

CERVICAL LENGTH ULTRASOUND: IMPROVING THE QUALITY OF A TOOL FOR PREDICTION AND PREVENTION FOR PRETERM BIRTH

By: Rupsa C. Boelig, MD, Vincenzo Berghella, MD

Transvaginal cervical length ultrasound has been increasingly shown to be an important tool in the prediction and prevention of preterm birth. In singletons without prior preterm birth, singletons with a history of preterm birth, and twins, a short transvaginal ultrasound cervical length between 18-23 weeks has been shown to be predictive of preterm birth, and perhaps more importantly, there are now interventions available to prevent preterm birth in these populations.¹⁻³ Improper measurement of cervical length could lead to overtreatment or unnecessary procedures for an inaccurately measured short cervix, or lack of treatment and a potentially preventable preterm birth.

The Cervical Length Education and Review (CLEAR) which provides education as well as an avenue to certification if desired, was developed by the Perinatal Quality Foundation to document that providers performing cervical length measurements in pregnancy are properly trained and adhere to standardized criteria for the documentation of cervical length (<https://clear.perinatalquality.org>). The CLEAR program criteria were developed in conjunction with members from ACOG, ACOOG, ACR, AIUM, SDMS, and SMFM.

A recent study by our team found that 15% of trained imagers submitting images to the CLEAR program for certification failed to obtain an adequate image and/or measurement.⁴ This confirmed the findings of an earlier study by the MFMU.⁵ Importantly, we noted that the top reasons for image failure were related to key aspects of imaging and evidence of basic technical deficiencies. The most common deficiencies were in anterior and posterior width of cervix not being equal (33%), failure to visualize the internal or external os (29%), incorrect magnification of the cervix and /or failure to visualize of the bladder (33%), and incorrect caliper placement (24%).⁴ Additionally, we found that the majority (85%) of those who failed an initial submission then passed after receiving feedback through the CLEAR program. These findings highlight the importance of a standardized cervical length training and certification program.

As cervical length becomes more widely used in the prediction and prevention of preterm birth, a 1 mm difference in measurement may determine whether a patient receives an intervention or not; it is thus crucial that as obstetrical care providers we address the quality and consistency of our cervical length imaging. The fact

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a significant percentage of trained imagers failed to obtain adequate cervical length imaging highlights the need for the standardization of cervical length ultrasound measurement and the certification of appropriately trained imagers. The CLEAR program provides an avenue for educating imagers and health care providers, addresses a deficiency in quality control of cervical length measurement, and establishes a protocol for quality review.⁵

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FETAL CARDIAC AXIS: A USEFUL SCREENING TOOL FOR CONGENITAL HEART DEFECTS IN EARLY GESTATION

By: Elena Sinkovskaya MD, PhD

Approach to the ultrasound examination in the first trimester has evolved over the last 30 years from a simple assessment of the crown-rump length and heartbeat to a comprehensive protocol including screening for chromosomal abnormalities using nuchal translucency as well as evaluation of basic fetal anatomy.

Several mostly indirect sonographic markers were proposed for cardiac screening between 11+0 and 13+6 weeks gestation including increased nuchal translucency, abnormal flow in ductus venosus and tricuspid regurgitation.¹ In addition diagnostic algorithms using different combinations of these markers were developed to estimate patient-specific risk for major CHD allowing a detection rate of cardiac anomalies up to 58%.

Recent studies demonstrated that the direct visualization of fetal cardiac planes is a feasible method of screening for congenital heart defects at 11-14 weeks' gestation. Assessment of the transverse plane of the fetal chest at the level of the four chamber view is therefore now recommended by the ISUOG Practice Guidelines for performance of first-trimester fetal ultrasound scan to document the normal position of the heart (levocardia).² This view is also useful for evaluation of cardiac axis. Several research teams, including ours, have demonstrated that cardiac axis measurement in early gestation can be reliably achieved in most cases, using either the transabdominal or transvaginal approach^{3,4}. It was also noted that fetal cardiac axis establishes its position by 12th week gestation and remains unchanged during pregnancy measuring approximately $45^{\circ} \pm 15^{\circ}$ in most cases.

