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 test for open neural tube defects (ONTD), T21, and T18
Maternal Serum Screen, Integrated
• Combined first- and second-trimester screening test for ONTD, T21, and T18
Maternal Serum Screen, Quad
• Second-trimester (>14 weeks) screening test for ONTD, T21, and T18 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
    ▪ Anti-estriol 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 inhibit 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
• Posttest risks – calculations by a multivariate log Gaussian model
  o Risk estimates for T21 and T18 are strongly influenced by maternal age
  o Refer to table for first- and second-trimester screening options

Tests to Consider

Primary tests
Maternal Serum Screen, First Trimester 0081150
• First trimester – screens for T21 and T18
• Does not include AFP for ONTD screening
• Requires nuchal translucency (NT) measurement performed by an ultrasonographer certified by the Fetal Medicine Foundation (FMF) or the Nuchal Translucency Quality Review (NTQR)

Maternal Serum Screening, Integrated, Specimen #1 0081062 (first trimester) AND
Maternal Serum Screening, Integrated, Specimen #2 0081064 (second trimester)
• Requires a previously submitted first-trimester specimen
• Screening tests for T21, T18, and ONTD
• Risks determined using a combination of first- and second-trimester serum markers, with or without first-trimester NT measurement
• Risks provided after second-trimester specimen is received

Maternal Screening, Sequential, Specimen #1 0081293 (first trimester) AND
Maternal Screening, Sequential, Specimen #2 0081294 (second trimester)
• Requires a previously submitted first-trimester specimen
• First trimester – screens for T21 and T18
• Second trimester – screens for T21, T18, and ONTD
• Requires NT measurement performed by an ultrasonographer certified by FMF or NTQR
• Risks provided in both first and second trimesters
Maternal Serum Screen, Alpha Fetoprotein, hCG, Estriol, and Inhibin A 0080269
• Second trimester – screens for T21, T18, and ONTD

Related tests
Non-Invasive Prenatal Testing for Fetal Aneuploidy 2007537
• Screening for common fetal aneuploidy disorders – trisomy 13, 18, 21, Turner syndrome, sex chromosome aneuploidies (XXX, XXY, XYY), or triploidy, in pregnant women (9w0d-term)
Non-Invasive Prenatal Testing for Fetal Aneuploidy with 22q11.2 Microdeletion 2013142
• Screening for whole chromosome fetal aneuploidy disorders involving chromosomes 13, 18, 21, X, Y, and triploidy in pregnant women (9w0d-term)
• Also screens for microdeletions causing 22q11.2 deletion syndrome (DiGeorge/velocardiofacial syndrome [VCFS])
• Useful when the fetus is identified as having a heart defect and/or other findings suggestive of del22q11.2
• May identify presence of 22q11.2 deletion in the patient
Non-Invasive Prenatal Testing for Fetal Aneuploidy with Microdeletions 2010232
• Screening for whole chromosome fetal aneuploidy disorders involving chromosomes 13, 18, 21, X, Y, and triploidy in pregnant women (9w0d-term)
• Also screens for microdeletions causing
  o 22q11.2 deletion syndrome (DiGeorge/VCFS)
  o 1p36 deletion syndrome
  o Angelman syndrome
  o Prader-Willi syndrome
  o Cri-du-chat (5p-) syndrome
Chromosome Analysis, Chorionic Villus 2002291
• Prenatal chromosome analysis on chorionic villi when individual
  o Is at increased risk for fetal aneuploidy based on maternal age, abnormal NIPT, abnormal multiple marker screening, or abnormal fetal ultrasound
  o Has a family history of chromosome abnormality or genetic disorder
  o Desires diagnostic testing instead of screening
Chromosome Analysis, Amniotic Fluid 2002293
• Prenatal chromosome analysis on amniotic fluid when individual
  o Is at increased risk for fetal aneuploidy based on maternal age, abnormal NIPT, abnormal multiple marker screening, or abnormal fetal ultrasound
  o Has a family history of chromosome abnormality or genetic disorder
  o Desires diagnostic testing instead of screening
Alpha Fetoprotein (Amniotic Fluid) with Reflex to Acetylcholinesterase and Fetal Hemoglobin 0080427
• Evaluate possibility of a fetal ONTD at 13-36 weeks of gestation

Disease Overview
Incidence
• ONTD – 1/900 pregnancies
• T21 – 1/600 births
• T18 – 1/3,000 births

Background
ONTD
• Most common ONTDs include
  o Spina bifida
    ▪ Often results in some degree of paralysis of lower limb, loss of bowel and bladder control, ventriculomegaly
  o Anencephaly
    ▪ Incompatible with life
• Risk – independent of maternal age
T21
• Extra copy of chromosome 21
• Features
  o Moderate intellectual disability
  o Characteristic facial features
  o Variety of medical conditions (eg, cardiac abnormalities)
• Risk – increases with maternal age
  o ~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
  o Severe to profound intellectual disability
  o Small size at birth/poor growth
  o 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
  o Targeted ultrasound (US)
  o Other prenatal diagnostic procedure(s)
  o 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
  o T21 and T18 screen – 1/25 or worse, reported as abnormal
  o Second-trimester specimen not required if first-trimester result is abnormal
• Second trimester
  o T21 screen – 1/110 or worse, reported as abnormal
  o T18 screen – 1/100 or worse, reported as abnormal
  o 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
  o uE3 <0.15 MoM – increased risk for congenital steroid sulfatase deficiency or Smith-Lemli-Opitz syndrome
  o hCG >3.5 MoM – increased risk for poor fetal outcome

Maternal Serum Screen, Integrated
• See maternal screen sequential for second trimester

Maternal Serum Screen, Quad
• See maternal screen sequential for second trimester

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

<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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</thead>
<tbody>
<tr>
<td></td>
<td>First trimester</td>
<td>First and second trimester</td>
<td>First and second trimester</td>
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<tr>
<td>measurements</td>
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<tr>
<td>Gestational age</td>
<td>42–85 mm (~11w0d–13w6d)</td>
<td>10w0d-13w6d (by US or LMP)</td>
<td>36-85 mm (~10w3d-13w6d)</td>
<td>42-85 mm (~11w0d-13w6d); will not reject if CRL is between 36 and 42 mm</td>
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<td></td>
<td>N/A</td>
<td>AFp, hCG, uE3, DIA</td>
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<tr>
<td>Gestational age</td>
<td>N/A</td>
<td>15w0d-24w6d (by previous CRL or LMP)</td>
<td>15w0d-24w6d (by previous CRL)</td>
<td>15w0d-24w6d (by previous CRL)</td>
<td>14w0d-24w6d</td>
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| Down syndrome (T21) | Detection rate | 85% | 85% | 87% | 86% (63% – first draw; 23% – second draw) | 81% |
| Screen-positive rate | 4-5% | 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% | 80% | 1-2% |
| Results reported       | First trimester | Second trimester | Second trimester | Both first and second trimesters | Second trimester |