First Trimester Ultrasonography in Screening and Detection of Fetal Anomalies

JIRI SONEK*

An obstetrical ultrasound examination provides invaluable information regarding the fetus. Until the mid-1980s, ultrasound in the first trimester was limited to localization of the pregnancy, establishing viability, and accurate dating. With the advent of high-resolution ultrasound and transvaginal scanning, a significant amount of information about the fetus can be gained and provided to the patient at a very early stage in gestation. This article provides an overview of the role of first trimester (11–13 + 6 weeks’ gestation) ultrasound in screening and diagnosis of fetal anomalies. The first trimester is an ideal time for screening for aneuploidy, primarily due to the advantages that nuchal translucency (NT) measurement provides. NT measurement is also useful in establishing the risk of congenital cardiac disorders and a number of genetic and non-genetic syndromes. Significant NT thickening is associated with an increase in perinatal morbidity and mortality. Potential mechanisms resulting in increased NT are discussed. A number of new ultrasound markers for fetal aneuploidy have been investigated over the past several years, some of which appear to improve the screening efficacy of early ultrasonography. The role of these is reviewed. A number of fetal anomalies can now be consistently diagnosed in the first trimester. Their appearance at this early gestational age is discussed as well. It is clear that, data obtained by first trimester ultrasound are useful in counseling expectant parents and in planning the appropriate follow-up.

KEY WORDS: first trimester obstetrical ultrasound; fetal markers; fetal anomalies

INTRODUCTION

Obstetric ultrasound examination at any stage in pregnancy serves two important functions: diagnostic and screening. While many major fetal defects can be diagnosed in the first trimester, the diagnostic accuracy of an ultrasound scan is significantly greater in the mid-second trimester due to the larger size and more advanced development of the fetus. On the other hand, the performance of a second trimester scan as a screening tool is generally considered less reliable. The first trimester is an ideal time for screening for fetal aneuploidy [Cuckle et al., 2005]. This is primarily due to the availability of the first trimester-combined screen, with the nuchal translucency (NT) measurement being the most important component. Moreover, the NT measurement is not only useful for detection of aneuploidy, but a thickened NT also raises a suspicion of a wide range of fetal defects, genetic syndromes, and an overall increase in morbidity and mortality.

Common sense, supported by objective studies, tells us that parents want to know about any fetal problems as early in pregnancy as possible [Mulvey and Wallace, 2000; de Graaf et al., 2002]. This review looks at the screening and diagnostic capabilities of first trimester ultrasound. For the purpose of this review, this is defined as 11–13 + 6 weeks’ gestation since this is when NT screening is done. Markers of fetal aneuploidy other than NT will also be discussed. Out of these, the most promising ones are nasal bone (NB) evaluation, Doppler evaluation of blood flow across the tricuspid valve (TCV), Doppler evaluation of blood flow through the ductus venosus (DV), and measurement of the fronto-maxillary facial (FMF) angle. The diagnostic capabilities of first trimester ultrasound will be discussed both in connection with screening and independently.

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NUCHAL TRANSLUCENCY

Overview

Between 11 and 13 + 6 weeks’ gestation, a layer of fluid is present beneath the nuchal skin extending for variable distance over the fetal head and back [Nicolaides et al., 1992a]. For reasons that are not entirely clear, at this point in gestation, the amount of this fluid is highly sensitive to fetal problems. An antero-posterior measurement of this layer of fluid with the fetus in a longitudinal view gives an accurate estimate of the amount of fluid present, provided that it is done in a strictly standardized fashion (Table I and Fig. 1) [Snijders et al., 1998]. Since an increase in the amount of this fluid is associated with a number of apparently unrelated fetal problems, it is safe to assume that there are a number of mechanisms which cause its increase. It is also likely that in some circumstances, more than one mechanism is at play. In order to understand the versatility of NT as a marker, it is important to review the variety of mechanisms, which may increase its thickness. These include cardiac dysfunction, abnormalities of the heart and great arteries, venous congestion of the head and neck, altered composition of the extracellular matrix, failure of lymphatic drainage due to abnormal or delayed development of the lymphatic system or impaired fetal movements, fetal anemia or hypoproteinemia and congenital infection.

PATHOPHYSIOLOGY OF INCREASED NUCHAL TRANSLUCENCY

Cardiac Dysfunction

Cardiac dysfunction (failure) is an attractive explanation for NT thickening. Fluid accumulation within bodily cavities is a well-recognized clinical feature of this condition. Direct evaluation of cardiac performance in the first trimester is very difficult. For example, there does not appear to be a direct correlation between cardiac size or left ventricular ejection fraction and NT thickening in fetuses with cardiac defects [Simpson and Sharland, 2000]. However, chromosomally normal fetuses with a history of increased NT do show reduced diastolic function in the second trimester [Rizzo et al., 2003], suggesting that perhaps our ability to evaluate the cardiac function directly in the first trimester is not sensitive enough.

Indirect evidence of cardiac strain in fetuses with increased NT measurement comes from molecular biology studies. Trisomic fetuses with an increased NT have been shown to have increased levels of atrial and brain natriuretic peptide mRNA [Hyett et al., 1996b]. It is known that during the postnatal period, congestive heart failure is associated with upregulation of these peptides [Tsuchimochi et al., 1988]. However, changes in some other biochemical markers of cardiac failure (e.g., increased expression of sarcoplasmic reticulum calcium ATPase in the heart) have not been found [von Kaisenberg et al., 1997].

Evidence of altered cardiac performance and myocardial compliance also come from Doppler studies. Both aneuploidy and cardiac defects are associated with the absence or reversal of the A-wave in the DV [Matias et al., 1998, 1999; Bilardo et al., 2001]. A possible explanation for this finding is decreased compliance of the ventricular walls. Similarly, the association between aneuploidy and cardiac defects with tricuspid regurgitation [Huggon et al., 2003] may reflect a certain degree of ventricular dilation, which may act as the cause of the TCV incompetence.

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However, these Doppler abnormalities can be seen in association with cardiac problems that are not generally associated with overt heart failure such as ventricular septal defects [Hyett et al., 1996], suggesting that myocardial dysfunction may be only a partial explanation.

There are physiological reasons why the heart of a first trimester fetus does not require a severe impairment for its hemodynamics to be altered. Fetal ventricles are limited in their elasticity and, as such, develop much greater tension when stretched. Also, the placental resistance in the first trimester (the afterload) is significantly higher than it will become later in pregnancy causing the heart to operate at the upper end of the Starling’s curve, therefore being closer to the point of failure. Furthermore, the lack of any significant intrinsic renal function at this point in pregnancy takes away from the fetus an extremely important tool to combat fluid retention.

