Incorporating First-Trimester Down Syndrome Studies Into Prenatal Screening

Executive Summary of the National Institute of Child Health and Human Development Workshop

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The National Institute of Child Health and Human Development (NICHD), the Society for Maternal–Fetal Medicine, and the American College of Obstetricians and Gynecologists (ACOG), cosponsored a workshop on December 16–17, 2004, to discuss the evidence for first-trimester Down syndrome screening and to explore the effects of combining first- and second-trimester screening, given the results of recent U.S. trials. The experts evaluated the evidence for offering first-trimester screening to provide individual risk assessment for Down syndrome. First-trimester screening has been demonstrated to provide efficient Down syndrome risk assessment, with a detection rate of 84% (95% confidence interval 80–87%), which is clinically comparable to the second-trimester quadruple screen at a fixed false-positive rate of 5%. The participants at the workshop concluded that at this time there is sufficient evidence to support implementing first-trimester Down syndrome risk assessment in obstetric practice in the United States, provided that certain requirements can be met. These requirements include training and quality control standards for first-trimester nuchal translucency measurement and laboratory assays, access to chorionic villus sampling, and appropriate counseling regarding screening options.

See related editorial on page 2.

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This workshop was cosponsored by the National Institute of Child Health and Human Development, Society for Maternal–Fetal Medicine, and the American College of Obstetricians and Gynecologists. Workshop participants are listed in the appendix.

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Prenatal screening for Down syndrome has been undergoing rapid development, with alternative approaches extending testing into early pregnancy. The National Institute of Child Health and Human Development (NICHD), the Society for Maternal–Fetal Medicine, and The American College of Obstetricians and Gynecologists (ACOG) held a workshop on December 16–17, 2004. Experts were asked to summarize the available studies on first-trimester and second-trimester screening for Down syndrome and to discuss the impact of clinical implementation of various combinations of screening tests in the United States. The development of guidance for clinical practice was *not* a goal of the workshop. The conference included representation from the relevant fields covered by this topic, including obstetricians, maternal–fetal medicine specialists, radiologists, geneticists, genetic counselors, developmental pediatricians, epidemiologists, ethicists, and public health experts. This report summarizes the discussions at this workshop.

Fetal aneuploidy complicates pregnancies of women of all ages, races, and ethnic backgrounds. It accounts for a large proportion of pregnancy loss, as well as perinatal morbidity and mortality. Down syndrome is the most frequent chromosomal disorder among liveborn children, with an expected prevalence of 1/600–800 live births.[1] Down syndrome is the most common identifiable cause of mental retardation and is associated with high rates of structural congenital anomalies, such as congenital heart defects. In addition, there are important developmental and social needs of children with Down syndrome.

Risk factors for Down syndrome include advanced maternal age, the birth of a previously affected child, and balanced parental structural rearrangements of chromosome 21. Although the majority of couples with one of these risk factors will have a normal child, many choose to have an invasive diagnostic test

Down Syndrome Risk Assessment Approaches

First trimester
Nuchal translucency, PAPP-A, hCG

Second trimester
Triple screen: MSAFP, hCG, uE_3
Quadruple screen: MSAFP, hCG, uE_3, inhibin-A
Genetic sonogram: ultrasound markers
Extended sonogram: serum + ultrasound markers

Integrative (nondisclosure of first-trimester results)
Integrated (NT, PAPP-A, quad screen)
Serum integrated (PAPP-A, quad screen)

Sequential (disclosure of first-trimester results)
Independent: independent interpretation of first- and second-trimester tests
Step-wise:
  First-trimester test:
    Positive: diagnostic test offered
    Negative: second-trimester test offered; final risk estimate incorporates first- and second-trimester results
Contingent:
  First-trimester test:
    Positive: diagnostic test offered
    Negative: no further testing
    Intermediate: second-trimester test offered; final risk estimate incorporates first- and second-trimester results

PAPP-A, pregnancy associated plasma protein-A; hCG, human chorionic gonadotrophin; MSAFP, maternal serum alpha-fetoprotein; uE_3, unconjugated estriol; NT, nuchal translucency.

