

Ultrasound screening in the first trimester of pregnancy

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Abstract

Fetal nuchal translucency thickness (NT) at 11–13+6 weeks scan has been combined with maternal age to provide an effective method of screening for trisomy 21; for an invasive testing rate of 5%, about 75% of trisomic pregnancies can be identified. When maternal serum free β -human chorionic gonadotropin (β -hCG) and pregnancy-associated plasma protein-A (PAPP-A) at 11–13+6 weeks are also taken into account, the detection rate of chromosomal defects is about 85–90%. It was found that in 60–70% of fetuses with trisomy 21, the nasal bone is not visible in the 11–13+6 weeks scan and examination of the nasal bone can increase screening detection rate by the first trimester scan and serum biochemistry to more than 95%.

In addition to its role in the assessment of risk for trisomy 21, increased nuchal translucency thickness can also identify a high proportion of other chromosomal defects and is associated with major abnormalities of the heart and great arteries, and a wide range of genetic syndromes.

Key words: Ultrasound screening for chromosomal abnormalities, fetal nuchal translucency thickness, trisomy 21, human chorionic gonadotropin (hCG), pregnancy-associated plasma protein-A (PAPP-A), amniocentesis.

INTRODUCTION

In 1866 Langdon Down noted that common characteristics of patients with trisomy 21 are skin deficient in elasticity, giving the appearance of being too large for the body, and flat face with a small nose. In the 1990s, it was realized that the excess skin of individuals with Down's syndrome can be visualized by ultrasonography as increased nuchal translucency in the third month of intrauterine life.

translucency (NT) thickness and 60–70% have absent nasal bone (Figures 1 and 2).

Non-invasive diagnosis

Extensive research has aimed at developing a non-invasive method for prenatal diagnosis based on the isolation and examination of fetal cells found in the maternal circulation.



Figure 1. Fetus with subcutaneous collection of fluid at the back of the neck

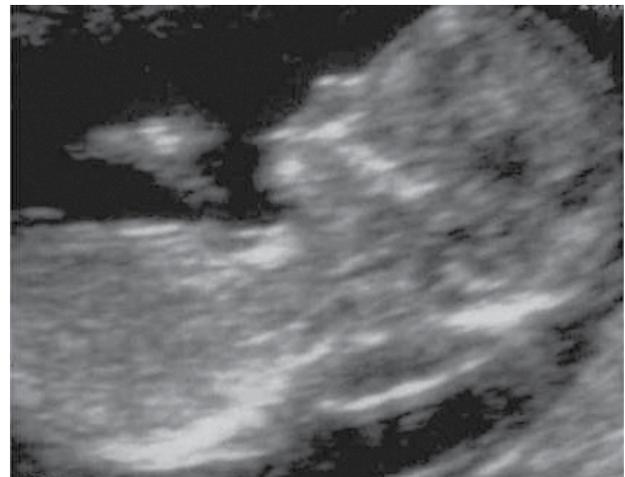


Figure 2. Ultrasound picture of a 12-week fetus with trisomy 21, demonstrating increased nuchal translucency

First trimester diagnosis of chromosomal defects

About 75% of trisomy 21 fetuses have increased nuchal

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On the basis of currently available technology, examination of fetal cells from maternal peripheral blood is more likely to find application as a method of risk assessment, rather than non-invasive prenatal diagnosis of chromosomal defects. The sensitivity of this method is comparable to serum screening. However, unlike serum biochemistry testing,

which is relatively easy to apply for mass population screening, analysis of fetal cells from maternal blood is both labor intensive and requires highly skilled operators. Recent interest has focused on the presence of cell-free fetal DNA in maternal plasma and the ability to quantify the concentration of male fetal DNA in male-fetus pregnancies using real-time quantitative PCR. The extent to which cell-free fetal DNA will become another maternal serum marker in screening for trisomy 21 remains to be seen.

Invasive diagnosis

Amniocentesis

There is only one randomized trial, which compared the risks of amniocentesis to controls (Tabor et al 1986). Total fetal loss rate in patients having amniocentesis was 1% higher than in controls. The study also reported that amniocentesis was associated with an increased risk of respiratory distress syndrome and pneumonia. Amniocentesis is also possible at 10–14 weeks of gestation. However, randomized studies have demonstrated that after early amniocentesis the rate of fetal loss is about 2% higher and the incidence of talipes equinovarus is 1.6% higher than after first-trimester chorionic villus sampling or second-trimester amniocentesis.

