

## Prenatal Diagnosis in the 21<sup>st</sup> Century

*From the Editor and Authors*

*Since our last Update on Prenatal Diagnosis in 1994, there have been significant advances in the use of prenatal screening procedures and options. This includes the use of ultrasound and maternal serum analysis in the first trimester of pregnancy. Some of these options have reported a 90% or higher sensitivity rate in the detection of Down syndrome. This has caused a shift in the use of invasive procedures for diagnostic purposes. In this issue, we will describe some of these options in detail. We will also discuss the need for comprehensive guidance and counseling when these options are presented to the patient.*

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### Update on Prenatal Screening Options

#### **Combined ultrasound with serum screening**

Recently screening has focused both on moving the gestational age window earlier in the pregnancy as well as using a combination of screening techniques to enhance detection and decrease the screen positive rate.

#### **Maternal age Screening**

Historically the original screening tool for identifying chromosome risk, particularly Down syndrome, was maternal age. The fact that Down syndrome children were more likely born to older women was recognized as early as 1909. In the late 1950's Lejeune and Jacobs first noted that Down syndrome is caused by an extra acrocentric

chromosome and by late 1960's prenatal diagnosis of Down syndrome by amniocentesis was described. By the 1970's the United States standardized the clinical practice of screening by maternal age and offered amniocentesis to women older than 35 years old. At that time, this represented about 5% of the pregnant population and was felt to be reasonable "screen positive rate". Currently, about 10-11% of the pregnancy population is over age 35, resulting in a doubling of the screen positive rate when using maternal age alone.

It was quickly recognized that the majority of Down syndrome cases were missed when screening by maternal age alone. About 30% of Down syndrome pregnancies are detected using age related risk cut off of 35 while 70% are missed.

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## Maternal Serum Screening

Maternal serum screening was added to the screening armamentarium as way to address the percentage of Down syndrome cases missed when using age related risk alone. The clinically relevant serum analytes are alpha-feto protein (AFP) human chorionic gonadotropin (HCG), estriol (uE3) and inhibin. When used in combination these make up the components of the double, triple and quad marker screens. Using universal serum screening on a population basis represented a significant improvement over age alone. By the mid 1980's, offering this type of enhanced screening to low risk women became standard. Using a 5% screen positive rate for the overall population, the performance of these serum screening strategies is as follows:

- Double marker (AFP, HCG) – 59%
- Triple marker (AFP, HCG, estriol) – 69%
- Quad marker (AFP, HCG, estriol, inhibin) – 76%

While this represents a significant improvement over age related screening alone, these screening strategies are not perfect and miss a substantial number of cases. In addition, the actual screen positive rate in many populations is much higher related primarily to dating issues. Finally, these markers are only valid in the second trimester- 15-22 weeks. This has led to interest in better and earlier screening strategies.

## First trimester screening for chromosome disorders

Advances in serum and ultrasound techniques now allow very effective screening to be performed in the first trimester. Advantages of this approach include:

- Increased time for performing genetic testing.
- May increase options for therapeutic intervention in the future.
- Alleviates anxiety earlier in the pregnancy. Increased time for decisions.
- Termination of pregnancy is safer and may be more acceptable to the couple

Recent large studies also indicate that screening strategies which include first trimester screening may be more effective due both to an increased detection rate as well as a lower screen positive rate. There are a variety of options available for first trimester screening. No standard for clinical practice has been established leaving the decision for mode of testing up to the practitioner and the patient. This is likely to change over the coming years as a more uniform testing strategy becomes established based on a variety of issues including detection rates, screen positive rates, cost of serum testing, cost of ultrasound screening and availability of appropriate resources for the testing.

Currently, the first trimester maternal serum analytes that have been clinically validated are PAPP-A, total B-HCG or free BHCG. Free beta HCG (measurement of only the free beta subunit of the HCG molecule) is the one analyte that appears to have utility in both the first and second trimesters. Total beta HCG can also be used however with somewhat lower efficacy in the first trimester as a single marker. The useful range of free beta HCG is from 9-22 weeks gestation. Levels are noted to be increased in trisomy 21, and decreased in trisomy 13 and 18. Pregnancy Associated Protein A (PAPP-A) is a placentally derived protein that is useful in the first trimester only; between 9-13 weeks. Levels are noted to be decreased in trisomy 21, 18 and 13.

One unique feature of first trimester screening is that it most commonly involves the combination of maternal serum analytes with a quantitative ultrasound measurement of the nuchal translucency. Although ultrasound has been used for many years as a screening tool for birth defects, this is the first screening algorithm where ultrasound technique has been rigorously standardized in order to be used quantitatively in risk assessment.

The nuchal translucency refers to the subcutaneous space between the fetal skin and the soft tissue covering the cervical spine measurement in a midline sagittal plane. An increased diameter of this space is associated with an increased risk of chromosome abnormalities as well as congenital heart disease, and a variety of other syndromes.

This measurement is only valid in the first trimester, from about 11- 13 weeks and should not be confused with the nuchal fold measurement. The nuchal fold is the thickness of the back of the neck from the occipital bone to the outer skin surface measured in a transverse diameter. The nuchal fold is valid in the second trimester- 15-22 weeks, as a soft marker for Down syndrome.

The nuchal translucency (NT) has been found to be the single most powerful ultrasound screening parameter for chromosome risk. The detection rates in various studies with this marker alone in the 1<sup>st</sup> trimester vary between 78- 90% depending in the population studied. By combining NT measurements with maternal serum screening it is possible to increase the detection rate as well as decrease the screen positive rate. Another advantage of using NT with maternal serum screening is the elimination of false positives due to dating errors. This problem may increase the actual screen positive rate to as high as 12-15% for triple marker or quad marker testing. With 1<sup>st</sup> trimester screening using maternal serum and NT, dating issues are eliminated so that actual false positive rates would be significantly reduced in clinical practice.