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for reassurance. Invasive procedures potentially detect Down syndrome and other aneuploidies with a high degree of accuracy but are associated with a small risk of pregnancy loss. The National Institutes of Health Consensus Development Conference Statement in 1978 stated that women over 35 years of age at delivery should be offered second-trimester amniocentesis, establishing this age cutoff as the screening criterion for Down syndrome.[2] This cutoff attempted to balance procedure-related losses against the Down syndrome risk. Lower total postprocedure loss rates have been reported more recently by experienced practitioners with the use of ultrasound guidance, although the procedure-related loss rate has not been reevaluated by prospective studies. Chorionic villus sampling (CVS), introduced a decade later, provides an alternative for first-trimester diagnosis. Although safe, CVS is generally associated with a slightly higher risk of procedure-related loss than second-trimester amniocentesis.[3,4] Some operators believe that CVS and second-trimester amniocentesis may have comparable clinical safety when performed by individuals who are highly experienced with both procedures.[5]

Maternal age alone is a poor screening criterion for Down syndrome because the majority of children with Down syndrome are born to women who are less than 35 years of age. The observation of reduced maternal serum alpha-fetoprotein (MSAFP) associated with aneuploidy in 1984 enabled a woman's individual risk of Down syndrome to be further refined.[6] As a result, some older women at lower risk choose not to have an invasive procedure, and younger women identified at increased risk can choose diagnostic testing if they perceive the risk-benefit ratio of the invasive procedure as favorable. The sensitivity of maternal serum screening has progressively improved with the addition of sev-

eral other serum analytes. The "triple test" measures MSAFP, human chorionic gonadotropin (hCG), and unconjugated estriol, and more recently the "quadruple test" added measurement of inhibin-A. The evaluation of ultrasonographic markers in the second trimester, such as shortened humerus or increased nuchal skin fold thickness, provides additional quantitative information to modify risk assessment. By 1995, 63% of all pregnant women in the United States had serum screening performed.[7] This is often supplemented by ultrasonography of the second-trimester fetal anatomy or a "genetic sonogram" to look specifically for markers of aneuploidy.

From 1989 to 2001, live births to women over 35 years of age increased from 8.4% to 13.6%.[1] First births to 35- to 39-year-old women increased by 36% and to 40- to 44-year-old women by 70% between 1991 and 2001.[8] In addition to maternal age, the prevalence of Down syndrome infants is affected by the availability and uptake of screening and prenatal diagnosis. Second-trimester screening technologies have had a greater impact in the younger population because many women who are 35 years of age of older have been offered invasive testing since the 1970s. Thus, despite the older maternal age distribution in more recent years, there has been a 7.8% decline in reported number of Down syndrome neonates, and the decrease in observed-to-expected rates of Down syndrome live births is most dramatic for women under the age of 35.[1]

Although definitive noninvasive prenatal diagnosis remains an elusive goal, technological refinements continue to focus on improving individual patient risk assessment so that the number of invasive diagnostic procedures and procedure-related losses can be minimized. This is best achieved by maximizing the sensitivity for Down syndrome detection while maintaining the lowest possible false-positive rate.

In 1992, Nicolaides helped move Down syndrome screening from the second to the first trimester, when he reported that first-trimester nuchal translucency measurement was increased in 35% of aneuploid fetuses, compared with only 1% of euploid fetuses.[9] Other investigators subsequently confirmed this association. Studies have examined the use of nuchal translucency measurement either alone or in combination with maternal serum analytes (pregnancy-associated plasma protein-A [PAPP-A] and hCG) as a first-trimester screening test for Down syndrome. Several large prospective studies have compared first- and second-trimester screening and combining the results of testing in both the first and second trimesters.

The wider implementation of first-trimester Down syndrome screening may have significant effects on the interpretation of second-trimester screening results.