Chorionic villus sampling

The rate of fetal loss following first-trimester transabdominal chorionic villus sampling is the same as with second-trimester amniocentesis. There is an association between chorionic villus sampling before 10 weeks and fetal transverse limb abnormalities, micrognathia and microglossia. It is therefore imperative that chorionic villus sampling be performed only after 11 weeks.

Screening for chromosomal defects

The first method of screening for trisomy 21 was based on the association with advanced maternal age. In the late 1980s, a new method of screening was introduced that takes into account not only maternal age, but also the concentration of various fetoplacental products in maternal circulation. At 16 weeks of gestation, the median maternal serum concentrations of α -fetoprotein (AFP), unconjugated estriol (uE3), human chorionic gonadotropin (hCG) (total and free- β) and inhibin-A (INH-A) in trisomy 21 pregnancies are sufficiently different from normal to allow the use of combinations of some or all of these substances to select a 'high-risk' group. This method of screening is more effective than maternal age alone and, for the same rate of invasive testing (about 5%), it can identify about 50–70% of the fetuses with trisomy 21. Screening by a combination of maternal age and fetal NT thickness at 11–13+6 weeks of gestation was introduced. This method has now been shown to identify about 75% of affected fetuses for a screen-positive rate of about 5%.

Subsequently, maternal age was combined with fetal NT and maternal serum biochemistry (free β -hCG and PAPP-A) in the first-trimester to identify about 85–90% of affected fetuses.

In 2001, it was found that in 60–70% of fetuses with trisomy 21, the nasal bone is not visible by ultrasound at 11–13+6

weeks and preliminary results suggest that this finding can increase the detection rate of the first trimester scan and serum biochemistry to more than 95%.

Patient-specific risk for chromosomal defects

Every woman has a risk that her fetus/baby has a chromosomal defect. In order to calculate individual risk, it is necessary to take into account the background or a priori risk, which depends on maternal age and gestation, and multiply this by a series of factors or likelihood ratios, which depend on the results of a series of screening tests carried out during the course of the pregnancy to determine the patient-specific risk.

Maternal age and gestation

The risk for many of the chromosomal defects increases with maternal age. Additionally, because fetuses with chromosomal defects are more likely to die in utero than normal fetuses, the risk decreases with gestational age.

The rates of spontaneous fetal death in trisomy 21 between 12 weeks (when NT screening is carried out) and 40 weeks is about 30% and between 16 weeks (when second trimester maternal serum biochemical testing is carried out) and 40 weeks is about 20%.

Similar methods were used to produce estimates of risks for other chromosomal defects. The risk for trisomies 18 and 13 increases with maternal age and decreases with gestation; the rate of miscarriage or fetal death between 12 weeks and 40 weeks is about 80%.

Previous affected pregnancy

The risk for trisomies in women who have had a previous fetus or child with a trisomy is higher than the one expected on the basis of their age alone. In women who had a previous pregnancy with trisomy 21, the risk of recurrence in the subsequent pregnancy is 0.75% higher than the maternal and gestational age-related risk for trisomy 21 at the time of testing. Thus, for a woman aged 35 years who has had a previous baby with trisomy 21, the risk at 12 weeks of gestation increases from 1 in 249 (0.40%) to 1 in 87 (1.15%), and, for a woman aged 25 years, it increases from 1 in 946 (0.106%) to 1 in 117 (0.856%). Currently available evidence suggests that recurrence is chromosome-specific and, therefore, in the majority of cases, the likely mechanism is parental mosaicism.

