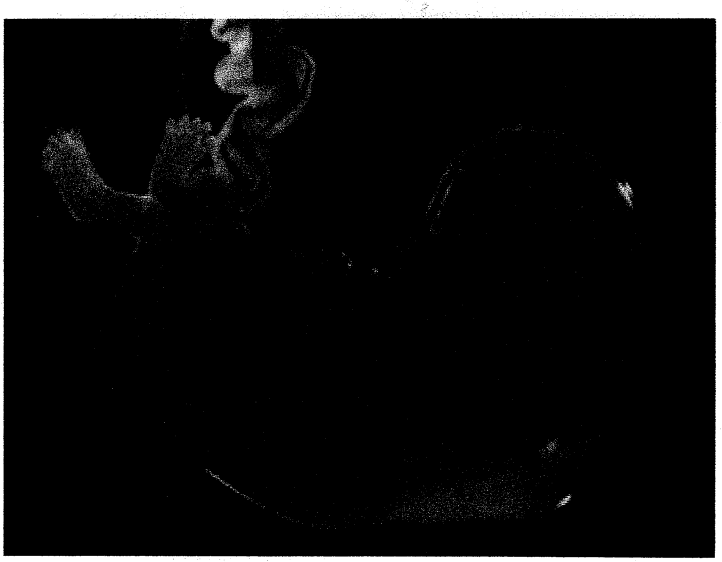
FETAL MALFORMATIONS

Ultrasound diagnosis and screening

Review paper in Preventive medicine



by

Tone Tjørnhom

CHARLES UNIVERSITY, 3rd FACULTY OF MEDICINE

Prague, March 2006

"The hair is not black, as in the real mongol, but of brownish color, straight and scanty. The face is flat and broad, and destitute of prominence. The cheeks are roundish, and extended laterally. The eyes are obliquely placed, and the internal chanti more than normally distant from another. The palpebral fissures is very narrow. The forehead is wrinkled transversely from the constant assistance which the levatores palpebrarum derive from the occipito-frontalis muscle in opening of the eyes. The lips are large and thick with transverse fissures. The tongue is long, thick and is much roughened. The nose is small. The skin has a slightly dirty yellowish tinge, and is deficient in elasticity, giving the appearance of being too large for the body."

The above is an extract from the paper "Observations on an ethnic classification of idiots" by Langdon Dawn, published in 1866. (7)

INTRODUCTION

Most hospitals in Europe practice a routine scan between 16 and 22 weeks. There is now a tensdency to delay this to between 20 and 22 weeks, as this improves the oppurtunity to diagnose cardiac and late developmenting abnormalities, such as microcephaly.
An increasing numbers of hospitals are also offering an early scan at about 11to 14 weeks gestation. A routine two scan policy is also recommended by the royal college of Obstetricians and Gynecologists (9).

In 1866, Langdon Down reported that the skin of individuals with trisomy 21 appears to be too large for their body. 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 first 3 months of intrauterine life. Fetal nuchal translucency thickness at the 11–14-week 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. The abcence of nasal bone has also played a role in the screening programme. When maternal serum free-b human chorionic gonadotropin and pregnancy-associated plasma protein-A at 11–14 weeks are also taken into account, the detection rate of chromosomal defects is about 90%. In addition to these measures later studies demonstrate the importance

of using Doppler ultrasond in the detection of chromosomal abnormalities, particulary when it comes to early detection of trisomy 21. (7)

Other benefits of the 11–14-week scan include confirmation that the fetus is alive, accurate dating of the pregnancy, early diagnosis of major fetal defects, and the detection of multiple pregnancies. The early scan also provides reliable identification of chorionicity, which is the main determinant of outcome in multiple pregnancies.

As with the introduction of any new technology into routine clinical practice, it is essential that those undertaking the 11–14-week scan are adequately trained and their results are subjected to rigorous audit. The Fetal Medicine Foundation, under the auspices of the International Society of Ultrasound in Obstetrics and Gynecology, has introduced a process of training and certification to help to establish high standards of scanning on an international basis. The Certificate of Competence in the 11–14-week scan is awarded to those sonographers that can perform the scan to a high standard and can demonstrate a good knowledge of the diagnostic features and management of the conditions identified by this scan. (9)

Chromosomal abnormalities:

The most common chromosomal abnormalities can be classified as either aneuploidis (usually trisomies) or sex-chromosome abnormalities.