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**TABLE I. Requirements for a Standardized NT Measurement**

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Details</th>
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<tr>
<td>1. Gestational age</td>
<td>11 + 0 to 13 + 6 weeks (CRL 45–84 mm)</td>
</tr>
<tr>
<td>2. View</td>
<td>mid-sagittal (the fetus can be either facing toward or away from the transducer)</td>
</tr>
<tr>
<td>3. Image size</td>
<td>the upper thorax and the fetal head should occupy 75% of the image (measurement accuracy of 0.1 mm)</td>
</tr>
<tr>
<td>4. Caliper placement</td>
<td>on-to-on fashion (see Figure 1)</td>
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<tr>
<td>5. The maximum NT measurement</td>
<td>should be used for risk calculation</td>
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<tr>
<td>6. If a nuchal cord is present, NT should be measured above and below the nuchal cord and the average of the two measurements should be used for risk calculation</td>
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<tr>
<td>7. The fetus should be away from the amnion</td>
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<tr>
<td>8. The fetus should be in a neutral position</td>
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NT, nuchal translucency.
Abnormalities of the Great Vessels

The aortic isthmus is the portion of the aorta that extends between the left subclavian artery and the ductus arteriosus. It is known to be narrowed in certain fetal conditions, notably Turner syndrome and Down syndrome [Hyett et al., 1996]. Increased blood flow to the head and neck region is a natural consequence of this narrowing. Other abnormalities of the great vessels have also been associated with nuchal thickening (Hyett et al., 1996).

Venous Congestion in the Head and Neck

Compression of intrathoracic organs, whether due to a mass effect of a lesion within the thorax such as a diaphragmatic hernia [Sebire et al., 1997] or the constrictive effect of short rib skeletal dysplasias [Ben Ami et al., 1997] can lead to an increase in intrathoracic pressure and to venous congestion of the fetal head and neck. Evaluation of NT helps in establishing the prognosis in the case of diaphragmatic hernias: those fetuses that have an increased NT have a significantly higher chance of dying during the neonatal period as compared to those with a normal NT.

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Altered Composition of the Extracellular Matrix

Many of the protein components of the extracellular matrix are encoded on chromosomes 21 (collagen type VI), 18 (laminin), and 13 (collagen type IV) [von Kaisenberg et al., 1998b]. Immunohistochemical studies of the skin of chromosomally abnormal fetuses demonstrated specific alterations of the extracellular matrix which may be attributed to gene dosage effects [von Kaisenberg et al., 1998a,b]. Chromosome 21 also encodes superoxide dismutase. This enzyme protects hyaluronic acid from free radical-mediated degradation [Aliakbar et al., 1993]. Hyaluronic acid, a component of the extracellular matrix, can entrap a large amount of water. The over-production of superoxide dismutase in trisomy 21 fetuses leads to an increase in hyaluronic acid, which in turn may lead to an increase in subcutaneous fluid and thick NT [Bohlandt et al., 2000]. One may speculate that altered composition of the extracellular matrix may also be the underlying mechanism for increased fetal NT seen in a number of skeletal dysplasias that are thought to be associated with alterations in collagen metabolism (e.g., achondrogenesis type II [Soothill et al., 1993]), Nance–Sweeney syndrome [Brady et al., 1998], osteogenesis imperfecta type II [Makrydimas et al., 2001], abnormalities of fibroblast receptors for growth factors (e.g., achondroplasia [Hernadi and Torocsik, 1997], thanatophoric dysplasia [Hernadi and Torocsik, 1997; Mangione et al., 2001; Souka et al., 2001]), and disturbed metabolism of peroxisome biogenesis factor (e.g., Zellweger syndrome [Bilardo et al., 1998; de Graaf et al., 1999; Christiaens et al., 2000; Johnson et al., 2001]). However, as mentioned, earlier, constriction of the thorax also contributes to nuchal thickening in many cases of skeletal dysplasia and may...
be the primary underlying pathology leading to increased NT measurements.

**Failure of Lymphatic Drainage**

Accumulation of lymphatic fluid within the nuchal area may result from either an intrinsic problem with the lymphatic development or due to a decrease in lymphatic drainage secondary to impaired fetal movements. The lymphatic system primarily develops independently of the venous system with subsequent formation of anastomoses [van der Putte and van Limborgh, 1980; Rodriguez-Niedenfuhr et al., 2001]. A delay in the development of the lymphatic system or aplasia and hypoplasia of the lymphatic vessels can occur in both chromosomally abnormal and euploid fetuses. These phenomena can be identified to a varying degree in most fetuses with aneuploidy. Examples of chromosomally normal fetuses where deficient lymphatic drainage is found include Noonan syndrome [van Zalen-Sprock et al., 1992b; Johnson et al., 1993; Trauffer et al., 1994; Reyniders et al., 1997; Bilardo et al., 1998; Adekunle et al., 1999; Achiron et al., 2000; Hiippala et al., 2001; Souka et al., 2001], and congenital lymphedema [Souka et al., 2002b]. In congenital neuromuscular disorders such as fetal akinesia deformation sequence, [Ville et al., 1992; Nadel et al., 1993; Pandya et al., 1995; Hyett et al., 1997a], myotonic dystrophy [Bilardo et al., 1998; Souka et al., 2001], and spinal muscular atrophy, [Rijhsinghani et al., 1997; Bilardo et al., 1998; Van Vuugt et al., 1998; Stiller et al., 1999; Souka et al., 2001; de Jong-Pleij et al., 2002] increased NT may be the consequence of impaired lymphatic drainage due to reduced fetal movements. Nuchal thickening due to severe amniotic band sequence is probably due to a combination of limited fetal movement and a constriction of the fetal body. For example, more than 80% of fetuses with a body stalk defect have an increased NT [Daskalakis et al., 1997; Smrcek et al., 2003b].

**Fetal Anemia**

Genetic causes of fetal anemia (α-thalassemia [Lam et al., 1999b], Black-fan-Diamond anemia [Souka et al., 2002], congenital erythropoietic porphyria [Pannier et al., 2003], dyserthropoietic anemia [Souka et al., 2002], Fanconi anemia [Tercani et al., 2001]), and congenital infection-related anemia [Petrikovsky et al., 1996; Smulian et al., 1998; Markenson et al., 2000; Sohan et al., 2000], can present with increased fetal NT. Severe red blood cell alloimmunization does not usually occur prior to 16 weeks of gestation, presumably because the fetal reticuloendothelial system is too immature to cause sufficient RBC destruction [Nicolaides et al., 1988]. Consequently, red blood cell alloimmunization is not associated with increased fetal NT.