Presentations at the workshop included a review of the development and contribution of different components of first-trimester and second-trimester screening for detection of fetal aneuploidy, the role of invasive testing, recent studies performed in the United States, the economic and public health consequences of implementation of first-trimester screening, and the ethical issues surrounding various Down syndrome screening strategies. An issue of *Seminars in Perinatology* has been devoted to publication of manuscripts from these presentations.[10] Given the number of potential markers at various gestational ages, a myriad of approaches for risk assessment are possible. An outline of the approaches is provided in the box, "Down Syndrome Risk Assessment Approaches."

First trimester screening (nuchal translucency, hCG, and PAPP-A) is performed between 11 and 13 weeks and 6 days of gestation. Fetal nuchal translucency increases with crown-rump length, so it is important to take

Table 1. Combined First-Trimester Screening: Prospective Study Outcomes

	First-Trimester Detection Rate at 5% of False-Positive Rate		
Study*	Patients (n)	Down Syndrome Cases (n)	Detection Rate (%)†
BUN	8,216	61	79
FASTER	33,557	84	83
SURUSS	47,053	101	83
OSCAR	15,030	82	90
Total	103,856	328	84

* These numbers, presented at the time of the workshop, may differ from those presented in later publication.
† 95% Confidence interval 79.7–87.0%.
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gestational age into account when determining measurement cutoffs for an increased nuchal translucency measurement. First-trimester screening has been demonstrated to provide efficient Down syndrome risk assessment with a detection rate of 84% (95% CI 80–87%), which is clinically comparable with the second-trimester quadruple screen at a fixed false-positive rate of 5%. (Table 1).[11]

Timing of the performance of the components of the first-trimester screen is important to maximize sensitivity. The median nuchal translucency, PAPP-A, and hCG levels in affected pregnancies change with gestational age during the first trimester, as do their standard deviations in unaffected pregnancies. The optimal time to perform nuchal translucency measurement appears to be at 11 weeks.[12–14]

In the first trimester, the maternal serum concentration of hCG is higher in pregnancies with Down syndrome than in pregnancies with chromosomally normal fetuses, whereas PAPP-A is lower.[12] Two forms of hCG are used in Down syndrome serum screening: free β-hCG and total hCG (free + intact β-hCG). As an independent serum marker, free β-hCG performs better than total hCG up to 13 weeks,[15] but when combined with nuchal translucency and PAPP-A as part of the first-trimester screen, there does not appear to be a clinically significant advantage.[16]

The discrimination of hCG improves with increasing gestational age during the first trimester and is greatest at 13 weeks, whereas the sensitivity of PAPP-A is optimal at 10 weeks and declines thereafter. Although screening may be performed between 10 and 13 weeks, 11 weeks appears to be the optimal time.[13,14]

Second trimester screening began with the triple screen, composed of MSAFP, hCG, and unconjugated estriol, usually performed between 15 and 22 weeks. Quad screen (MSAFP, hCG, unconjugated estriol, and inhibin) demonstrates increased sensitivity for Down syndrome detection. Estimates from 2 of the most recent large studies, SURUSS and FASTER, are similar (Table 2). The incremental gain in detection by going from the triple to the quad marker test is between 7 and 11 percentage points, with a detection rate of approximately 80% for 5% false-positive rate.[17]

The *genetic sonogram* is a systematic algorithm combining multiple individual ultrasound markers during the second trimester to improve Down syndrome risk assessment. Markers that are evaluated include major structural malformations, shortened humerus or femur, and other anatomic findings that have been associated with Down syndrome, such as increased nuchal skin thickness, pyelectasis, echogenic intracardiac focus, hypoplastic fifth digit, sandal gap toe, echogenic bowel, and widened iliac angle. An abnormal genetic sonogram results when there is abnormal biometry, a major structural anomaly, or another anatomic finding suggestive of Down syndrome. Risk is adjusted in the presence of multiple sonographic markers by multiplying age-related risk by the product of the respective ultrasound markers' likelihood ratios. This "screening" concept was developed and applied almost exclusively in high-risk referral populations.[18] A large meta-analysis of second-trimester Down syndrome markers concluded that sonographic markers are not of practical value in the low-risk population.[19] This finding is likely due to the lack of uniformity in obtaining and interpreting these markers, variability in operator experience and sonographic equipment, and lack of quality control.

