[A technical review]

Advances in Screening for Fetal Chromosomal Abnormalities

Introduction

The goal of maternal serum screening is to identify women who have an increased risk for fetal Down syndrome or open neural tube defects and to offer these women diagnostic testing. At the same time, the combination of markers is used to identify women at increased risk for fetal trisomy 18. Traditionally, maternal serum screening has been offered in the second trimester of pregnancy. Recent multi-center trials in the US and Europe have demonstrated that effective screening for fetal chromosome abnormalities can now be performed in the first trimester and that combining markers from both the first and second trimester results in improved detection rates.[1]

American College of Obstetricians and Gynecologists

Several Down syndrome screening strategies have been developed in the past decade, giving physicians and women an unprecedented number of choices. In January 2007, the American College of Obstetricians and Gynecologists (ACOG) published management guidelines for implementing Down syndrome screening in clinical practice.[1]

Notable recommendations and conclusions include[1]:

- Screening and invasive diagnostic testing for aneuploidy should be made available to all women who present for prenatal care before 20 weeks of gestation regardless of maternal age.
- First trimester screening using both nuchal translucency (NT) measurement and biochemical markers is an effective screening test for Down syndrome in the general population.
- Ideally, women seen early in pregnancy should be offered aneuploidy screening that combines first and second trimester testing (integrated and sequential).
- Options for women who are first seen during the second trimester are limited to quadruple screening (AFP, hCG, uE3, DIA) and ultrasound examination.

Maternal Serum Screening Options

LabCorp offers a comprehensive menu of maternal serum screening options that provides physicians with the flexibility to meet the needs and preferences of each woman (Table 1).

First and Second Trimester Combination Screening

First and second trimester combination screening tests provide Down syndrome, open spina bifida, and trisomy 18 risk assessments using first and second trimester maternal serum markers and first trimester measurement of the fetal nuchal translucency (NT). The NT is a collection of fluid behind the fetal neck as visualized by ultrasound.[1] Consistent with recommendations of ACOG, LabCorp only accepts NT values from sonographers credentialed specifically in the performance of NT measurements by the NTQR, Fetal Medicine Foundation, or equivalent entity.[1]

Integrated Screening requires measurements from two blood specimens, one collected in the first trimester and one in the second trimester.[2,3] Integrated Screening combines maternal age risk, first trimester NT, and maternal serum pregnancy-associated plasma protein A measurements with second trimester measurements of alpha-fetoprotein (AFP), unconjugated estriol (uE3), human chorionic gonadotropin (hCG), and dimeric inhibin A (DIA). After all testing is completed, a single risk assessment for Down syndrome is provided in the second trimester based on all markers. A screening result is provided for open spina bifida, and the screening markers are also used to identify pregnancies at high risk of trisomy 18. Integrated Screening detects an estimated 92.4%[4] of pregnancies with Down syndrome (with a 3.3%[4] false-positive rate), providing the highest detection rate and lowest false-positive rate of tests generally available.

Serum Integrated Screening is identical to Integrated screening, except that an NT measurement is not used in the risk assessment.[2,3,5] Serum Integrated Screening combines maternal age risk and first trimester maternal serum PAPP-A measurement with second trimester measurements of AFP, uE3, hCG, and DIA. This test may be beneficial for women without access to an NT measurement or for women in whom an NT measurement cannot be obtained for technical reasons. Serum Integrated screening has an estimated Down syndrome detection rate of 88.1%[4] (with a false-positive rate of 6.0%[4]), representing a significant improvement when compared to AFP Tetra.

Sequential Screening requires measurements from two blood specimens, one collected during the first trimester and the other in the second trimester.[5] In the first stage of Sequential Screening, an initial Down syndrome risk assessment is performed using maternal age, first trimester NT, PAPP-A, and hCG. Women with an exceptionally high Down syndrome risk (≥1:45) are reported as screen-positive with the recommendation to refer them for genetic counseling and diagnostic testing. Women whose Down syndrome risk assessment is below the cut-off (<1:45) proceed with the second stage of Sequential Screening (second trimester maternal serum AFP, uE3, hCG, and DIA analysis), at which time a final risk assessment for Down syndrome is provided based on NT, PAPP-A, and the four second trimester markers. A screening result is provided for open spina bifida, and the screening markers are also used to identify pregnancies at high risk of trisomy 18. Sequential Screening provides an estimated Down syndrome detection rate of 92.3%[4] (with a 3.5%[4] false-positive rate). Sequential Screening maintains the option of earlier diagnostic testing and pregnancy intervention for women found to be screen-positive after the first stage of the Sequential screen, while achieving a higher detection rate at a lower false-positive rate than the First Trimester Screen with Nuchal Translucency.

First Trimester Screening

The First Trimester Screen With Nuchal Translucency (FTS With NT) for Down syndrome combines maternal serum levels of human chorionic gonadotropin (hCG), pregnancy-associated plasma protein A (PAPP-A), and dimeric inhibin A (DIA) with maternal age risk and fetal nuchal translucency measurement. First trimester screening identifies 86%[3] of Down syndrome (with a 5%[3] false-positive rate) and about 75%[6] of trisomy 18 pregnancies (with a 0.5%[6] false-positive rate). Screening for open spina bifida (OSB) cannot be performed in the first trimester. Maternal serum AFP screening for open spina bifida in the second trimester is recommended with an optimal gestational age of 16 to 18 weeks.[1,7]

Second Trimester Screening

AFP Tetra screening for Down syndrome is offered in the second trimester of pregnancy and combines maternal serum measurements of AFP, uE3, hCG, and DIA with maternal age risk. AFP Tetra screening has an estimated Down syndrome detection rate of 75%-80%[9] (with a 5%[9] false-positive rate) and an estimated trisomy 18 detection rate of 73%[8] (with a 0.5%[8] false-positive rate). A risk assessment for open spina bifida is provided as well.

