Maternal Serum Screening

Indications for Ordering

Low-risk individuals
Maternal Serum Screen, First Trimester
• First-trimester screening test for Down syndrome (trisomy 21 [T21]) and trisomy 18 (T18)

Maternal Serum Screen, Sequential
• Combined first- and second-trimester screening tests for T21, T18, and open neural tube defects (ONTD)

Maternal Serum Screen, Integrated
• Combined first- and second-trimester screening tests for T21, T18, and ONTD

Maternal Serum Screen, Quad
• Second-trimester (>14 weeks) screening test for T21, T18, and ONTD for individual who did not have first-trimester screening performed

High-risk individuals
All high-risk pregnant women should consider noninvasive prenatal testing (NIPT), chorionic villus sampling (CVS), or amniocentesis instead of the tests listed above
• High risk defined as
  o Women ≥35 years at delivery
  o Previous pregnancy with chromosome aneuploidy
  o Either parent is a known carrier of a chromosomal translocation or inversion
  o Abnormal fetal ultrasound
  o Increased risk of ONTD due to family history, patient use of specific medications (eg, valproic acid or carbamazepine), or diabetic status

Test Description

Methodology depends on test components
• Alpha fetoprotein (AFP) and human chorionic gonadotropin (hCG)
  o Noncompetitive (sandwich) immunoassay
    ▪ Antibodies — capture protein to a solid phase and detect presence of protein
    ▪ External calibrators used

• Unconjugated estriol (uE3)
  o Solid phase competitive immunoassay
    ▪ Antiestriol polyclonal antibody (labeled estriol)
    ▪ Solid phase antibody directed against the estriol antibody
    ▪ External calibrators

• Dimeric Inhibin-A (DIA)
  o Noncompetitive (sandwich) microtiter immunoassay
    ▪ Capture antibody to inhibin subunit βA
    ▪ Detection antibody to subunit α
    ▪ External calibrators

• Pregnancy-associated plasma protein-A (PAPP-A)
  o Sequential immunoenzymatic assay
  o Measures protein using monoclonal antibodies and external calibrators

• Post-test risks — calculations by a multivariate log Gaussian model
  o Risk estimates for T21 and T18 are strongly influenced by maternal age

• Refer to table for first- and second-trimester screening options

Tests to Consider

Primary tests
Maternal Serum Screen, First Trimester, hCG, PAPP-A, NT 3000145
• First-trimester screening test for T21, T18
• Does not include AFP for ONTD screening
• Requires NT measurement performed by an ultrasonographer certified by the Fetal Medicine Foundation (FMF) or the Nuchal Translucency Quality Review (NTQR)

Maternal Screening, Sequential, Specimen #1, hCG, PAPP-A, NT 30000146
• First-trimester screening test for T21 and T18
• Requires NT measurement performed by an ultrasonographer certified by the FMF or NTQR
• Risks provided in both first and second trimesters

Maternal Screening, Sequential, Specimen #2, Alpha Fetoprotein, hCG, Estriol, and Inhibin A 3000148
• Second-trimester screening test for T21, T18, and ONTD
• Requires a previously submitted first-trimester specimen, Maternal Screening, Sequential, Specimen #1, hCG, PAPP-A, NT (3000146)
• Requires NT measurement performed by an ultrasonographer certified by the FMF or NTQR
• Risks provided in both first and second trimesters
Maternal Serum Screening, Integrated, Specimen #1, PAPP-A, NT 3000147
- First-trimester screening test for T21, T18, and ONTD
- Risks determined using a combination of first- and second-trimester serum markers, with or without first-trimester nuchal translucency (NT) measurement
- Risks provided after testing is completed for second-trimester specimen, Maternal Serum Screening, Integrated, Specimen #2, Alpha Fetoprotein, hCG, Estriol, and Inhibin A (3000149)

Maternal Serum Screening, Integrated, Specimen #2, Alpha Fetoprotein, hCG, Estriol, and Inhibin A (Quad) 3000143
- Second-trimester screening test for T21, T18, and ONTD
- Requires a previously submitted first-trimester specimen, Maternal Serum Screening, Integrated, Specimen #1, PAPP-A, NT (3000147)
- Risks are determined after second-trimester specimen is received, using a combination of first- and second-trimester serum markers with or without first-trimester NT measurement

Maternal Serum Screen, Alpha Fetoprotein, hCG, Estriol, and Inhibin A (Quad) 3000143
- Second-trimester screening test for T21, T18, and ONTD

Related tests (screening)
Non-Invasive Prenatal Testing for Fetal Aneuploidy 2007537
Non-Invasive Prenatal Testing for Fetal Aneuploidy with 22q11.2 Microdeletion 2013142
Non-Invasive Prenatal Testing for Fetal Aneuploidy with Microdeletions 2010232

Related tests (diagnostic)
Chromosome Analysis, Chorionic Villus 2002291
Chromosome Analysis, Amniotic Fluid 2002293
Cytogenomic SNP Microarray – Fetal 2002366

