A mid-sagittal view of a 12.5 week fetus showing an abnormal profile with a maxillary protuberance (arrow) characteristic of a facial cleft. The Perinatal Quality Foundation supports research demonstrating the value of first trimester ultrasound.

IN THIS ISSUE

- 1st Trimester Sonographic Markers of Aneuploidy.
- Cervix Measurement Image Criteria.
- Tips for Quality Monitoring Within Practices
- 1st Trimester Sonographic Markers: Are They Being Done?
- Non-Invasive Prenatal Screening: A Primer.
- Impact of a Required Remediation Program.
- Can We Predict Providers Assigned to RQM?
- Does Practice Size Impact Measurements?
- What Does the Literature Say About Transvaginal and Transabdominal Measurements of the Cervix?

Prenatal detection of aneuploidy is one of the major objectives of screening sonography, and although nuchal translucency is one methodology, there are other sonographic markers that have been proposed to evaluate risk of aneuploidy. Advances in diagnostic ultrasound technology and technique have led to improved visualization of fetal anatomy at earlier gestational ages as well as identification of other first trimester markers of aneuploidy.

Absent Nasal Bone:

Earlier work examining facial characteristics of individuals with trisomy 21 noted a shorter than average nasal bridge (1). This led to an interest in detecting this feature prenatally and assessing its predictive value in diagnosing aneuploidy. Cicero et al published the first large prospective trial and studied fetal profile in 701 high-risk pregnancies at 11-14 weeks and found that 73% of fetuses with trisomy 21 had an absent nasal bone as compared to only 0.5% of chromosomally normal fetuses (2). In their follow-up work of more than 5851 cases they again noted association with trisomy 21 with 68.8%

CERVIX MEASUREMENT IMAGE CRITERIA:

1. Transvaginal Image
2. Cervix is approximately 75% of image
3. Anterior = Posterior Width
4. Maternal Bladder Empty
5. Internal Os is Seen
6. External Os is Seen
7. Cervical Canal Visible Throughout
8. Caliper Placement Correct
9. Cervix Mobility Considered
of trisomy 21 fetuses having an absent nasal bone and 32.3% of fetuses with other chromosomal abnormalities presenting with this finding (3). This study also noted an ethnic discrepancy associated with absent nasal bone, with the finding more likely to be a normal variant (up to 9%) in those of Afro-Caribbean ancestry, compared with 2% for Caucasians and 5.0% for Asians. The prevalence also decreased as CRL and gestational age increased. More recently, Rosen et al reviewed current literature on this marker and included over 35,000 (from nine studies) of first trimester nasal bone ultrasound assessments in selected and unselected populations. Overall, they reported a 65% rate of absent nasal bone in fetuses with trisomy 21 compared to 0.8% of euploid fetuses and a wide range in the ability to perform a successful examination (76-100%), varying by the institution (4). One of the proposed explanations for this wide variation is difficulty in obtaining an appropriate image for nasal bone assessment and the high level of training required to achieve competence. Many experts have described obtaining nasal bone images as much more challenging than nuchal translucency since nasal bones require a perfect mid-sagittal image and optimal angle of insonation with the fetal profile (4). In conclusion, while non-visualization of the nasal bone in the first trimester and trisomy 21 have a definitive relationship, the use and value of this marker in the general population has not been fully determined. Lack of widespread sonographic expertise to accurately assess this marker adds another challenge. Cicero et al suggested a reasonable 2-stage approach, where NT and maternal serum analytes are first assessed and women with intermediate risk (defined by the authors as having between 1 in 100 and 1 in 1000 risk of aneuploidy) undergo a nasal bone examination. The investigators also published formulas which integrate race, gestational age and nuchal translucency into the overall risk assessment of an absent nasal bone.

A-wave in the Ductus Venosus:

Another sonographic finding noted more commonly in aneuploid fetuses is absent or reversed A-wave in the ductus venosus (DV). Murta et al studied 372 high risk pregnancies with suspected chromosomal abnormality, 29 of which had confirmed aneuploidy. Of the chromosomally abnormal fetuses, 93.1% had either absent or reversed ductus venosus flow compared to 1.7% in chromosomally normal fetuses (5). Oh et al performed Doppler assessment of DV in over 2500 cases and noted a relationship of abnormal flow with not only aneuploidy, but cardiac defects, IUGR and renal anomalies as well (6). Maiz and colleagues screened over 19,000 pregnancies comparing performance of traditional first trimester screening with screening that included DV flow. They found an improved overall performance of first trimester aneuploidy screening with inclusion of DV with detection rate of 96% of trisomy 21 cases and false positive rate of 3% (7). While this data seems promising, the utility and application of this sonographic finding to the general population remains uncertain. Ductus venosus in the first trimester may be as small as 2 mm and due to both the small size and risk of Doppler contamination from neighboring vessels, accurate Doppler assessment is very challenging (8). Extensive and specialized training is required to accurately find and measure the flow in the vessel and until further studies confirm its applicability in aneuploidy screening of the general population, its clinical application is limited. Similar to Cicero, Maiz suggested a 2-stage approach with screening of only “intermediate-risk” (defined as 1 in 51 to 1 in 1000) population and this tactic may be not unreasonable in institutions with experienced providers (7).