Trisomies occur in the majority of cases due to non-disjunction during meiosis. This abnormality of gametogenesis is known to occur more frequently with advancing maternal age. Rarely, trisomies may occur due to unbalanced translocations (6%). Although any chromosome may be affected, the majority of trisomies result in first trimester miscarriage except for trisomies 13 (Patau's), 18 (Edward's) and 21 (Down's). Down's syndrome is associated with characteristic mental (mental retardation, deafness, short-sihtedness) and physical features (flat facies, macroglossia, cardiac septal defects, intestinal atresias) in addition to post-natal outcomes like premature ageing, reduced immunity, leukaemia and reduced life-span. Trisomies 13 and 18 ara associated with such major structural defects that their diagnosis is usually suspected on antenatal ultrasound. Since trisomies 13 and 18 have a

very high intrauterine lethality (90-95%), screening programmes are geared mainly towards the antenatal detection of Down's syndrome, which is the commonest chromosomal abnormality at birth. (9)

Screening tests for Down's syndrome

Screening for chromosomal defects in the first trimester instead of the second has the advantage of earlier prenatal diagnosis and consequently less traumatic termination of pregnancy for those couples who choose this option. On the other hand it also identifies those pregnancies with chromosomal abnormalities that are destined to miscarry. Approximately 30% of affected fetuses die between 12 weeks of gestation and term. (7)
In the process of screening for chromosomal abnormalities the approaches taken into account ldepend on geographical location and it's policy and resources available (equipment, skilled physicians, economy): maternal risk factors (history), maternal serum bioochemistry and ultrasound investigation is the leading approaches best documented at this point.

Maternal history:
The pravalence of Down's syndrome increases with advancing maternal age, therefore women over 35 are routinely screened. However, 90 per cent of pregnant women are younger than 35 years and despite beeing at lower risk they give birth to 75-80 per cent of Down's syndrome babies. Women who have allready had a pregnancy affected by Down's syndrome are also offered prenatal diagnosis, based on the finding that their background risk for trisomy is slightly increased. (3)

Maternal serum biochemistry:

In maternal serum B-hCG (beta human chorionic gonadotropin) and PAPP-A (pregnancy associated plasma protein A) is routinely measured in the time period between 10-14 week of gestation. This is called the double test.
In trisomy 21 during the first semester of pregnancy the maternal serum concentration of free b-hCG is higher than normal and PAPP-A is lower. In normal pregnancies b-hCG decreases after the 10^{th} week,whereas. PAPP-A normally increases with gestation. Pregnancy-specific

b-1 glycoprotein (SP1), Alfa-fetoprotein and inhibin-A do not provide a useful distinction between affected and normal pregnancies. (5)

Diagnostic ultrasound

The use of ultrasound imaging has provided a number of basic facilities that are employed as a routine in establishing the precence of fetal life, gestational age, multiple pregnancy and developmental abnormalities.

This technique employs high frequency (3-7,5 MHz), low intensity sound waves, which are transmitted through the abdomen or pelvis by an ultrasound transducer. The transducer consists of piezo electric crystals usually mounted in a curved array. Small groups of crystals are triggered in sequence and each emits a focused ultrasound beam in series of pulses and then receives the reflected signals from within the uterus between the pulses. (ten teachers). There are three forms of real time scanners: linear array, mechanical array and phased array. Only linear and phased array methods are now commonly used. These techniques enable positive identification of moving or pulsatile parts, particular fetal movements and fetal heartbeats. Transvaginal probes of higher frequency are now widely used as they give better imaging of the pelvis. The use of Doppler ultrasound, either pulsed or continous has enabled the measurement of velocity of blood flow through the uterine vessels, umbilical vessels and now, especially in the investigation of chromosomal abnormalities, the flow in ductus venosus. (9)

The routine ultrasound scan:

The scan is usually performed transabdominally, but in some countries the transvaginal route is preferred. The principal aim of this scan is:

-To provide an accurate estimation of gestational age by measurements of the fetal CRL (crown-rump lenght).

-To diagnose multiple gestation, and in particular to identify monochronic twins which are at increased risk of fetal abnormality.