Maternal serum analyte screening remains the standard for second-trimester Down syndrome screening. As expected, efforts have been made to combine genetic sonography with these biochemical markers in the form of the "extended genetic sonogram" to improve detection. By the same method traditionally used for serum markers, the correlations between biometry and other markers, eg, hCG, can be calculated, and individual risk of Down syndrome based on combinations of maternal age, ultrasound biometry, and serum markers can be determined. As observed with first-trimester screening, the combination of ultrasonography and biochemistry may result in increased Down syndrome detection compared with that obtained from either group of markers by themselves.[20]

Integrative testing involves the performance of first- and second-trimester testing and reporting a single risk to the patient in the

Table 2. Second-Trimester Test Performance

	Detection Rate at 5% of False-Positive Rate	
	SURUSS (%)	FASTER (%)
Triple markers:		
AFP + hCG + uE_3	74	70
Quad markers:		
AFP + hCG + uE_3 + inh A	81	81

AFP, maternal serum alpha-fetoprotein; hCG, human chorionic gonadotrophin; uE_3, unconjugated estriol; inh A, inhibin-A.

Adapted from Canick JA, Macrae AR. Second trimester serum markers. Semin Perinatol 2005;29:205; with permission from Elsevier

second trimester. The patented "integrated test" involves measurement of nuchal translucency and PAPP-A in the first trimester. The results of the first-trimester screen are not disclosed to the patient. Patients return at 15 weeks of gestation, when the quad markers are obtained, and results of nuchal translucency, PAPP-A, and quad markers are combined to provide a single Down syndrome risk assessment in the second trimester. In studies of this approach, the hCG results from the first trimester were not included in the integrated risk assessment calculation. Integrated screening yields a high detection rate with a low false-positive rate. In the FASTER and SURUSS trials, such an integrated screening program had a sensitivity of 95% and 94%, with false-positive rates of 4.0% and 4.9%, respectively.[13,14] When nuchal translucency scan is not available, the integrated serum screen may be performed (PAPP-A, quad screen). This "integrated serum" test is projected to yield a screening performance similar to, or slightly better than, the first-trimester combined test (detection rate of 85% at a 3.9 % false-positive rate).[13]

Sequential testing involves the performance of both first- (PAPP-A, hCG, and nuchal translucency) and second-trimester testing (MSAFP, unconjugated estriol, hCG, and inhibin) with the disclosure of first-trimester results so the patient can act upon these results. There are 3 approaches to sequential screening: 1) independent, 2) stepwise, and 3) contingent. Significantly different risks may be reported to the same patient depending on which approach is used.

Independent sequential testing involves the independent interpretation of first- and second-trimester tests. The first-trimester test result is given to the patient, and second-trimester testing is offered unless the patient has undergone CVS. However, the second-trimester test is interpreted without taking into account the first-trimester test results, ie, maternal age is used as the a priori risk for second-trimester testing. Although the sensitivity is high, this is the least efficient risk assessment strategy because the additive false-positive rate is unacceptably high.[14,21]

In *stepwise sequential testing* an early invasive procedure is offered if the first-trimester result is above a specified cutoff. If the first-trimester screening result is below the cutoff, then the patient is offered second-trimester testing, and the final risk in the second trimester is determined using all markers. In the FASTER Trial, such a stepwise sequential screening program detected 95% of Down syndrome cases at a 4.9% false-positive rate.[14] The advantage of this approach is a sensitivity and a false-positive rate approaching those obtained with integrated screening, but with the option of early results being available for the highest risk patients in the first trimester.

Contingent sequential testing also begins with the performance of first-trimester screening. Based on the first-trimester screening results, women are then grouped in 1 of 3 risk categories: high, intermediate, and low risk. The cutoff points of the groups and their specific risks vary depending upon how these groups are defined. Table 3 presents one example of how these groups may be defined.[22] The highest risk group (above designated cutoff, eg, > 1 in 65 Down syndrome risk) is offered early diagnosis. The lowest risk group (low cutoff, eg, < 1 in 1,300 Down syndrome risk) is reassured and does not undergo second-trimester testing. The intermediate risk group (eg, risk between 1 in 65 and 1 in 1,300) is offered second-trimester testing (quad screen). The final reported risk in the second trimester in this group is estimated using all 7 markers.