Tricuspid Regurgitation and Mitral-Tricuspid Offset:

More recently, researchers have reported on another first trimester marker of aneuploidy – tricuspid regurgitation (TR). Kagan et al screened over 19,000 pregnancies and reported that TR was noted in 0.9% of chromosomally normal fetuses and 55%, 33% and 30% of fetuses with trisomies 21, 18, 13, respectively (9). Despite positive association, limitations of efficacy of this marker exist and are similar to those of DV assessment. Lack of technical experience with first trimester fetal cardiac anatomy, small caliber of the valve as well as the possibility of contamination from adjacent valves are all limitations of wide-spread use of this marker. Another marker that has been suggested is that of decreased mitral valve-tricuspid valve distance (MTD) as MTD is
associated with endocardial cushion defects. In a study of 691 fetuses, MTD was found to have a detection rate of 70% with a 3.8% false positive rate.(10)

**Conclusion:**
While the performance of these first trimester sonography screening tests seems promising, the application of this data to the general population is still uncertain. In the largest reported study to date, Ghaffari and colleagues published a report on 13,706 pregnancies and concluded that detection rate of chromosomally abnormal fetuses was 100% when utilizing maternal serum markers plus nuchal translucency, nasal bone, ductus venosus and tricuspid regurgitation. Their reported false positive rate was 3.4% (11). Lack of expertise in evaluating these markers may lead to increased false positive rate which, in turn, can lead to increased patient anxiety. As ultrasound technology continues to improve and as experience is gained, the applicability of these more recent markers may become more realistic and feasible.

**References**
As summarized in the article in this issue by Gilmandyar and Thornburg, prospective studies have shown that first trimester sonographic assessment of the nasal bone (NB), tricuspid valve (TV), and ductus venosus (DV) have the potential to improve the performance of aneuploidy screening with higher detection rates and decreased false-positive rates. In addition to these promising statistics, however, the literature also demonstrates that there is a significant learning curve associated with accurate assessment of these markers. Specifically, it has been shown that sonographers learning to perform either NB or DV assessments in the first trimester require approximately 80 scans to achieve competence in image acquisition and interpretation (Cicero 2003, Maiz 2008). The significant training required undoubtedly impacts the feasibility of performing these assessments in the general population, but the frequency with which these first trimester aneuploidy markers are being evaluated in clinical practice is unknown. Accordingly, the Education Committee of the Nuchal Translucency Quality Review (NTQR) sought to examine practice patterns related to first trimester aneuploidy markers including the nasal bone, tricuspid valve, and ductus venosus.

Surveys were emailed to 7,218 NTQR participants, and responses were received from 17.4%. Of the respondents, 21.7% were physicians and 78.3% were sonographers. When asked about imaging of the fetal nasal bone in the first trimester, 56.6% of respondents reported that they perform NB assessment if it is “technically feasible” at the time of the NT scan. Of those who perform NB assessment at the time of the NT scan, 51.5% state that they use the results in the initial risk assessment and 48.5% state that the NB is used as a contingency (or secondary) risk element. Interestingly, only 30% of respondents report being credentialed to perform first trimester nasal bone (NB) assessment.
The vast majority of respondents - 91.1% - report not assessing either tricuspid regurgitation (TR) or ductus venosus (DV) for first trimester aneuploidy screening, whereas 3.9% perform both, 0.7% assess TR alone, and 4.3% assess the DV only. Of those respondents who evaluate TR and/or DV, 89.7% state that it is completed within the standard exam allotment, whereas 10.3% allow extra time if needed. In total, only 69 respondents report altering recommendations based on TR and/or DV results. Of all respondents, only 32 reported being credentialed to perform either TR or DV in the first trimester; of those who report performing either TR or DV evaluations, 84.1% report that they are not credentialed to perform these assessments in the first trimester. Overall, only 23.7% of all respondents report being interested in learning TR and/or DV techniques.