-To identify markers which would indicate a risk of fetal chromosome abnormality, such as Down's syndrome. This is principially achieved by measuring the small pool of fluid underneath the skin at the back of the neck (nuchal translucency)

-To identify fetuses with gross structural abnormalities, such as anencephaly or encephalocele. (3)

Crown-Rump lenght in chromosomally abnormal fetuses

In the first 90 days of pregnancy, the most accurate measurement for estimation of gestational age is the measurement of crown-rump lenght.

Chromosomal abnormalities is often associated with low birth weight. Studies examining first trimester growth in chromosomally abnormal fetuses have demonstrated that trisomy 18 and triploidy are associated with moderately severe growth restriction, trisomy 13 and Turner syndrome with mild growth restriction, whereas in trisomy 21 growth is essentially normal (side6). Therefore, a policy of routine pregnancy dating by measurement of crown-rump lenght will not affect the interpretation of results in screening by nuchal translucency thickness for trisomy 21, whereas in the other chromosomal abnormalities it will actually improve their detection, since nuchal translucency normally increases with gestation. (7)

Two phenotypic features described by Dr Langdon Down in 1866 have been currently implemented into fetal Down syndrome screening. These are poor skin elasticity, and a flat face with a small nose. The excess skin of Down syndrome individuals can be assessed by ultrasond as either nuchal translusency in the first trimester or increased nuchal fold in the second.

Nuchal translucency

Nuchal translucency is an increase in the thickness and translucency of the skin over the neck. It is more specific for Down¨s syndrome and is best detected between 10-14 week of gestation.

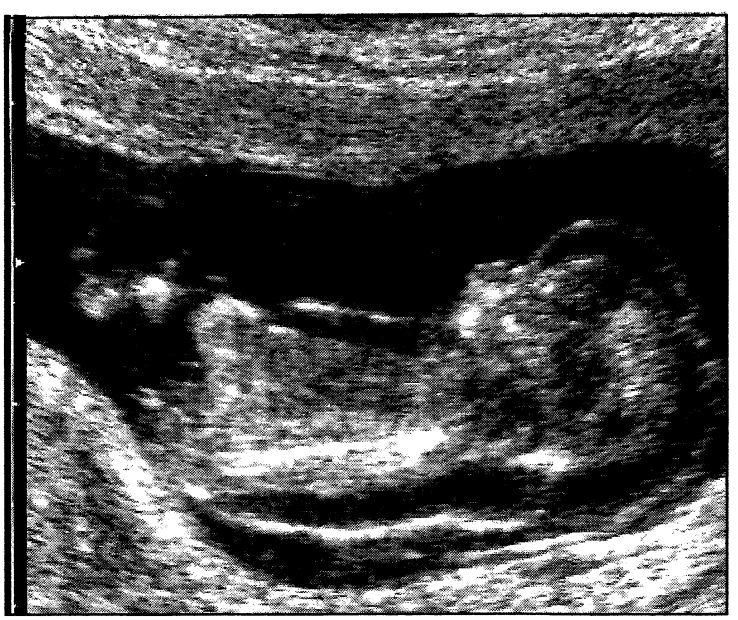
In addition to its role in the assessment of risk for trisomy 21, increased nuchal translucency thickness can also identify a high proportion of other chromosomal abnormalities and is associated with major defects of the heart and great arteries, and a wide range of skeletal dysplasias and genetic syndromes. Possible mechanisms for increased nuchal translucency include cardiac failure, venous congestion in the head and neck due to superior mediastinal

compression, altered composition of the extracellular matrix, abnormal or delayed development of the lymphatic system, failure of lymphatic drainage due to impaired fetal movements, fetal anemia or congenital infection.

The term translucency is used the first trimester, because this is the feature observed ultrasonographically, but during second semester it may develop into either nuchal edema or cystic hygromas with or without generalized hydrops.

Nuchal translucency is in 95 % of the cases measured successfully by transabdominal ultrasound, in the remainig transvaginal ultrasound is neccesary to obtain a satisfactory result.

The equipment must be of good quality, it should have a video loop function and the callipers should be able to provide measurements to one decimal point. The average time for each ccan should be at least 10 minutes. And all sonographers should be able to obtain a correct crown-rump length and a proper saggital view of the fetal spine for measurement of the nuchal translucency.



