Nuchal Translucency and Prenatal Diagnosis of Congenital Heart Disease: Progress and Future Directions

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Nuchal translucency thickness is an important component of prenatal screening programs, which exist to help quantify the risk of certain chromosomal and anatomical abnormalities in a fetus in utero. Abnormally increased nuchal translucency thickness has been used as a soft marker for Down’s Syndrome and other aneuploidies for more than a decade. Recently, an association has been identified between increased nuchal translucency thickness and congenital heart disease, raising the possibility that nuchal translucency thickness may help identify affected fetuses as early as 11-14 weeks gestation. However, the pathophysiological mechanism which produces an abnormal nuchal translucency thickness in the fetus is not well understood and an abnormal measurement is not specifically associated with any one type of lesion. Therefore, nuchal translucency thickness cannot be used for diagnosis of congenital heart disease in utero, but may be very helpful in identifying fetuses at risk, which may help improve diagnostic accuracy and direct resource-efficient use of diagnostic methods such as fetal echocardiography.

Introduction

Although it has long been the holy grail of prenatal care to be able to assure every woman a healthy infant at term, 2-3% of infants are born with at least one anatomical deformity. The congenital heart diseases are collectively the most common congenital defects, with a combined incidence estimated at approximately 1/100 at term, and higher in the prenatal population. Cardiac lesions may occur in isolation, or alternately as part of a genetic syndrome. Even in isolated cases, there appears to be a genetic, likely multifactorial, component to their etiology. They range from incidental findings of no great functional significance (e.g. small atrial septal defects) to lesions which, if left untreated, are immediately life-threatening to the neonate (e.g. transposition of the great arteries). Structural heart defects are thought to contribute to up to 20% of all neonatal deaths and up to 50% of all infant deaths.

Recently, attention has focused on the utility of ultrasound measurement of the free fluid behind the neck of the fetus—termed the “nuchal translucency” (NT)—in predicting congenital heart disease in the fetus. It has been suggested that the subset of fetuses with abnormal NT measurements is at increased risk for congenital heart defects; therefore the NT thickness may be of use in prenatal diagnosis of congenital heart disease.

What is Nuchal Translucency?

The NT measurement is a measurement of the thickness of the free fluid layer behind the fetal neck. This is measured by ultrasonography between 11 and 14 weeks gestation. There are strict criteria to establish an ultrasound image as adequate for the assessment of nuchal translucency and the normal limit to the measurement is dependent upon gestational age. The NT measurement was first suggested as a soft marker for fetal aneuploidy by Nicolaides and colleagues in 1994, and this association was later confirmed by other researchers. It is now known that the nuchal translucency measurement is 77% sensitive and 95% specific for Down’s Syndrome/Trisomy 21, the most common of the...
three autosomal aneuploidies that are compatible with life.\(^4\)

However, the NT measurement is also associated with a host of other abnormalities in the fetus. Even in chromosomally normal fetuses, increasing NT is associated with adverse fetal outcomes.\(^7,8\) Bilardo and colleagues report that up to 20% of chromosomally normal fetuses with increased NT experienced an adverse outcome, defined as miscarriage, intrauterine death, parental choice to terminate the pregnancy, or one or more structural or genetic disorders in the fetus. Of the 86 adverse outcomes, 14 (16%) were pregnancy terminations. The likelihood of adverse outcome appeared to correlate with increasing degrees of NT abnormality.\(^8\)

**Nuchal Translucency and Congenital Heart Disease**

Recently, in both euploid\(^9-12\) and aneuploid\(^13-16\) fetuses, an abnormally elevated NT measurement has been described in association with congenital heart disease in the fetus. There is increasing risk of cardiac lesions as the NT becomes progressively more abnormal.\(^12\) Ghi and colleagues report the overall incidence of major cardiac defects to be 4.5% in fetuses with NT above 2.5 mm, with 7% incidence in fetuses with nuchal translucency thickness equal to or greater than 3.5 mm.\(^12\) They suggest that abnormal NT may be more of a risk factor for major congenital cardiac lesions than maternal diabetes, positive family history of congenital heart disease or exposure to teratogenic agents, and that therefore fetal echocardiography is indicated for all fetuses with elevated NT measurements. At a NT thickness at or above 3.5 mm (roughly the 99\(^{th}\) percentile), major cardiac anomalies appear to be present in 5-10% of screen-positive fetuses.\(^12,17-19\) Hyett and colleagues\(^11\) propose a cutoff of between the 95\(^{th}\)-99\(^{th}\) percentiles as the optimum point to initiate referral for fetal echocardiography. Hyett suggests the nuchal translucency measurement could contribute to the detection of approximately 30% of all cases of congenital heart defects.\(^19\)

