Summer 2011

With this issue, Dr. Karin M. Fuchs from Columbia University assumes the editorship of the NT Examiner. Dr. Steven Warsof from Eastern Virginia Medical School provided excellent stewardship as editor between 2007 and 2011. On behalf of NTQR committee members and participants we extend a welcome to Dr. Fuchs and a grateful salute to Dr. Warsof.

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Top Tip: New Epi Report Teaching Tool

Four times each year the NTQR provides a NT measurement monitoring report to participants. The statistical analysis of participant measurements provides feedback that is useful for improving measurement accuracy and practice quality. The interpretation and implications of the epidemiologic report may not be apparent. To answer questions the NTQR benefit committee with the support of Perkin Elmer Laboratories has developed an "Epi Report Teaching Tool." The presentation is available on the NTQR home page, http://www.ntqr.org. The presentation is approximately 15 minutes in length and may be watched in short segments or repeated as needed. NTQR strongly recommends that every participant reviews the "Epi Report Teaching Tool," and regularly monitors their reports. Participants may be assigned to required quality maintenance (RQM) based on their NT median MoM or standard deviation Log 10 MoM. Monitoring and understanding your epi reports is important to achieve and maintain NT measurement quality.

REPORTING THE NT MEASUREMENT: HOW MANY DIGITS AFTER THE DECIMAL?

By Bryann Bromley, MD and the NTQR Quality Assessment Committee

The image on the left reports one digit after the decimal; the image on the right reports two digits after the decimal.

The NTQR data monitoring program provides an epidemiologic analysis of data submitted for each participant and provides information on the performance of individual practitioners. In the process of reviewing this data, it has become apparent that some practices and practitioners are reporting NT measurements with one digit after the decimal (x.y0) while others are reporting their data with two digits (x.yz) after the decimal.

In order to investigate why this was occurring, we surveyed the ten largest practices in each of these two categories. It became apparent that the practices reporting two digits after the decimal (x.yz) had machines that were pre-set to display these. The majority of practices reporting a single number after the decimal (x.y0) had machines set to only display one digit. In this small sample, no practice was rounding or truncating numbers to report one digit after the decimal nor were practices averaging NT measurements to report two digits after the decimal. All practices, reported properly using the largest of several technically good images as the NT that was reported.

Laboratories to which measurements are sent, generally input data exactly as written by the provider. Several large laboratories provide requisitions that only allow one digit after the decimal while others have an open ended prompt for the NT, so that as many digits as desired may be entered. In the event that a laboratory receives two digits after the decimal, there is no uniform method of handling the information. Some laboratories enter the two decimal data exactly as written; others enter one decimal by rounding or truncating.

Using two digits after the decimal (x.yz) for reporting NT measurements is not useful, either clinically or statistically. Additionally, those practices reporting the NT measurement with two digits after the decimal were more likely to be identified in our epidemiologic monitoring process to be measuring below expected values. With this in mind, the NTQR oversight committee met and concluded that uniformity in data collection is optimal and suggests that all machines be set to report one digit after the decimal. In the event that this is not possible, the NT should be reported to the laboratories with only one digit after the decimal. This requires the practitioner to round the value up or down to the next single significant digit.

For example:
If the best largest NT measurement is displayed as 2.14 or less, it should be rounded down to 2.1.
If the best largest NT is displayed as 2.15 or above, it should be rounded up to 2.2.

This will provide national uniformity in data management.
What is Wrong With Image #1?

A. Not magnified enough.
B. Fetus not in midsagittal
C. NT line not crisp and clear.
D. Amnion not seen.
E. Head flexed or over-extended.
F. Calipers not placed properly on inner aspect of lines.
G. Calipers not oriented at right angles to the fetus.
H. + calipers not used.
I. Calipers not measuring the widest distance.
J. Good image, nothing wrong.

What is Wrong With Image #2?