Fetal nuchal translucency

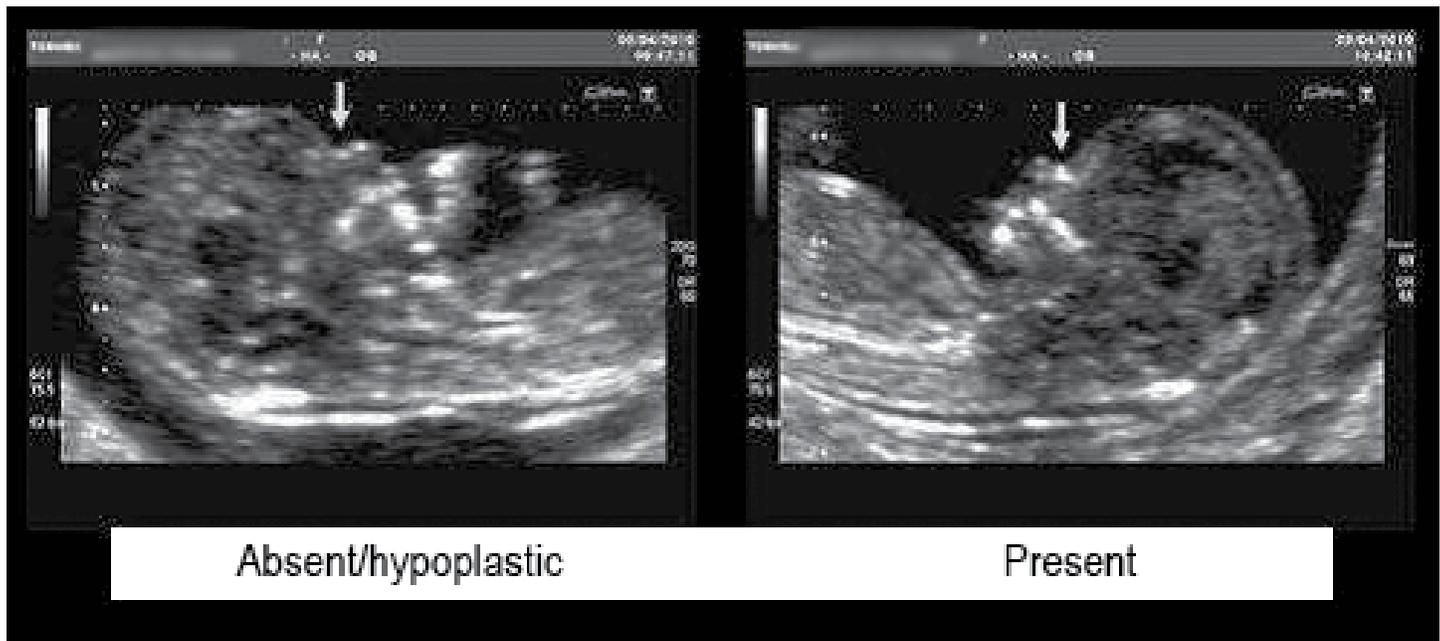
Fetal NT normally increases with gestation (crown–rump length). In a fetus with a given crown–rump length, every NT measurement represents a likelihood ratio which is multiplied by the a priori maternal and gestational age-related risk to calculate a new risk. The larger the NT, the higher the likelihood ratio becomes and therefore the higher the new risk. In contrast, the smaller the NT measurement, the smaller the likelihood ratio becomes and therefore, the lower the new risk.

Nasal bone and other first-trimester sonographic markers

At 11–13+6 weeks the nasal bone is not visible by ultrasonography in about 60–70% of fetuses with trisomy 21 and in about 2% of chromosomally normal fetuses. Abnormalities in the flow velocity waveform from the ductus venosus are observed in about 80% of fetuses with trisomy 21 and in 5% of chromosomally normal fetuses. Similarly, the prevalence of other sonographic markers, such as exomphalos, megacystis and single umbilical artery, are higher in certain chromosomal abnormalities than in chromosomally normal fetuses. Each of these sonographic markers is associated with a likelihood ratio, which can be multiplied by the a priori risk to calculate a new risk.

the minimum gestational age is 11 weeks. For example, diagnosis or exclusion of acrania and therefore, anencephaly cannot be made before 11 weeks because sonographic assessment of fetal skull ossification is not reliable before this gestational age. Examination of the four-chamber view of the heart and main arteries is possible only after 10 weeks. At 8–10 weeks all fetuses demonstrate herniation of the midgut that is visualized as a hyperechogenic mass in the base of the umbilical cord, and it is therefore unsafe to diagnose or exclude exomphalos at this gestational age. The fetal bladder can be visualized in only 50% of fetuses at 10 weeks, in 80% at 11 weeks and in all cases by 12 weeks.

The reasons for selecting 13 weeks and 6 days as the upper limit are: first, to provide women with affected fetuses the



Maternal serum biochemistry in the first-trimester

The level of free β -hCG in maternal blood normally decreases with gestation. In trisomy 21 pregnancies free β -hCG is increased. The level of PAPP-A in maternal blood normally increases with gestation and in trisomy 21 pregnancies the level is decreased. For a given gestation, each β -hCG and PAPP-A level represents a likelihood ratio that is multiplied by the a priori risk to calculate the new risk. The higher the level of β -hCG and the lower the level of PAPP-A the higher the risk for trisomy 21.