Previously, Hyett and colleagues\(^13\) have suggested that the nuchal translucency measurement may be related to failure of the fetal heart rather than to the direct effects of aneuploidy. As cardiac lesions are seen in many of the genetic syndromes, this is certainly a plausible explanation for the close association seen between increased nuchal translucency, aneuploid conditions and congenital heart disease. However, this interpretation is by no means unanimously accepted, and multiple authors\(^20,21\) report that the degree of NT abnormality is not specifically associated with any particular heart lesion. Makrydimas and colleagues\(^21\) report that there is considerable overlap between the average NT measurement for different cardiac lesions and the identity of the lesion; thus, the NT measurement is not helpful for the specific diagnosis of fetal congenital heart disease except to indicate that a cardiac lesion may be present. The underlying pathophysiology remains unclear, and alternate explanations for the elevated NT in cases of congenital heart disease include venous congestion in the head and neck of the fetus, abnormalities of lymphatic drainage, altered distribution of subcutaneous tissue, glycosaminoglycan and proteoglycan accumulation, fetal anemia and/or decreased fetal movement.\(^22,23\) Therefore, the NT may indeed identify fetuses who are at increased risk of congenital heart defects so that these can be referred on for more specialized diagnostic testing (e.g. fetal echocardiography). However, in isolation, it does not appear to be sensitive or specific enough to be a diagnostic test for congenital heart disease.\(^17\)

Mol\(^24\) has suggested that relying on nuchal translucency to identify fetuses with Down’s Syndrome may in fact preferentially identify fetuses in whom there is an associated cardiac defect. Given the relative incidence of congenital heart disease (1/100) and Down’s syndrome (1/800-1000 overall)\(^25,26\), the NT measurement may in fact pick up more babies with congenital heart disease who incidentally have Down’s syndrome than babies with Down’s syndrome who have an associated cardiac defect.
The clinical implications of this finding are less clear. It could be argued that, even if increased NT is a marker for congenital heart disease in the fetus, it is not useful clinically as it is a standard of care to offer all pregnant women (regardless of NT measurement) a morphological ultrasound scan at 18-20 weeks during which structural cardiac lesions can be identified. The current recommendation is a four-chamber view of the heart and imaging of the ventricular outflow tracts in an attempt to identify major anomalies. However, it has been previously noted in population studies of prenatal patients that morphological echocardiography is dependent upon the expertise of the ultrasonographer and consequently an inexperienced one may miss a significant proportion of major cardiac defects. In their study, Hyett and colleagues report abnormal NT measurement in 55% of fetuses with major congenital heart disease, compared to an abnormal four-chamber view on prenatal ultrasound in 26% of those same babies. The 26% detection rate in that study was consistent with prior estimates. Wald and colleagues have suggested, based on a meta-analysis of studies of the utility of nuchal translucency measurements and congenital heart disease, a detection rate of 52% and a false-positive rate of 5% using a screening cutoff of 1.7 multiples of the median. This is greater than that achieved using a four chamber view alone, and, therefore, the nuchal translucency shows great promise as a potential screening tool for congenital heart disease which can help direct appropriate and resource-efficient use of fetal echocardiography.

Summary

Nuchal translucency is typically measured at 11-14 weeks as part of prenatal screening programs in order to help estimate maternal risk of bearing a child with aneuploidy or neural tube defects. In recent years, an association has been demonstrated between abnormally elevated nuchal translucency and a group of structural, genetic and chromosomal abnormalities in the developing fetus, including the congenital heart diseases, as well as poorer pregnancy outcomes for the fetus, and this is seen even in fetuses with normal chromosomes. Routine measurement of the nuchal translucency shows great promise in helping to identify fetuses at increased risk of congenital heart disease, and therefore may help direct resource-efficient use of fetal echocardiography. However, by itself, increased nuchal translucency does not predict the diagnosis of a specific type of cardiac defect in the fetus.

References