

Maternal Screening, Sequential

TEST COMBINES A FIRST- AND SECOND-TRIMESTER SPECIMEN WITH ULTRASOUND TO SCREEN LOW-RISK PREGNANCIES FOR DOWN SYNDROME, OPEN NEURAL TUBE DEFECTS, AND TRISOMY 18

Overview

- About half of the families who have a child with an open neural tube defect (ONTD), Down syndrome (DS), or trisomy 18 (T18) have no prior family history of the condition or any other obvious risk factor, such as advanced maternal age.
- The sequential screen, while not diagnostic, helps identify pregnancies at increased risk for the above disorders.
- The sequential screen typically combines analyte data from two specimens.
 - First-trimester sample:
 - Serum levels of pregnancy-associated plasma protein A (PAPP-A) and total human chorionic gonadotropin (hCG) are measured and the results evaluated in combination with the fetal nuchal translucency (NT) ultrasound measurement to determine the fetal risk for T21 and T18.
 - A final interpretation is provided in the first trimester if the pregnancy is at high risk (one in 25 or worse) for DS or T18. No second-trimester sample is required in these cases.
 - Preliminary results, including the date range for required second-trimester specimen draw, are reported in the first trimester for pregnancies not at increased risk (better than one in 25) for DS or T18.
 - Second-trimester sample
 - Serum levels of alpha fetoprotein (AFP), hCG, unconjugated estriol (uE3), and dimeric inhibin A (DIA) are measured and the results combined with the PAPP-A and NT measurements from the first-trimester sample. The patient's risk for T21, T18, and ONTD is evaluated and reported.
 - Abnormal results require follow-up with targeted ultrasound, genetic counseling, and consideration of fetal-diagnostic testing.

Disease Overview

- DS is caused by an extra copy of chromosome 21. People with DS usually have moderate to severe mental retardation, characteristic facial features, and a variety of medical problems.
- T18 is caused by an extra copy of chromosome 18. Most newborns with T18 die at birth, but approximately 5–10 percent survive at least one year. Long-term survivors have profound mental retardation and are neither ambulatory nor articulate.
- The most common ONTDs include spina bifida and anencephaly. Spina bifida often results in some degree of paralysis of the lower limbs, difficulty with bowel and bladder control, and ventriculomegaly. Anencephaly is incompatible with life.

Epidemiology

- DS (1:700 births) and T18 (1:6,000 births) occur regardless of race or geographical location.
- The risk of DS and T18 increases with increasing maternal age, but approximately 50 percent of mothers with affected children are under 35 years of age.
- ONTDs occur independently of maternal age (~1:1,000–1,700 pregnancies in the United States) and vary with ethnic background, geographical location, and folic acid consumption.

Indication for Ordering

This test is indicated in any low-risk pregnant patient who presents before 14 weeks gestation.

Contraindications

- For high-risk pregnancies, a diagnostic procedure (e.g., chorionic villus sampling or amniocentesis) should be considered instead of maternal serum screening. High-risk pregnancies include:
 - Women of advanced maternal age (≥ 35 years at delivery).
 - Women with a prior pregnancy affected with an ONTD, DS, or T18.
 - Women taking valproic acid or carbamazepine.
- If a cystic hygroma or a significantly increased NT (>3.5 mm) is found on ultrasound, direct fetal karyotyping is recommended. Approximately 70 percent of first-trimester cystic hygromas are associated with a fetal aneuploidy, most commonly DS and Turner syndrome.
- If diagnostic testing is declined, patients need to be informed that screening misses some cases of ONTD, DS, and T18.

Additional Ordering Notes

- Collection of two blood specimens and an ultrasound are routinely required for this test.
- An ultrasound and collection of the first-trimester sample must occur between 11 weeks, 0 days and 13 weeks, 6 days of pregnancy (crown-rump length [CRL] must measure between 4.2 and 8.5 cm at the time of draw and ultrasound. Although the two can be done on different days, both must be performed within the specified gestational window).
- The sonographer performing the scan must be NT-certified by the Fetal Medicine Foundation (FMF) or the Nuchal Translucency Quality Review Program (NTQR).

- CRL and NT measurements must be performed on the same calendar day. The NT should be reported to the nearest 0.1 mm, along with the date of ultrasound, gestational age, and the sonographer's name and certification number. Test reporting may be delayed if this information is not received.
- If the sonographer is not certified or is otherwise unable to obtain an NT, the serum-only integrated screen (ARUP test code 0081062) may be ordered. Please see the ARUP Laboratory Test Directory or the Maternal Serum Screening Integrated Test technical bulletin, or contact an ARUP genetic counselor for test details.
- Specimen #2 collection occurs between 15 weeks, 0 days and 22 weeks, 6 days (based on the CRL). Acceptable date ranges to draw the second sample will be provided in the sequential-1 report.
- Patient demographics are required. The Patient History for Maternal Serum Testing
- Form is available at http://www.aruplab.com/guides/ug/tests/iconpdf_17.pdf; forms may be ordered from ARUP Client Services using requisition number #289-1101 or GP#41130.