For contingent sequential screening to be successful, careful determination of risk cutoffs is required. The first-trimester cutoff must identify a significant proportion of Down syndrome pregnancies with only a small number of false positives. Similarly, the group having no further testing should contain few affected pregnancies but should be large enough to minimize the number of patients requiring second-trimester screening. The intermediate cutoff should identify the majority of the remaining Down syndrome pregnancies after second-trimester screening, with a limited number of patients being offered amniocentesis.

The sensitivities of first- and second-trimester screening at a 5% false positive rate from large prospective trials are summarized in Tables 1 and 2, respectively. The participants at the workshop concluded that, at this time, there is

Table 3. Example of Risk Groups for Contingent Screening

Trisomy 21 Risk Group	Estimated Percentage of Total Population	Estimated Percentage of Total Trisomy 21
High (> 1 in 65)	1	70
Intermediate (1 in 65 to 1 in 1,300)	18	25
Low (< 1 in 1,300)	81	5

sufficient evidence to support implementation of first-trimester Down syndrome risk assessment in obstetric practice in the United States, provided that certain requirements can be met. These requirements include training and quality-control standards for first-trimester nuchal translucency measurement and laboratory assay and appropriate counseling regarding various options. Implementation of widespread first-trimester screening also necessitates the availability of early sonogram for more accurate ultrasound dating and also access to CVS. Discussion of various screening strategies followed taking into consideration patient preference and choice, available resources, practical implementation, and effectiveness of risk assessment. Although integrated screening provides high sensitivity and a low false-positive rate, there was concern that routine nondisclosure of first-trimester screening might not be acceptable to patients in clinical practice and that withholding results violates sound ethical principles of medical practice. For this reason the participants generally agreed that contingent sequential screening, a strategy that has not been studied prospectively, merits further evaluation.

The wider implementation of first-trimester Down syndrome screening may have significant effects on the interpretation of second-trimester screening results. Increased use of first-trimester screening will likely lead to decreased prevalence of Down syndrome in the second trimester. Without modification of second-trimester serum marker cutoffs for the subpopulation having already undergone first-trimester screening, the decreased prevalence will decrease the positive predictive value and increase the false-positive rate of the second-trimester serum screening and genetic sonogram. With contingent screening the highest risk group will have first-trimester diagnosis, and the prevalence of Down syndrome will also be decreased in the second trimester. However, because the remaining patients who have second-trimester screening are an intermediate risk group, cutoffs may be established so that the performance characteristics of the risk assessment may not be substantively changed. When first-trimester Down syndrome screening is performed, strategies that eliminate second-trimester screening for Down syndrome will still require that we offer screening for open neural tube defects.

For patients, choosing a risk assessment approach from the large array of possible strategies is a complex decision-making process. It requires information about the sensitivity, false-positive rate, comparative procedure-related risk of first- and second-trimester diagnostic procedures, and timing in gestation that the information will become available to patients. Some couples might choose a more sensitive risk assessment scenario to reduce the risk of procedure-related loss, even if that means the information will not be available until the second trimester. Others may opt for risk assessment that has a higher false-positive rate and, therefore, a higher risk of procedure-related loss, to obtain information at an earlier time in pregnancy. The argument that patients are being deprived of an opportunity to make decisions about their pregnancy management at an early gestational age is avoided when women are able to select the testing protocol before testing begins. These decisions are value laden and can only be made by patients.

Health care providers will also need additional education to be able to appropriately counsel women about the different risk assessment approaches. The difficulties in offering these complex choices are likely to require a gradual transition in clinical practice. Newer tests are being developed, and risk assessment approaches will continue to increase and evolve. Our role as health care providers will be to inform couples in a nonjudgmental manner of the available options and allow them to select the best risk assessment approach for their unique set of circumstances.

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APPENDIX

The following is an alphabetical list of participants at the workshop:

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