**Fetal Hypoproteinemia**

Hypoproteinemia is implicated in the pathophysiology of both immune and non-immune hydrops fetalis [Nicolaides et al., 1985a,b]. In the first trimester, the underlying mechanism for the increased NT in fetuses with congenital nephrotic syndrome of the Finnish type and diffuse mesangial sclerosis may be hypoproteinemia due to severe proteinuria [Souka et al., 2002]. Relative hypoproteinemia may be a contributing factor to the genesis of nuchal thickening in a number of fetal disorders, including aneuploidy [Nicolaides et al., 1985b].

**Fetal Infection**

Maternal and fetal infection can be found in approximately 10% of cases with non-immune hydrops fetalis seen in the second or third trimesters where no other cause is evident. However, in the first trimester, serologic studies in mothers carrying chromosomally normal fetuses with thickened NT do not show an increased prevalence of a recent infection when compared to mothers whose fetuses have normal NT [Sebire et al., 1997]. Therefore, with the exception of Parvovirus B19, maternal evaluation for infectious causes of thick NT is not warranted. The thickened NT associated with Parvovirus B19 infection is felt to be due to a combination of fetal anemia and myocarditis-related cardiac dysfunction [Petrikovsky et al., 1996; Smulian et al., 1998; Markenson et al., 2000; Sohan et al., 2000].

**IMPLICATIONS OF A THICK NUCHAL TRANSLUCENCY**

**Overview**

There is a direct correlation between the NT thickness and the prevalence of chromosomal defects [Suijders et al., 1998], major fetal abnormalities, miscarriage, and fetal and neonatal death [Souka et al., 1998, 2001; Michailidis and Economides, 2001]. By performing a systematic ultrasound evaluation of the fetus at 11–13 + 6 weeks of gestation starting with the NT measurement, one can accurately estimate the likelihood of chromosomal abnormalities and a wide range of non-chromosomal defects including malformations, deformations, and genetic syndromes.

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Just as the prevalence of fetal problems increases with nuchal thickening, finding a thin NT is associated with a reduction of risk in women with an increased priori risk. In fetuses with a thickened NT, once the presence of aneuploidy has been ruled out, the risk of other fetal abnormalities does not statistically increase until the NT measurement reaches the 99th centile. The NT measurement representing this centile throughout the 11–13 + 6 weeks time period is essentially steady at 3.5 mm [Michailidis and Economides, 2001].
**Nuchal Translucency and Aneuploidy**

The prevalence of chromosomal defects increases exponentially with increasing NT thickness. The relation between fetal NT and chromosomal defects was derived from a multicenter screening study involving 96,127 singleton pregnancies [Snijders et al., 1998]. It is this distribution of NT measurements which is used most commonly for quality assurance by comparing operator specific distributions to it. It is now recognized that measuring the NT is an excellent screening method for fetal aneuploidy. The performance of the test can be improved even further by combining it with first trimester biochemical markers (free-beta hCG and PAPP-A) and other sonographic markers such as the NB, TCV Doppler flow evaluation, or DV Doppler flow (see below). Briefly, for a 5% screen positive rate, the detection rate for Down syndrome is approximately 75% for maternal age and NT, 90% for combined screening using maternal age, NT, free-beta hCG, and PAPP-A, and 94% using combined screening consisting of maternal age, NT, free-beta hCG, PAPP-A, and either NB, TCV flow, or DV flow [Nicolaides et al., 2005]. NT screening is also highly effective in screening for other types of aneuploidy such as trisomies 18 and 13, Turner syndrome, and triploidy [Snijders et al., 1998]. (For further details of combined screening, see Prof. K. Spencer's review in this issue.)

**Nuchal Translucency in Euploid Fetuses—Fetal Structural Defects**

Several studies have reported that increased fetal NT thickness is associated with a high prevalence of major fetal abnormalities [Ville et al., 1992; van Zalen-Sprock et al., 1992; Hewitt, 1993; Johnson et al., 1993; Nadel et al., 1993; Shulman et al., 1994; Trauffer et al., 1994; Salvesen and Goble, 1995; Hewitt et al., 1996; Moselhi and Thalghanathan, 1996; Reynolds et al., 1997; Bilardo et al., 1998; Fukada et al., 1998, 2002; Pajkrt et al., 1998; Souka et al., 1998, 2001; Van Vugt et al., 1998, 2001; Adekunle et al., 1999; Schwarzler et al., 1999; Maymon et al., 2000; Bilardo et al., 2001; Hiippala et al., 2001; Mangione et al., 2001; Michailidis and Economides, 2001; Senat et al., 2002; Cheng et al., 2004; Bahado-Singh et al., 2005]. The prevalence of major fetal abnormalities in chromosomally normal fetuses increases proportionately with NT thickness, from 1.6%, in those with NT below the 95th centile [Michailidis and Economides, 2001] to 2.5% for NT between the 95th and 99th centiles and exponentially thereafter to about 45% for NT of 6.5 mm or more [Souka et al., 1998, 2001]. Statistically, the risk of major fetal abnormalities does not increase until the NT reaches 3.5 mm or above.