The appropriate combination of ultrasound, 1<sup>st</sup> and second trimester serum screening has not been standardized. A variety of strategies currently exist:

1. NT alone or 1<sup>st</sup> trimester serum screen alone
2. Combined screen- NT plus PAPP-A, free BHCG
3. Sequential- Combined screen and then Quad screen
4. Integrated- NT, PAPP-A plus Quad
5. Serum Integrated- 1<sup>st</sup> and 2<sup>nd</sup> trimester serum
6. Contingency screening- 1<sup>st</sup> trimester combined screen followed by Integrated testing only in intermediate risk group
7. Sequential screening- 1<sup>st</sup> trimester combined screen followed by Integrated screen.

Standardization of testing options will require clarification of the data- predictive values, false positive rates, cost/ benefit analysis based on large clinical trials that have recently been completed. New ultrasound markers, such a nasal bone, tricuspid valve regurgitation and ductus venosus flow patterns are also being validated and may eventually become part of the screening algorithm.

Universal implementation of first trimester screening will require infrastructure support. This would include a shift to early enrollment in prenatal care, PR. Cost /benefit analysis. Appropriate training and standardization of sonographers to perform NT measurements would need to be implemented and is in fact currently being implemented through several organizations including the Society of Maternal Fetal Medicine (SMFM) and the Fetal Medicine Foundation. Another important feature would be expanding the availability of CVS as the follow-up diagnostic test for a positive first trimester screen.

**Table 1. Summary of Screening Options**

	<b>First Trimester Screening</b>	<b>Quad Marker Screening</b>	<b>Combined, Integrated Screening</b>
Timing	10-13 weeks	15-22 weeks	10-13 weeks, then 15-22 weeks
NTD Screening	No	Yes	Yes
False Positive Rate	5%-6%	5%-6%	1%-2%
Detection Rate	85%-90%	75%-80%	93%
Trisomy 18 Screening	No	Yes	Yes
Testing Options	CVS, U/S, Amniocentesis	U/S, Amniocentesis	U/S, Amniocentesis

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## **Prenatal Screening for Chromosome Abnormalities: The Need for Anticipatory Guidance & Follow-up – One Genetic Counselor’s Perspective**

To many providers, prenatal screening tests are useful tools for sorting patients into categories of risk, minimizing the use of invasive diagnostic procedures, and deciding what tests to offer. As providers we may assume that the desire for risk information is universal. As it turns out, the simple fact that screening tests present no physical risk to the patient does not mean that they are the proper choice for everyone. Like diagnostic tests such as amniocentesis, the offering of prenatal screening tests should be accompanied by at least a minimum of counseling and anticipatory guidance.

One concept that can be challenging for consumers of prenatal tests is the difference between a screening and diagnostic test. Among genetic counselors, stories abound about clients who say they were told their baby has Down syndrome based on a screening test. Of course, it is unlikely that the providers in these situations actually told the patient that the test diagnosed Down syndrome. Nonetheless, it is clear that many consumers hear the worst as they are responding to the emotional shock of having an abnormal result on a test that was not fully explained beforehand. The chances of this type of miscommunication can be reduced by a simple conversation about the nature of screening tests vs. diagnostic tests, *before* any screen is ordered. If given a few minutes of time to discuss the issue, most consumers can grasp the fact that the test looks for warning signs that are alone inconclusive, and that are meant to be used for later decision-making.

On the other hand, downplaying the ability of screening tests to detect fetal problems can also cause confusion. Some patients may have had a provider who was so emphatic beforehand that a screening test can be wrong that the patient completely disregards the implications of an abnormal test (see, for example, “Genetic counseling gone awry: Miscommunication between prenatal genetic service providers and Mexican-

origin clients” by Browner et al.) Others have interpreted that screening tests were done to *ensure* the baby’s health. It is common for a genetic counselor to hear a client say they were completely unaware they were being tested for Down syndrome risks until they found out the test was positive. Some consumers say that they would not have wanted the test if they had completely understood what it was looking for, especially when they learn that the next steps include provider offer of amniocentesis and pregnancy termination. There are some expectant parents who simply do not want to know before delivery if the baby is affected with a chromosome condition. For those patients, prenatal screening tests are not necessarily appropriate.

Another complaint from some consumers of prenatal genetic testing is that results are delivered in an insensitive and unsupportive manner (see, for example, “Prenatally diagnosed Down syndrome: Mothers who continued their pregnancies evaluate their health care providers” by Skotko). Of course, it is difficult to win any popularity points when one is the bearer of bad news. However, we can try to deliver diagnoses in a compassionate, non-judgmental manner, and be ready with contact information for support organizations in the community. We can also educate ourselves about the true spectrum of outcomes for fetal diagnoses and refrain from painting only a worst-case scenario for our patients. Families report that they want accurate information, but also help maintaining a healthy, realistic hope that they can manage whatever challenge lies ahead.

In summary, the issues surrounding prenatal screening and diagnostic testing require compassionate and articulate communication between provider and consumer. Genetic counselors are not only trained in medical genetics, but also in the delicacies of communicating about complex and emotionally charged medical issues. Thorough genetic counseling can help consumers make choices based on their own values and individual situations, provide patients with coping strategies and a sense of control over a frightening situation, and connect with support resources in the community. To find a genetic counselor in your

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area, visit the National Society of Genetic Counselors website at [www.nsgc.org](http://www.nsgc.org) or the Mountain States Regional Genetics Collaborative Center website at [www.msgrcc.org](http://www.msgrcc.org).

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