Increased nuchal translucency and exomphalos in a trisomy 18 fetus at 12 weeks of gestation (7)

The optional gestational age for nuchal translucency measurement is between 11 to 13 week. The success rate is then 98-100%. At 14 week the success rate falls to 90% and later than that the investigation is getting more difficult due to the fetal vertical position.The crown-rump lenghth should be within range 45mm to 84mm. (7)

The nuchal translucency should be measured with the fetus in the neutral position. If the neck is flexed, the measurement can be decreased with 0,4 mm and if the neck is hyperextended it can be increased with 0,6mm. Care must be taken to distinguish between fetal skin and amnion because at this time of gestation, both structures appears as thin membranes.

The ability to measure nuchal translucency and to obtain reproducible results improves with training. Good results are achieved after 80 and 100 scans for the transabdominal and the transvaginal routes, respectively.

Recent studies is published to determine the performance of screening for Down's syndrome and other major chromosomal abnormalities using nuchal translucency, free ß-human chorionic gonadotropin and pregnancy associated plasma protein-A (double test). The studies show that the double test alone detected 73% of chromosomal abnormalities whilst together with Nuchal translucency 91% was detected. (6)

Nasal bone

It has been shown that ultrasound can be used to assess the nasal abnormality that manifests as absent nasal bone in the first trimester or more usually nasal hypoplasia in the second trimester. Later studies has now reported that a new parameter called prenasal thickness hypothesized associated with the poor skin elasticity, in combination with nasal bone lenght could yield a higher screening detection rate than nasal bone alone. (8)

Doppler Ultrasound

The ability to study blood flow non-ivasively in the fetus, in the two placental circulations, and in thenewborn is a major development in perinatal medisine. Clinical applications for this technology are still being established as the necassity evaluative studies and clinical trials are carried out. Perinatal blood flow studies are now a potentially widely available clinical tool.

Doppler ultrasound makes use of the phenomenon of the Doppler frequency shift, where the reflected wave will be at a different frequency from the one transmitted if it interacts with moving structures, such as red blood cells flowing along a blood vessel. If the red blood cells are moving towards the beam, the reflected signal will be at a higher frequency than the transmitted one and lower if the flow is away from the beam. The y-axis records the height of the doppler shift and the x-axis records the time. Color coding of frequency shifts make blood flow easily seen. The measurements from the venous waveforms obtained are demonstrated in the figure below: (2)

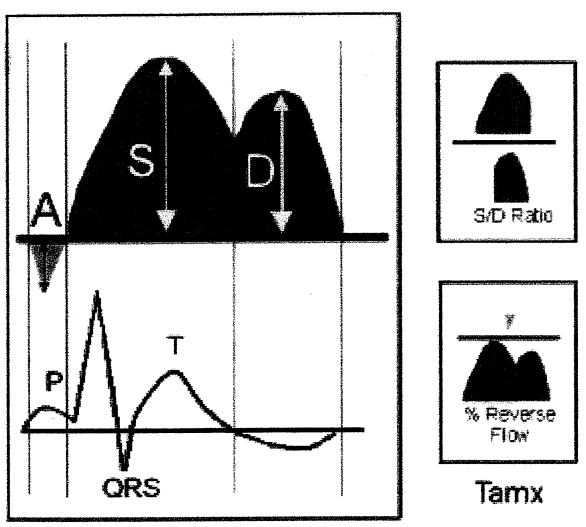


Figure 1 The upper panel represents the venous waveform, correlated with the EKG in the lower panel. A = atrial systole, S = ventricular systole, D = early ventricular diastole. The colored portions of the waveform represent the Tamx for atrial systole (gold), ventricular systole (red), and early ventricular diastole (blue). The yellow arrows represent the measurement of the peak velocity for ventricular systole and early ventricular diastole. The black arrow represents the peak velocity for atrial systole.

Recent studies has demonstrated an increased importance in using the ductus venosus flow in the detection of chromosomal abnormalities. Other vessels like umbilical vein, inferior vena cava and middle cerebral arteries have also been studied but turned out to reflect lower sensitivity thsn ductus venosus.

