

Maternal Serum Screen, Quad

MATERNAL SERUM QUAD SCREENING SHOULD BE OFFERED TO WOMEN WHO ARE AT LOW RISK FOR ONTD, DS, AND T18

Clinical Background

- Most 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 quad screen helps identify pregnancies at increased risk for these disorders. It is not a diagnostic test. Abnormal results require follow-up with targeted ultrasound and consideration of a prenatal diagnostic procedure.
- Many pregnant patients request screening for these fetal defects. Choices include the maternal serum quad screen, the first-trimester screen, the integrated screen, and the sequential screen. The quad screen is indicated for patients in the second trimester who have not had first-trimester aneuploidy screening.

Disease Overview

- 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. ONTD occurs in approximately one in 900 pregnancies and is independent of maternal age.
- An extra 21st chromosome causes DS. People with DS usually have moderate mental retardation, characteristic facial features, and a variety of medical problems. DS occurs in approximately one in 700 births regardless of race or geographical location.
- An extra 18th chromosome causes T18. Most newborns with T18 die at birth, but approximately 5 percent survive at least one year. Long-term survivors have severe mental retardation and are neither ambulatory nor articulate. T18 occurs in approximately one in 5000 births.
- The risk of DS and T18 increases with increasing maternal age, but approximately 50 percent of mothers having affected children are under 35 years of age.

Indications for Ordering

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

Contraindications

High-risk women should consider skipping screening and instead have a diagnostic procedure, such as amniocentesis. This includes women of advanced maternal age (35 years or older at the expected time of delivery); those with a prior pregnancy affected with an autosomal trisomy, triploidy or ONTD; those who are diabetic or needing medication for glucose control; and women taking valproic acid or carbamazepine. If diagnostic testing is declined, patients need to be informed that the quad screen misses approximately 20 percent of fetuses with ONTD, DS, and T18.

Additional Ordering Notes

- The serum specimen should be collected between 14 weeks 0 days and 24 weeks 6 days. In order to provide accurate risks, ARUP requires patient demographic information. Please use the Patient History for Maternal Serum Testing form, which can be found on our Web site at http://www.aruplab.com/guides/ug/tests/iconpdf_17.
- Weight: A current patient weight is required to interpret the test.
- Due date: Please provide the most current due date and if it was determined by LMP or ultrasound.
- Race: Caucasian will be assumed if this is left blank.
- Insulin-dependant diabetic: Please mark "yes" if the patient has type I or type II diabetes and needs either insulin or oral medications for glucose control.
- Family history of NTD: If there is a family history, please tell us the relationship of the affected person to the fetus. For example: If the patient's sister had spina bifida, the relationship to the fetus would be "aunt."
- Previous pregnancy with a chromosome abnormality: Please include stillborn, miscarried, or terminated fetuses with known karyotypes. Any autosomal aneuploidy and triploidy affect the risk in the current pregnancy.
- IVF using a donor egg: Please mark "yes" if the egg used came from a donor or was retrieved from the patient one year or more prior to current pregnancy. Age of donor or age of patient at retrieval must be provided.
- Valproic acid or carbamazepine: If the patient is currently taking one of these medications (or was taking at any point during the pregnancy), or any derivative thereof, please mark "yes" and tell us the name of the medication.

Interpretation

- The quad screen measures alpha fetoprotein (AFP), human chorionic gonadotropin (hCG), unconjugated estriol (uE3), and dimeric inhibin A (DIA).
- Patient demographics are used to calculate the multiples of the median (MoM) values for each of the laboratory tests. The pattern of the MoM values is used to calculate post-test risks for ONTD, DS, and T18.
- If the interpretation is “high AFP,” the patient is at increased risk for ONTD. High AFP also occurs in an unrecognized twin pregnancy and an underestimated gestational age. A high AFP occurs at an AFP MoM of 2.5 or greater.
- Screens with a DS risk of one in 150 or worse are “abnormal.” Using these risk cutoffs will have an initial positive rate of 4–5 percent and a DS detection rate of ~80 percent.
- Other abnormal screens include those at increased risk for T18, or risk of NTD greater than one in 250, with an AFP MoM of less than 2.5 (usually due to a family history of NTD or other history, which increases a patient’s a priori risk for ONTD).
- Increased risk of congenital steroid sulfatase deficiency or Smith-Lemli-Opitz syndrome (uE3 < 0.15 MoM) and poor fetal outcome (hCG \geq 3.5 MoM) is reported as “see note.”

Limitations

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

Follow-up Testing

- Recommended follow-up testing depends on the type of abnormal screen. A thorough ultrasound examination is almost always indicated. Women who screen positive for DS or T18 require follow-up with targeted ultrasound examination and consideration of amniocentesis for determination of fetal karyotype.
- Women with a high AFP between 2.5 and 3.0 MoM can have a repeat AFP test or be evaluated as for those with AFP \geq 3.0 MoM. If a repeat test is ordered, please redraw no sooner than two weeks after the quad was drawn and order an MS AFP only [ARUP test Maternal Serum Screen, Alpha Fetoprotein (Only) (0080434)]. Do not request a second quad screen.

- Women with AFP \geq 3.0 MoM should have a targeted level II ultrasound, which has 97 percent sensitivity and 100 percent specificity for NTD when performed by experienced operator. The patient should also be offered amniocentesis to measure amniotic fluid AFP and acetylcholinesterase (ACHE) to further reduce the risk of an open neural tube defect by 99 percent.

Methodology

- AFP and hCG are both measured using a non-competitive (sandwich) 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 (sandwich) microtiter immunoassay that uses a capture antibody to inhibin subunit β A, 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.

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. Malone FD, et al. First- and second-trimester evaluation of risk (FASTER) trial: principal results of the NICHD multicenter Down syndrome screening study. *Am J Obstet Gynecol* 2003; 189:S56.
3. Wald NJ, Rodeck C, Hackshaw AK, and Rudnicka A. SURUSS in perspective. *BJOG* 2004; 111:521–31.
4. Haddow JE, et al. Second trimester screening for Down syndrome using maternal serum dimeric inhibin A. *J Med Screen* 1998; 5:115–9.

Test Information

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Maternal Serum Screen, Alpha Fetoprotein, hCG, Estriol, & Inhibin A

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

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