**INCREASED NUCHAL TRANSLUCENCY—TYPES OF ABNORMALITIES**

**Overview**

A wide range of fetal abnormalities has been reported in fetuses with increased NT. The prevalence of major cardiac defects, [Gembruch et al., 1993; Achiron et al., 1994; Hyett et al., 1996, 1997, 1999; Bilardo et al., 1998; Joseffson et al., 1998; Souka et al., 1998, 2001; Schwarzler et al., 1999; Zosmer et al., 1999; Ghi et al., 2001; Mavrides et al., 2001; Michailidis and Economides, 2001; Orvos et al., 2002; Galindo et al., 2003; Hafner et al., 2003; Lopes et al., 2003; Makrydimas et al., 2003; McAuliffe et al., 2003; Smrcek et al., 2003], diaphragmatic hernia, [Bulas et al., 1992; Nadel et al., 1993; Pandya et al., 1995; Van Vugt et al., 1998; Mangione et al., 2001; Souka et al., 2001; Varlet et al., 2003], exomphalos [Ville et al., 1992; Nadel et al., 1993; Pandya et al., 1995; Snijders et al., 1995; Cha’Ban et al., 1996; van Zalen-Sprock et al., 1997; Adekunle et al., 1999; Mangione et al., 2001; Souka et al., 2001; Senat et al., 2002; Schemm et al., 2003], body stalk anomaly [Van Vugt et al., 1998; Smrcek et al., 2003], skeletal defects [Fisk et al., 1991; Hewitt, 1993; Soothill et al., 1993; Trauffer et al., 1994; Meizner and Barnhard, 1995; Ben Ami et al., 1997; Elyahu et al., 1997; Hernadi and Torocsik, 1997; Petrikovsky et al., 1997; den Hollander et al., 1997; Brady et al., 1998; Fukada et al., 1998; Hafner et al., 1998; Hill and Leary, 1998; Souka et al., 1998, 2001; Adekunle et al., 1999; Lam et al., 1999; Hiippala et al., 2001; Hull et al., 2001; Makrydimas et al., 2001; Mangione et al., 2001; Percin et al., 2001; Fukada et al., 2002; Monteagudo et al., 2002; Souka et al., 2002; Souter et al., 2002; Clementschitsch et al., 2003; Viora et al., 2003b], and certain genetic syndromes, such as congenital adrenal hyperplasia [Masturzo et al., 2001; Fincham et al., 2002; Flores Anton et al., 2003], fetal akinesia deformation sequence, [Ville et al., 1992; Nadel et al., 1993; Pandya et al., 1995; Hyett et al., 1997; Souka et al., 2001], Noonan syndrome [van Zalen-
Sprock et al., 1992; Johnson et al., 1993; Trauffer et al., 1994; Reynders et al., 1997; Bilardo et al., 1998; Adekunle et al., 1999; Aichiron et al., 2000; Hiippala et al., 2001; Souka et al., 2001]. Smith–Lemli–Opitz syndrome [Hobbins et al., 1994; Hyett et al., 1995; Pandya et al., 1995; Sharp et al., 1997; Souka et al., 2001], and spinal muscular atrophy [Rijhsinghani et al., 1997; Bilardo et al., 1998; Van Vugt et al., 1998; Stiller et al., 1999; Souka et al., 2001; de Jong-Pleij et al., 2002], appears to be substantially higher in fetuses with a thickened NT compared to the general population. However, in other cases the association is less definite, primarily due to the extremely rare nature of many of these disorders.

Cardiac Defects

The pathophysiologic reasons why cardiac lesions may be associated with nuchal thickening are discussed earlier (see above). Clinical studies have proven this association. In three studies with a combined total of 30 fetuses with major cardiac defects diagnosed by echocardiography at 11–14 weeks, 83% had increased NT [Aichiron et al., 1994; Smrcek et al., 2003]. In screening studies the prevalence of major cardiac defects in fetuses with NT below the 95th centile was in 1.6 per 1,000 based on examination of 63,894 fetuses [Hyett et al., 1997, 1999; Ghi et al., 2001; Mavrides et al., 2001; Michailidis and Economides, 2001; Lopes et al., 2003; McAuliffe et al., 2003]. The NT measurements in fetuses with a thickened NT were stratified and the prevalence of major cardiac defects for various NT ranges was determined: NT of 2.5–3.4 mm, 1%; NT of 3.5–4.5 mm, 3%; NT of 4.5–5.4 mm, 7%; NT of 5.4–6.4 mm, 20%; NT of 6.5 mm or more, 30%. Combining the results of eight studies dealing with a total of 67,256 low-risk pregnancies shows a detection rate of 37.5% for a false positive rate of 4.9% [Bilardo et al., 1998; Josefsson et al., 1998; Hyett et al., 1999; Schwarzer et al., 1999; Mavrides et al., 2001; Michailidis and Economides, 2001; Orvos et al., 2002; Haﬁner et al., 2003]. Based on a meta-analysis of screening studies, the detection rates of congenital cardiac defects of about 37% and 31% for NT cut-offs of the 95th and 99th centiles, respectively, could be achieved. It was estimated that fetal echocardiography in all chromosomally normal fetuses with NT above the 99th centile would identify one major cardiac defect in every 16 patients examined [Makrydimas et al., 2003]. Additionally, this analysis showed that the performance of screening by increased NT does not vary with the type of cardiac defect. Similar results were obtained in a multicenter study where nuchal thickening was found to be increased in all types of heart defects: left as well as right heart lesions, septal defects, outflow tract disorders, laterality disorders, and complex heart lesions [Makrydimas et al., 2005].

Improvements in the resolution of ultrasound machines have now made it possible to perform a detailed fetal cardiac evaluation even in the first trimester of pregnancy [Gembruch et al., 1993; Carvalho et al., 1998; Zosmer et al., 1999; Simpson et al., 2000]. In fetuses with major defect, the early scan can either lead to the correct diagnosis or at least raise suspicions so that follow-up scans are carried out. Conversely, a majority of cardiac defects can be ruled out if the heart is normal in its ultrasound appearance even at this early stage of pregnancy. It must be stressed that an echocardiogram, whether it is performed in the first trimester or later, needs to be done by individuals trained to do so (for further details on ultrasound screening and diagnosis of congenital heart defects, see Prof. Allan’s review in this issue).

Is Increased Nuchal Translucency in Euploid Fetuses Associated With Developmental Delay?

A number of studies have reported on the long-term follow up of chromosomally and anatomically normal fetuses with increased NT with an overall rate of developmental delay of 2.6% [Nadel et al., 1993; Brady et al., 1998; Van Vugt et al., 1998; Adekunle et al., 1999; Maymon et al., 2000; Hiippala et al., 2001; Senat et al., 2002; Cheng et al., 2004]. Only one of the studies had a control arm [Nadel et al., 1993]. No difference was noted in the rate of developmental delay between the study group and controls.

Does the Appearance of Nuchal Translucency Change Prognosis?

In the second and third trimesters of pregnancy, abnormal accumulation of fluid behind the fetal neck can be classified as either a cystic hygroma or nuchal edema [Chervenak et al., 1983; Benacerraf et al., 1987]. About 75% of fetuses with a cystic hygromas in the second trimester have a chromosomal abnormality, out of which 95% is Turner syndrome [Azar et al., 1991]. Nuchal edema in the second trimester has a number of potential causes. Chromosomal abnormalities are found in about one-third of these fetuses with about 75% being trisomies 21 or 18 [Nicolaides et al., 1992]. Nuchal edema can also be associated with non-chromosomal disorders such as fetal cardiovascular and pulmonary defects, lymphatic abnormalities, skeletal dysplasias, congenital infection and metabolic, and hematological disorders [Nicolaides et al., 1992].