A. Not magnified enough.
B. Fetus not in midsagittal
C. NT line not crisp and clear.
D. Amnion not seen.
E. Head flexed or over-extended.
F. Calipers not placed properly on inner aspect of lines.
G. Calipers not oriented at right angles to the fetus.
H. + calipers not used.
I. Calipers not measuring the widest distance.
J. Good image, nothing wrong.

What is Wrong With Image #3?

A. Not magnified enough.
B. Fetus not in midsagittal
C. NT line not crisp and clear.
D. Amnion not seen.
E. Head flexed or over-extended.
F. Calipers not placed properly on inner aspect of lines.
G. Calipers not oriented at right angles to the fetus.
H. + calipers not used.
I. Calipers not measuring the widest distance.
J. Good image, nothing wrong.
What is Wrong With Image #4?

A. Not magnified enough.
B. Fetus not in midsagittal
C. NT line not crisp and clear.
D. Amnion not seen.
E. Head flexed or over-extended.
F. Calipers not placed properly on inner aspect of lines.
G. Calipers not oriented at right angles to the fetus.
H. + calipers not used.
I. Calipers not measuring the widest distance.
J. Good image, nothing wrong.

What is Wrong With Image #5?

A. Not magnified enough.
B. Fetus not in midsagittal
C. NT line not crisp and clear.
D. Amnion not seen.
E. Head flexed or over-extended.
F. Calipers not placed properly on inner aspect of lines.
G. Calipers not oriented at right angles to the fetus.
H. + calipers not used.
I. Calipers not measuring the widest distance.
J. Good image, nothing wrong.

What is Wrong With Image #6?

A. Not magnified enough.
B. Fetus not in midsagittal
C. NT line not crisp and clear.
D. Amnion not seen.
E. Head flexed or over-extended.
F. Calipers not placed properly on inner aspect of lines.
G. Calipers not oriented at right angles to the fetus.
H. + calipers not used.
I. Calipers not measuring the widest distance.
J. Good image, nothing wrong.
NTQR epidemiologic reports now include a graph on which is plotted a provider’s median NT multiple of the median (MoM) value for the reporting period against the standard deviation (SD) of log10 MoM from the same data. The graph includes a box representing the limits of acceptable practice, bordered by a median of 0.90-1.10 MoM and an SD of 0.08-0.12. Depending on the number of scans included in the calculation it is possible to be outside the target box by chance alone so a provider is only explicitly alerted by NTQR if there is a statistically significant finding. In this article we will explain the consequences of being outside the box on the Down syndrome risk calculated for a screened individual and on the detection and false-positive rates in the screened population.

The median and the SD are performance indicators of two different types of error; inaccuracy or systematic error and imprecision or random error. The median should be 1.00 MoM even for a quality assessment data, like in NTQR, where Down syndrome cases have not been removed. A median of 0.90 MoM, the lower limit of acceptability, indicates an inaccurate under-measurement on average of 10% and 1.10 indicates over-measurement. In the literature the SD for unaffected pregnancies from large multi-center studies has been about 0.12, but for an individual centre it can be expected to be about 0.10 and for most individual operators it is 0.09. For a center and certainly for a provider an SD of 0.12 would indicate imprecise measurement. A provider with an SD of 0.08 could be measuring particularly precisely but another possibility is that they are not discriminating different NTs sufficiently. This could be as serious as measuring imprecisely.

For the purposes of this article screening is assumed to be carried out at 12 weeks either with NT alone or a Combined test using NT, PAPP-A and free beta hCG or intact hCG, and a 1 in 270 (mid-trimester) risk cut-off. Risk is assumed to be calculated with a model based on published meta-analysis parameters except that the NT unaffected SD is reduced to 0.10 and in Down syndrome variance reduced by the same amount. Model predicted detection rate (DR) and false positive rate (FPR) uses a standardized maternal age distribution.