The ductus venosus is a tiny vein connecting the umbilical circulation directly to the inferior vena cava. Highly oxygenated blood from the placenta flows through the ductus venosus directly towards the foramen ovale and the left atrium. Flow velocity waveforms in the ductus venosus are characterized by a peak during ventricular systole (S-wave), another peak during venricular diastole (D-wave) and a nadir during atrial contraction in late diastole (A-wave). In contrast to the neighboring inferior vena cava and hepatic veins, the blood flow normally remains orthograde during atrial contraction. Doppler studies of the fetal circulation have demonstrated the importance of the ductus venosus in the continous monitoring of fetuses with intrauterine growth restriction due to placental insufficiency. Studies demonstrating an association between abnormal flow patterns and fetal chromosomal abnormalities, congenital cardiac defects or adverse pregnancy outcome in high risk patients and in the general population have recently raised interrest in ductus venosus Doppler studies at 10-14 weeks of gestation. In these studies, increased values of the pulsatile index for veins (PIV) and absent or reversed flow during atrial contraction were correlated with abnormal pregnancy outcome. (4)

An article published in 2005 Borell et al reported that the median PIV in Down's syndrome was 1,70 times higher than in unaffected pregnancies. And that modelling predicts that for a fixed 5% false-positive rate, the addition of PIV to nuchal translucency alone will increase the detection rate from 76 to 85%, and combined with serum markers, from 88 to 92%. (1)

CONCLUSION

Examination of ductal flow is time consuming and require skilled operators. It is therefore unlikely that this assessment will be incorporated into the routine first-trimester scan. However, the data suggest that the assessment of ductal flow can potentially play a role as a secondary method of screening in order to achieve a major reduction in the false-positive rate of primary screening for chromosomal abnormalities by a combination of maternal age, nuchal translucency and maternal serum free b-hCG and PAPP-A at 11-14 weeks. A policy of reserving invasive testing only for those with abnormal ductal flow could reduce the overall need for chorionic villus sampling from 5%, with a small reduction in the estimated sensitivity of 90%.

REFERENCES

1. **Antoni Borell, Anna Gonce, Josep M. Martinez, Virginia Borobio, Albert Fortuny, Oriol Coll and Howard Cuckle.** 2005
First-trimester screening for Down syndrome with ductus venosus Doppler studies in addition to nuchal translucency and serum markers
Prenatal diagnosis 2005; **25**: 901-905

2. **Creasy and Resnik**
Maternal – Fetal medicine, principles and practice
Third edition

3. **E.Malcolm Symonds and Ian M.Symonds**
Essential obstetrics and gynaecology, Churchill Livingstone
Fourth edition

4. **F.Prefumo, D.Risso, P.L. Venturini and P.De Biaso.** 2002
Reference values for Ductus venosus Doppøer flow measurements at 10-14 weeks of gestation
Ultrasound Obstet Gynecol 2002; **20**: 42-46

5. **Kevin Spenser, Christina K.H, Nicolas J. Cowans, Chineze Otigbah and Kypros H.Nicolaides.** 2005
Prediction of pregnancy complications by first-trimester meternel serum PAPP-A and free ß-hCG and with second trimester uterine artery doppler
Prenatal diagnosis 2005; **25**: 949-953

6. **K.R.Wøydemann, A:C: Shalmi, M. Christiansen, S.O. Larsen, K. Sundberg, V.Brocks, J. Bang, B. Nørgaard-Pedersen and A. Tabor** 2005
Improved first-trimester Down syndrome screening performance by lowering the false-positive rate: a prospective study of 9941 low-risk women
Ultrasound Obstet Gynecol 2005; **25**: 227-233

7. **Kypros H. Nicolaides, Neil J. Sebire, Rosalinde J.M. Snijders and Renato Ximenes**

The 11-14 weeks scan

Diploma in fetal medicine series, ISUOG educational series

8. **Ron Maymon, Orna Levinsohn-Tavor, Howard Cuckle, Yosef Tovbin, Eli Draezen, Yifat Wiener and Arie Herman** 2005

Second trimester ultrasoundprnasal thickness combined with nasal bone length: a new method of Down syndrome screening

Prenatal diagnosis 2005: **25**: 906-911

9. **Stuart Campbell and Christoph Lees**

Obstetrics by ten teachers

Seventeenth edition