in utero interventions

2. Molecular/Exome Sequencing:

- o   Useful when CMA is normal but anomalies exist.

Yields a diagnosis in ~8–10% of such cases

3. Chorionic Villus Sampling (CVS)

- **Procedure:**
  - o   Performed after 10 weeks gestation
  - o   Sample taken transabdominally or transcervically under ultrasound
  - o   Analyzes *trophoblast* cells (placental tissue)
- **Timing:**
  - o   Earliest diagnostic test available
  - o   Can be used late in pregnancy if others aren't possible
- **Risks:**
  - o   Loss rate ≈ 0.2%
  - o   Early CVS (<10 weeks) → risk of limb reduction or oromandibular defects
- **Mosaicism:**
  - o   Seen in ~2% → may require confirmatory amniocentesis
- **Results:**
  - o   Cytotrophoblast analysis: ~2 days
  - o   Cultured trophoblast cells: 8–12 days

4. Amniocentesis

- **Procedure:**
  - o   Typically done at 16–20 weeks (can be done after 10 weeks)
  - o   Amniotic fluid is removed via ultrasound-guided needle
  - o   Fluid regenerates within 24 hours
- **Risks:**
  - o   Loss rate: 0.3% procedure-related; 0.9% total
  - o   Membrane rupture (1%) → usually resolves in 3 weeks
  - o   Early amniocentesis (<13 weeks): ↑ risk of clubfoot & miscarriage (1–2% loss)
- **Biochemical Markers:**