Figure 1 shows what would happen to the Down syndrome risk based on NT alone in a 25 year old if the accuracy of the NT in the screened population is altered by systematically shifting the mean up or down by 10%. At this age the practical consequences are in moderate-to-very high NT values. For example, using the risk calculator which assumes complete accuracy and average precision, a value of 1.73 MoM would yield a mid-trimester risk of 1 in 270 – exactly at the cut-off. But if the operator is under-measuring by 10% the true risk would be much higher at 1 in 100. A consequence of under-measurement is that the DR and FPR will both be reduced. The model predicted rates assuming complete accuracy and precision are for NT alone 73% and 3.8%. For a Combined test the predicted rates are 82% and 3.5% if it uses free beta hCG or 80% and 3.5% if the intact molecule is measured. If NT is 10% under-measured the predicted rates are: NT alone 67% and 1.8% and Combined test 77% and 2.0% (free beta hCG) or 75% and 2.0% (intact hCG).

Figure 1 also shows the consequences on risk calculation if the operator is over-measuring by 10%. The true risk for an NT measured as 1.73 MoM, when in this example the calculated risk is 1 in 270, would be only 1 in 560. The DR and FPR will both be increased and the model predicted rates are: NT alone 78% and 7.3% and Combined test 85% and 5.8% or 84% and 6.0%.

Figure 2 shows what would happen in the same circumstances if the precision where to be changed by a 0.020 reduction or increase in SD in unaffected pregnancies (and a corresponding change in the NT variance for Down syndrome). For an NT of 1.73 MoM in comparison to the 1 in 270 calculated risk, the true risk would be a much higher 1 in 120 risk if the operator had greater than average precision and much lower, 1 in 420, if the precision was low. This will mainly affect the FPR which will be reduced in a tighter distribution and increased if wider: NT alone 2.0% and 6.2% respectively; Combined test 2.3% and 5.0% (free beta hCG) or 2.3% and 5.2% (intact hCG).
In a very large medical center it is possible to directly monitor performance by the calculating the DR and FPR. To do this the observed rates have to be compared with those predicted by modelling with a maternal age distribution comparable with the screened population. But the diagnosis of potentially non-viable Down syndrome pregnancies which are subsequently terminated will necessarily lead to an upward bias in the observed detection and could lead to false reassurance. The FPR can also be misleading. Using NT alone a particularly high rate may indicate either an upwards shift in values, a broader spread of results or both. A low rate could relate to a downward shift in values but could also mean that NT is being measured more precisely than expected. For a Combined test an excess or a deficit may be contributed to by the biochemical marker distributions. And there may be a problem with NT even when the positive rate is consistent with the expected rate if the biochemical markers are performing particularly well.

Therefore, the new graph on the NTQR report may be your first indication that there is a problem. Don’t be discouraged, many more providers are under-measuring than are over-measuring and studies in the literature show that measurements can be increased within a relatively short period of time [3-8]. The first step if your results are outside the target box is to have yourself assessed by experienced colleagues in the same center. Perhaps they are out of target too, in which case you need to be in touch with Jean Spitz of the NTQR staff for advice.

REFERENCES

GENETIC SYNDROMES ASSOCIATED WITH INCREASED NT MEASUREMENTS:
SMITH-LEMLI-OPTIZ (SLO)

By Kathleen Hays Devary, MS, CGC
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Genetic Counselor and Member
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Nuchal translucency (NT) measurements greater than the 95th percentile have been associated, not only with an increased chance for aneuploidy but also with a significantly increased risk for structural defects, especially congenital heart defects and diaphragmatic hernia, and with genetic syndromes. In this issue of the NT Examiner we will review Smith-Lemli-Optiz in a continuing series of articles reviewing the genetic syndromes most frequently reported in association with increased NT measurements.