Disease Overview

Incidence
- ONTD – 1/900 pregnancies
- T21 – 1/600 births
- T18 – 1/3,000 births

Background
ONTD
- Most common ONTDs include
  - Spina bifida
    - Often results in some degree of paralysis of lower limb, loss of bowel and bladder control, ventriculomegaly
  - Anencephaly
  - Incompatible with life
- Risk – independent of maternal age

T21
- Extra copy of chromosome 21
- Features
  - Moderate intellectual disability
  - Characteristic facial features
  - Variety of medical conditions (eg, cardiac abnormalities)
- Risk – increases with maternal age
  - ~50% of babies with T21 are born to women <35 years

T18
- Extra copy of chromosome 18
- Most newborns die within their first year of life
- Features
  - Severe to profound intellectual disability
  - Small size at birth/poor growth
  - Variety of medical conditions (eg, cardiac abnormalities) which are generally more severe than those seen in T21
- Risk – increases with maternal age

Screening/detection
- Maternal serum screening helps to identify pregnancies at risk for ONTD, T21, or T18
- Most families who have a child with ONTD, T21, or T18 have no obvious risk factor for the condition (eg, advanced maternal age, previous history)
- Refer to table for first- and second-trimester screening options
- Abnormal results for any screen requires followup
  - Targeted ultrasound (US)
  - Other prenatal diagnostic procedures
  - Genetic counseling

Test Interpretation

Results
T21 cutoffs listed below are ARUP default cutoffs
- Clients may request a different T21 cutoff

Maternal Serum Screen, First Trimester
- T21 screen – 1/230 or worse, reported as abnormal
- T18 screen – 1/100 or worse, reported as abnormal

Maternal Serum Screen, Sequential
- First trimester
  - T21 and T18 screen – 1/25 or worse, reported as abnormal
  - Second-trimester specimen not required if first-trimester result is abnormal
- Second trimester
  - T21 screen – 1/110 or worse, reported as abnormal
  - T18 screen – 1/100 or worse, reported as abnormal

ONTD screen
- AFP >2.5 MoM – increased risk for ONTD
- AFP <2.5 MoM – screen will be reported as abnormal when the ONTD risk is 1/250 or worse
- uE3 <0.15 MoM – increased risk for congenital steroid sulfatase deficiency or Smith-Lemli-Opitz syndrome
- hCG >3.5 MoM – increased risk for poor fetal outcome
### Maternal Serum Screen, Integrated
- See maternal serum screen sequential for second trimester

### Maternal Serum Screen, Quad
- See maternal serum screen sequential for second trimester

### Limitations
- A screen interpreted as “normal” misses approximately 15-20% of ONTD cases, 10-20% of T21 cases, and 10-20% of T18 cases, depending on the test and maternal age
- AFP false positives occur with multiple gestation pregnancies, fetal ventral wall defects, fetal demise, and underestimated gestational age

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### First- and Second-Trimester Prenatal Screening Options

<table>
<thead>
<tr>
<th>Specimen(s) collected</th>
<th>First Trimester Only</th>
<th>Serum Integrated (without NT)</th>
<th>Full Integrated (with NT)</th>
<th>Sequential Screen</th>
<th>Quad</th>
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</table>

| Gestational age | Blood – 43.83.9 mm (11w0d–13w6d) NT – 38.83.9 mm (10w3d–13w6d) | Blood – 32.4–83.9 mm (10w0d–13w6d) by US or LMP | Blood – 32.4–83.9 mm (10w0d–13w6d) NT – 38.83.9 mm (10w3d–13w6d) | Blood – 43.83.9 mm (11w0d–13w6d) NT – 38.83.9 mm (10w3d–13w6d) | N/A |

| Second-trimester measurements | N/A | AFP, hCG, uE3, DIA | AFP, hCG, uE3, DIA | AFP, hCG, uE3, DIA | AFP, hCG, uE3, DIA |
| Gestational age | N/A | 14w0d-24w6d (by previous CRL or LMP) | 14w0d-24w6d (by previous CRL) | 14w0d-24w6d (by previous CRL) | 14w0d-24w6d |

| Down syndrome (T21) | Detection rate | 85% | 85% | 87% | 86% (63% – first draw; 23% – second draw) | 81% |
| Screen-positive rate | 6% | 3-4% | 1% | 1.6% (0.6% – first draw; 1% – second draw) | 4-5% |

| Trisomy 18 | Detection rate | ~80% | 90% | 90% | 90% | ~80% |
| Screen-positive rate | <1% | 0.01% | 0.01% | 0.01% | <0.5% |

| Open neural tube defect | Detection rate | N/A | 80% | 80% | 80% | 80% |
| Screen-positive rate | N/A | 1-2% | 1-2% | 1-2% | 1-2% |

| Results reported | First trimester | Second trimester | Second trimester | Both first and second trimesters | Second trimester |

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