The survey data above suggest that the NB, TR, and the DV are not being routinely assessed in clinical practice as part of first trimester aneuploidy screening. Furthermore, the survey shows a significant proportion of the providers who do perform these first trimester assessments in clinical practice are not credentialed to do so, and that a minority of respondents were interested in further education. While explanation for the low rates of credentialing and lack of interest in further education is likely multifactorial, it is possible that these findings are influenced by the emerging role of non-invasive prenatal screening for fetal aneuploidy. In fact, more than half of respondents agreed that non-invasive prenatal screening using cell-free fetal nucleic acids would replace first trimester screening using NT within the next 3-5 years. While the role of non-invasive prenatal screening in clinical practice remains to be seen, the promise this technology holds may make providers reluctant to pursue the training and credentialing required for more widespread utilization of first trimester nasal bone, tricuspid valve, and ductus venosus assessment in aneuploidy screening.

References:

What is non-invasive prenatal screening (NIPS)?
New molecular genetic techniques such as massively parallel shot gun sequencing (MPSS) have made it possible to take advantage of the presence of cell free fetal DNA in the maternal bloodstream to determine whether a fetus is likely to have a major aneuploidy with a very high degree of accuracy and without the increased chance for a miscarriage associated with chorionic villus sampling and amniocentesis. In October of 2011 the first clinical test using this technology to test for fetal Down syndrome in a sample of maternal blood became available. In the six months since then, other laboratories have come on the market and the testing has expanded to include trisomy 18 and trisomy 13.

How is NIPS done?
Anytime after 10 weeks of pregnancy, a sample of maternal blood is collected in tubes provided by the laboratory. Fragments of cell-free DNA are sequenced in order to determine what chromosome they originate from. The amounts of material from chromosomes 13, 18 and 21 are measured and compared to the expected amounts. If there is more DNA present from one of these chromosomes, it is reported as an over-representation, which is associated with a very high likelihood of a diagnosis of fetal trisomy. Results are usually available in about 10 business days.

How reliable is NIPS?
With currently available tests quoting sensitivities of 99.1% or greater for Down syndrome, 97.2% or greater for trisomy 18 and 78.6% or greater for trisomy 13 and specificities greater than 99% for each, these are clearly excellent screening tests. At this time it is recommended that results be confirmed by a traditional prenatal diagnostic test (CVS or amniocentesis) if a definitive result is desired or needed, as when a patient plans to have a pregnancy termination of an affected fetus.

Who is it for?
Participants in the scientific studies leading up to the launch of NIPS tests were considered to be high-risk patients with one or more of the following indications for prenatal testing: advanced maternal age, positive NT/ maternal serum screening test result (such as first trimester or quad-screening), ultrasound abnormality, or other maternal indication, such as positive personal or family history of aneuploidy. Thus, at this time NIPS is considered to be a second-tier screening test for those with an increased risk. However, studies to validate the use of these technologies in the general obstetric population are underway and it is expected that the screening will soon be an option for all pregnant women.

It is important to bear in mind, that currently the tests can only provide information about the presence or absence of trisomy 13, 18 or 21. Women who are at risk for other chromosome abnormalities, such as Turner syndrome, translocations, or microdeletions should be counseled that these conditions are not currently detected by NIPS. Women at risk for Mendelian conditions or those for whom additional testing, such as microarray, might be requested need to be counseled that these conditions will not be detected by NIPS and they may opt to have CVS or amniocentesis.
How does NIPS compare to the current nuchal translucency-based screening tests?

While the specificity and sensitivity of NIPS techniques have been demonstrated to be superior to those for current screening options in high-risk populations, NIPS does have some limitations. On the one hand, not requiring an ultrasound examination makes the test simple to do for any patient presenting to provider’s office for a prenatal visit. However, first trimester NT ultrasound examination is valuable for many reasons including accurate dating, early identification of multiple gestations, diagnosis of up to 60-70% of structural fetal anomalies, and screening for congenital heart disease. In addition, NIPS is not suitable for multiple gestation pregnancies.

What should I tell my patients?

In 2011 women were surveyed in their obstetrician’s waiting room regarding their interest in the future possibility of a prenatal test that would be 100% safe for the fetus, would be as accurate as amniocentesis, and could be completed as early as 10 weeks gestation. Of the 114 women surveyed, 71.9% stated they would be interested if such a test was available and 22.7% were not sure. Only 5.4% stated they would not be interested in such a test. Interestingly, the respondents were evenly divided on what they would do if they learned their fetus had Down syndrome. 33.9% indicated they would probably terminate the pregnancy, 33% said they would probably not, and 33% were unsure. This suggests that the majority of pregnant women would appreciate having the option of NIPS regardless of how they would use the results. As with all other screening and diagnostic testing options, patients should receive genetic counseling to help them understand the benefits and limitations of NIPS in order to make an informed decision.

If you would like more information or if you want to make a referral, you can locate a genetic counselor in your area at the National Society for Genetic Counselors’ website, nsgc.org, under the find a counselor tab.