Measurement of nuchal translucency

The optimal gestational age for measurement of fetal NT is from 11 weeks to 13 weeks and 6 days. The minimum fetal crown–rump length should be 45 mm and the maximum 84 mm.

There are two reasons for selecting 11 weeks as the earliest gestational age for measurements of NT. Firstly, screening necessitates the availability of a diagnostic test and chorionic villus sampling before this gestational age is associated with transverse limb reduction defects. Secondly, many major fetal defects can be diagnosed by the NT scan, provided

option of first rather than second trimester termination; second, the incidence of abnormal accumulation of nuchal fluid in chromosomally abnormal fetuses is lower at 14–18



weeks than before 14 weeks, and third, the success rate for a measurement taken at 10–13 weeks is 98–100%, falling to 90% at 14 weeks because the fetus adopts vertical position

making it more difficult to obtain an appropriate image.

Fetal NT increases with crown–rump length and therefore, it is essential to take gestational age into account when determining whether a given NT thickness is increased. In a study involving 96,127 pregnancies, the median and 95th centile at a crown–rump length of 45 mm were 1.2 and 2.1 mm and the respective values at crown–rump length of 84 mm were 1.9 and 2.7 mm (Snijders et al 1998).

Nuchal translucency thickness and risk for chromosomal defects

Studies demonstrated that: first, in normal pregnancies, fetal NT thickness increases with gestational age; second, in trisomy 21 and other major chromosomal defects fetal NT is increased, and third, the risk for trisomies can be derived by multiplying the a priori maternal age and gestation related risk by a likelihood ratio, which depends on the degree of deviation in fetal NT measurement from the normal median for that crown–rump length (Nicolaides et al., 1994; Pandya et al., 1995). It was estimated that, in a pregnant population with a mean maternal age of 28 years, using the risk cut-off of 1 in 300 to define the screen positive group would detect about 80% of trisomy 21 fetuses for a false positive rate of 5%.

Screening for chromosomal defects in the first, rather than the second trimester, has the advantage of earlier prenatal diagnosis and, consequently, less traumatic termination of pregnancy for those couples who choose this option. A potential disadvantage is that earlier screening preferentially identifies those chromosomally abnormal pregnancies that are destined to miscarry. Approximately 30% of affected fetuses die between 12 weeks of gestation and term. This issue of preferential spontaneous death in fetuses with chromosomal defects is, of course, a potential criticism of all methods of antenatal screening, including second trimester maternal serum biochemistry, because the rate of fetal death between 16 weeks and term is about 20%.

A statistical model combining first-trimester fetal NT and maternal serum PAPP-A with second-trimester free β -hCG, uE3 and INH-A, estimated that for a false positive rate of

5% the detection rate of trisomy 21 could be 94% (Wald et al 1999).

Sonographic features of chromosomal defects

At 11–13+6 weeks, all major chromosomal defects are associated with increased NT thickness (Snijders et al 1998). In addition to increased NT, in trisomy 21, 60–70% of fetuses have absent nasal bone, 25% have a short maxilla, and 80% have abnormal Doppler waveforms in the ductus venosus. In trisomy 18, there is early onset fetal growth restriction, a tendency for bradycardia and exomphalos in 30% of cases, absent nasal bone in 55% and single umbilical artery in 75%. In trisomy 13, there is tachycardia in about 70% of the cases and early onset fetal growth restriction, megacystis, holoprosencephaly or exomphalos in about 40% of the cases. In Turner syndrome, there is tachycardia in about 50% of cases and early onset fetal growth restriction. In triploidy, there is early onset asymmetrical fetal growth restriction, bradycardia in 30% of cases, holoprosencephaly, exomphalos or posterior fossa cyst in about 40% and molar changes in the placenta in about 30%.