In the first trimester, the term increased NT is used irrespectively of whether the collection of fluid contains septations and regardless of how far down the fetal back the fluid layer extends [Nicolaides et al., 1992]. A report on 29 fetuses with abnormally large nuchal fluid accumulations at 10–13 weeks’ gestation showed that the appearance of the nuchal fluid could neither predict the prevalence of chromosomal abnormalities nor the overall prognosis [Cullen et al., 1990a]. In a recent study involving 386 fetuses with NT measurement at or above the 95th centile, septations were demonstrated in a transverse suboccipitobregmatic view in each case [Molina et al., 2006]. The FASTER trial excluded those cases where septations were seen and in a separate study, with the authors controversially concluding that outcome of fetuses with thickened NT differ according to
appearance [Malone et al., 2005]. A critical evaluation of the statistical analysis used in this article was subsequently published [Sonien et al., 2006]. Furthermore, subsequent analysis of the data did show that NT size rather than appearance is most important [Comstock et al., 2006]. The risk of fetal abnormalities and perinatal morbidity and mortality are related to the NT thickness and not to its appearance.

**Why Is 11–13+6 Weeks an Optimal Time for Nuchal Translucency Measurement?**

Even at this early stage in pregnancy, an ultrasound evaluation is more than just estimation of gestational age and NT measurement. Therefore, it is prudent to choose a time in early gestation when the most information can be gathered about a fetus in a single examination and still fulfill requirements for NT screening. It is clear that fetal anatomic evaluation is very gestational-age dependent and its benefit prior to 11 weeks of gestation is limited. Specifically, the following structures have been shown not to lend themselves for an adequate evaluation prior to 11 weeks: presence or absence of normally ossified fetal skull (important in detection of acrania/anencephaly) [Green and Hobbins, 1988], evaluation of cardiac anatomy (cardiac anatomy cannot be evaluated prior to 11 weeks gestation) [Johnson et al., 1992; Gembuch et al., 1993; Braithwaite et al., 1996], evaluation of the abdominal umbilical cord insertion (presence of the physiologic gut herniation prior to 11 weeks gestation makes the diagnosis of an omphalocele difficult) [Snijders et al., 1995; van Zalen-Sprock et al., 1997], identification and size of the urinary bladder (see below) [Braithwaite et al., 1996; Rosati and Guariglia, 1996; Sebire et al., 1996] NB (lack of ossification of the NB prior to 11 weeks renders its evaluation useless in screening for Down syndrome [Sandicallyoglu et al., 1994]).

There are three main reasons why the upper limit of 13+6 weeks was selected. One is due to the fact that the screening by measuring the NT becomes less efficient beyond this point: the prevalence of increased fluid accumulation within the nuchal area in chromosomally abnormal fetuses decreases beyond this point in gestation [Benacerraf et al., 1987; Nicolaides et al., 1992a,b; Souka et al., 2001]. Furthermore, the acquisition of an appropriate NT measurement becomes much more difficult at 14 weeks and beyond (only 90% of the cases) as compared to earlier gestational ages (98–100%) [Whitlow and Economides, 1998; Mulvey et al., 2002]. Thirdly, by placing a relatively early gestational age limit on the timing of the screen, one allows for the option of an earlier and therefore safer form of termination of the affected fetuses.

In women who did not have a previous scan to date the pregnancy, it is best to schedule the NT scan at 12–13 weeks’ gestation, which allows for small errors in dating [Mulvey et al., 2002].

**OTHER MARKERS FOR FETAL ANEUPLOIDY**

**Nasal Bone Evaluation**

In 1866 Langdon Down noted that a common characteristic of patients with trisomy 21 is a small nose [Down, 1866]. Anthropometric [Farkas et al., 2001], radiological [Keeling et al., 1997; Stempfle et al., 1999; Larose et al., 2003; Tuxen et al., 2003], and histological studies [Minderer et al., 2003; Tuxen et al., 2003], have demonstrated an objective difference in NB findings between euploid individuals and those with trisomy 21. Since the initial description of this phenomenon by ultrasound [Sonien and Nicolaides, 2002], a number of studies have been published indicating that absence of the NB in the first trimester [Cicero et al., 2001, 2003c, 2004b; Otano et al., 2002; Orlandi et al., 2003; Viora et al., 2003; Wong et al., 2003; Zoppi et al., 2003] is highly associated with trisomy 21.

**Association of NB Absence With Chromosomal Abnormalities**

Combined data from the ultrasound studies mentioned above shows that that the fetal profile was successfully examined in 15,046 (97.4%) cases and the NB was absent in 185 of 15,048 (1.2%) chromosomally normal fetuses and in 282 of 412 (68.4%) fetuses with trisomy 21 [Sonien et al., 2006].

The prevalence of NB absence changes with ethnicity (it is highest in individuals of African origin), NT thickness (it increases as the NT measurement increases), and the crown rump measurement (it decreases with gestational age). Therefore, likelihood ratios in screening for trisomy 21 must be adjusted to account for these factors [Cicero et al., 2003, 2004]. If the NB is found to be absent between 11 and 12 weeks, it is appropriate to examine the fetus 1 week later. The results of that scan can be used to calculate the risk of trisomy 21, thus reducing the false positive rate. (For further details of combined screening using additional ultrasound markers, see Prof. Spencer’s review in this issue.)

In order for the NB evaluation to perform reliably as a screening tool, a strict scanning protocol has to be followed (Table II). This requires training and ongoing audit. As expected, the ability to evaluate the NB improves with time [Cicero et al., 2003]. Nonetheless, ultrasound NB evaluation should be achievable without extending the length of ultrasound examination as both NT and NB are obtained in the midsagittal plane [Kanellopoulos et al., 2003].
In contrast to the above studies, the NB was felt to be present in all nine trisomy 21 fetuses identified in the FASTER trial [Malone et al., 2004] and questions were raised whether this marker could be implemented in broad screening programs. However, they were able to examine only 76% of the 6,316 fetuses scanned at 10–13 weeks. Potential differences in techniques used are illustrated in another publication [Welch and Malone, 2003]. Despite these differences, there is strong consensus among leading authors that failure to adopt a strict protocol can result in a very low detection rate. Certainly, a significant lack of standardization accounts for the finding of a retrospective study of stored images where NB was present in all five trisomy 21 fetuses [De Biasio and Venturini, 2002]. Nevertheless, in many experienced centers, at 11+0–13+6 weeks the fetal profile can be successfully examined in more than 95% of cases. The NB is absent in about 70% of trisomy 21 fetuses, 55% trisomy 18 fetuses, and 34% trisomy 13 fetuses, making NB evaluation an important addition to our armamentarium of markers for fetal aneuploidy [Cicero et al., 2004].

