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
  - 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
    - Anti-estriol 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 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
  - 22q11.2 deletion syndrome (DiGeorge/VCFS)
  - 1p36 deletion syndrome
  - Angelman syndrome
  - Prader-Willi syndrome
  - Cri-du-chat (5p-) syndrome

Chromosome Analysis, Chorionic Villus 2002291

- Prenatal chromosome analysis on chorionic villi when individual
  - Is at increased risk for fetal aneuploidy based on maternal age, abnormal NIPT, abnormal multiple marker screening, or abnormal fetal ultrasound
  - Has a family history of chromosome abnormality or genetic disorder
  - Desires diagnostic testing instead of screening

Chromosome Analysis, Amniotic Fluid 2002293

- Prenatal chromosome analysis on amniotic fluid when individual
  - Is at increased risk for fetal aneuploidy based on maternal age, abnormal NIPT, abnormal multiple marker screening, or abnormal fetal ultrasound
  - Has a family history of chromosome abnormality or genetic disorder
  - 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
  - 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 procedure(s)
  - 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 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

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 (preferred) Blood – PAPP-A	US – CRL , NT Blood – PAPP-A	US – CRL, NT Blood – PAPP-A, hCG	N/A
Gestational age	42–85 mm (~11w0d–13w6d)	10w0d-13w6d (by US or LMP)	36-85 mm (~10w3d-13w6d)	42-85 mm (~11w0d-13w6d); will not reject if CRL is between 36 and 42 mm	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	15w0d-24w6d (by previous CRL or LMP)	15w0d-24w6d (by previous CRL)	15w0d-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	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