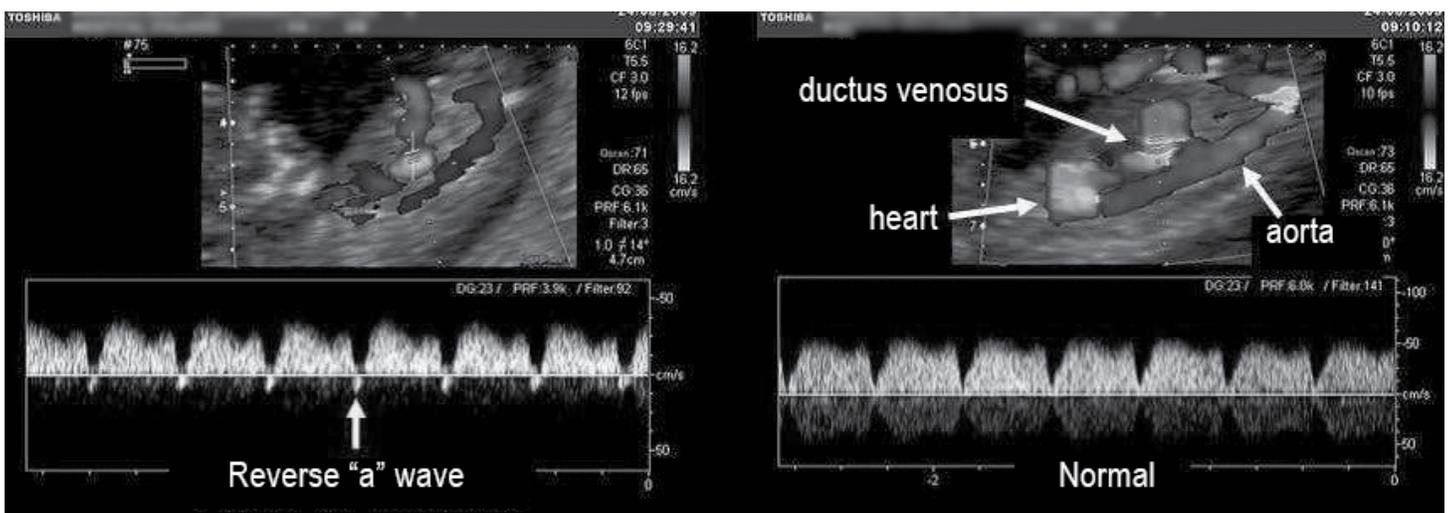
Absence of fetal nasal bone

The fetal nasal bone can be visualized by sonography at 11–13+6 weeks of gestation (Cicero et al 2001). Several studies have demonstrated a high association between absent nasal bone at 11–13+6 weeks and trisomy 21, as well as other chromosomal abnormalities (Nicolaides 2004).

A case-control study at 11–13+6 weeks of gestation examined the potential performance of screening for trisomy 21 by a combination of sonography for measurement of fetal NT and assessment of the presence or absence of the fetal nasal bone and measurement of maternal serum free β -hCG and PAPP-A (Cicero et al 2003). It was estimated that for a false positive rate of 5%, the detection rate of trisomy 21 would be 97%.

Doppler in the ductus venosus

The ductus venosus is a unique shunt directing well-oxygenated blood from the umbilical vein to the coronary and cerebral circulations by preferential streaming 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), and forward flow during atrial contraction (a-wave). In the second and third trimesters of pregnancy abnormal flow with absent or reverse a-wave is observed in impending or overt cardiac failure.

At 10–13+6 weeks abnormal ductal flow (Figure 6) is associated with chromosomal defects, cardiac abnormalities and adverse pregnancy outcome (Matias et al 1998, Borrell et al 2003).

Studies, have demonstrated that at 10–13+6 weeks there is abnormal flow in the ductus venosus in about 80% of trisomy 21 fetuses and in about 5% of chromosomally normal fetuses (Nicolaidis 2004). There is no or only a weak association between increased fetal NT and the incidence of abnormal ductal flow. These findings indicate that assessment of the ductus venosus can be combined with measurement of fetal NT to improve the effectiveness of early sonographic screening for trisomy 21.

CONCLUSION

In addition to its role in the assessment of the risk of having trisomy 21, increased nuchal thickness can also identify a high proportion of other chromosomal defects and is associated with major abnormalities of the heart, great arteries, and a wide range of genetic syndromes.

Other benefits of performing the ultrasound scan during weeks 11 to 13.6 weeks of pregnancy include: confirmation that the fetus is alive, accurate dating of the pregnancy, early diagnosis of major fetal abnormalities, and detection of multiple pregnancies. The early scan also provides reliable identification of chorionicity, which is the main determinant of the outcome in multiple pregnancies.

Respect for autonomy is a central principle in medical ethics and law. This ethical principle obliges the physician to elicit and implement the patient's preferences. The relevance of respect for autonomy to first trimester screening is two-fold. First, early diagnosis of fetal abnormality and the option of early termination of pregnancy are important to many women. Second, most first trimester screening tests provide reassurance for many women who would prefer not to have an invasive procedure to determine fetal abnormality be done if the risk is low. Consequently, provision of high-quality first trimester screening service significantly enhances the autonomy of pregnant women.

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