Smith-Lemli-Optiz (SLO) has an estimated prevalence of 1 in 10000 to 1 in 60000 in individuals of European ancestry. It is less common in other ethnic groups. SLO is caused by a metabolic defect in the cholesterol pathway that results in a deficiency of 7-dehydrocholesterol reductase (DHCR7) leading to a surplus of 7-dehydrocholesterol (7-DHC). Features of the condition include prenatal and postnatal growth retardation, microcephaly, cardiac defects, underdeveloped external genitalia in males, postaxial polydactyly, cleft palate, and distinctive facial features including temporal narrowing, epicanthal folds, broad nasal bridge, anteverted nares, micrognathia, and low-set and posteriorly rotated ears. Cognitive impairment
is typically moderate to severe and behavioral problems are common. Affected females are under ascertained due to the lack of genital abnormalities present in males. Neonatal death is common, of those that survive 20% die in the first year or life. There is a broad clinical spectrum and individuals with milder features and low normal intellectual function have been described.

SLO may be suspected in a pregnancy due to an increased NT, second trimester ultrasound findings, as well as abnormally low levels of serum unconjugated estriol found in second trimester maternal serum screening.

SLO is inherited in an autosomal recessive manner. Biochemical prenatal diagnosis is possible by detecting abnormal concentrations of 7-DHC in amniotic fluid or chorionic villi with a greater than 99% detection rate. DHCR7 is the only gene known to be associated with SLO, sequence analysis of the gene detects 96% of known mutations. Therefore a negative mutation analysis does not rule out the diagnosis. In families in which there is no history of SLO or in families in which a mutation has not been identified, biochemical prenatal diagnosis is the first tier of testing.

As ultrasound findings consistent with SLO can be nonspecific and overlap with features of other syndromes, it is important to carefully review family and medical history for diagnostic clues of other possible syndromes to consider in the differential diagnosis. Consultation with a genetic counselor is appropriate to further evaluate the family and medical history as well as provide patient support, education, and guidance. With access to appropriate resources and information, patients will be empowered to make the decisions that best fit their family in both their current and future pregnancies.

REFERENCES


2. Gene Reviews - NCBI Bookshelf


REQUIRED QUALITY MAINTENANCE (RQM) UPDATE

In 2010 the Nuchal Translucency Quality Review Program assigned 75 participants to required quality maintenance (RQM). In 2011, 669 participants have been assigned. Participants with two epidemiologic reports outside the expected range for NT median MOM or standard deviation are selected. The RQM web-based module currently consists of the following steps:

- Updating practice information.
- Reviewing image tips to prevent high or low measurements.
- Reviewing the NT measurement technical lecture.
- Passing an image review test.
- Submitting an initial batch of 5 NT images and passing image review.
- For sonographers, providing the name and NT # of an NT credentialed supervising physician. The physician is contacted to verify supervision.

Review of NTQR’s new epi report teaching tool is a recommended addition to these steps as understanding and monitoring measurements using the epidemiologic report is essential to maintaining accurate measurements.

The goal of NTQR required quality maintenance is to educate and reinforce key concepts that improve the accuracy of NT measurements. The steps are available for participants who are not assigned to RQM. Participants may voluntarily submit images and complete the image review test by going to Performance Improvement menu within their account. It is NOT the aim of NTQR to remove NT credential numbers however we have begun to deactivate the credentials of those who do not complete the process in a reasonable time.

The effectiveness of NTQR’s required quality maintenance to improve NT measurement quality is under investigation. Early analysis is supportive. NTQR is investigating cumulative sum analysis as a feedback tool for participants after RQM. This tool will visually demonstrate measurement improvements.

The NTQR has also been investigating factors that may predict assignment to RQM. It appears that sonographers who submit data with a supervising physician number are less likely to be assigned to remediation than those sonographers who do not report a supervising physician. A full report of these investigations will be available shortly.

Participants who receive an e-mail with an assignment to RQM are encouraged to start the process immediately and work through the steps sequentially at a steady pace. NTQR staffs are available by phone or e-mail to answer questions.
Patient Information Video (Spanish version)

On September 14, 2011 we posted a Spanish version of the patient education video on First Trimester Risk Assessment for Down Syndrome. This was in direct response to the requests of our Providers. Please check out the video when you get a moment.