To perform cardiac axis measurement the following criteria should be met (Figure 1 and 2):

- Appropriate image magnification: cross-section of the fetal chest occupies majority of the image;
- Anatomic landmarks including one complete rib on each side of the fetal lateral chest wall are demonstrated;
- Clear visualization of the cardiac chambers;
- Measurement of the cardiac axis as the angle between the line that traces the long axis of the heart and the line that bisects the thorax in an anteroposterior direction;
- Color or directional power Doppler can be used briefly to confirm the location of the interventricular septum which is important for accurate measurement.
- Thermal Index for BONE should be displayed and the ratio should be less than 0.7.

Abnormal cardiac axis is observed in association with CHD as well as with thoracic and abdominal abnormalities (Figure 3). Based on recent case-control study involving 197 fetuses with confirmed CHD diagnosed prior to 15 weeks gestation, abnormal cardiac axis was found in 74.1% of affected fetuses and in 2.8% of normal controls.⁵ Three types of cardiac axis abnormalities were described including left-axis deviation (measurement is above 60 degrees), right-axis deviation (measurement is below 30 degrees) and non-identifiable cardiac axis when measurement was impossible to perform secondary to absent/non-visualized interventricular septum.

In contrast to nuchal translucency, cardiac axis performs equally well in detecting CHD in fetuses with normal and abnormal karyotypes. Furthermore performance of cardiac axis measurement in detection of major CHD in fetuses with a normal karyotype seems to be significantly better than enlarged NT, tricuspid regurgitation or reversed A-wave in ductus venosus used alone or in combination. Incidence of abnormal cardiac axis has been reported to be dependent on type of congenital heart disease. Our experience demonstrated that an abnormal cardiac axis is more likely to be found in fetuses with conotruncal anomalies and complex congenital heart disease including univentricular hearts. Assessment of the cardiac axis can be particularly helpful in early detection of conotruncal anomalies such as Tetralogy of Fallot and common arterial trunk, because these are commonly characterized by a normal four-chamber view.

In summary, addition of cardiac axis assessment to the nuchal translucency measurement can be helpful in defining a population at risk for fetal congenital heart disease. Identification of abnormal cardiac axis during routine ultrasound evaluation in early gestation should be considered an indication for fetal echocardiogram.

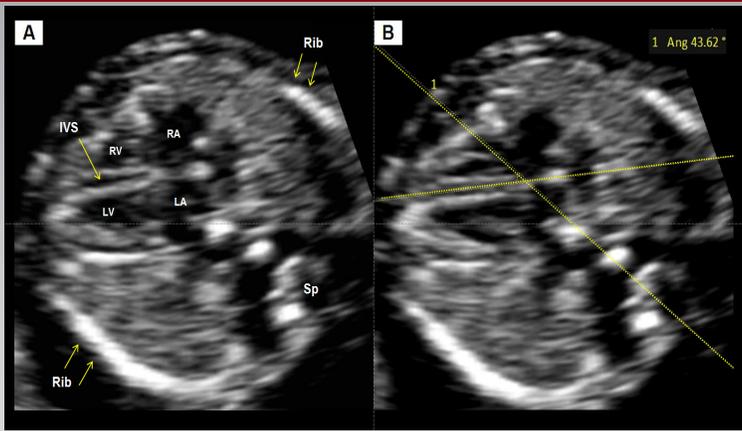


Figure 1. Axial view of the fetal chest at the level of the four-chamber view of a normal fetus at 12 6/7 weeks of gestation and CRL of 65.8 mm. Anatomic landmarks of correct image (A) and measurement of the cardiac axis (B) is demonstrated. IVS - interventricular septum; LA - left atrium; LV- left ventricle; RA - right atrium; RV - right ventricle; Sp - spine.

