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
  - Women ≥35 years at delivery
  - Previous pregnancy with chromosome aneuploidy
  - Either parent is a known carrier of a chromosomal translocation or inversion
  - Abnormal fetal ultrasound
  - 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)
  - Noncompetitive (sandwich) immunoassay
    - Antibodies: capture protein to a solid phase and detect presence of protein
    - External calibrators used
- Unconjugated estriol (uE3)
  - Solid phase competitive immunoassay
    - Antiestriol polyclonal antibody (labeled estriol)
    - Solid phase antibody directed against the estriol antibody
    - External calibrators
- Dimeric Inhibin-A (DIA)
  - Noncompetitive (sandwich) microtiter immunoassay
    - Capture antibody to inhibin subunit βA
    - Detection antibody to subunit α
    - External calibrators
- Pregnancy-associated plasma protein-A (PAPP-A)
  - Sequential immunoenzymatic assay
  - Measures protein using monoclonal antibodies and external calibrators
- Posttest risks: calculations by a multivariate log Gaussian model
  - 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 and 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 3000149
- 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-Optiz 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

- T21 screen: 1/150 or worse, reported as abnormal
- T18 and ONTD screen: 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

First- and Second-Trimester Prenatal Screening Options					
	First Trimester Only	**Serum Integrated (Without NT)**	**Full Integrated (With NT)**	**Sequential Screen**	**Quad**
Specimen(s) collected	**First trimester**	**First and second trimester**	**First and second trimester**	**First and second trimester**	**Second trimester**
First-trimester measurements	US – CRL, NT Blood – PAPP-A, total hCG	US – CRL (optional) Blood – PAPP-A	US – CRL , NT Blood – PAPP-A	US – CRL, NT Blood – PAPP-A, hCG	N/A
Gestational age	Blood – 43-83.9 mm (11w0d–13w6d) NT – 38-83.9 mm (10w3d-13w6d)	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