References


SMFM Abstract (Feb 2012): “Impact of a required remediation program on nuchal translucency measurements: Experience of the Nuchal Translucency Quality Review (NTQR) Program”

submitted by Karin Fuchs MD, Jean Spitz MPH RDMS, Gregory Toland, Bryann Bromley MD, Beryl Benacerraf MD, Lawrence Platt MD, and Mary D’Alton MD

In February 2012, NTQR presented an abstract at the annual meeting of the Society for Maternal-Fetal Medicine (SMFM) that assessed the impact of its remediation program - Required Quality Maintenance (RQM) - on epidemiologic analysis of participants’ nuchal translucency (NT) measurements. This was an observational study of NT measurements submitted by physicians and sonographers who were assigned to RQM in 2010 due to a low median NT MoM and/or a high SD. Of 3557 monitored NTQR participants, 279 (7.8%) were assigned to RQM in 2010. Of the participants who completed the RQM process prior to March 2011, 47% were within range and 53.1% had decreased their SD by at least 0.02 on their July 2011 report. Of the remediated participants who had submitted > 30 NT measurements after completing
RQM, 88.5% had increased their median NT MOM by > 0.05 above their pre-RQM MOM and 61.5% had a post-RQM NT median MOM of 0.89-1.1. These data indicate that NTQR participants demonstrate improved performance after completing a required quality maintenance program, and suggest that ongoing quality review after remediation is an essential part of a quality monitoring program.

**AIUM Abstract (April 2012): “Can we predict those providers assigned to Required Quality Maintenance based on initial credentialing and practice parameters: The experience of the Nuchal Translucency Quality Review (NTQR) Program”**

submitted by Bryann Bromley MD, Jean Spitz MPH RDMS, Loralei Thornburg MD, Gregory Toland, Beryl Benacerraf MD, Karin Fuchs MD, Lawrence Platt MD, and Mary D’Alton MD

At the annual meeting of the American Institute of Ultrasound in Medicine (AIUM) in April 2012, NTQR presented an abstract exploring whether initial credentialing performance or specific practice characteristics could predict which NTQR participants would later be assigned to Required Quality Maintenance (RQM) due to “low range” measurements.

In this case-control study, credentialing performance and practice characteristics were compared between 122 providers assigned to RQM for “low range” NT median MOMs and 282 credentialed participants with “within range” NT median MOMs. The groups were compared with respect to the number of image batches required to complete the credentialing process, the scores of passing batches, number of NT measurements submitted and, for sonographers, the presence of a supervising credentialed physician.

While there was no significant difference between the groups when comparing number of NT measurements performed, performance on initial NT credentialing did seem to predict which providers will be assigned to RQM. Specifically, participants assigned to RQM were more likely to have submitted more than one batch of images for credentialing than those who did not require RQM (27.0% vs 18.4%; p= 0.002). Batch scores were also higher for those participants who did not require RQM than for participants later assigned to RQM (p= 0.048). In addition, data suggest that sonographers with a credentialed supervising physician are less likely to be placed in RQM than sonographers without a credentialed supervising physician (p<0.001).

**AIUM Abstract (April 2012): “Do the number of providers within a practice influence the quality of NT measurements: The experience of the Nuchal Translucency Quality Review (NTQR) Program”**

submitted by Bryann Bromley MD, Jean Spitz MPH RDMS, Gregory Toland, Beryl Benacerraf MD, Karin Fuchs MD, Lawrence Platt MD, and Mary D’Alton MD

In another abstract submitted at the April 2012 annual meeting of the American Institute of Ultrasound in Medicine (AIUM) in April 2012, NTQR evaluated whether the number of providers within a practice group influenced provider performance on epidemiologic monitoring.

The study group was comprised of 1315 practices and 2744 individual providers. Overall, 26.8% of providers had an NT median MOM that was “out of range” (< 0.9 or > 1.1). An “out of range” NT MOM was identified in 17.8% of providers in practice groups of ≥ 10 compared with 24.1% in groups of 5-9, 29% in groups of 2-4, and 30.9% for single providers. Overall, 32.4% of practices had ≥ 50% of providers with an “out of range” NT median MOM. In practices with ≥ 10 providers, 13.8% had ≥ 50% of providers “out of range” compared with 23.8% in practices with 5-9 providers and 38.4% in practices with 2-4 providers.

In summary, this study showed that that providers working in larger group practices are more likely to have an NT median MOM that is within range. Similarly, practices with a larger number of providers are more likely to have a majority of their providers with “within range” epidemiologic monitoring. Although further data is needed to confirm the findings, these data suggest that peer monitoring may influence NT.
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Transabdominal evaluation is the least reliable method

Major studies & RCTs over >10 years have all used TVU