**Fetal Measurements as Markers in the First Trimester**

A novel method for evaluating the relative position of the fetal maxilla with respect to the forehead was recently introduced [Sonek et al., 2006]. This is done by measuring the FMF angle, which is defined as the angle between the upper surface of the upper palate and the frontal bone. The apex of the angle is the anterior most aspect of the maxilla (Fig. 2). In this study, three-dimensional (3D) volumes of the fetal head which were obtained before fetal karyotyping at 11–13+6 were retrospectively reviewed. A precise midline sagittal view of the face was generated using a multi-planar mode and the FMF angle was measured in 100 fetuses with trisomy 21 and 300 chromosomally normal fetuses. The mean FMF angle was significantly larger in the trisomy 21 fetuses than in the chromosomally normal fetuses (mean 88.7°, range 75.4–104° vs. mean 78.1°, range 66.6–89.5, P < 0.001). Sixty-nine percent of the trisomy 21 fetuses had an FMF angle, which was greater than 95th centile (85°) of the euploid population. Forty percent of the trisomy 21 fetuses had an FMF angle which was above the upper limit of the range of angles (90°) of the euploid population. Only 2% of the affected fetuses had an FMF angle below the 50%. There was no significant association between the FMF angle and crown-rump length, NT thickness, or presence/absence of the NB in either the trisomy 21 or the chromosomally normal fetuses. The authors postulated three possible mechanisms for the increased FMF angle in trisomy 21 fetuses. First, it may be due to a dorsal displacement of the upper palate with respect to the forehead. Second, the increased angle can be produced by

**TABLE II. Requirements for a Standardized View to Evaluate the NB in the First Trimester**

1. Gestational age: 11 + 0 to 13 + 6 weeks (CRL 45–84 mm)
2. View: mid-sagittal (the fetus must be facing toward the transducer)
3. Image size: the upper thorax and the fetal head should occupy 75% of the image
4. The angle of insonation should be at 90 degrees with the longitudinal axis of the NB (i.e., the face of the transducer should be parallel to the longitudinal axis of the NB)
5. Two echogenic lines (skin of the nasal bridge and the NB underneath it) forming the so-called “equal sign” must be seen in order to document the presence of the nasal bone
6. The line representing the nasal bone should be at least as echogenic as the overlying skin
7. A third echogenic line representing the skin of the tip of the nose is seen located anteriorly to the “equal sign” in the mid-sagittal view

NB, nasal bone; CRL, crown-rump length measurement.

![Figure 2. A: FMF angle in a chromosomally normal fetus. B: FMF angle in a trisomy 21 fetus.](image-url)
Frontal bossing, though this is not recognized a feature of trisomy 21. Finally, the difference in the FFM angles could result from differences in the direction of the longitudinal axis of the upper palate—a deviation of this axis toward the base of the skull would lead to an increase in the FFM angle. However, the third hypothesis does not lend itself easily to an objective evaluation. A prospective evaluation of this technique with two-dimensional ultrasound is ongoing.

There are several other measurements in the first trimester, which are more common in chromosomally abnormal fetuses compared with chromosomally normal population. Growth can be reduced even in the first trimester in trisomy 18, triploidy and, to a lesser degree in trisomy 13 and Turner syndrome. However, in the case of trisomy 21, the crown-rump lengths are not different from the euploid fetuses [Dru- gan et al., 1992; Kuhn et al., 1995; Nicolaides et al., 1996; Bahado-Singh et al., 1997; Jaimiaux et al., 1997; Schemmer et al., 1997; Sherrod et al., 1997]. Several other fetal measurements have been investigated as possible markers for trisomy 21: maxillary length, [Cicero et al., 2004] ear length, [Sacchini et al., 2003], femur length [Longo et al., 2004], and humeral length [Longo et al., 2004]. Even though statistical differences between trisomy 21 and euploid fetuses have been shown to exist, the actual differences in these measurements are so small that they are not clinically useful. Likewise, differences in fetal heart rate have been shown between euploid and aneuploid fetuses: relative tachycardia in trisomy 13 and Turner syndrome and bradycardia in trisomy 18 and triploidy. However, the slight increase in FHR in trisomy 21 is not significant enough to be clinically useful [Liao et al., 2000].

**Fetal Structural Defects as Markers in the First Trimester**

The finding of a two-vessel cord in the first trimester is not associated with an increased prevalence of trisomy 21 but increases the risk of trisomy 18 approxi- mately sevenfold [Rembouskos et al., 2003]. Since the presence of a single umbilical artery in the first trimester can be demonstrated only with the aid of color Doppler mapping, adherence to the ALARA principle (radiation exposures As Low As Reasonably Achievable) suggests that routine evaluation of the number of umbilical vessels at this point in gestation may not be warranted.

The fetal urinary bladder can be visualized in approximately 50% of fetuses at 10 weeks’ gestation and in essentially all normal fetuses by 13 weeks’ gestation [Braithwaite et al., 1996; Rosati and Guariglia, 1996; Sebire et al., 1996]. Finding megacystis (longitudinal diameter of 7 mm or more) in the first trimester is associated with an increased risk of a wide range of chromosomal abnormalities. Bladder measurements of 7–15 mm are associated with an approximately 24% chance of aneuploidy, primarily trisomies 18 and 13 [Liao et al., 2003].

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In chromosomally normal fetuses, 90% of megacystis in this range resolves spontaneously [Liao et al., 2003]. Greater degrees of megacystis (>15 mm) are less likely to be associated with aneuploidy (11.4%) [ Favre et al., 1999]. Unfortunately, they lead to progressive obstructive uropathy even in the chromosomally normal group. It is interesting to note that megacystis is associated with an increased NT regardless of the karyotype [Liao et al., 2003].