Interpretation

- Patient demographics and analyte/ultrasound measurements are used to calculate multiple of the median (MoM) values for each of the laboratory analytes and the NT. The pattern of the MoM values is used to calculate post-test risks for ONTD, DS, and T18.
- Markers used for assessment of risk during the first trimester include NT, PAPP-A, and total hCG. Analytes measured in the second trimester include AFP, hCG, uE3, and DIA, which are combined with first trimester PAPP-A and NT results for the second-trimester risk assessment.
- First-trimester reporting:
 - Preliminary results, including the date range for required second-trimester specimen draw, are reported in the first trimester for pregnancies not at increased risk (risk better than one in 25) for DS or T18.
 - A final interpretation is provided in the first trimester if the pregnancy is at high risk (risk is one in 25 or worse) for DS or T18. No second-trimester sample is required.
- Second-trimester reporting:
 - A DS risk of one in 110 or worse is reported as abnormal. This risk cutoff predicts a detection rate of 86 percent at a screen positive rate of 1.6 percent.
 - A T18 risk of one in 100 or worse is reported as abnormal. This risk cutoff predicts a detection rate of 90 percent at a screen positive rate of < 0.5 percent.
 - ARUP uses a singleton AFP MoM cutoff of ≥ 2.5 . If the interpretation is "high AFP," there is an increased risk of an ONTD in the pregnancy. This cutoff value predicts a detection rate of 80 percent at a screen positive rate of 1.5 percent. High AFP also occurs in unrecognized twin pregnancies and with underestimated gestational age.
 - Pregnancies at an increased risk for ONTD with an AFP MoM of < 2.5, but a risk of one in 250 or worse, are also reported as abnormal. This is usually due to a family history of NTD, the use of certain seizure medications by the patient during pregnancy, or the presence of maternal insulin-dependant diabetes, any of which increases a patient's a priori risk for ONTD.
- An increased risk of congenital steroid sulfatase deficiency or Smith-Lemli-Opitz syndrome ($uE3 \leq 0.14$ MoM) and poor fetal outcome ($hCG \geq 3.5$ MoM) is reported as "see note."

Limitation

A screen interpreted as "normal" misses approximately 15 percent of DS, 20 percent of ONTD, and 10 percent of T18 cases.

Follow-Up Testing

- Recommended follow-up for a positive DS or T18 screen includes a targeted ultrasound examination and consideration of chorionic villus sampling (CVS) or amniocentesis for determination of fetal karyotype.
- For an $AFP \geq 3.0$ MoM, a targeted, level II ultrasound is recommended, which has 97 percent sensitivity and 100 percent specificity for ONTD when performed by an experienced sonographer. The patient should also be offered amniocentesis to measure amniotic fluid AFP and acetylcholinesterase (ACHE) to further assess the risk of ONTD.
- A high AFP between 2.5 and 3.0 MoM may represent a transient state; these women can have a repeat AFP test or be evaluated as those with an $AFP \geq 3.0$ MoM. If a repeat test is ordered, please redraw no sooner than two weeks after the second sequential draw was done and order an MS AFP-only (ARUP test code 0080434).

Methodology

- PAPP-A is a pregnancy-associated plasma protein A and is a sequential immunoenzymatic assay that uses monoclonal antibodies and external calibrators.
- AFP and hCG are both measured using a non-competitive immunoassay that uses one antibody to capture the protein to a solid phase, another antibody to detect the protein, and external calibrators.
- The estriol assay is a solid-phase competitive immunoassay that uses an anti-estriol polyclonal antibody, labeled estriol, a solid-phase antibody directed against the estriol antibody, and external calibrators.
- Inhibin-A is measured using a non-competitive microtiter immunoassay that uses a capture antibody to inhibit subunit βA , a detection antibody to subunit α , and external calibrators.
- Calculation of post-test risks uses a multivariate log Gaussian model. Risk estimates for DS and T18 are influenced strongly by maternal age.

Related Tests

- Maternal Serum Screen, Alpha Fetoprotein (only) (0080434)
- Maternal Serum Screen, Alpha Fetoprotein, hCG and Estriol (0080108)
- Maternal Serum Screen, Alpha Fetoprotein, hCG, Estriol, and Inhibin A (0080269)
- Maternal Serum Screening, Integrated, Specimen #1 (0081062)
- Maternal Serum Screening, Integrated, Specimen #2 (0081064)
- Maternal Serum Screen, First Trimester (0081150)

References

1. Ashwood ER, Knight GJ. Clinical chemistry of pregnancy. In *Tietz textbook of clinical chemistry and molecular diagnostics*, 4th ed. Burtis CA, Ashwood ER, Bruns DE, eds. 2006. Philadelphia: W.B. Saunders Co., 2153–206.
2. D'Alton M, Cleary-Goldman J. First and second trimester evaluation of risk for fetal aneuploidy: the secondary outcomes of the FASTER trial. *Semin Perinatol* 2005;29:240–6.
3. Gagnon A, et al. Society of Obstetricians and Gynaecologists of Canada Genetics Committee. Obstetrical complications associated with abnormal maternal serum markers analytes. *J Obstet Gynaecol Can* 2008;30:918–49.
4. Wald NJ, et al. SURUSS in perspective. *Semin Perinatol* 2005;29:225–35.

Test Information

0081293 **Maternal Screening, Sequential, Specimen #1**

0081294 **Maternal Screening, Sequential, Specimen #2**

For specific collection, transport, and testing information, refer to the ARUP website at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.