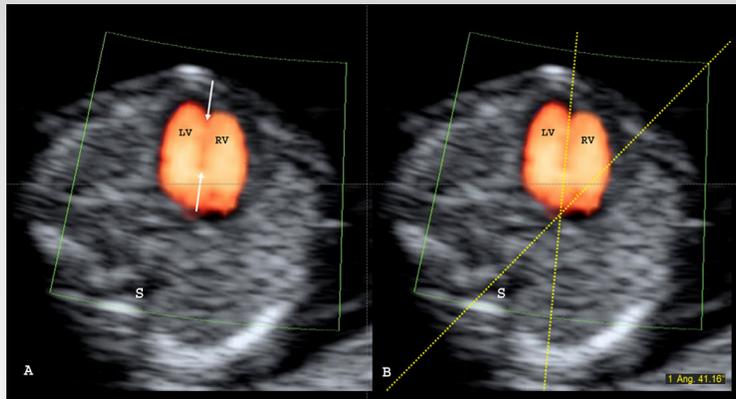


Figure 2. Axial view of the fetal chest at the level of the four-chamber view of a normal fetus at 13 1/7 weeks of gestation and CRL of 72.3 mm. Identification of the interventricular septum using power Doppler (A) and measurement of the cardiac axis (B) is demonstrated. LV- left ventricle; RV - right ventricle.

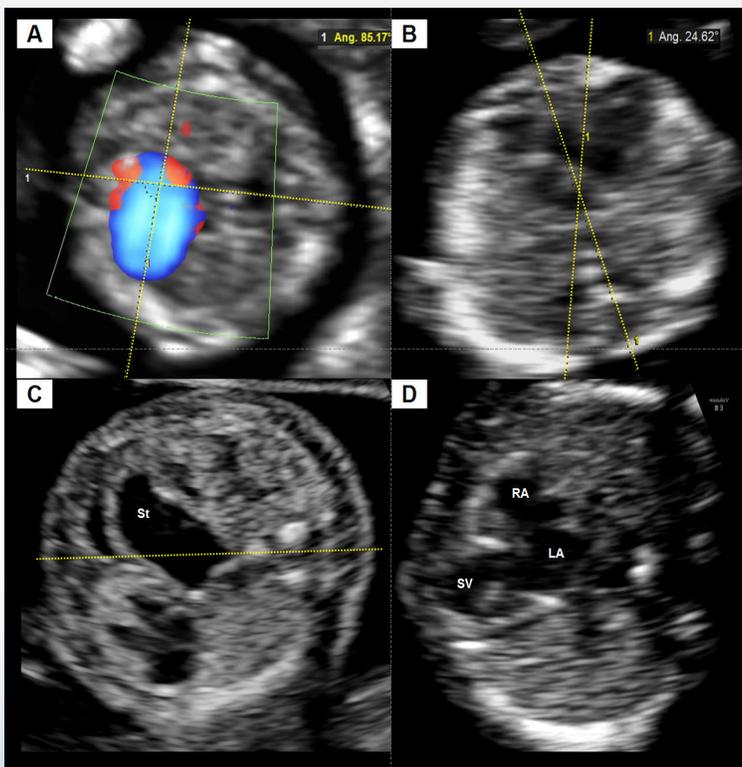


Figure 3. Axial view of the fetal chest at the level of the four-chamber view in four fetuses with abnormal cardiac axis and cardiac position. (A) Fetus at 11 1/7 weeks with tetralogy of Fallot. Note left deviation of the cardiac axis (CAX is 85°); (B) Fetus at 12 3/7 weeks with pulmonary atresia with intact interventricular septum. Note right deviation of the cardiac axis (CAX is 25°); (C) Fetus at 13 4/7 weeks gestation with large left sided congenital diaphragmatic hernia. Note abnormal position of the heart in the right chest. St - stomach; (D) Fetus at 13 1/7 weeks gestation with univentricular heart physiology (tricuspid atresia with pulmonary atresia). Cardiac axis cannot be measured secondary to not visualized interventricular septum. LA - left atrium; RA - right atrium; SV - single ventricle.