An omphalocele is an abnormality that has a high association with chromosomal defects, most commonly trisomy 18 [van Zalen-Sprock et al., 1997]. Since trisomy 18 has such a high rate of mortality, its association with an omphalocele decreases significantly with gestational age: 61% at 11–13 + 6 weeks gestation, 30% in the second trimester, and 15% at term [Maymon et al., 2000]. It appears that omphalocles that contain bowel only confer the highest risk of aneuploidy. The presence of a physiological mid-gut herniation can be a confounding variable and is one of the reasons why NT screening should be delayed until 11 weeks’ gestation [Braithwaite et al., 1996; van Zalen-Sprock et al., 1997]. Omphalocles are associated with an increased prevalence of nuchal thickening regardless of karyotype [van Zalen-Sprock et al., 1997].

Holoprosencephaly results from the failure of the forebrain (prosencephalon) to cleave normally. Based on the degree to which the failure of cleavage occurs, three types of holoprosencephaly exist. In its most extreme form (alobar holoprosencephaly), only a single cerebral ventricle is present and the thalami are fused, making the diagnosis even in the first trimester relatively reliable. This condition is associated with a significantly increased risk of aneuploidy (30%), most commonly trisomy 13 [Snijders et al., 1999]. The semilobar and lobar types of holoprosencephaly show segmentation of the lateral ventricles to varying degrees, making the diagnosis by prenatal ultrasound difficult.

**USE OF DOPPLER IN SCREENING**

**Blood Flow Across the Tricuspid Valve**

Regurgitant flow across the TCV is significantly more common in the presence of chromosomal defects, especially at 11–13 + 6 weeks [Huggon et al., 2003; Faiola et al., 2005]. It has been
shown that at this gestational age the prevalence of TCV regurgitation in fetuses with trisomy 21 is about 74% whereas only 7% of chromosomally normal fetuses have this finding [Faiola et al., 2005].

The evaluation begins by obtaining an apical view of the four-chamber heart. The ideal angle of insonation with respect to the longitudinal axis of the ventricular septum is 0° (i.e., the ventricular septum is positioned vertically on the image) but angles of up to 30° are acceptable. A relatively large (approximately 3 mm) Doppler gate is placed over the TCV in order to be able to evaluate the blood flow in both directions. The biphasic forward flow across the valve is identified during the cardiac diastole and the atrial contraction. During the ventricular systole, however, there should be very little if any flow back across the closed TCV. Significant TCV regurgitation is diagnosed if reversed flow is noted and lasts for more than 50% of ventricular systole. Since the outflow tracts are in such a close proximity to the ativoventricular valves, it is not unusual to have their Doppler footprint superimposed on the region of the TCV. However, they are relatively easy to differentiate from TCV regurgitation because of the differences in their peak velocities and shapes of their waveforms (for further details see www.fetalmedicine.com).

An additional benefit of evaluating the flow across the TCV is that there is an association between an increased prevalence of cardiac defects and TCV regurgitation, irrespective of the presence or absence of aneuploidy [Huggon et al., 2003; Faiola et al., 2005]. Therefore, if TCV regurgitation is noted and the fetal chromosomes prove to be normal, a more careful evaluation of the cardiac anatomy is indicated.

**Ductus Venosus**

The DV directs well-oxygenated blood, which arrives through the umbilical vein, to the coronary and cerebral circulation. It does so by preferentially streaming it through the foramen ovale into the left atrium. Blood flow in the ductus has a characteristic waveform with high velocity during ventricular systole (S-wave) and diastole (D-wave). There is a rapid decrease in velocity during the atrial contraction (a-wave) but forward flow is normally maintained. The a-wave is considered abnormal if there is a complete cessation of forward flow or a reversal of flow [Kiserud et al., 1994; Hecher et al., 1995].

Abnormal ductal flow is associated with chromosomal abnormalities, cardiac defects and adverse pregnancy outcome. In the combined data from six studies, abnormal ductal flow was observed in 273/5,462 (5.0%) chromosomally normal fetuses, 108/131 (83.3%) with trisomy 21 and in 205/277 (74.0%) of all chromosomal abnormalities [Antolin et al., 2001; Mavrides et al., 2002; Murta et al., 2002; Zoppi et al., 2002; Borrell et al., 2003]. There may be an association between increased fetal NT and the presence of abnormal ductal flow but it appears to be a weak one. These findings suggest that Doppler evaluation of the DV flow can be combined with NT screening [Murta et al., 2002; Zoppi et al., 2002; Borrell et al., 2003]. However, examination of ductal flow requires highly skilled operators since the interference from adjacent vessels is a commonly encountered.

**Other Doppler Evaluations**

Doppler evaluation of the uterine arteries [Bindra et al., 2001], umbilical artery [Iusiniaux et al., 1996; Martinez et al., 1997; Brown et al., 1998; Borrell et al., 2001], umbilical vein [Brown et al., 1999], jugular vein [Martinez et al., 2003], and carotid artery [Martinez et al., 2003] have been evaluated as possible markers for fetal aneuploidy. Thus far, these modalities have not been shown to be clinically useful.

**Integrated Sonographic and Biochemical Screening in the First Trimester**

In order for new ultrasound markers to be included in the combined screen (NT and free beta hCG and PAPP-A), a sufficient degree of independence has to be present. This has been shown to be the case with NB [Cicero et al., 2003], TCV Doppler [Falcon et al., 2006], and DV [Borrell et al., 2003]. The Fetal Medicine Foundation has developed algorithms which allow for both NB and TCV Doppler to be integrated in the first trimester combined screen. It is estimated that for a false positive rate of 5%, the detection rate of trisomy 21 would be approximately 95% and for a false positive rate of 2.5% the detection rate would be approximately 90% if the combination of maternal age, NT, maternal serum biochemistries, and either NB or TCV Doppler are used.

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This level of detection may be achieved either if the new markers are evaluated in all fetuses or if a two tiered approach is taken [Nicolaides et al., 2005]. The latter approach is based on segregating patients into three risk groups based on a combined (NT and biochemistries) risk assessment: high-risk (>1:100), intermediate (101–1,000), and low risk (<1,000). The high-risk group is offered an invasive diagnostic test and the low-risk group is reassured. Additional markers (NB or TCV) are evaluated in the intermediate group. If the evaluation is...
The diagnosis of a meningocoele/encephalocele is based on the presence of a defect in the skull, usually in the occipital region. It may either be an isolated finding or be a part of a syndrome such as Meckel–Gruber syndrome [Pacheco et al., 1989; Sepulveda et al., 1997]. Either just meninges (meningocoele) or meninges and brain tissue (encephalocele) protrude through this opening [Bronstein and Zimmer, 1991; van Zalen-Sprock et al., 1992]. The diagnosis of this defect can be made in early pregnancy, though it may be difficult prior to the time of ossification of the cranial vault. A confounding variable may be that the size of the protrusion and its contents may vary with gestational age. A case of a temporary resolution of the lesion has also been reported [Bronstein and Zimmer, 1991].