SMFM Abstract: "NTQR Toughens Criteria for Review of Images"
by Beryl Benacerraf, Jean Spitz, Lawrence Platt and Alfred Abuhamad

In an effort to reduce the number of practitioners with NT medians below the target range, the NTQR-Image Review committee changed the image review criteria starting in April 2009 to emphasize caliper placement. Under the new criteria, 5 images were required instead of 10, but criteria related to caliper placement had to be correct on all images and each image had to receive an overall score of at least 7/9.

In February 2011, NTQR presented an abstract at the annual meeting of the Society for Maternal-Fetal Medicine comparing the pass/fail rate between image batches submitted under the old criteria (in 2008) and the new criteria (first half of 2010). The initial pass rates were noted to decrease from 71% to 47% (p < 0.001) and final pass rates decreased from 85% to 68% (p < 0.001). Although the new image review criteria have resulted in a decreased pass rates, future research is required to determine the impact this change may have on the number of participants falling outside the expected range; stay tuned!

ISUOG Abstract: “Nuchal Translucency Education and Quality Review (NTQR) program: First One Million Results”
submitted by Howard Cuckle, Loralei Thornburg, Bryann Bromley, Karin Fuchs, Lawrence Platt, Ronald Wapner, and Mary D’Alton

Since its inception over one million NT measurements have been submitted to NTQR from from 3631 providers at 1433 sites in North America. Using the first million NT measurements submitted, NTQR assessed the variability in NT measurements between different NTQR participants.

The overall median was 0.926 MoM and standard deviation of 0.105. Physician participants had higher medians than sonographer participants. There was considerable variability in MoMs according to ethnic origin with the lowest values in African-Americans and the highest in Asian women, as well as an independent tendency for levels to increase with maternal weight and age. The median for 51,910 scans in twin fetuses was identical to singletons with a strong correlation between each fetus and the co-twin. These data and more will be presented at the annual meeting of the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) in September 2011; links to the manuscript will be provided when it is published!

Maternal Fetal Medicine Foundation to change name

The Maternal Fetal Medicine Foundation (MFMF) will change its name to Perinatal Quality Foundation effective January 1, 2012. The parent foundation for NTQR will be found at http://www.perinatalquality.org. The Nuchal Translucency Quality Review program and the NTQR website and contact information will not change.

Join NTQR and Get Credentialed

The Nuchal Translucency Quality Review Program (NTQR) is a United States based effort seeking to establish a NT quality control system and help formalize set standards. NTQR offers a unique opportunity to learn about the proper techniques and theories involved in obtaining accurate and reproducible NT measurements from the 11-14 week ultrasound scan and first trimester risk assessment for Down Syndrome, while also offering a method to evaluate and track provider proficiency though ongoing NT quality monitoring reports.

Two ways to join NTQR and get credentialed!

1. On Line
   - Go to www.ntqr.org
   - Register
   - On your computer, watch the same lectures given at NTQR's land-based courses. (This doesn't have to be done in one sitting)
   - Take the same on-line test as land-based course participants
   - Submit 5 NT images for quality review
   - Get credentialed

2. Plan to attend one of these upcoming NTQR land-based courses:
   - Register and attend a planned Land-Based Courses (see below)
   - Take the on line exam
   - Submit 5 NT images for quality review
   - Get credentialed
Program Statistics 10/10/2011

- 6,657 providers of NT measurements have registered with the Nuchal Translucency Quality Review Program
- 4,904 providers have been credentialed through NTQR
- Over 33,100 NT images have been reviewed by NTQR's Expert Reviewers
- Over 1.5 million data sets have been provided by participants or by our partner laboratories. Valid data sets were analyzed to produce individual epidemiologic reports. Over 3850 personalized reports were sent to participants in July 2011.
- To see a list of our partner laboratories, go to www.NTQR.org

Answers to Image Review Questions

- Image 1: E
- Image 2: F, I
- Image 3: C, D, F
- Image 4: F
- Image 5: B, C, F
- Image 6: B