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THE UTILITY OF NT IN IDENTIFYING RARE CHROMOSOMAL ABNORMALITIES NOT DETECTABLE BY CFDNA SCREENING

By: Mary Norton, MD

Prenatal screening using cell free DNA (cfDNA) was introduced into clinical practice in 2011, and has been clearly demonstrated to have very high sensitivity and specificity for the common aneuploidies. However, these common aneuploidies comprise only about 75-80% of all chromosomal abnormalities. Given that nuchal translucency (NT) measurement is increased with a number of different chromosomal and structural anomalies, it has been debated whether NT ultrasound would be of benefit in detecting the remaining 20-25%. We therefore conducted a study in a large, population based cohort in order to determine the utility of NT measurement in detection of chromosomal abnormalities not screened by cfDNA. We were also interested in the utility of different NT cutoffs, including NT greater than or equal to 3.0 mm or 3.5 mm, or 2.0 MoM.

The study population included all participants in the California Prenatal Screening Program who had singleton pregnancies and underwent sequential screening between March 2009 (when NT was added to the program) and December 2012. Outcomes of all screened pregnancies were collected through the California Chromosome Registry, which collects outcomes through state mandated reporting of all chromosomal abnormalities diagnosed in a fetus or an infant through one year of age. The number of fetuses with an NT of 3.0 mm or more, 3.5 mm or more, or 2.0 MoM or more was determined. Karyotypes were flagged as normal or abnormal; abnormal results were categorized by type of abnormality and whether the abnormality is detectable by cfDNA. Non-mosaic trisomy 13, 18, or 21, or sex-chromosomal aneuploidy were considered detectable, while other chromosome abnormalities were considered not detectable. For chromosomal abnormalities not detectable by cfDNA, the number that had enlarged nuchal translucency was determined.

Over 1.3 million women were screened during the study period ($n = 1,324,607$), and of those, 452,901 had first trimester screening including NT. In all, 5105 (1.1%) had an NT ≥ 3.0 mm, 2461 (0.54%) were ≥ 3.5 mm, and 3672 (0.81%) were ≥ 2.0 MoM. Of the 2572 chromosomally abnormal cases that were detected prenatally or during the first year of life, 1032 (40.0%) had an NT ≥ 3.0 mm, 836 (32.5%) were ≥ 3.5 mm, and 936 (36.3%) were ≥ 2.0 MoM. Of the 650 (25.2%) fetuses with an abnormality that was not detectable by cfDNA, 108 (16.6%) had an NT > 3 mm; 87 (13.4%) were ≥ 3.5 mm and 104 (16.0%) were ≥ 2.0 MoM. We calculated that adding NT to cfDNA screening at a cutoff of 3.0mm would detect an additional 108 chromosomal abnormalities and increase the detection rate for all abnormalities from 74.8% to 79.0%. For each additional abnormality detected, 4484 women would have to undergo NT screening and 51 would have diagnostic testing.

Overall, we calculated that the addition of NT to cfDNA screening would detect 16.6% of the uncommon abnormalities not identified by cfDNA alone. However, in an average risk population, these abnormalities are rare and most are not associated with an enlarged NT.



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INCREASED NUCHAL TRANSLUCENCY BEYOND THE KARYOTYPE: CONGENITAL HEART DISEASE

By: Renée Chard , MSc, CGC

In this issue of the NT Examiner we continue the “Increased Nuchal Translucency: Beyond the Karyotype” series by reviewing the role of nuchal translucency (NT) measurement in screening for structural congenital heart disease. Nearly 1% of babies born in the United States have a congenital heart defect (CHD). CHD accounts for an estimated 4.2% of neonatal deaths overall and 24.5% of neonatal deaths attributed to the presence of a birth defect.¹

In a meta-analysis that pooled data from 20 studies, Sotiriadis et al report that 537 of 205,232 euploid fetuses were prenatally diagnosed with major CHD.² The prevalence of major CHD in fetuses with a normal karyotype was 1 in 48 (almost 2%) if the NT was above the 95th percentile and 1 in 19 (approximately 5%) if the NT was above the 99th percentile.