**Hydranencephaly** is a lethal condition which is caused by a complete occlusion of the internal carotid artery and its branches resulting in an absence of cerebral hemispheres. This condition can be diagnosed early in pregnancy. In one report, its appearance at 12 weeks' gestation included a large head with small hemispheres and a fluid filled intracranial cavity with no midline echo [Lin et al., 1992].

The diagnosis of an open spine defect can be made by ultrasound in the mid-second trimester with a high degree of certainty. This is due to the fact that this condition is essentially invariably accompanied by typical cranial findings at this point in gestation: scalloping of the frontal bones which give the skull a lemon-like shape in the transverse view and caudal displacement of the cerebellum giving it a banana-like shape in the transverse view and causing the transverse diameter to be diminished [Nicolaidis et al., 1986]. Unfortunately, these signs do not appear to be reliably present in the first trimester. However, the presence of a lemon sign has been reported in some fetuses with an open spine defect even in the first trimester [Sebire et al., 1997].

Pathognomonic feature of hydrocephaly is enlargement of the ventricles. It appears that ventriculomegaly generally does not develop until after the 14th week of gestation. As such, hydrocephaly is not a condition, which can be reliably diagnosed in the first trimester [Mangione et al., 2001].

Dandy-Walker malformation (DWM) is diagnosed if the cerebellar vermis is partially or completely absent, leading to a posterior fossa cyst. The normal formation of the cerebellar vermis extends well into the second trimester making the diagnosis of DWM in the first trimester very difficult [Babcock et al., 1996; Ulm et al., 1997].

**Gastrochisis** is a result of a defect involving the entire thickness of the abdominal wall. It is usually located to the right of the umbilical cord insertion. Usually, only small bowel protrudes through this opening, though other abdominal organs have been noted to do so. Unlike in the case of an omphalocele, the cord insertion itself is normal and this condition is not associated with an increased risk of aneuploidy. The diagnosis of a gastrochisis is relatively simple to make at the 11–13+6 week scan, as long as care is taken to insonate the cord insertion [Guzman, 1990; Kushnir et al., 1990].

Bilateral renal agenesis invariably results in oligohydramnios after 16 weeks of gestation. However, at the 11–13+6 week scan, the amount of amniotic fluid will be normal. The inability to see the kidneys after a careful search will raise a suspicion of bilateral renal agenesis. However, the adrenals can to some extent mimic the presence of kidneys and the fetal bladder can be visualized at this early gestational age even in the presence of bilateral renal agenesis making the definite diagnosis very difficult [Bronstein et al., 1994]. Other renal abnormalities have been diagnosed at 11–13+6 weeks of gestation: infantile polycystic kidney disease [Bronstein et al., 1992], multicystic dysplastic kidney disease, [Bronstein et al., 1990; Economides and Brathwaite, 1998], and hydronephrosis [Cullen et al., 1990; Hernadi and Toroskik, 1997].

However, since all of the latter conditions are variable in onset during gestation and do not have a consistent...
ultrasound appearance in the first trimester, they cannot be reliably diagnosed at this early gestational age.

**Multiple Gestations**

There are several advantages of detection and ultrasound evaluation of multiple gestations at 11–13 + 6 weeks of gestation. Firstly, the accuracy of determination of chorionicity at this gestational age is essentially 100% [Monteagudo et al., 1994; Sepulveda et al., 1996]. Early in gestation, the chorion leave is covered by chorionic villi, which atrophy as the pregnancy progresses. Therefore, in the first trimester, the dividing membrane in dichorionic gestations is not only much thicker overall compared to monochorionic gestations, but it also demonstrates a characteristic thickening at the point of its junction with the placenta (so-called lambda sign). In a pregnancy where the dividing membrane is difficult to see, differentiation between a monochorionic/diamniotic and monoamniotic gestations can be made based on the number of yolk sacs [Bromley and Benacerraf, 1995]. Second, use of biochemical screening for fetal abnormalities in twins is limited by its inability to differentiate between the two fetuses, increasing the importance of the sonographic component of screening. This is especially true in dichorionic/diamniotic gestations. However, the addition of biochemical markers to NT screening in twins does reduce the false positive rate [Noble et al., 1997; Spencer, 2000; Spencer and Nicolaides, 2003]. In higher order multiple gestations, the use of biochemical markers for clinical use is not yet available [Maymon et al., 1999]. Third, multiple gestations are at an increased risk for fetal anomalies, especially midline defects. Therefore, an early fetal anatomic evaluation is especially useful. When using NT measurements for screening, in monochorionic gestations, one of the twins can have a thickened NT due to an imbalance in blood volumes between the two fetuses (an early form of twin–to–twin transfusion) [Spencer and Nicolaides, 2003]. This has to be taken into consideration when estimating the risk of aneuploidy. (For further details of combined screening in multiple gestations, see Prof. Spencer’s review in this issue.)

**CONCLUSION**

Ultrasound provides a window through which invaluable information about the fetus, amniotic fluid, and the placenta can be gained even in the first trimester. Clearly, the days when a first trimester obstetric ultrasound simply meant a crown-rump measurement are over.

An early systematic evaluation of the fetus is best done between 11 and 13 + 6 weeks of gestation. At this point in time, a measurement of the NT is obtained, thus providing us with the most robust fetal marker for aneuploidy currently available. Incorporation of this marker in a combined screen with biochemical markers and/or other ultrasound marker such as NB evaluation or TCV blood flow leads to detection rates of over 90% for 5% screen positive rates for trisomy 21. In multiple gestations, NT screening is of even greater value since biochemical markers do not perform as well as in singletons.

The often-underestimated benefit of measuring the NT is its correlation with other fetal defects and the overall risk of fetal morbidity and mortality. Therefore, its importance lies not only in its robustness as a marker but also in a high degree of versatility, which cannot be duplicated by using biochemical markers. High-resolution ultrasound, especially when transabdominal and transvaginal approaches are combined, allows for an early and accurate evaluation of fetal anatomy.

In order for the various components of ultrasound-based screening programs and fetal evaluation to be effective, it is imperative that sonographers receive the appropriate training and accreditation. The overall result is that prospective parents are provided with significant amount of useful information about the fetus at an early gestational age with clear medical and psychological benefits.

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