Implementing a Strategy

ACOG acknowledges that not all tests will be available in all areas and that each practice will have to determine which screening strategies best meet the needs of their patients.[1] In determining which tests to offer, gestational age at presentation, availability of personnel trained in nuchal translucency measurement, and the availability of CVS should be considered.[1]

Abbreviations	
ACOG	American College of Obstetricians and Gynecologists
AFP	Alpha-fetoprotein
CRL	Crown-rump length
CVS	Chorionic villus sampling
DIA	Dimeric inhibin A
FTS	First trimester screening
hCG	Human chorionic gonadotropin
NT	Nuchal translucency
NTQR	Nuchal Translucency Quality Review program
OSB	Open spina bifida
PAPP-A	Pregnancy-associated plasma protein A
uE3	Unconjugated estriol

Table 1. Comparison of Screening Options for Down Syndrome, Trisomy 18, and Open Spina Bifida

Test (Number)	Markers	Gestational Age	Down Syndrome		Trisomy 18		Open Spina Bifida		Specimen Requirements	CPT
			Detection Rate	False-positive Rate	Detection Rate	False-positive Rate	Detection Rate	False-positive Rate		
First and Second Trimester Combination Screening*										
Integrated 1† (017100)	NT; PAPP-A	10-13 weeks	92.4%[4]	3.3%[4]	90%[8]	0.1%[8]	80%[7]	1%-3%[10]	3 mL serum, gel-barrier tube (without thrombin additive). Avoid hemolysis. Submit original tube refrigerated; do **not** pour off. Provide CRL (45-84 mm), CRL date, NT, and sonographer's ID.	84163
Integrated 2 (017170)	AFP; uE3; hCG; DIA	15-21 weeks							5 mL serum, gel-barrier tube (without thrombin additive). Avoid hemolysis. Submit original tube refrigerated; do **not** pour off.	82105; 82677; 84702; 86336
Serum Integrated 1 (017200)	PAPP-A	10-13 weeks	88.1%[4]	6.0%[4]	90%[8]	0.1%[8]	80%[7]	1%-3%[10]	3 mL serum, gel-barrier tube (without thrombin additive). Avoid hemolysis. Submit original tube refrigerated; do **not** pour off.	84163
Serum Integrated 2 (017270)	AFP; uE3; hCG; DIA	15-21 weeks							5 mL serum, gel-barrier tube (without thrombin additive). Avoid hemolysis. Submit original tube refrigerated; do **not** pour off.	82105; 82677; 84702; 86336
Sequential 1† (017700)	NT; PAPP-A; hCG	10-13 weeks	92.3%[4]	3.5%[4]	90%[8]	0.1%[8]	80%[7]	1%-3%[10]	3 mL serum, gel-barrier tube (without thrombin additive). Avoid hemolysis. Submit original tube refrigerated; do **not** pour off. Provide CRL (45-84 mm), CRL date, NT, and sonographer's ID.	84163; 84702
Sequential 2 (017750)	AFP; uE3; hCG; DIA	15-21 weeks							5 mL serum, gel-barrier tube (without thrombin additive). Avoid hemolysis. Submit original tube refrigerated; do **not** pour off.	82105; 82677; 84702; 86336
First Trimester Screening (FTS)										
First Trimester Screen With Nuchal Translucency† (017500)	NT; PAPP-A; hCG; DIA	10-13 weeks	86%[3]	5%[3]	75%[6]	0.5%[6]	—	—	3 mL serum, gel-barrier tube (without thrombin additive). Avoid hemolysis. Submit original tube refrigerated; do **not** pour off. Provide CRL (45-84 mm), CRL date, NT, and sonographer's ID.	84163; 84702; 86336
Second Trimester Screening										
AFP Tetra (017319)	AFP; uE3; hCG; DIA	15-21 weeks	75%-80%[9]	5%[9]	73%[8]	0.5%[8]	80%[7]	1%-3%[10]	5 mL serum, gel-barrier tube (without thrombin additive). Avoid hemolysis. Submit original tube refrigerated; do **not** pour off.	82105; 82677; 84702; 86336
Maternal Serum AFP (010801)	AFP	15-23 weeks	—	—	—	—	80%[7]	1%-3%[10]	3 mL serum, gel-barrier tube (without thrombin additive). Avoid hemolysis. Submit original tube refrigerated; do **not** pour off.	82105

*For a risk assessment, these test options require two blood specimens: one collected between 10 to 13 weeks of gestation, the other collected between 15 to 21 weeks of gestation. Optimal screening for OSB is 16 to 18 weeks of gestation. Down syndrome detection rates and false-positive rates for Integrated, Serum Integrated, and Sequential Screening are based on first trimester markers measured at 11 completed weeks of gestation and second trimester markers measured at 14 to 20 weeks of gestation.
†The NT measurement should be performed by a health care professional credentialed by the Fetal Medicine Foundation, the Nuchal Translucency Quality Review Program, or an equivalent entity.

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