Prenatal detection of congenital heart disease has the benefits of allowing a provider to inform expectant parents of the diagnosis and prognosis, giving parents options in regards to pregnancy management and allowing appropriate adjustment of delivery plans. In a review of relevant literature, Holland et al compared preoperative outcomes among infants with prenatally diagnosed CHD with outcomes of those diagnosed postnatally. Of 1316 infants with CHD and no other risk factors for infant death and planned surgical intervention, 3% of those diagnosed with CHD after birth died before surgery could be done, while only 0.7% of those diagnosed prenatally died preoperatively.³

Because of the increased risk of CHD in the setting of increased NT measurement and the benefit of prenatal diagnosis of CHD on postnatal outcomes, increased NT is an indication for detailed evaluation of the fetal cardiac anatomy.⁴ Patients identified to have an increased NT – either above the 95th or 99th percentile for gestational age – should be referred for fetal echocardiogram to screen for congenital heart disease.

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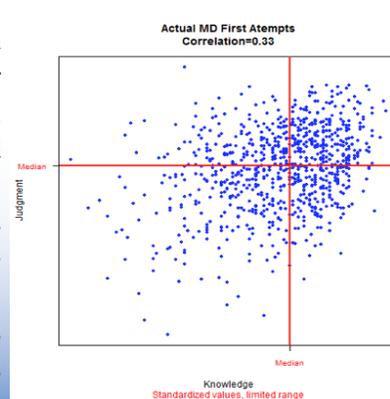
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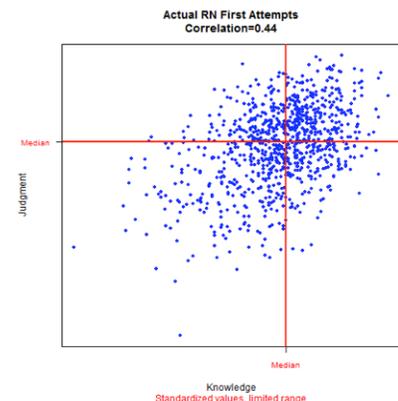
Conventional examinations that focus on fetal heart rate monitoring only assess practitioner knowledge. The PQF FMC exam, however, assesses judgment, or how the practitioner would apply their knowledge in the face of uncertainty. FMC data has shown that individual physicians and nurses (blue dots) can demonstrate discrepant degrees of knowledge and judgment. The diversity among individual provider's knowledge and judgment scores demonstrates the value of an fetal monitoring examination that assesses both measures.

MEASURING MULTIPLE COMPONENTS OF PROFICIENCY WITH FETAL MONITORING

PHYSICIAN JUDGMENT VS. KNOWLEDGE



NURSE JUDGMENT VS. KNOWLEDGE



WHOLE EXOME SEQUENCING IN THE EVALUATION OF FETAL STRUCTURAL ANOMALIES

By: Ronald Wapner, MD

It is well known at this point that identifying chromosomal aneuploidies and copy number variants relevant to fetal structural anomalies has significant value. Although whole-exome sequencing (WES) has been applied to select prenatal cases, its incremental value in regular clinical settings has not been previously assessed in an unselected prospective cohort of anomalies. Existing small studies have only enrolled select prenatal patients expected to have a high likelihood of having a genetic abnormality. These studies have identified pathogenic WES variants in 10-30% of this limited population.^{1,2}

In our ongoing study, we are prospectively evaluating the incremental value of WES in routine prenatal diagnosis in an unselected cohort of patients with anomalies. All sequential patients with a fetal structural anomaly are offered WES as part of the prenatal genetic evaluation. Study participants also had diagnostic prenatal testing with karyotype and chromosomal microarray testing performed on amniotic fluid or CVS.

At SMFM 2017, we reported on over 300 completed cases of which approximately 15% had an abnormal array or karyotype. Of the remaining cases, 7.7% were found to have a causal pathogenic variant identified, and an additional 20% had a “genomically plausible” but unproven variant.”³ All of our pathogenic findings were confirmed in a CLIA laboratory and communicated to the families.

Our work continues to demonstrate the incremental value that WES may add in the evaluation of fetal structural anomalies. However, WES should be used with caution in prenatal testing since at the present time interpretation is difficult and requires an interdisciplinary team of geneticists and MFM specialists. The relationship between many de novo genetic variants and fetal phenotypes is frequently uncertain and more experience is required before WES can be recommended for introduction into routine practice.

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