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First-Trimester Screening

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All patients have a 2% to 3% risk of birth defects, regardless of their prior history, family history, maternal age, or lifestyle [1]. Chromosome abnormalities account for approximately 10% of birth defects, but are important because of their high mortality and morbidity. Trisomy 21 (Down syndrome) is the most common serious chromosome abnormality at birth, occurring in approximately 1 of 500 pregnancies in the United States. The actual risk varies with maternal and gestational age and whether there is a history of previous pregnancies affected by chromosomal abnormality, although, as with other birth defects, all patients are at risk for fetal Down syndrome.

A detailed fetal anatomic survey performed at 18 to 22 weeks remains the primary means for detecting the majority of serious "structural" birth defects; however, first-trimester screening at 11 to 14 weeks has developed into the initial screening test for many patients. A wealth of information can be obtained at this time, including detection of many structural defects, as well as screening for fetal aneuploidy, including Down syndrome. The major advantage of first-trimester screening is the earlier gestational age of detection so that diagnostic testing (chorionic villous sampling [CVS] or genetic amniocentesis) can be made available for patients considered at highest risk for chromosome abnormalities. First-trimester screening can also help identify patients at increased risk for a variety of other abnormalities, including cardiac defects, that may be seen later. In this way, first-trimester screening can help triage patients for subsequent testing.

Older screening methods relied on clinical risk factors, particularly maternal age, to determine which patients might benefit from a diagnostic invasive test for fetal aneuploidy; however, maternal age alone is a poor screening method for determining who is at risk for chromosome abnormalities.

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First-trimester screening has proved to be very effective in screening for fetal aneuploidy. The accuracy of both first-trimester and second-trimester ultrasound can be improved by also considering various biochemical markers. As a result, there are currently four main components to screening for fetal aneuploidy and other birth defects: (1) first-trimester ultrasound, (2) first-trimester biochemistry, (3) second-trimester ultrasound, and (4) second-trimester biochemistry. These four components of contemporary screening can be used in isolation or can be combined with one another for greater accuracy.

This article focuses on first-trimester ultrasound screening, but also describes related screening protocols that can be used.

First-trimester aneuploidy screening

It is now well-known that increased fluid or thickening beneath the skin at the back of the neck is associated with a higher risk for fetal aneuploidy and other birth defects. This sonographic observation mirrors the clinical description of Down syndrome made more than 100 years ago by Dr. Langdon Down, who reported that the skin of affected individuals is "too large for their bodies" [2].

During the 1980s, many ultrasound studies described the typical appearance of cystic hygromas in the second trimester, and their association with aneuploidy, particularly Turner's syndrome [2–12]. At the same time, it was observed that cystic hygromas seen during the first trimester may have different appearances (nonseptated), and different associations (trisomies) than those seen during the second trimester. It was also observed that "cystic hygromas" seen during the first trimester can resolve to nuchal thickening alone, or even normal nuchal thickness, and still be associated with aneuploidy [13,14]. In a related observation, Benacerraf and colleagues [15,16] noted that second-trimester nuchal thickening was associated with an increased risk of Down syndrome.

In 1992, Nicolaides and colleagues [17] proposed the term "nuchal translucency (NT)" for the sonographic appearance of fluid under the skin at the back of the fetal neck observed in all fetuses during the first trimester [Fig. 1]. They further reported an association between the thickness of the translucency and the risk of fetal aneuploidy, especially trisomies. This concept of measuring NT in all fetuses formed the basis for first-trimester screening by ultrasound. By 1995, the first large study of NT was published [18]. Subsequent studies have confirmed that NT thickness can be reliably measured at 11 to 14 weeks gestation and, combined with maternal age, can produce an effective means of screening for trisomy 21 [19].

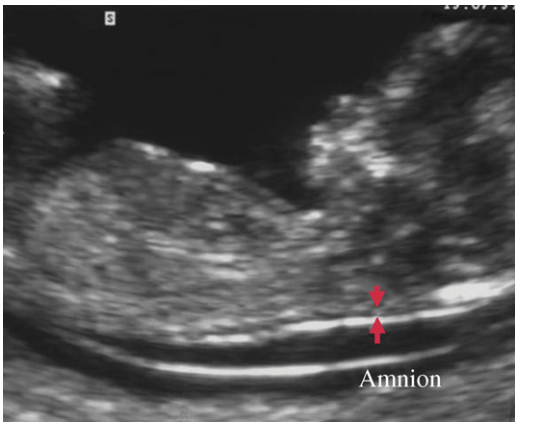

Fig. 1. Normal nuchal translucency measurement (*arrows*) at 12 weeks, 5 days.

The mechanism for increased NT may vary with the underlying condition. The most likely causes include heart strain or failure [20,21] and abnormalities of lymphatic drainage [22]. Evidence for heart strain includes the finding of increased levels of atrial and brain natriuretic peptide mRNA in fetal hearts among trisomic fetuses [23]. Also, some Doppler ultrasound studies of the ductus venosus at 11 to 14 weeks in fetuses who have increased NT have reported absent or reversed flow during atrial contraction in the majority of chromosomally abnormal fetuses and in chromosomally normal fetuses who have cardiac defects [24,25].

Abnormal lymphatic drainage may occur because of developmental delay in the connection with the venous system, or a primary abnormal dilatation or proliferation of the lymphatic channels. Fetuses who have Turner's syndrome are known to have hypoplasia of lymphatic vessels [26,27]. Lymphatic drainage could also be impaired by lack of fetal movements in various neuromuscular disorders, such as fetal akinesia deformation sequence [28].

An alternative explanation for increased NT is abnormal composition of the extracellular matrix. Many of the component proteins of the extracellular matrix are encoded on chromosomes 21, 18, or 13. Immunohistochemical studies of the skin of chromosomally abnormal fetuses have demonstrated specific alterations of the extracellular matrix that may be attributed to gene dosage effects [29,30]. Altered composition of the extracellular matrix may also be the underlying mechanism for increased fetal NT in certain genetic syndromes that are associated with alterations in collagen metabolism (such as achondrogenesis Type II), abnormalities of fibroblast growth factor receptors (such as achondroplasia and thanatophoric dysplasia), or disturbed metabolism of peroxisome biogenesis factor (such as Zellweger syndrome).